REVIEW ARTICLE

CONTENTS

The role of menopausal hormone therapy in hormone-dependent carcinogenic mechanisms in the oral cavity: A literature review

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ABSTRACT

Across the world, the incidence of oral squamous cell carcinoma (OSCC) is increasing, establishing it as one of the most prevalent cancers originating in the oral cavity. Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ) expression were identified and analyzed in normal oral mucosa as well as in squamous cell carcinoma. On a molecular level, estrogens and progestogens, as steroid hormones, influence various biological processes, including reproduction and behavior, by binding to their intracellular receptors. Hypotheses suggest that oral cavity malignancies could be hormonally induced. Periodontal inflammation, mediated by TREM-1, IL-1β, and reduced salivary antibacterial function during hormonal fluctuations, is important in evaluation of etiology of oral cancers and is correlated to hormonal levels. Focal adhesion kinase (FAK) signaling activates ERα through phosphorylation, increasing its transcriptional activity and promoting cell proliferation. Menopausal hormone therapy (MHT) offers both hormonal and non-hormonal treatments, with concerns about overprescription and potential off-label use. In this literature review we aimed to analyze whether there is a link between MHT which consists of estrogen or both estrogen and progesterone and oral cancer risk. A review of the scientific literature covering the years 2018–2025 was carried out, whether estrogens, identified as carcinogens, may be suggested as the potential therapeutic target for OSCC in the future, similar to their well grounded role in the standard management of estrogen receptor-positive breast cancer.

KEY WORDS: carcinogenesis, hormone replacement therapy, oral squamous cell carcinoma, menopausal hormone therapy

Wiad Lek. 2025;78(8):1677-1683. doi: 10.36740/WLek/209542 DOI

INTRODUCTION

Estrogens have been identified as carcinogens, and their action in promoting cancer is the result of complex molecular mechanisms. Recent studies show that a variety of tumors could be hormonally induced during pregnancy or in young female patients without the established risk factors of alcohol or tobacco use [1]. Researchers highlight the impact of estrogen signaling in various cancers, including non-small cell lung cancer (NSCLC), where estrogen may influence tumor progression, potentially modifying patient prognosis and therapeutic outcomes. Additionally, studies in colorectal carcinoma reveal the variable expression of ERβ isoforms, shedding light on their possible clinicopathological and molecular significance. Furthermore, hypermethylation of the promotor region of the ER gene leads to reduction of the expression as well as deregulation of growth of colonic mucosa [2]. Estrogens may reduce serum insulin-like growth factor-I (IGF-I), which is a crucial factor in the pathophysiology of colorectal and other cancers. Estrogens were observed to participate in mechanisms of tumor volume increase, as shown in an experiment on laryngeal carcinoma [3]. ERβ directly regulates the NOTCH1 gene expression during differentiation *via* RNA polymerase II pause release, whereas mutations in NOTCH1 are linked to the onset of squamous cell carcinoma [4]. Selective estrogen receptor modulators (SERMs), such as tamoxifen, effectively target estrogen receptors and inhibit cancer proliferation [5, 6] and have become the gold

standard of anti-estrogen treatment in breast cancer in postmenopausal women [7, 8]. Other widely used drugs are Aromatase inhibitors; anastrozole, letrozole, and exemestane and Selective estrogen receptor down regulators (SERDs); fulvestrant and elacestrant. Furthermore, for malignancies not exclusively hormone-dependent (like endometrial cancer or ovarian cancer), such as colon cancer, glioma, or lung cancer, estrogen receptor-mediated impacts on the pathogenesis are documented [9].

AIM

The aim of this review is to provide information whether the estrogens used in menopausal hormone therapy have the possible impact on carcinogenic mechanisms in the oral cavity. In consequence, whether there are more possible uses of the potential anti-tumor benefits of estrogen-related medicines, which are now being examined. Together, these findings emphasize the need to understand the nuanced role of estrogen receptors in tumor biology to better assess clinical implications of novel targeted therapies [10].

MATERIALS AND METHODS

In this literature review we aimed to analyze whether there is a link between MHT which consists of estrogen or both estrogen and progesterone and the risk of oral cancer development. A review of the scientific literature covering the years 2018–2025 was carried out, whether estrogens may be suggested as the potentially carcinogen for OSCC in the future. We used search of the PubMed and Scopus databases. Keywords used in the search included „menopause", „estrogen", „periodontal inflammation", „gingivitis" and „oral squamous cell carcinoma".

The search included both peer-reviewed articles published in English as well as original articles.

