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Review

Hormone therapy and melanoma in women

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ABSTRACT

Although primary cutaneous melanoma accounts for approximately 3% of all malignant skin tumors, it has the greatest contribution to skin cancer–related death. Sex-specific differences in melanoma tumor behavior have been described, and melanoma pathogenesis may be hormonally mediated. This review aims to summarize the literature to date regarding the effects of hormone therapy on melanoma in women. Women's exogenous hormone use has changed dramatically over the past few decades. Thus, we focus on studies investigating the associations between oral contraception, fertility treatments, menopausal hormone therapy (MHT), and melanoma. Across hormone therapy types, there does not appear to be a well-established association between exogenous female hormones and melanoma incidence. However, MHT practices and formulations vary significantly across countries. Although MHT does not appear to increase melanoma risk in studies from the United States, conflicting results have been observed in Europe. Unopposed estrogen MHT formulations require further investigation to determine a clear pattern between hormone use and the development of melanoma.

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Introduction

The worldwide incidence of melanoma has increased rapidly over the last 50 years (Guy et al., 2015). Although primary cutaneous melanoma accounts for approximately 3% of all malignant skin tumors, it has the greatest contribution to skin cancer–related death (Aung et al., 2017). There are important differences in the clinical presentation of melanoma with respect to sex, including anatomic location and age of onset (Olsen et al., 2020). Environmental factors such as sun exposure and biological factors such as sex hormones have been postulated to mediate these differences. Melanocytes are known to respond to estrogen stimulation, and in vitro studies have found that skin treated with estrogen can express up to three times the amount of melanin (McLeod at al., 1994; Natale et al., 2016). This concept is well established in

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melasma pathogenesis because the development of this skin hyperpigmentation has been linked to increased estrogen both in oral contraceptive users and pregnant women (Fernandes and Amaral, 2015; Resnik and Collumb, 1967).

The role of estrogen-containing therapies in the development of melanoma has been explored in oral contraceptive pills, assisted reproductive technology, and menopausal hormone therapy, but inconsistent results between studies have been reported. Knowledge of sex-specific differences in melanoma tumor behavior is essential to inform accurate patient prognostication and subsequent evaluation and management. Herein, we summarize the literature to date regarding commonly used estrogen hormone therapies and their influence on melanoma incidence in women.

Recent trends in hormone therapy use

Female exogenous hormone use has changed dramatically over the past few decades. Hormonal contraception usage has increased substantially since 1970, with its prevalence almost doubling from 36% in 1970 to 64% in 2015 (United Nations, 2015). Although oral contraceptive pill use has slowly declined since 2002 in women age 20 to 34 years, its use has increased in women aged 15 to 19 during the same period. Oral contraceptive pills remain the most commonly prescribed method of contraception (Doherty et al., 2017). In addition, within the last decade, many new treatments have been integrated into routine assisted reproductive technology (ART), which describes any fertility treatments in which either eggs or embryos are handled. The overall use of ART has increased worldwide, with in vitro fertilization (IVF) being the most effective and commonly used form (Audibert and Glass, 2015; Kushnir et al., 2017). Women who conceive using IVF go through an average of 2.7 cycles of IVF, with data suggesting that the odds of pregnancy increase after three cycles (Audibert and Glass, 2015). ART gives women the option to start families later; as such, this technology has contributed to a sharp increase in the mean age at first childbearing.

Hormone replacement therapy use has changed dramatically since it became integrated into clinical practice in 1942. Its use in menopausal women peaked in 1999 with 35 million prescriptions in the United States (Crawford et al., 2019). Following the results of two randomized clinical trials initiated by the Women's Health Initiative, however, there was a rapid and subsequent substantial decline in the use of hormone therapies due to the discovered risks associated with its use (Chlebowski et al., 2020; Crawford et al., 2019). The first of the Women's Health Initiative studies examined the risks and benefits of conjugated equine estrogen (CEE) combined with medroxyprogesterone acetate for women with an intact uterus. This study was stopped in 2002 after a median intervention period of 5.6 years, when the risks were deemed to exceed the benefits. Risks of combined therapy included increases in cardiovascular disease and invasive breast cancer (diagnosed at a more advanced stage; Chlebowski et al., 2020; Crawford et al., 2019).

