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Review

Is There a Role for Sex Hormone Receptors in Head-and-neck Cancer? Links with HPV Infection and Prognosis

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Abstract. *Background/Aim: Head-and-neck squamous cell carcinoma (HNSCC) is the fifth most common cancer in the world and human papillomavirus (HPV) is an important risk factor for this neoplasm. Recent studies showed an association between sex hormone receptors and pathogenesis and/or prognosis in patients with HNSCC. The aim of this study was to clarify the expression patterns of sex hormone receptors in HPV-positive and HPV-negative HNSCC and their associations with tumour biopathology and biological behaviour. Materials and Methods: Scientific literature indexed in PubMed about sex hormone receptors in HNSCC was retrieved and critically analyzed, to obtain an overview of expression patterns and their possible implications for tumour biopathology and prognosis. Results: Sex hormone receptors were more frequently detected in oropharyngeal tumours compared with HNSCC from other locations. ERα was associated with HPV-positive tumours. The androgen and progesterone receptors were associated with poor patient prognosis. Estrogen receptor alpha (ERα) is implicated in the biopathology of HNSCC in different ways, by promoting DNA hypermutation and facilitating HPV integration thus contributing to an immunogenic phenotype, but also by cooperating with the epithelial growth factor receptor (EGFR) to promote resistance to therapy. Conclusion: The expression of sex hormone receptors may be of prognostic value in specific tumour subgroups, but the use of hormonal therapies for HNSCC is still not in close sight.*

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Head-and-neck cancer comprises a group of malignancies affecting multiple sites including the oral cavity, the oropharynx, nasopharynx, hypopharynx, larynx and the salivary glands. Histologically, these lesions are most commonly squamous cell carcinomas (HNSCC) (1). An estimated 650,000 new cases occur yearly worldwide, along with 330 000 deaths from HNSCC (2). In the USA, HNSCC corresponds to 3% of all cancers with approximately 53,000 new cases and 10,800 deaths yearly. Males seem to be at higher risk, with a male to female ratio varying between 2:1 and 4:1 (3). Classically, alcohol and tobacco consumption have been identified as major risk factors for developing HNSCC (4, 5). Recently, infection with high-risk human papillomavirus (HPV) has been recognized as a risk factor for developing HNSCC (6). HPV-positive HNSCC is preferentially located at oropharyngeal sites, especially the tonsils and the tongue base, and shows distinguishing clinico-pathological features (7). Other risk factors for developing HNSCC include dietary or workplace exposure to environmental toxicants and genetic predisposition (8-10). Between 2005 and 2014, the incidence of HPV-positive HNSCC increased by 3% while that of classical lesions decreased by 2% (11). The increasing incidence of HPV-positive HNSCC motivated a significant effort to understand the biopathology of these lesions and adapt the current therapeutic approaches (12). A number of markers is currently in use or under study for identifying these lesions (*e.g.*, immunohistochemistry for $p16^{INK1A}$) or to predict response to

specific therapies (*e.g.*, infiltration of T lymphocytes to predict response to immune checkpoint inhibitors) (13, 14). However, the role of hormonal receptors in HNSCC remains poorly defined.

Hormonal receptors play a major role in some malignancies like breast (15) and prostate (16) cancers and have also been implicated in HPV-driven lesions like cervical cancer (17, 18). Multiple studies have addressed the expression patterns of hormonal receptors in HNSCC, as well as their association with HPV and their potential clinical significance, but the data concerning this subject remains dispersed and difficult to interpret. The present review brings together those data, contributing to clarify the expression patterns of hormonal receptors in HPV-positive and HPV-negative HNSCC. The contributions of hormonal receptors for the biopathology of these cancers and their potential impact on therapy are also discussed. For these purposes, PubMed-indexed research articles and reviews were retrieved and critically analyzed. Preference was given to recent literature published between 2015 and 2020, but older studies were included whenever useful to define the timeline of research in this field.