REVIEW AND DISCUSSION

Menopause is a normal phase in a woman's life characterized by the cessation of the monthly cycle and a considerable decline in hormone levels, particularly estrogen. This life stage often manifests in women aged 45 to 55 and is frequently linked with many symptoms, including hot flashes, nocturnal sweats, sleeplessness, vaginal dryness, mood fluctuations, and an elevated risk of osteoporosis and cardiovascular disease [11]. Indications for menopausal hormone therapy (MHT) include severe vasomotor symptoms, such as hot flashes, and the genitourinary syndrome of menopause, characterized by vaginal dryness and associated issues. This medication may also aid in the prevention of osteoporosis, especially in women at elevated risk of fractures when other treatment options are insufficient or inaccessible [12]. MHT encompasses a broad spectrum of therapeutic options, which can be categorized into both hormonal and non-hormonal approaches. The hormonal therapies include tibolone, combined estrogen and progestin formulations provided by manufacturers, estrogen alone, combinations of estrogen and progestin prescribed by physicians, and localized estrogen treatments. On the other hand, non-hormonal alternatives, often utilized for symptom management, include medications such as citalopram, desvenlafaxine, escitalopram, gabapentin, paroxetine, and venlafaxine [13]. The treatment is widely offered to patients and is often proposed in the private healthcare sector, raising concerns about the potential risk of overprescription [14].There is a debate, whether there is an area of off-label use of the hormone therapy for prolonging the positive self-esteem due to the eradication or covering of symptoms of womens' ageing [15]. The practices outlined above are remnants of an era characterized by limited scientific data when celebrities proclaimed MHT as "the fountain of youth" [14]. Since the introduction and authorization of the first combination oral contraceptive pill, formulations have changed from including high-dose estrogen (150 mcg) to much lower levels (10 and 20 µg). Contraindications mostly include current or historical hormone-dependent malignancies (e.g., breast cancer), uncontrolled hypertension, thromboembolic disorders, active hepatic illness, and gestation. The choice to apply MHT must be personalized, considering the patient's age, duration after menopause, and other risk factors [11]. Hormone treatment may result in side effects such as an elevated risk of venous thrombosis, particularly with oral estrogen.The increased cancer risk, including breast cancer, is associated with prolonged use of combination therapy (estrogen combined with progestogen). The risk of endometrial cancer is also hormone-dependent. The impact on the risk of developing malignancy in endometrial tissue varies depending on the method of hormone treatment. Sequential combined MHT, longer duration of the use with fewer days of progestogen per cycle and higher doses of estrogen slightly increases the risk, while continuous combined estrogen/progesterone therapy decreases the risk when taken orally [16, 17]. Additional potential adverse effects include headaches, nausea, edema, and mood fluctuations [11, 12].

PERIODONTAL INFLAMMATION

Periodontal inflammation has recently been proposed as an additional factor contributing to the increased risk

of cancer development [18]. In the article by Yakar et al. [19], the pathomechanism of periodontal inflammation during menopause is discussed, with emphasis on molecular mediators like TREM-1, PGLYRP1, and IL-1β. The study highlights that TREM-1, a receptor expressed on myeloid cells, plays a significant role in the inflammatory process of periodontal disease, specifically by amplifying inflammatory signals. This mechanism is relevant in both chronic and acute periodontal inflammation. In initial stage, pathogens in dental plaque trigger the immune response, leading to the release of cytokines and inflammatory mediators, which includes interleukin-1β (IL-1β). This response marks the beginning of tissue inflammation. In amplification stage, TREM-1 is activated on the surface of myeloid cells, intensifying the inflammatory response by further promoting cytokine release. This receptor enhances the activity of pro-inflammatory mediators, thus amplifying the immune response against periodontal pathogens. In chronic inflammatory stage, continuous activation of TREM-1 and related pathways leads to prolonged inflammation. PGLYRP1, another mediator, works alongside TREM-1 and IL-1β to sustain the inflammatory process, which can lead to tissue destruction if not controlled. TREM-1 is a critical component in the pathomechanism of periodontal inflammation, serving as a receptor that amplifies immune responses during both chronic and acute phases of periodontal disease. This receptor's activity is associated with an enhanced inflammatory response, which is particularly relevant during menopause and may affect immune responses and inflammation in the gingival tissues. The findings suggest that targeting TREM-1 might offer therapeutic potential in managing periodontal inflammation, especially for menopausal women who may experience heightened inflammatory responses due to hormonal shifts [19]. Additionally, estrogen plays a role in angiogenesis by enhancing the expression of vascular endothelial growth factor (VEGF), subsequently impacting gingival vascularization [20].