The second study examined CEE alone for women after hysterectomy, and it was also stopped after a median intervention period of 7.2 years owing to increased stroke risk and no overall coronary heart disease benefit, although breast cancer incidence was actually decreased with CEE alone (Chlebowski et al., 2020; Crawford et al., 2019). Overall, MHT has continued to decrease over the past 2 decades, but it is still considered the most effective treatment for menopausal symptoms because it is known to prevent bone loss and reduce fractures in postmenopausal women. Current practice is to carefully weigh the risks and benefits of hormone therapy for each individual patient. The trends in exogenous female hormone use are important to consider in evaluating the incidence of melanoma in women.

Melanoma and oral contraception

A multitude of oral contraception options exist as effective birth control for women (Ely and Hamilton, 2018). Combined estrogen-progestin contraceptives (COCs), also known as oral contraception pills, can provide reliable contraception with additional noncontraceptive benefits for most women (Sech and Mishell, 2015). At a low dose of <50 μg ethinyl estradiol, COCs are a reliable and safe form of contraception until menopause (Brynhildsen, 2014; Hannaford et al., 2010). For women who cannot or prefer not to use estrogen-containing contraception, progestin-only contraception is available in the form of progestin-only oral pills (POPs), an implant, injection, or intrauterine device. POPs are also an appropriate contraceptive option for most women with contraindications for COCs, except individuals with a known or suspected pregnancy, breast cancer, abnormal uterine bleeding, or liver abnormalities (Curtis et al., 2016). Much of the literature to date has focused on the association between the use of COCs and POPs and the risk of malignant melanoma (MM), whereas non–hormonally active contraceptive options have been less well studied.

The hormonal effects of oral contraceptives are known to affect malignancies across multiple organ systems. Oral contraceptive use is inversely associated with ovarian, endometrial, and colorectal cancer incidence, but positively associated with breast, cervical, and liver cancer (Gierisch et al., 2013). The association between oral contraceptive use and melanoma has been controversial. The majority of data on oral contraceptives and melanoma are based on epidemiologic studies evaluating the risk of developing melanoma associated with the use of oral contraceptives (Driscoll et al., 2016). Early case-control studies in the 1980s found that extended oral contraceptive use was associated with melanoma (Beral et al. 1984). In the past 3 decades, multiple cohort studies and three meta-analyses have been performed. Despite significant study heterogeneity, none of the meta-analyses demonstrated an association between oral contraceptive use and risk of melanoma, even when considering important parameters such as age at first use and duration of use (Gandini et al., 2011; Gefeller et al., 1998; Karagas et al., 2002).

A recent prospective cohort study by Cervenka et al. (2018) investigated the association between oral contraceptive use and melanoma risk. The investigators noted 539 melanoma cases among 79,365 women and found no association between oral contraceptive use and melanoma risk. However, oral contraceptive use was positively associated with tanning bed use (odds ratio: 1.14; confidence interval [CI], 1.01–1.29) and sunburns ($p = .05$; Cervenka et al., 2018). These findings highlight the potential confounding effect of environmental factors in the relationship between oral contraceptive use and melanoma.

The literature to date suggests that oral contraceptive use is not associated with increased melanoma risk. Women seeking contraceptive options should be linked to appropriate providers, and history of melanoma should not be viewed as a contraindication for use.

Melanoma and fertility treatments

Fertility drugs are of interest in the context of hormonal influence on malignancy because they expose women to supraphysiological hormone levels. A large prospective cohort of French women born between 1925 and 1950 found that although fertility drug users were more likely to report tanning bed use and sunburn, there was no association between fertility drug use and MM risk, nor was there an effect modification by ultraviolet light exposure (Cervenka et al., 2020). Although most studies do not observe a clear relationship between fertility treatments and melanoma risk, some studies have demonstrated associations within specific

subgroups of patients. Rossing et al. (1995) showed that the risk was increased only among patients who had used clomiphene during 12 or more cycles. Similarly, a study by Calderon-Margalit et al. (2009) found that only women treated with clomiphene experienced a significantly increased risk of MM. A study by Young et al. (2001) demonstrated that exposure to fertility drugs was positively associated with MM in women whose partners were infertile, and negatively associated with melanoma in women with low doses of fertility drugs. Althuis et al. (2005) did not find that clomiphene use significantly raised melanoma risk, but the authors noted that clomiphene use was associated with a heightened risk of melanoma in nulliparous women who were followed for >15 years. Although the results of these studies are inconsistent, they do suggest that clomiphene may be an initiator of carcinogenesis.

