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Review

Biological roles and clinical significance of estrogen and androgen receptors in head and neck cancers

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Abstract

Head and neck cancers (HNC) include malignant tumors that grow in and around the mouth, larynx, throat, sinuses, nose, and salivary glands. Accumulating evidence in malignancies suggests the aberrant expressions of the estrogen receptor (ER) and the androgen receptor (AR) in HNC, such as in laryngeal cancer and cancer of the salivary gland. Moreover, the signaling pathways involving these receptors that mediate tumorigenesis, proliferation, apoptosis, migration, and invasion have been elucidated. This review summarizes the roles of ER and AR with the putative signaling pathways involved in HNC. We also discuss the potential application of ER- and AR-related therapies in HNC. However, most of the mechanisms underlying AR and ER involvement in the development of HNC remain elusive and warrant further studies. A comprehensive understanding of the functional roles and mechanisms of action of AR and ER in HNC will facilitate the development of better therapeutic strategies for this disease. Overall, studies on AR and ER provide a promising potential for the diagnosis and treatment of HNC in the future.

Key words: Androgen receptor; Estrogen receptor; Head and neck cancer; Molecular target; Biomarker; Cancer treatment

Background

Head and neck cancers (HNC) are one of the most lethal and predominant tumors, worldwide, accounting for 5.7% of the total global mortality due to cancers [1-3]. Its potential epidemiological trend shows an uneven regional distribution of disease burden. For instance, the Swedish Head and Neck Cancer Register (SweHNCR) report suggests that among the 9733 patients diagnosed with HNC between 2008 - 2015, approximately 10% died within six months of diagnosis [4]. In 2019, an estimated 66,630 new cases of HNC were diagnosed and 14,620 individuals died due to this disease in the United States [5]. Based on the epidemiological research data from 2008 to 2012, in Shanxi Province, China, the average annual incidence rate of laryngeal cancer was $0.70/10^5$ [6]. Remarkably, the essential risk factors of HNC include tobacco and alcohol use, and infection by the human papillomavirus (HPV) [7, 8]. Additionally, other factors have been identified by the epidemiological studies of HNC, including genetics, toxic exposure, diet, and environmental conditions [3, 9, 10].

Radiotherapy and chemotherapy are the most predominant adjuvant treatments for HNC [11].

Radiotherapy can facilitate clinical outcomes to a certain extent but also is accompanied by some side effects of radiation, such as dry mouth symptoms and difficulties in chewing/swallowing [12, 13]. Recently, the use of cetuximab and taxane has been on the rise [14], and the combined induction using gemcitabine and cisplatin suggests a new possibility for improving the recurrence-free survival rate [15]. Despite these benefits, the disadvantages of chemoresistance, toxic side effects, and acute adverse events [16] have not been addressed, thus warranting further studies. In the past few years, due to the low toxicity of combination chemotherapy, that is, the integration of chemotherapy and combined androgen blockade (CAB) using the androgen receptor (AR) antagonist, the research attention for its clinical applicability has gained traction [17]. For example, patients with advanced AR-positive salivary duct carcinoma exhibit increased overall survival after undergoing androgen-deprivation therapy (ADT) [18]. Correspondingly, in breast cancer, the estrogen receptor-α66 (ERα66) serves as a molecular target for endocrine therapy and binds estrogen to mediate metastasis [19]. Taken together, these studies indicate that AR and ER have promising roles in the management of cancers including HNC.

In this review, we have summarized the current knowledge on the functional roles of ER and AR in HNC (Fig. 1) and discussed their putative applications in treatment and diagnosis. Moreover, as anti-androgen and anti-estrogen therapies continue to be regarded as potential therapeutic strategies, targeting ER and AR signaling pathways may prove useful for the treatment of patients with HNC.

