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The relationship between menopausal hormone therapy and keratinocyte carcinoma: A review☆

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ABSTRACT

Introduction: Keratinocyte carcinoma (KC) is the most common malignancy in the United States. The two most common forms of KC are basal cell carcinoma and squamous cell carcinoma (SCC), which account for 80% and 20% of cases, respectively.
Objective: There are many well-established risk factors for KC, but a more controversial risk factor for KC development is menopausal hormone therapy (MHT). This review synthesizes existing information on this topic and identifies knowledge gaps for future study.
Methods: A systematic review of the literature using the Medical Subject Headings terms "menopausal hormone therapy; skin neoplasms" was conducted in the PubMed database from March 19, 2018 to April 1, 2018. This yielded 168 articles, case reports, and reviews, which were further refined for inclusion during the development of this manuscript. Additional articles were identified from cited references.
Results: Four studies pertaining to this topic were identified. The results were evaluated in the context of these studies' strengths and weaknesses. MHT contributes to an increased risk of basal cell carcinoma in Caucasian subjects and may make these tumors histologically more aggressive. There is not enough evidence to make a conclusion with regard to a potential relationship between MHT and SCC. However, one study suggested an increased risk of SCC with MHT use and another demonstrated a temporal association with prolonged MHT use and increased risk of SCC development.
Conclusion: Ever users of MHT should be screened more frequently for KC. This issue is of importance to dermatologists because patients who receive earlier diagnoses of KC will have a better opportunity to pursue treatment.

Introduction

Background

Keratinocyte carcinoma (KC) is the most common malignancy in the United States. The two most common forms of KC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which account for 80% and 20% of cases, respectively (Albert and Weinstock, 2003). Between 2007 and 2011, the treatment costs for KC in the United States averaged $4.8 billion annually and demonstrate the significant burden of the disease on the U.S. health care system (Guy et al., 2015).

An estimated 20% of 70-year-old adults living in the United States have had at least one KC in their lifetime (Stern, 2010). This percentage will likely increase over the years as the average number of adults who are treated for KC in the United States is increasing (Guy et al., 2015). When considering the prevalence of these tumors, understanding risk factors that contribute to their development is extremely important.

Well-established risk factors for KC include solar ultraviolet radiation exposure, fair skin, exposure to ionizing radiation, prior history of skin cancer, and genetic factors. A more controversial risk factor for the development of these cutaneous neoplasms is menopausal hormone therapy (MHT). Case control studies have reported an association between ever using MHT and an increased risk of KC. One study suggests that women who have taken hormone therapy represent a high-risk population in need of more frequent skin cancer screening (Cahoon et al., 2015). This issue is of particular importance to

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women's health because MHT in lower doses continues to be an accepted treatment for menopausal symptoms (Birkhäuser and Reinecke, 2008).

Objective

The primary objective of this systematic review is to provide a summary of the body of evidence available with regard to the potential relationship between hormone therapy and the development of BCC and SCC as reported in clinical trials to date. This area has received increased attention in the past 10 years, and consolidating findings in one place will facilitate for clinicians to better understand the risk profiles of their patients. Additionally, synthesizing the literature will help identify knowledge gaps for further study.

Methods

A review of the literature using the PubMed database was conducted with the search terms "menopausal hormone therapy skin neoplasms." The Medical Subject Headings terms used in the search were "hormone replacement therapy; skin neoplasms." The search was conducted from March 19, 2018 to April 1, 2018. The search yielded 168 articles, case reports, and reviews, which were further refined for inclusion during the development of this manuscript. Additional articles were identified from cited references. Only English-language articles were included.

General principles

The average age of women at the onset of menopause in the United States is 49.1 years (Nichols et al., 2006). Due to an increased life expectancy, Western women can now expect to spend more than one-third of their lifetime after menopause, which underscores the importance of postmenopausal health care (Brincat et al., 2005).

Notably, 60% to 80% of women experience vasomotor symptoms of warmth, flushing, and perspiration at some point during the menopausal transition, and a sizable minority report symptoms that persist well into their sixth and seventh decades of life (Barnabei et al., 2005; Thurston and Joffe, 2011). Vasomotor symptoms are associated with poorer quality of life, negative mood, and sleep problems during midlife (Thurston and Joffe, 2011). Estrogen was approved by the U.S. Food and Drug Administration in 1942 to treat symptoms of menopause.