HPV-positive *Versus* HPV-negative HNSCC

Classical HNSCC is strongly associated with tobacco and alcohol consumption: data from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) show that cigarette smoking increases HNSCC risk by 50% and smoking more than 5 cigarettes per day increases HNSCC risk by over two-fold (19). Alcohol is another well-known risk factor for HNSCC, oesophageal and gastric cancer, and cooperates with tobacco to increase HNSCC risk (20-22). Genetic polymorphisms have been suggested to increase the risk of HNSCC associated with alcohol (23). Similarly, tobacco consumption seems to cooperate with HPV infection to increase the risk of HNSCC (24, 25). In fact, mice transgenic for the HPV16 *E6* and *E7* oncogenes showed increased susceptibility to oral carcinogenesis induced by the tobacco-related carcinogen 4-nitroquinoline-1-oxide (26).

The connection between HPV and certain HNSCC subtypes was first pointed out twenty years ago (6). This seminal study identified HPV in 25% of HNSCC samples and in 62% of those located in the tonsils and the tongue base, with HPV16 being most commonly found. HPV-positive tumours showed a more favourable biological behaviour compared to HPV-negative HNSCC. Over the years, these initial observations were reinforced by multiple reports from different groups and oral infection with high-risk HPV, especially HPV16, was consistently associated with increased HNSCC risk (27-29). Studies on bovine (30), canine (31), feline (32) and murine (33) models showed the ability of papillomaviruses to infect and induce different types of lesions in the oral cavity, as previously reviewed (34-36). More recently, our group demonstrated the ability of HPV16 to specifically induce tongue base HNSCC in transgenic mice (37), providing experimental evidence to support the etiologic role of HPV16 in this type of cancer. There are over 200 HPV types, which are transmitted by direct contact and most often cause benign lesions (38). The host's immune system is generally able to clear HPV infections, leading to spontaneous regression of lesions within two years, as previously reviewed (39, 40). However, some HPV types, known as high-risk HPVs (*e.g.*, HPV16, 18 and 31) show increased ability to establish persistent infections and induce lesions that may progress towards anogenital and oropharyngeal cancers (41-43). The carcinogenic activity of high-risk HPVs is largely attributed to their E6 and E7 oncoproteins with some less-understood contributions by the E5 oncoprotein (44, 45), as recently reviewed (46). The E6 and E7 oncoproteins interact with two tumour suppressor proteins, p53 and the retinobastoma protein (pRb), inducing their degradation and dysregulating key cellular functions such as proliferation, survival and DNA repair (46). High-risk HPVs also have mechanisms to promote the immune evasion of infected cells (47, 48) and are able to interfere with the epigenetic modulation of gene expression through microRNA networks, as previously reviewed (49).

Histologically, HPV-positive HNSCC tends to be less differentiated than HPV-negative tumours (50). Since the beginning of the XXI century, the incidence of HPV-positive HNSCC has been steadily increasing while that of HPV-negative HNSCC decreased a trend that is speculated to be caused by changing sexual habits (51). HPV-positive tumours tend to respond better to therapy (52-54) and specific therapeutic modalities, including de-escalation of aggressive chemo-radiation treatment, are currently under study (11, 55, 56).

Hormone Receptors in HNSCC

The role of hormone receptors is well characterized in several types of cancers. This is particularly true in the case of sex hormone (estrogen, androgen, progesterone) receptors in malignancies like breast cancer (15, 57) and prostate cancer (16), where the expression of sex hormone receptors is critical to define tumour subtypes with distinguishing biopathological characteristics and different responses to therapy. The use of hormonal therapies for treating androgen-dependent prostate cancer (*e.g.*, enzalutamide) and some types of breast cancer (*e.g.*, tamoxifen) is well established (58-60). Androgen receptors (AR) were detected in the normal oral mucosa using immunohistochemistry on frozen samples (61). More recently, Fei *et al.* (2018) reported low levels of AR expression in only a minority of laryngeal samples (62). The same authors reported similar results