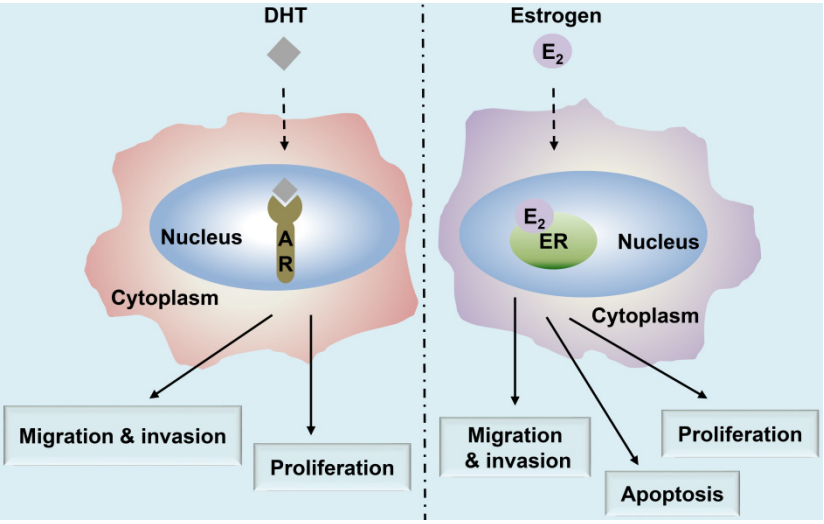

Figure 1. Summary of the major functions of androgen and estrogen receptors in HNC. The androgen receptor (AR)/estrogen receptor (ER)-mediated signaling pathways are activated upon binding with the corresponding ligands, androgen dihydrotestosterone (DHT) or estrogen (17β-estradiol, E_2), respectively, resulting in the regulation of HNC behavior, including cell proliferation, apoptosis, migration, and invasion.

ER-mediated signaling pathways

Estrogen receptors (ERs) are typical members belonging to the superfamily of nuclear receptors that include receptors involved in the action of steroid hormones, thyroid hormones, vitamin D, and several orphan receptors [20]. These receptors are primarily classified into two categories, namely the classical nuclear receptors, comprising ERα and ERβ, localized in the nucleus and mediating the effects of estrogen and the membranous receptors, including the membranous components of the classical nuclear receptor and the G protein-coupled estrogen receptor 1 (GPER1) [21, 22].

Estrogen either enters the cell or is synthesized within. It binds with the nuclear ER, thereby forming an ER homodimer or heterodimer [21]. The activated ER interacts with the DNA enhancer estrogen response element (ERE) resulting in the ER-ERE complex, which further facilitates the formation of a transcription initiation complex that induces transcription, and thus, the ER exerts its functions [23]. Estrogen can produce biological effects through the rapid activation of intracellular secondary signaling systems through the ER membrane [24]. These effects include (1) the rapid activation of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathway, (2) stimulation of adenylate cyclase (cAMP), thereby promoting the activity of cAMP-regulated gene transcription, and (3) activation of protein kinase C (PKC) increasing in endogenous Ca^{2+} [23-28] levels. Additionally, there are other ER-mediated pathways, including the c-Jun N-terminal kinase (JNK) pathway, which induces apoptosis, and the phosphatidyl-inositol 3 kinase (PI3K) pathway that inhibits apoptosis (Fig. 2) [22, 29, 30]. Finally, the classical estrogen signaling is through the membrane-associated 17β-estradiol (E_2)-ER binding, which triggers multiple rapid signal transduction cascades [24, 31] (Fig. 3).

AR-mediated signaling pathways

The AR is similar to the ER in that they belong to the superfamily of nuclear receptors [32]. The length of the AR gene, located on xq11-12, is greater than 90 kb. It has eight exons, wherein exon 1 is at the amino-terminus and is responsible for stimulating the gene transcription [33, 34]. Thus, AR acts as a transcription factor and consequently translocates to