In 1991, the Women's Health Initiative (WHI) was initiated by the United States National Institutes of Health to study the effects of MHT, which is an umbrella term for both estrogen-only and estrogen-plus-progesterone treatments. The trial found an association between MHT and increasing rates of cardiovascular disease and breast cancer in post-menopausal women; however, MHT in lower doses continues to be an accepted treatment for menopausal symptoms (Birkhäuser and Reinecke, 2008; Shook, 2011). In fact, a survey of 600 European and U.S. gynecologists, obstetrician/gynecologists, and general practitioners found that 97% of providers concluded that the majority or all of their patients experienced positive benefits from MHT (Birkhäuser and Reinecke, 2008).

Currently, the initiation of MHT is considered a safe option for healthy, symptomatic women who are within 10 years of menopause or <60 years of age and do not have contraindications to MHT (Stuenkel et al., 2015; North American Menopause Society [NAMS], 2017). Contraindications to the initiation of MHT include a history of breast cancer, coronary heart disease, previous venous thromboembolic event or stroke, or active liver disease. MHT in women with an intact uterus should consist of estrogen-plus-progesterone therapy as opposed to estrogen alone to prevent the occurrence of endometrial hyperplasia and carcinoma (Beral et al., 2005). Women who have undergone a hysterectomy receive estrogen alone because there is no known health benefit to adding a progestin in this population.

With regard to the recommended duration of menopausal hormone therapy, both the NAMS and the American College of Obstetrics and Gynecology agree that the use of MHT should be individualized, with use after age 60 years or even 65 years deemed reasonable when benefits outweigh the risks (American College of Obstetrics and Gynecology, 2014; NAMS, 2017).

The benefits of MHT include the treatment of vasomotor symptoms and genitourinary syndrome of menopause. Additionally, MHT has been shown to prevent bone loss and fracture (NAMS, 2017). The risks of MHT include an increased likelihood of developing heart disease, myocardial infarction, stroke, and breast cancer. As a result, the U.S. Food and Drug Administration added a black-box warning in 2003 to outline these risks on labels of estrogen-plus-progesterone and estrogen-alone drug products intended for use in postmenopausal women (Anderson et al., 2004; Manson et al., 2013; Rossouw et al., 2002).

Relationship between menopausal hormone therapy and skin cancer

Mechanistic understanding

Estrogens and progestins play an important role in skin physiology and pathophysiology, including improving the content and quality of collagen, increasing skin thickness, enhancing vascularization, and increasing mitotic activity in the epidermis of women (Brincat, 2000; Punnonen, 1972). Estrogens and progestins are photosensitizing agents (Cooper and George, 2001; Harber and Baer, 1972; Sedee and van Beijersbergen, 1985; Silver et al., 2003) known to induce keratinocyte proliferation, and important modulators of epidermal carcinogenesis (Thornton, 2002; Urano et al., 1995).

Many studies have attempted to elucidate the relationship between estrogens and KC. Exogenous estradiol administration has been shown to enhance the development of BCC and SCC in rodents (Lupulescu, 1981). The effects of estradiol and other estrogens are mediated by estrogen receptors. The two known forms of estrogen receptors are alpha and beta. Keratinocytes express both estrogen receptors (ER)-α and ER-β, and at physiological concentrations, estradiol only upregulates the level of ER-α receptors (Verdier-Sevrain et al., 2004).

ER-β is an important tumor suppressor and its expression is lost in various cancers. In murine skin, the ER-β agonist Erb-041 downregulates Wnt/β-catenin, which is a pathway known to be associated with the pathogenesis of skin cancer (Di Piazza et al., 2012). Because estrogen-induced isolated ER-α upregulation reduces the relative effects of ER-β, this could explain the relationship between estrogen and epidermal carcinogenesis. This is in accordance with the findings by Mancuso et al., who proposed a potential association between ER-α/ER-β imbalance and KC in mouse models of the skin (Mancuso et al., 2009). Interestingly, this phenomenon has been studied in ovarian cancer as well, with progression to ovarian cancer associated with a change in the ratio of ER-α to ER-β, with ER-α generally higher than ER-β (O'Donnell et al., 2005; Pujol et al., 1998; Rutherford et al., 2000).