concerning the expression of prolactin receptors in normal laryngeal mucosa. There are two types of oestrogen receptors commonly located in the cell nucleus, the well-known alpha and beta (ERα and ERβ), located in the cell nucleus (63) in contrast, the G-protein-coupled estrogen receptor (GPER) is associated with the cell membrane rather than the nucleus and triggers a number non-genomic effects (64). Although GPER has been implicated in some types of cancer (65), its role is not so well characterized as that of ERα and ERβ. Initial studies performed in the 1980s showed conflicting results regarding the expression of ER or the progesterone receptor in the laryngeal mucosa (66, 67). In the early 2000s, Valimaa *et al*. reported that normal oral mucosa and salivary glands express ERβ (68), but another study using paraffin-embedded samples from a small patient cohort (n=5) reported that the oral mucosa was negative for ERα and progesterone receptors (69). Lukits *et al*., using frozen and paraffin-embedded samples from 10 patients obtained different results. When analyzing frozen samples, both the oral mucosa and the glottis were positive for ERα, ERβ and progesterone receptors on the mRNA level. Using immunofluorescence techniques, the authors observed expression of ERα on the oral and glottic mucosa while ERβ was more abundant in the glandular epithelium (70). These findings suggest that the methods for studying the expression of those markers in the oropharyngeal cavity need to be standardized, especially the use of frozen *versus* paraffin-embedded material and the immunohistochemical techniques employed. Due to the complexity of the oropharyngeal and laryngeal cavities, it is also possible that specific anatomic areas (*e.g*., larynx *versus* tongue) express some hormone receptors while others do not.

The expression patterns of sex hormone receptors in HNSCC is also unclear, which is unsurprising considering these difficulties and the heterogeneity of these tumours. Androgen receptor was found to be expressed in salivary gland duct carcinomas and other non-squamous head and neck cancers, as recently reviewed (71). The present review will focus on data concerning HNSCC.

An initial study performed in 1984 using a dextran-coated charcoal method for determining oestrogen and progesterone receptors in HNSCC samples found ER in only 2 out of 75 samples and no progesterone receptors (66). Virolainen *et al*. (1986) detected AR, ER and PR in 31%, 69% and 35% respectively of frozen laryngeal squamous cell carcinoma (SCC) samples, using hormone binding assays (72). In contrast, Ferguson *et al*. (1987) using immunohistochemistry on frozen samples reported that neither ER nor PR were expressed by laryngeal carcinomas (67). Twenty years later, Lukits *et al*. studied the expression of progesterone receptors (PR), and the two distinct estrogen receptors, ERα and ERβ in 67 frozen oral, laryngeal and hypopharyngeal SCC samples at the mRNA and protein levels (70). The authors observed that all three receptors were expressed by epithelial cells in these cancers and that ERα was more frequently expressed than ERβ. These two receptors were expressed in their wild-type form or as splice variants δ3 and δ5 for ERα and ERβ, respectively. Most lesions expressed both ER and PR (41.8% of lesions), rather than ER or PR alone (8.9%). Almost 10 years later, another study compared the expression on the progesterone receptor (PR) and ERα in male and female patients and in normal oral mucosa, intraepithelial lesions and oral SCC, and only observed expression of ERα in 11% of intraepithelial lesions and SCCs (69). In the same year, Grsic *et al*. (2016) studied the expression of ERβ in a larger cohort (174 patients, 165 of which were male). Interestingly, this study showed ERβ expression in 42% of patients (73). Most negative tumours were laryngeal primaries (p=0.04), and the expression of ERβ was consistently higher in tumours from other sites (oral cavity, hypopharynx, oropharynx) without further anatomy-related differences. Another study found that 16% of oropharyngeal cancers expressed AR, 27% expressed PR and 63% expressed ERβ, while ERα expression was not detected (74). In contrast, Kano *et al*. (2019) detected both ERα and ERβ in 29% and 36% of oropharyngeal cancer samples, respectively (75). Using immunohistochemistry on paraffin-embedded materials, Wu *et al*. (2014) reported that AR was expressed in two-thirds (14/21) specimens of oral squamous cell carcinoma (OSCC). AR knockdown using short hairpin RNA reduced the proliferation of representative cell lines *in vitro* and abolished their growth when xenografted in mice (76). More recently and in line with these findings, 10/23 OSCC patients were found to be positive for AR using paraffin-embedded material (77). The same authors reported that AR expression was significantly associated with increased phosphorylated epidermal growth factor receptor (EGFR). Using *in vitro* systems, AR pharmacological inhibition reduced EGFR phosphorylation while AR agonists had the opposite effect, suggesting AR promotes EGFR signalling in those tumours. Those *in vitro* observations also associated AR signalling with enhanced cell migration, potentially increasing tumour aggressiveness. Another recent study using a larger cohort (total n=196) of metastatic and non-metastatic OSCC patients suggested that AR cytoplasmic accumulation associates with moderately increased risk of metastasis (78). The significance of AR cytoplasmic immunostaining in this context requires additional clarification, especially considering that AR splice variants play an important role in prostate cancer and some of those variants may accumulate in the cytoplasm (Zhan *et al*., 2017) (79). Overall, although AR is expressed in a majority of HNSCC samples, its role in tumour biopathology and its implications for patient outcome remain largely obscure. Table I summarizes data on the expression of sex hormone receptors in HNSCC.