the nucleus following the binding of the active androgen dihydrotestosterone (DHT) [33] (Fig. 1). The AR contains four functional regions as follows: the N-terminal domain, DNA-binding domain (DBD), ligand-binding domain, and a hinge [34]. A typical signaling pathway involving AR consists of different stages [35]. First, the AR binds to androgen (DHT) causing a conformational change, and thus, the AR separates from the heat shock proteins and enters the nucleus through the nuclear pore [34]. In the nucleus, AR undergoes phosphorylation and dimerization and can recognize the androgen response elements (AREs) on target genes, thereby binds to them and causing chromatin remodeling in an effect to open up the regulatory regions of promoters, eventually recruiting co-activators for the formation of transcriptional complexes, ultimately leading to transcription of the target gene [33, 35]. Forkhead box protein A1 (FOXA1) is a transcription factor of the AR target gene, which regulates its transcription as well as facilitates the interactions of AR with the chromatin [36]. The contribution of AR and FOXA1 to the process of tumorigenesis [37] is illustrated in Fig. 4. Moreover, studies on salivary duct carcinoma show that treatment with DHT increases cell proliferation, migration, and invasion, while the AR inhibitor, fluorouracil, blocks the effects of DHT, suggesting that the androgen-AR signaling axis exerts effects on cellular proliferation, migration, and invasiveness [38].

Functional roles of ER in the biological behavior of HNC

Recent studies show that the expression of ERα in laryngeal squamous cell carcinoma (LSCC) is higher relative to the corresponding normal tissues [39]. A similar finding has been reported in malignant minor salivary gland tumors of the sinonasal tract, the majority of which are ER-positive [40]. Likewise, the expression of ERβ is higher in head and neck squamous cell carcinoma (HNSCC) as compared to the normal epithelium [41]. Besides, numerous reports confirm that ER immunoreactivity is present in approximately 50% - 80% of the cases in some HNC types [42-46]. Taken together, these findings demonstrate that ERs are highly expressed in most HNC and are closely associated with its development. The roles and underlying mechanisms of action of ER in HNC progression are listed in Table 1.