The proposed mechanism of the relationship between progestins and skin cancer is more straightforward, as progesterone has been shown to downregulate Wnt/β-catenin signaling (Kim et al., 2018; Wang et al., 2009).

Further study is needed to better characterize the effect of exogenous estrogen therapy in cutaneous models. In the meantime, understanding the available information on the potential association of

Table 1
Summary of studies reviewed

Research study	Type of study	Methods	Findings	Limitations	Takeaway
Tang et al., 2011	Post hoc analysis of multisite, double-blind, randomized placebo-controlled WHI study	27,347 postmenopausal women in United States with no history of cancer other than previous KC identified. Women randomly assigned to conjugated equine E (0.625 mg/d) plus P (2.5 mg/d) or placebo in the E + P trial if intact uterus (n = 16,608) or conjugated equine estrogen alone or placebo in E-alone trial if hysterectomy (n = 10,739). Mean follow-up 5.6 and 7.1 years, respectively.	1800 KC cases identified. No effect of combined E + P alone or E-alone on number of incident cases of self-reported KC. E + P vs. placebo: 494 vs. 486 cases, HR = 0.95, 95% CI: 0.83-1.07, $p = .38$ E-alone vs. placebo: 406 vs. 414 cases, HR = 1.03; 95% CI: 0.89-1.18; $p = .73$	Major risk factors for skin cancer (including sun exposure, sunburns, number of nevi, family history, and skin type) not collected. Post hoc analysis of the WHI hormone therapy trials (terminated early because of identified health risks of MHT. Follow-up time was limited and adherence low). All KC cases were self-reported and no validation occurred. KC was evaluated together with no distinction between BCC and SCC.	No relationship found between MHT and KC.
Birch-Johansen et al., 2012	Post hoc analysis of prospective Diet, Cancer, and Health cohort	Total of 29,875 cancer-free women born and residing in Denmark enrolled in study from 1993 to 2007. Participants completed lifestyle questionnaire. Total of 27,176 women with available information on MHT use at baseline identified and included in the analyses. Denmark KC skin cancer database used to retrieve all incident KC cases from the cohort. Median follow-up was 11.5 years.	Total of 1175 BCC cases and 76 SCC cases were diagnosed. BCC: Ever use of MHT at baseline associated with 15% significantly increased risk of BCC. BCC risk not associated with duration of MHT use. SCC: No association between MHT use at baseline and risk of SCC. Significantly increased SCC risk of 1.35 (95% CI: 1.05-1.72) associated with every 5 years of MHT use at baseline. No significant difference between different types of MHT ($p = .80$).	Risk estimates for SCC had relatively low precision due to the limited number of SCC cases diagnosed (n = 76.). Women required to recall details about timing and duration of MHT use (recall bias). Lack of diversity in study population.	Ever use of MHT associated with 15% increased risk of BCC. No relationship found between ever use of MHT and SCC risk, but every 5 years of MHT contributed to increased risk of SCC.
Cahoon et al., 2015	Post hoc analysis of prospective U.S. Radiologic Technologists cohort	Total of 143,517 Americans certified by American Registry of Radiological Technologists were enrolled. Participants completed 3 lifestyle questionnaires (one from 1983-1989, second from 1994-1998, third from 2003-2005). Total of 46,100 white women who had completed both second and third questionnaires and were cancer-free at time of second questionnaire identified and followed. Self-reported BCC from group was recorded; BCC discovered during medical record validation also included. Study authors estimated 10 years of follow-up time.	Total of 1730 BCC cases identified. Elevated risk of BCC associated with any MHT use compared with never users (HR: 1.16; 95% CI: 1.03-1.30). BCC risk most increased among women who used MHT for ≥10 years compared with never users (HR: 1.97; 95% CI: 1.35-2.87).	No information comparing demographics of ever and never users of MHT provided. Recall bias a factor because women had to remember details about baseline MHT use. Study population limited to white women. Non-validated self-reported BCC included in analysis.	MHT use associated with elevated BCC risk, especially among women who used MHT for ≥10 years.
Kuklinski et al., 2016	Retrospective case control study with cases identified from 1979-1980 and 1993-1994 New Hampshire Skin Cancer Study	Histologically confirmed cases of invasive newly diagnosed SCC and BCC identified near New Hampshire. Controls chosen from Center for Medicare enrollment lists or driver's license records provided by New Hampshire Department of Transportation. 84% of cases and 73% of controls interviewed to provide information about previous exposures. Dermatopathologists evaluated each case, documenting presence or absence of actinic keratosis for SCC, histology type for BCC (infiltrative, sclerosing, morpheaform, and micronodular vs. other), and level of solar elastosis (mild/moderate/severe) in tumor-adjacent dermis for BCC and SCC to determine whether tumor had aggressive histology.	Total of 570 SCC cases and 746 SCC controls, and 550 BCC cases and 633 BCC controls. Both current and former MHT use associated with increased risk of SCC (OR: 1.4; 95% CI: 1.1-1.8). Ever use of MHT associated with more aggressive BCC histology (OR: 3.3; 95% CI: 1.3-8.8).	True retrospective case control study, so recall bias more of a limitation in this study than all other studies. Study population limited to Americans on U.S. East Coast.	Current and former MHT use associated with increased risk of SCC. Former MHT use associated with more aggressive BCC histology.