Other etiological factor of possible hormonal impact is the fact that estrogens may suppress the physiological salivary flow rate. This leads to a reduced natural antibacterial efficacy of saliva, hence disturbing local microbial homeostasis and increasing predisposition to gingivitis and dental caries in the affected women [21, 22]. The authors of cohort study with 103 participants did not found the correlation between hormonal contraception and significant changes in salivary microbiome together with mentioning in the same work that there is present an amount of evidence suggesting a connection between the menstrual cycle and alterations in the microbiome of dental plaque; however, a clear consensus is lacking, and the sample sizes of the cohorts were relatively limited [23].

Other studies also follow the arguments regarding development of gingivitis and suggest the more possible negative outcomes of using of hormonal contraception for oral cavity health. Main observed risks were osteitis following tooth extraction and presence of the Candida species [24]. Jensen et al. reported that women who are taking oral contraceptives had up to sixteen times higher level of Bacteroides species in their dental plaque than the control group [25].

The cross-sectional comparative study conducted among 200 females showed that hormonal contraceptives influence gingival and periodontal disease progression. The methodology was thoroughly and effectively developed, and as the study group only females aged 18 years and above of Jaipur city were included, and the exclusion criteria were consumption of alcohol and tobacco in any form, medical illnesses, being under any type of medications other than OCP, as well as having a periodontal problem or a history of any periodontal treatment prior to 6 months before the study. The study subjects were divided into two groups, i.e., contraceptive users and non-contraceptive users, each group consisting of 100 females. Periodontal status was examined using the Community Periodontal Index (CPI) and Loss of Attachment (LOA), where the use of CPI was particularly appropriate given its status as a validated index enabling scientific comparisons and enhancing the value of the conclusions drawn. Mean CPI score in contraceptive users and non-contraceptive users was 2.34 ± 0.81 and 1.16 ± 0.89 respectively. Mean LOA score in each group was 0.28 ± 0.45 and 0.19 ± 0.50 respectively [26].

The other pathologies connected to inflammation are the oral ulcerations. Altaee et al. in case-control study involving 30 female participants, aged between 18 and 45 years old, found, inter alia, that hormones in oral contraceptive pills markedly elevate the risk of mechanisms that contribute to the development of periodontal diseases. There is increase in the prevalence of oral symptoms, including ulcerative lesions and mucosal discolouration, particularly pyogenic granulomas. Inflammation-associated oral pathologies also include the development of ulcerative lesions. In a case-control study of thirty women aged 18–45 years, Altaee et al. demonstrated that hormonal components of oral contraceptive pills significantly increase risk factors for periodontal disease. Participants using progesterone-containing oral contraceptive pills exhibited a higher prevalence of oral symptoms—most notably ulcerative lesions, mucosal discoloration and pyogenic granulomas—than non-users. The authors propose that progesterone promotes gingival inflammation both by upregulating pro-inflammatory cytokines and

prostaglandin production and by increasing the volume of gingival crevicular fluid in pill users [27].

A cross-sectional analysis of 125 Saudi women (94 oral contraceptive users) by Jawad et al. found that users of combined hormonal pills experienced significantly higher rates of gingival bleeding, dental caries, and oral ulcerations than non-users [28]. Similarly, AlGhamdi et al. confirmed these associations and further concluded that chronic exposure to exogenous estrogen and progesterone in contraceptives leads to measurable increases in gingival crevicular fluid volume and shifts in its inflammatory cytokine profile [29].

ORAL SQUAMOUS CELL CARCINOMA (OSCC)

Oral squamous cell carcinoma (OSCC) is the most widespread oral malignancy. It is the representative of the group of oral cancers that still contributes a substantial disease burden. The first volume of Lancet Oncology Journal in the year 2025 even in its Editorial section discussed the importance of oral cancer incidence and management. The crucial part in the first steps of the oral cancer diagnostic pathway is always played by dentists worldwide. In 2022 more than 350 000 new cases along with 180 000 deaths due to oral cancer were recorded globally; moreover, in Papua New Guinea and Bangladesh oral cancer is the second most common cancer [30].