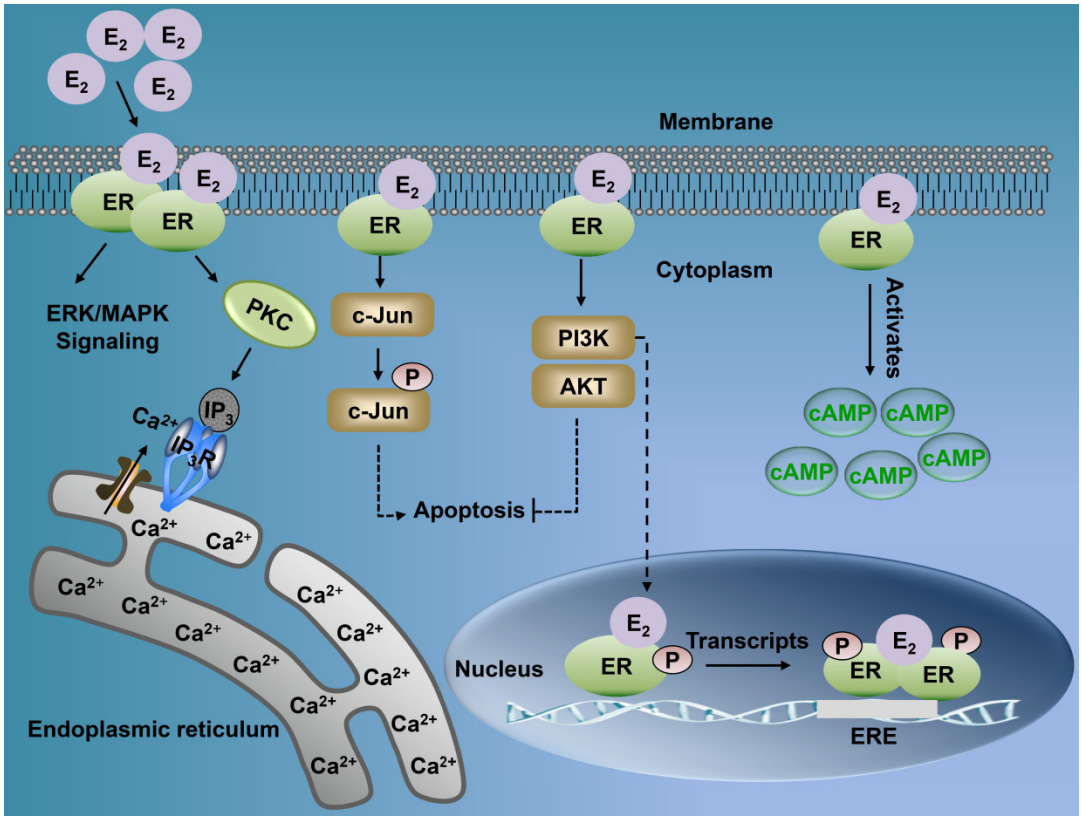

Figure 2. Multiple signaling pathways of nuclear ER and membrane ER. Membrane-associated E_2-ER signaling pathway. (1) E_2-ER activates ERK/MAPK signaling pathway; (2) The activation of PKC increases endogenous levels of Ca^{2+}, which can induce tumorigenesis and metastasis; (3) E_2-ER activates JNK pathway and eventually promotes apoptosis; (4) E_2-ER involved in the PI3K/AKT pathway suppresses apoptosis; (5) E_2-ER activates Camp; E_2-ER signaling pathway in the nucleus. Phosphorylation of ER combined with E_2 mediates the formation of ER-ERE complex, leading to transcription. ER: estrogen receptor; ERK: extracellular signal-regulated kinase; MAPK: mitogen-activated protein kinase; PKC: protein kinase C; IP_3: inositol triphosphate; IP_3R: inositol triphosphate receptor; cAMP: activation of adenylate cyclase; ERE: estrogen response element.

Table 1. The estrogen receptor (ER) expression, functions, and mechanisms in head and neck cancers (HNC)

Receptor	HNC Type	Expression	Prognosis	Function	Mechanism	Ref.
ER	Laryngeal cancer	Upregulation	Unfavorable	NA	NA	[78]
ERβ	Oropharyngeal cancer	Upregulation	Favorable	NA	NA	[79]
ERα	Laryngeal cancer	Upregulation	Unfavorable	NA	NA	[39]
ERα	HPV-positive oropharyngeal cancer	Upregulation	Favorable	NA	NA	[80]
ER	Laryngeal cancer	Upregulation	NA	Promote proliferation and inhibit apoptosis	NA	[50]
ERα	Papillary thyroid cancer (PTC)	Upregulation	NA	Promote growth of PTC and inhibit apoptosis	Activate ERK1/2 and autophagy	[47]
ERα36	Laryngeal cancer	Upregulation	NA	Inhibit apoptosis and increase aggression	Activate PKC and phospholipase D	[31]
ERβ	Laryngeal cancer	Upregulation	Unfavorable	Increase invasion	NA	[102]
ERβ	Tongue cancer	Upregulation	NA	Inhibit apoptosis	NA	[41]
ERβ	Tongue cancer	Upregulation	NA	Inhibit apoptosis and increase aggression	NA	[48]
ERβ1	Papillary thyroid cancer	Upregulation	NA	Inhibit proliferation	NA	[52]
ERα	Papillary thyroid cancer	Upregulation	NA	Promote growth and progression	NA	[52]
ER	Thyroid cancer	Upregulation	NA	Promote proliferation	Non-genomic pathways	[101]
ER	Thyroid carcinoma	Upregulation	NA	Promote growth of tumor cells	Genomic and non-genomic pathways	[53]
ER	Salivary gland cancer	Upregulation	Unfavorable	NA	NA	[55]
ERα66	Laryngeal cancer	Downregulation	Unfavorable	Increase aggression	NA	[57]
ERβ	Laryngeal cancer	Upregulation	NA	Inhibit aggression	Upregulate E-cadherin, activate β-catenin	[58]

Abbreviations: NA, not available; EGFR: growth factor receptor; ERK: extracellular signal-related kinase; Ref: reference.