BCC, basal cell carcinoma; CI, confidence interval; E, estrogen; HR, hazard ratio; KC, keratinocyte carcinoma; MHT, menopausal hormone therapy; P, medroxyprogesterone acetate; SCC, squamous cell carcinoma; WHI, Women's Health Initiative.

MHT and skin cancer in humans is critical to provide optimal patient care.

Literature review: Keratinocyte carcinoma and menopausal hormone therapy

In recent years, four studies have examined the relationship between MHT and KC (Table 1). The results were somewhat disparate, with Tang et al. (2011) reporting no relationship between MHT and KC and all other groups identifying an increased KC-risk associated with MHT use. To obtain a nuanced understanding of this topic, a consideration of these four studies' results in light of their strengths and limitations is important.

From a clinical research perspective, the gold standard for study design is a multisite randomized controlled trial. Of all trials that examined the relationship between MHT and KC, only the findings by Tang et al. (2011) fit this category. Tang et al. ultimately found that there was no relationship between MHT and the risk of KC when patient groups taking either estrogen alone or estrogen plus progesterone were compared with placebo. This study had many strengths and was well-powered with a total of 24,347 ethnically diverse women and only 1146 participants (4.7%) lost to follow up. Furthermore, Tang et al. (2011) researched any effect of MHT on KC incidence within high-risk subgroups on the basis of the following characteristics: age, body-mass index (BMI), regional solar radiation, history of KC, smoking status, and nonsteroidal anti-inflammatory drug use. No associations were found.

However, this study was not without significant limitations. The study examined the association between MHT and KC without separating the incidences of BCC and SCC into two different outcomes. This is significant because other studies on this topic found associations between MHT and incidence of one of these KCs, but not necessarily the other. Additionally, major risk factors for skin cancer including individual sun exposure, history of sunburns, number of nevi, family history of skin cancer, and skin type were not collected in the trials.

Furthermore, and probably most importantly, this study was a post hoc analysis of the WHI hormone therapy trials, which were terminated early because the identified health risks of MHT, including stroke, were found to outweigh any potential benefits. Thus, the mean follow-up time of the estrogen-plus-progesterone trial was only 5.6 years, and the mean follow-up time of the estrogen-alone trial was not much longer at 7.1 years.

This is in contrast with cohort studies performed by Cahoon et al. (2015) and Birch-Johansen et al. (2012), who reported follow-up times of ≥10 years and included women who had been taking MHT for up to 10 years at baseline. Furthermore, cases of KC were self-reported by study participants and not validated. Finally, Tang et al. (2011) reported low participant adherence to therapy, and at the time each trial was terminated, 42% of estrogen-plus-progesterone and 54% of estrogen-alone trial participants had stopped taking the study pills.

Although a sensitivity analysis that was restricted to women who adhered to treatment did not show an effect of hormone therapy on the risk of skin cancer, a consideration of the climate and controversy surrounding the WHI trials and the concerns these women had about their health is important. A possibility exists that adherence to therapy, determined by the weighing of medication bottles at the time of the annual visits, was not accurately assessed. For example, women could have thrown away their pills before their appointments. Thus, the Tang et al. trial had the best initial study design, but its limitations could explain the disparate results between this group and others.