Table I. *Expression of sex hormone receptors in HNSCC.*

Hormone receptor	Positivity	Sample	Method	References
AR	8/21	Laryngeal SCC, frozen	HBA	Virolainen *et al*. (1986)
	31/199	OPSCC, FFPE	IHC	Mohamed *et al*. (2018)
	14/21	Oral SCC, FFPE	IHC	Wu *et al*. (2004)
	10/23	Oral SCC, FFPE	IHC	Liu *et al*. (2018)
	Unreported	Oral SCC, FFPE	IHC	Tomasovic-Longaric *et al*. (2019)
PR	None	Normal larynx, frozen	IHC	Ferguson *et al*. (1987)
	None	Laryngeal SCC, frozen	IHC	Ferguson *et al*. (1987)
	None	Oral SCC, FFPE	IHC	Grimm *et al*. (2016)
	21/43	Laryngeal and hypopharyngeal SCC, frozen	IHC	Lukits *et al*. (2007)
	8/15	Laryngeal SCC, frozen	HBA	Virolainen *et al*. 1986
	54/199	OPSCC, FFPE	IHC	Mohamed *et al*. (2018)
ERα	5/46	Oral SCC, FFPE	IHC	Grimm *et al*. (2016)
	16/43	Laryngeal and hypopharyngeal SCC, frozen	IHC	Lukits *et al*. (2007)
	None	OPSCC, FFPE	IHC	Mohamed *et al*. (2018)
	19/68	OPSCC, FFPE	IHC	Kano *et al*. (2019)
ERβ	73/174	Larynx, oral cavity, hypopharynx, oropharynx SCC, FFPE	IHC	Grsic *et al*. (2016)
	11/43	Laryngeal and hypopharyngeal SCC, frozen	IHC	Lukits *et al*. (2007)
	126/199	OPSCC, FFPE	IHC	Mohamed *et al*. (2018)
	23/64	OPSCC, FFPE	IHC	Kano *et al*. (2019)

IHC: Immunohistochemistry, FFPE: formalin-fixed paraffin embedded, HBA: hormone binding assays, SCC: squamous cell carcinoma, OPSCC: oropharyngeal squamous cell carcinoma, FFPE: formalin-fixed paraffin-embedded.

HPV and Hormonal Receptors

Mohamed *et al*. (2018) observed a correlation between HPV-positive tumours with increased expression of AR and reduced expression of PR ($p<0.001$ for both markers). Kano *et al*. (2019) reported that ERα expression is associated with HPV-positive oropharyngeal cancers ($p=0.018$ *versus* HPV-negative) and suggest that ERα facilitates the integration of HPV DNA into the host's genome by promoting DNA hypermutation through the apolipoprotein B mRNA-editing catalytic polypeptide 3 (APOBEC3). In fact, HPV-positive HNSCC has a specific mutational landscape associated with APOBEC, as previously described (80). In the cervical transformation zone, estrogen exposure promotes neoplastic transformation and the development of cervical cancer induced by HPV16 (17, 18). In 35% of cervical cancers, expression of aromatase, the rate-limiting enzyme involved oestrogen synthesis, is up-regulated compared to normal cervical mucosa and to precancerous lesions (81). Aromatase expression was associated with increased expression of ERα/ERβ and reduced PR expression, as well as with up-regulation of HPV oncogenes E6 and E7 and increased cell proliferation.