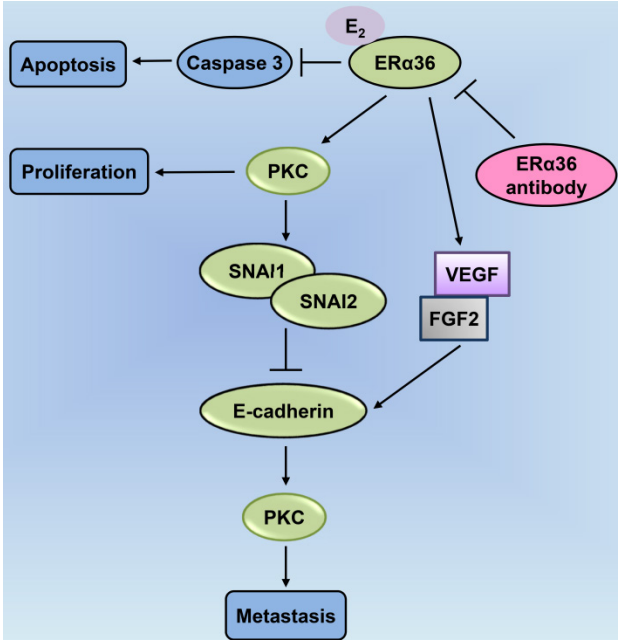

Figure 3. PKC-mediated ERα36-E_2 membrane signaling cascades are involved in cellular proliferation, anti-apoptosis, and metastasis in laryngeal cancer. ERα36-associated E_2 inhibits access of caspase-3 for promoting apoptosis; E_2 activation of ERα36 enhances the levels of expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2), blocked by the ERα36 antibody; ERα36-dependent E_2 signaling increases PKC activity associated with cellular proliferation; ERα36 activates PKC through E_2 that mediates the expression of the metastatic factors, SNAI1 and SNAI2; E_2 enhances the expression of the metastatic factor, Snail, and downregulates E-cadherin (CDH1); ERα36 antibodies block both of these effects, leading to epithelial-to-mesenchymal transition (EMT) and enhanced metastasis. PKC: protein kinase C.

Based on recent empirical evidence, ERs including ERα and ERβ, exert an anti-apoptotic effect in some HNC types [31, 47-49]. In particular, in papillary thyroid cancer, ERα induces autophagy, which is a pro-survival catabolic phase owing to the stimulation of reactive oxygen species and extracellular signal-regulated kinases, wherein the inhibition of autophagy promotes apoptosis [47]. Moreover, Shatalova et al. demonstrate high levels of ERβ expression in premalignant head and neck lesion cells MSK-Leuk1. Notably, exposure to E_2 results in lower cellular apoptosis, and this estrogen-dependent apoptosis can be restored through supplementation with the anti-estrogen drug. However, the association of exposure to E2 with the inhibition of apoptosis and ERβ remains enigmatic and needs further evaluation [41]. Although a group of researchers has provided considerable evidence suggesting that the activity of E_2 is associated with its receptor ER, resulting in the enhanced proliferation and conferring anti-apoptotic potential to cancer cells according to their receptor profiles, the role of ER remains controversial. A plausible explanation could be due to the uneven expressions of different membrane-related ERs in laryngeal cancer cells [50].

ERα and ERβ exhibit differential expression patterns even in the same HNC type and may exert various effects. For instance, ERα and ERβ may play different functions in the tumor growth and progression of the medullary thyroid carcinoma (MTC) [51]. Similarly, another study suggests that most cases of adenoid cystic carcinoma cases are positive for the expression of ERα and the five-year overall survival rate is significantly better in these cases relative to those with ERβ-positive expression [40]. Furthermore, the differential expression patterns of ERα and ERβ may induce opposite proliferative effects on the same type of HNC. For instance, the expression of ERα is positive for the growth of papillary thyroid cancer (PTC) cells due to autophagy [47], whereas ERβ exerts an inhibitory effect [52]. In thyroid carcinoma, ERs promote proliferation