Although the multisite, randomized, controlled trial is considered the gold standard for study design, other approaches continue to yield important information that can be useful for patient care. Birch-Johansen et al. (2012) and Cahoon et al. (2015) also examined the relationship between MHT and KC. Both groups conducted post hoc analyses on prospective cohort studies, and both found an increased risk of BCC in women taking MHT.

Birch-Johansen et al. (2012) conducted analyses on data gathered from the Diet, Cancer, and Health prospective cohort study of 29,875 cancer-free women who were born and resided in Denmark. These researchers found that ever use of MHT was associated with a 15% increased risk of BCC, but the number of years of MHT use was not determined to have an effect. No association was found between ever use of MHT and overall SCC risk, but every 5 years of MHT did contribute to an increased risk of SCC. The incidence rate ratio for SCC was 1.35 (95% confidence interval [CI]:1.04-1.72) for every 5 years of MHT use.

As previously mentioned, this trial was not randomized but is not without strengths. The demographics of MHT ever and never users were compared and grossly similar. MHT ever users at baseline had a higher level of alcohol consumption, but factors including distribution of skin reaction when exposed to strong sunlight, degree of freckles, degree of nevi, and BMI were similar between the groups. Probably the most significant strength of this trial is that it was conducted in Denmark, a country with an established KC database. This database is a compilation of information from the Danish Cancer Registry and Danish Registry of Pathology, and contains all incident BCC and SCC cases diagnosed in Denmark between 1978 and 2007. The authors reported virtually absent losses to follow up as a result of the precise linkage between their cohort and the Danish population-based registries. The median follow-up time was lengthy at 11.5 years.

As for this trial's weaknesses, women were required to recall details about the timing and duration of their MHT use, making recall bias a factor. Moreover, the significance of the SCC findings is dubious due to the low number of SCC diagnoses, with 1251 KC cases diagnosed in this cohort of which only 76 were SCC. Additionally, the trial was limited to the primarily white population of Denmark.

Cahoon et al. (2015) performed a post hoc analysis of data from the prospective U.S. Radiologic Technologists cohort study. In this study, 46,100 cancer-free, white American women who had completed two lifestyle questionnaires were identified and followed. Cahoon et al. found an increased risk of BCC associated with any use of MHT compared with never users, and the risk was most significantly increased in women who had used MHT for ≥10 years. A total of 1730 cases of BCC were diagnosed. SCC was not evaluated.

The most significant strength of this trial is its length of follow up. More than 20% of MHT users in this cohort reported a duration of MHT use of ≥10 years at baseline and were observed for up to an additional 10 years. Moreover, the study authors collected information on personal sun sensitivity characteristics; lifetime ambient ultraviolet radiation exposures on the basis of location of residence; and reproductive, lifestyle, and anthropometric factors. The final model for MHT use was adjusted for age, birth cohort (5-year incremental age groups), dental x-rays, BMI category, alcohol use, Celtic/Gaelic heritage, and ambient ultraviolet radiation.

With regard to this study's weaknesses, the study authors included demographic information that compared women who did and did not develop BCC, but no information to compare the demographics of ever and never users of MHT was provided. Additionally, the study population was exclusively composed of white American women and thus not diverse. Moreover, recall bias was a factor because women had to remember details about baseline MHT use. Finally, incident BCC was identified through self-reporting, and medical records were obtained only for 840 women (52%) of BCC cases. Of these 840 medical records, 809 cases (96%) were confirmed and 31 cases (4%) were denied. The authors found this confirmation

rate for self-reported BCC satisfactorily high and included the remaining 778 self-reported BCCs for which no medical records were obtained. The researchers also included an additional 112 BCC cases that were identified during a medical validation of the reported cancers other than BCC.

The final trial to examine the relationship between the use of MHT and KC was conducted by Kuklinski et al. (2016). This was a retrospective case control study with histologically confirmed cases of invasive newly diagnosed SCC and BCC obtained from the New Hampshire area in the United States. The controls were identified in the same region. Kuklinski et al. found a positive association between current and former MHT use and SCC risk. The study included a dermatopathologic assessment of the tumors and determined that former MHT use was associated with more aggressive BCC histology. Notably, the authors found no association between MHT use and BCC incidence, which is in accordance with the findings by Tang et al. (2011) but contradicts the findings by both Birch-Johansen et al. (2012) and Cahoon et al. (2015).