Overall, it is possible that estrogen signaling *via* ERα and/or ERβ plays a significant role in HPV-positive HNSCC, namely by promoting viral integration into the host cell's genome, as observed in cervical cancer (Figure 1). Additional evidence is needed to define the possible role of other hormone receptors such as AR and PR.

Therapeutic and Prognostic Relevance of Hormone Receptors in HNSCC

The clinical significance of sex hormone receptors in HNSCC has been addressed by multiple recent studies and pre-clinical studies of hormonal therapy have been attempted with limited success. As mentioned in the previous section, AR expression is associated with HPV infection in HNSCC (74). Interestingly, AR up-regulation was correlated with reduced survival ($p<0.005$) in HNSCC patients and was found to be driven by microRNA-21 (82). Concerning female sex hormone receptors, Lukits *et al*. (2007) did not find any significant associations between the expression of PR, ERα or ERβ and patient prognosis. However, PR expression was associated with reduced disease-specific survival ($p=0.001$) by a recent study (74). Egloff *et al*. (2009) suggested the

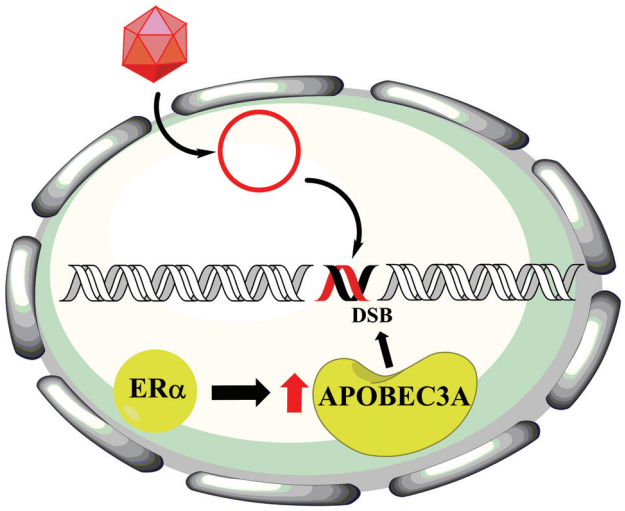

Figure 1. *A possible association between ERα and HPV-positive HNSCC, as proposed by Kano et al (75). Estrogen receptor alpha (ERα) up-regulates the apolipoprotein B mRNA-editing catalytic polypeptide 3 (APOBEC3), inducing DNA double-strand breaks which facilitate the integration of HPV DNA into the host cell genome.*