Oral cavity cancer, the sixth most common malignancy in the world, is also the 18th most commonly diagnosed malignancy globally, accounting for 2.0% of all cancer cases in 2020 according to the GLOBACAN database [31]. Oral cancers are more common in people older than 60 years but the prevalence is increasing in women and in younger people. Effective smoking control efforts may have contributed to the decline in oral cancer rates associated with tobacco use, a significant risk factor. Additional risk factors are alcohol consumption and human papillomavirus infection (HPV). The incidence is higher in men than in women. The study by Grimm et al. [32] did not find the expression of ER alpha in oral mucosa in OSCC samples from female patients whereas it was confirmed on male patients. ER alpha expression was also found in oral precursor lesions (squamous intraepithelial neoplasia). On the contrary, in a study conducted by Marocchio et al. [33] as well as by Doll et al. [34] ER alpha and beta were expressed in female oral mucosa cells, while ER beta was in female with OSCC in findings provided by Akyu Takei et al. [35]. Moreover, there is the cross-talk between ER and epidermal growth factor receptor (EGFR) in head and neck squamous cell carcinoma as well as relatively strong effect of estrogen and Epidermal Growth Factor (EGF). Chang et al. [36] examined the mechanism underlying ERα activation and showed the correlation with focal adhesion kinase (FAK) signaling, which activates the FAK/AKT pathway, enhancing the phosphorylation of ERα at Ser118 in OSCC cells. This phosphorylation increases ERα activity, promoting cell growth and proliferation in oral squamous cell carcinoma. Non-smoking and non-drinking (NSND) patients with oral cavity cancer are mainly observed among older women [37]. Farshadpour compared 195 NSND patients with HNC and 4209 patients with HNC retrospectively. Of the NSND patients with HNC, 142 (73%) were women, with a mean age of 73 years (median 76, range 20–97). Similarly, in a retrospective study on 287 patients with oral cavity cancer, 70 (24.4%) patients had NSND, of whom, 53 (18.5%) were women (M:F; 1:3.12). Moreover, of the 39 (13.6%) NSND patients, 28 (9.75%) were women over the age of 70. In that mentioned study, an increased risk was observed with increasing age (≥70 years) (HR: 3.219; 95% CI: 2.408–4.303), whereas smoking and alcohol consumption were not associated with the risk of oral cavity cancer in postmenopausal women [38]. In a screening examination conducted from 1 January 2002 to 31 December 2019, the number of participants diagnosed with oral cancer in retrospective cohort study by Yuk et al. in each group were as follows: 1782 (0.2%), 308 (0.2%), 159 (0.1%), 121 (0.3%), 15 (0.3%), and 4 (0.2%) in the non-MHT, tibolone, combined estrogen plus progestin by manufacturer (CEPM), oral estrogen, combined estrogen plus progestin by physician (CEPP), and topical estrogen groups, respectively [39]. In the Cox proportional hazard analysis adjusted for variables such as age, BMI, socioeconomic status (SES), region area, Charlson Comorbidity Index (CCI), parity, age at menarche, age at menopause, smoking, alcohol, physical exercise, and period from menopause to inclusion, the number of participants diagnosed with oral cancer increased in the tibolone (hazard ratio [HR]: 1.175, 95% confidence interval [CI]: 1.031–1.338) and oral estrogen groups (HR: 1.633, 95% CI: 1.35–1.976). That analysis of the results suggests that MHT increases the risk of oral cavity cancer in postmenopausal women. However, Fernandez et al., in a network analysis of case-control studies, which included 253 participants, showed a nonsignificant reduction in risk for cancers of the oral cavity, esophagus, pharynx and larynx, as well as for thyroid cancer, Hodgkins's, non- Hodgkin's lymphomas and myelomas. In that study there is mentioned that the reduction in risk for mentioned cancers should be considered always with the warnings about limited statistical power included in that study due to the low prevalence of HRT in that population and

low incidence for some of the cancers [40]. The same small number of participants are also in another study the factor of inconsistency in results analysis [41]. In the mentioned cohort study oral cancer diagnosed in HRT-use compared with non-use adjusted HR = 0.72 95% CI 0.55, 0.95).

CONCLUSIONS

In this literature review, we highlight the need for further research into the hormonal dependency of oral cancers. Specifically, the potential impact of endogenous versus artificial sex hormones, including molecular and clinicopathological aspects, requires in-depth evaluation. Additionally, alternatives to oral MHT should be explored to identify and evaluate the potential risks. Moreover, it must be highlighted that the globally-used MHT not only consists of oral estrogen, but there are alternative methods. Furthermore, it is critical to emphasize that MHT is not limited to oral estrogen, and individualization of treatment plans based on patient-specific risk factors is essential. This includes careful consideration of age, duration of therapy, and personal and family history of hormone-dependent cancers. The further research should also focus on new ways of pharmacotherapy, for example the potential use of tamoxifen or other drugs that target FAK. Other forms that seem not to share the same risk in cancer development are vaginal, topical estrogens and non-hormonal approaches, such as above mentioned antidepressants and gabapentin. In conclusion, understanding the nuanced interplay between hormonal treatments and cancer risk is vital to improving patient outcomes. Further studies should focus on clarifying the differences in carcinogenic potential between endogenous and artificial hormones, as well as evaluating the long-term safety of alternative therapies.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 18.05.205
ACCEPTED: 14.08.2025