through different molecular mechanisms. Previous studies show that membrane-bound ERs mediate growth-promoting effects through classical genomic and non-genomic pathways, which are linked to the tyrosine kinase signaling cascades, including transduction through MAPK and PI3K [53]. Another study demonstrates that 17beta-estradiol is an effective mitogen for benign and malignant thyroid tumor cells, as it can bind to the nuclear ERs, thereby promoting growth by activating the MAPK pathway [54]. In addition, the ligand activation for GPR30 signaling, coupled with the upregulation of specific GPER genes, is involved in the proliferation of tumor cells, which implies that GPER can contribute to the tumorigenesis process [55, 56]. Taken together, ERα and ERβ modulate the estrogen signaling at the genomic level, while the third membrane-bound estrogen receptor GPR30 is involved in non-genomic transduction mechanisms and occupies an equally important position in the development of HNC.

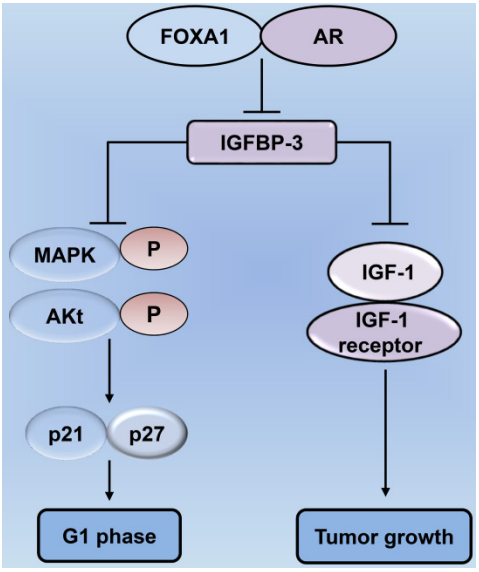

Figure 4. Forkhead box protein A1 (FOXA1) regulates tumor cell proliferation by modulating the expression of insulin-like growth factor-binding protein 3 (IGFBP-3) in prostate cancer. Decrease in the levels of FOXA1 and AR lead to an increase in IGFBP-3 expression, thereby inhibiting the proliferation of cancer cells. IGFBP-3 can suppress the biology of IGF-1 utilization, as well as inhibit the interaction between IGF-1 and the IGF-1 receptor, thereby exerting tumor-suppressive effects. Increased IGFBP-3 following FOXA1 depletion restrains the phosphorylation of signaling mediators, including MAPK and Akt, in the IGF-1 signaling pathway, thereby mediating cell cycle blockade in prostate cancer cells through p21 and p27. AR: androgen receptor; MAPK: mitogen-activated protein kinase.

The expression of ERα66 is lower in aggressive LSCC, while a high ESR1 (a gene encoding ER) expression is associated with improved survival of patients with LSCC [57]. Moreover, ERβ exhibits a significant role in the suppression of LSCC aggression, by reducing the aggressive epithelial-mesenchymal-transition (EMT) features including down-regulation of E-cadherin and concomitant activation of nuclear β-catenin [58]. In contrast, ER expression is indicative of more aggressive behavior. Numerous studies have highlighted the crucial role of ERs in the progression of HNC due to enhanced invasion and migration through the E_2 signaling [31, 59, 60]. Combined ER and EGFR inhibition *in vitro* reportedly reduce HNSCC invasion but not proliferation as compared to both of them targeted singly. Moreover, the combined inhibition of EGF and estrogen signaling pathways can augment the inhibition of invasion relative to the blockade of each pathway separately [61].