Although female infertility has been considered a risk factor for a number of cancers, there is insufficient evidence to support fertility treatment being associated with melanoma (Berk-Krauss et al. 2018; Kroener et al., 2017). A recent review of melanoma risk after IVF indicated a similar pattern of inconsistency among studies. Of the 11 studies that met the inclusion criteria for this review, five showed no increased risk of melanoma among IVF users compared with the general population (Berk-Krauss et al., 2018). Among these studies, there was no consistent pattern of association even after stratifying for specific categories and combinations of fertility drugs, as well as the number of cycles. The data did indicate, however, that there may be an increased risk for ever-parous women treated with IVF in general or with the use of the ovary-stimulating agents clomiphene and gonadotropins (Berk-Krauss et al., 2018). The authors recommended that although there is currently no indication to withhold IVF due to increased melanoma risk, physicians should still discuss the limited findings in current literature and evaluate the risk–benefit analysis carefully.

Melanoma and menopausal hormone therapy

Menopause occurs in women at a mean age of 51 years, with symptoms ranging from vaginal dryness and dyspareunia to hot flashes and night sweats (Pinkerton, 2020). Professional societies, including the Endocrine Society and the North American Menopause Society, recommend hormone replacement therapy for symptom relief within 10 years of menopause onset (Lumsden et al., 2016; Reid et al., 2014). The Endocrine Society recommends menopausal hormone therapy for the management of menopausal symptoms, but not for the prevention of cardiovascular disease or osteoporosis (Grossman et al., 2017; Stuenkel et al., 2015). MHT represents a significant source of exogenous hormone exposure, with many formulations available using unopposed or opposed estrogens with a progestin (The North American Menopause Society, 2017). As such, the association between MHT and melanoma is of clinical interest.

Findings regarding the effect of MHT on MM incidence have varied across research groups and study type. In 2010, Gupta and Driscoll (2010) identified 12 studies and reported that 10 of these showed no association between MHT and melanoma. The remaining two studies did not control for important confounders. One study failed to show an association between longer duration of MHT and increased melanoma risk, which would be expected in the setting of a true association (Gupta and Driscoll, 2010). A systematic review and meta-analysis of 5626 melanoma cases mirrored these findings and failed to detect a significant association between MHT and melanoma (Gandini et al., 2011).

In the past few years, newer European prospective studies have challenged these findings. A large Norwegian study reported a positive association between estrogen-only MHT and melanoma risk but not combined estrogen and progestin MHT and melanoma (Botteri et al., 2017). A recent prospective European cohort study from the European Prospective Investigation into Cancer and Nutrition examined the association between MHT and melanoma risk in 334,483 women. Among postmenopausal women, ever use of MHT was associated with a nonsignificant increase in melanoma risk overall (hazard ratio: 1.14; 95% CI, 0.97–1.43), which was heterogeneous across countries. The authors reported a 53% increased risk of melanoma in women using estradiol and no increased risk in women when using estrogens combined with a progestin. There was no association between duration of MHT use or age at the time of first use and melanoma risk (Cervenka et al., 2020). A Finnish cohort study of 293,570 women found similar results with a significant association between the use of unopposed estrogens and the risk of melanoma for 6 to 59 months (standardized incidence ratio: 1.20; 95% CI, 1.06–1.35), and no association between opposed estrogens and the risk of melanoma (standardized incidence ratio: 1.00; 95% CI, 0.87–1.14; Botteri et al., 2019).