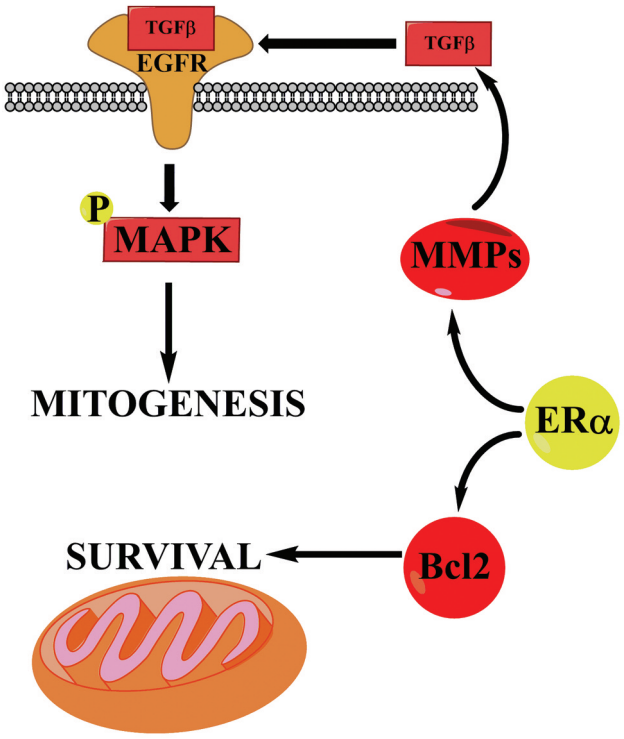

Figure 2. *Estrogen receptor alpha (ERα) was proposed to activate multiple signaling pathways leading to cell survival and proliferation. Up-regulation of B-cell lymphoma 2 (Bcl2) blocks the mitochondrial apoptotic pathway. The release of ligands for the epithelial growth factor receptor (EGFR) via matrix metalloproteinases leads to phosphorylation of mitogen-activated protein kinase (MAPK) and drives cell proliferation.*

existence of a cross-talk between ERα and the epidermal growth factor receptor (EGFR) in HNSCC and showed that the simultaneous expression of both receptors significantly reduced progression-free survival compared with tumours with only one of those receptors (hazard ratio 4.09, p=0.01). Interestingly, this was not observed for ERβ. In line with these observations, the authors also showed that a combined *in vitro* treatment of HNSCC cells with estradiol and EGF significantly increased cell invasion, compared with treatments with each single ligand (83). Lin *et al*. (2011) also reported that ERα cooperates with EGFR to promote chemoresistance of HNSCC cell lines *in vitro* (84). The authors reported that ERα up-regulates the anti-apoptotic protein B cell lymphoma 2 (Bcl-2) and rescues EGFR levels, promoting survival and proliferation (Figure 2). Early *in vivo* trials of anti-oestrogen therapies against cervical cancer in HPV-transgenic mouse models (85, 86) showed positive results. Trials of tamoxifen against HNSCC (87) allowed researchers to overcome cisplatin resistance *in vitro*. However, the mechanism of action of tamoxifen in ER-negative HNSCC cell lines remains unclear (88). If a rationale for hormonal therapy in HNSCC is to be found the role of hormonal receptors in this type of cancer needs to be clarified.

Interestingly, ERα was associated with improved overall survival in patients with HPV-positive oropharyngeal cancer (p=0.029) (75), possibly because the APOBEC mutational signature of these tumors makes them more immunogenic. More recently, Grsic *et al*. (2016) reported that ERβ expression in oropharyngeal cancer correlated with improved 5 years survival (35% *versus* 25% in patients with ERβ-negative cancers, p=0.045). The same was not observed in other anatomic sites. The HPV status of these tumours was not reported and may have been a confounding variable in this study. Grunow *et al*. (2017) made additional and more complex observations on the role of ERβ. Radiotherapy-treated oropharyngeal cancers expressing ERβ showed higher progression-free survival (p=0.002) and disease-specific survival (p=0.01), compared with negative cases. However, the authors also observed that ERβ up-regulated the submaxillary gland androgen-regulated protein 3A (SMR3A) and promoted the resistance to radiation therapy *in vitro* (89). Tumours expressing both ERβ and SMR3A had poor prognosis, similar to the ERβ-negative subgroup. These observations suggest that ERβ activates multiple pathways in HNSCC and may either play a protective role or, on the contrary, promote radio-resistance. The membrane associated GPER has also been implicated in laryngeal cancer, even if only by an *in vitro* study (90). GPER was shown to up-regulate interleukin-6 expression in response to bisphenol A *in vitro*, increasing cell proliferation and invasion.

Overall, sex hormone receptors seem to influence the biopathology of HNSCC mainly by promoting DNA hypermutation and facilitating HPV integration or by cooperating with EGFR in the case of ERα. The role of ERβ seems to be more complex and requires additional investigation. The expression of sex hormone receptors may be of prognostic value, if studied in the right tumour subgroups. The use of these receptors as therapeutic targets is still not in close sight. However, it is tempting to speculate that HNSCC subgroups may benefit from combination therapies of hormone receptor modulators with anti-EGFR drugs (*e.g.*, erlotinib).

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CP Oliveira Neto: article research, manuscript writing and submission; HO Brito: manuscript editing and review; RMG da Costa: article research, manuscript writing and drawing figures; LMO Brito: manuscript review.

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