The strengths of this trial include the fact that all cases were histologically validated, unlike other trials that included subject-reported non-validated cases. Additionally, this trial was the first to comment on the histologic profile of the KC cases. The effects of potential confounding factors were assessed, including skin reaction to first sun exposure, education level, family history of KC, number of hours spent outdoors between 9:00 a.m. and 5:00 p.m. during the summer and recreationally, number of lifetime painful sunburns, and smoking status. The final models were constructed using each hormone variable, and confounders that changed odds ratios (ORs) by >10% were deemed clinically relevant.

When considering the retrospective nature of the study, weaknesses included the effect of recall bias. Although participants were provided with photographic aids to assist in the recall of medications, the timing and duration of MHT use were solely based on subject recollection. Finally, because the study population was limited to Americans residing on the East Coast of the United States, the study population was not diverse. The study also did not report on ethnicity.

Conclusion

When considering the strengths and weaknesses of all trials, MHT use appears to contribute to an increased risk of BCC in Caucasian subjects, and may make these tumors more aggressive histologically (Birch-Johansen et al., 2012; Cahoon et al., 2015; Kuklinski et al., 2016). Birch-Johansen et al. (2012) and Cahoon et al. (2015) both performed post hoc analyses of prospective cohort studies, and both groups found an increased risk of BCC with MHT use. Birch-Johansen et al. reported a 15% significantly increased risk of BCC in MHT ever users and Cahoon et al. had similar findings (hazard ratio [HR]: 1.16; 95% CI: 1.03-1.30). Despite the limitations of the trial by Birch-Johansen et al. (2012), its findings with regard to BCC appear accurate when considering the following factors: adequate number of BCC diagnoses (n = 1175), no controversy surrounding the trial that resulted in premature termination (as with the WHI trial), median follow-up time was high at 11.5 years, and KC incidence was taken from a comprehensive national registry. The trial's weaknesses with regard to BCC primarily comprised recall bias and lack of a diverse patient population. These limitations were observed in all trials except the multisite, double-blind, randomized, controlled trial by Tang et al. that was conducted with WHI data (which was problematic for the reasons outlined). Particularly of note is the fact that Tang et al. studied an association between MHT and KC as a whole without separating BCC and SCC into separate outcomes. In terms of a potential association between MHT and more aggressive histological characteristics of BCC, the retrospective case control study by Kuklinski et al. (2016) found more aggressive BCC histology in users of MHT, but it was also the only study that commented on histology. Thus, further study is warranted to better characterize this relationship.

There does not yet appear to be enough information to make a conclusion with regard to the potential relationship between MHT and SCC, although one study suggested an increased risk of SCC with MHT use and another demonstrated a temporal association between length of MHT use and risk of KC development (Birch-Johansen et al., 2012; Kuklinski et al., 2016). Further study is warranted because not only were the findings disparate, there was also a low number of SCC cases diagnosed in the study by Birch-Johansen et al. while Cahoon et al. did not evaluate any cases of SCC, and Tang et al. studied KC as a whole without evaluating BCC and SCC as separate outcomes.

Of the four studies, the retrospective case control study by Kuklinski et al. was the only study to determine that ever use of MHT was associated with an increased risk of SCC (OR: 1.4; 95% CI: 1.1-1.8). In this study, an adequate number of SCC cases was reported (n = 570). The post hoc analysis of prospective cohort data by Birch Johansen et al. found no association between MHT use at baseline and risk of SCC but did report a significantly increased SCC risk of 1.35 (95% CI: 1.05-1.72) associated with every 5 years of MHT use at baseline. Notably, Birch-Johansen et al. (2012) identified only 76 cases of SCC. The multisite, double-blind, randomized, controlled trial conducted with WHI data by Tang et al. (2011) found no relationship between MHT and KC, and the post hoc analysis of a prospective cohort by Cahoon et al. did not report SCC.

The relationship between MHT and KC is an interesting topic that warrants further study. In the meantime, dermatologists should be aware of the plausible mechanistic relationship between hormones and these carcinomas, as well as the available findings that suggest a potential for increased KC risk in MHT ever users. Most women take MHT for ≤10 years, but some women with severe symptoms are prescribed prolonged MHT. When caring for these patients, both dermatologists and providers who prescribe MHT should be aware of the potential association with increased skin cancer in this population so that they can properly counsel patients and, taking other patient risk factors into consideration, adjust the screening frequency accordingly.

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.2018.07.002.

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