A recent French prospective cohort study found an association between any MHT use and melanoma risk (hazard ratio: 1.35; 95% CI, 1.07–1.71) but failed to demonstrate a difference in melanoma risk between MHT formulations (Cervenka et al., 2019). However, unlike breast cancer, the study did not find that melanoma risk increases linearly with MHT duration or decreases after cessation of use (Cervenka et al., 2019). A U.S. study of 167,503 women failed to replicate an association between MHT use and MM (Donley et al., 2019).

These inconsistent findings may reflect MHT formulation variability across the United States and Europe in terms of potency and proportion of estrogen versus progestin (Cervenka et al., 2019; Lowy and Weisz, 2005). Another possible reason for the inconsistent findings is the different ages of women included in these studies. Donley et al. (2019) had an inclusion criterion of women age >60 years, whereas the other studies did not have specific age-related inclusion criteria, which could suggest that melanoma risk in patients using MHT may be influenced by the age at which this therapy is started.

Progestins and estrogens might affect the melanoma risk in different directions, with estrogens exerting a detrimental effect. In the United States, CEE is widely used and U.S. studies to date have not determined an increased risk of melanoma with CEE, which was confirmed in the European Prospective Investigation into Cancer and Nutrition study (Cervenka et al., 2020). More multinational studies are needed to account for international differences in MHT formulation. Still, women experiencing substantial menopause symptom burden should be treated in accordance with major professional society guidelines. Current guidelines from the American Academy of Dermatology recommend against withholding hormonal therapy when medically appropriate in a patient with a history of cutaneous melanoma (Swetter et al., 2019).

Melanoma and hormone use after gynecologic surgeries

Several studies have investigated the association between the use of MHT and the risk of MM after gynecologic surgery. Hormone therapy is used more often by women after a hysterectomy than after natural menopause, and the use of postoperative estrogen has increased in the past decade (Hicks et al., 2019). However, oophorectomy, rather than hysterectomy, results in surgical menopause. A study by Holly et al. (1994) demonstrated that the risk of melanoma doubled with oral hormone use after hysterectomy, but the risk of melanoma was not increased with oral hormone use after natural menopause.

Holly et al. (1994) further examined the risk of hormone therapy after gynecologic surgery. The investigators observed that the effects of hormone use after hysterectomy were somewhat inconsistent. Women who had a hysterectomy with bilateral oophorec-

tomy were at increased risk for melanoma if they had taken hormones for ≤5 years, but women who had retained at least one ovary were at an increased risk if their hormone use exceeded 2 years. A duration effect of conjugated hormone use was observed for women who retained at least one ovary, but not for those with bilateral oophorectomy, although both groups were exposed to exogenous hormones. Although these inconsistencies may have been due to small sample size in some of the study subgroups, the authors reasoned that oophorectomy may reduce melanoma risk, whereas replacement hormone therapy may increase it (Holly et al., 1994).

Before menopause, estrogen is produced by the ovaries and estradiol predominates. After menopause, estrogen levels decrease significantly, and estrogens are produced mainly by converting androgens to estrone. After bilateral oophorectomy, women may retain estrogen in extraovarian tissues, although they no longer produce ovarian estrogens (Holly et al., 1994). Women who had taken estrogen after hysterectomy were only at increased risk in relation to women who had hysterectomy without hormone treatment. This study, however, did not report any analysis concerning known potential confounders, such as sun exposure. In addition, the length of use of hormone replacement therapy was not associated with an enhanced risk of melanoma, as might be expected if a causal relationship existed. A Canadian study noted an inverse association between bilateral oophorectomy and risk of superficial spreading melanoma (relative risk: 0.5; $p = .02$; Donley et al., 2019). Overall, current studies suggest that hormone therapy after gynecologic surgery is not associated with MM.

Conclusion

Melanoma may be associated with significant patient morbidity and mortality. Therefore, its potential responsiveness to hormones is of clinical interest. The use of exogenous female hormones has changed substantially over the past few decades. Yet, there is limited evidence to suggest oral contraception, fertility treatments, and hormone therapy after gynecologic surgery affects melanoma incidence. The effect of MHT on melanoma risk requires further investigation with multinational studies, given the differences in MHT formulation between countries. Still, the literature to date suggests that women should continue using hormone therapy as recommended by their physician without specific consideration of melanoma risk.

Conflicts of interest

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Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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