Effects of AR on the biological behavior of HNC

AR shows positive expression in HNCs, including oropharyngeal squamous cell carcinoma and salivary gland tumors. In a previous study, all six cases of salivary duct carcinoma and 14 cases of carcinoma ex pleomorphic adenoma (a subset of salivary gland carcinoma) showed strong nuclear immune reactivity for AR. Moreover, the uniform expression of AR in malignant salivary gland carcinoma has been demonstrated [62-66]. In another study, AR expression was detected in tumor samples from oropharyngeal squamous cell carcinoma (OPSCC) patients. The results indicated that 16% (31/199) of the tumors were positive for AR expression, of which 61% (19/31) exhibited a strong expression [67]. Tarakji et al. reported AR expression in 50% of the cases of pleomorphic salivary adenoma by immunohistochemical nuclear staining [68]. Additionally, the high expression of AR is associated with oncogenesis. Wu et al. have investigated the oncogenic role of AR in oral squamous cell carcinoma (OSCC) and reported a high level of expression of AR in premalignant and malignant lesions relative to the normal mucosal tissues. They examined the clinical specimens and observed that OSCC cells expressed functional AR which promoted their growth [69]. However, a few tumors show detectably lower rates [67, 70, 71] of 16% to 26% AR-positive expression. Despite the differential rates of AR expression, notably, the risk factors for malignant tumors are indispensable and deserve greater research attention. The potential functional roles of AR in HNC are listed in Table 2.

Higher expression of AR contributes to the proliferation of cells in different HNC types, including laryngeal carcinoma and juvenile nasopharyngeal fibroma. For instance, stimulation of AR by DHT in OSCC cells causes an increase in cyclin D1 expression, resulting in enhanced cell growth [69]. Moreover, AR exerts a growth-promoting effect on cells in the larynx cancer [72, 73]. In juvenile

nasopharyngeal fibroma, the expression of AR is higher in tumor fibroblasts relative to the genital cells. Consequently, the growth rate of tumor fibroblasts increases due to the action of androgen, while that of the tumor cells is suppressed upon the addition of anti-androgen drugs [74]. However, there is no definitive description of the mechanism underlying AR involvement in the proliferation of HNC, and little is known about how androgens impact proliferation upon binding to AR.

Table 2. The androgen receptor (AR) expression, functions, and mechanisms in head and neck cancers (HNC)

HNC Type	Expression	Prognosis	Function	Mechanism	Ref.
Oral carcinoma	Upregulation	NA	Promote proliferation	Upregulate cyclin D1 level and promote cell growth	[69]
Juvenile nasopharyngeal fibroma	Upregulation	NA	Promote proliferation	NA	[74]
Laryngeal cancer	Upregulation	NA	Promote proliferation	NA	[73]
Salivary duct cancer	Upregulation	NA	Increase invasion	NA	[76]
Micro-papillary salivary duct cancer	Downregulation	NA	Increase aggression	NA	[76]
Laryngeal cancer	Downregulation	Unfavorable	Increase invasion	NA	[102]
Differentiated thyroid cancer	Upregulation	NA	Increase aggression	NA	[77]

Abbreviations: NA, not available; Ref: reference.

Interestingly, ARs exert opposite effects on proliferation in some cancer types. Recently, Hickey et al. have demonstrated that AR activation exhibits antitumor activity in ER-positive breast cancer. They found that the activation of AR altered the genomic distribution of ER and its important co-activators, leading to the repression of ER-regulated cell cycle genes and upregulation of AR-regulated tumor suppressors, thereby inhibiting proliferation of cancer cells [75]. These opposing roles of AR may allow for the targeted development of new and better therapies for specific cancer types.

AR contributes to the migration of AR-positive OSCC cells [32]. DHT acts as an AR-ligand that promotes AR-positive cell migration of OSCC by enhancing the expression of phosphorylated EGFR and AKT. Furthermore, upon treatment of SCC9 cells (AR-positive OSCC cells) with bicalutamide (an AR inhibitor), migration rate and the phosphorylation of EGFR and AKT, reduce. AR plays an important role in OSCC cell migration by regulating the EGFR signaling transduction [32]. On the contrary, similar to ERs, ARs can also reduce invasion. The presence of an invasive micro-papillary component in salivary duct carcinoma that is AR-negative reportedly contributes to checking of the primary site; however, ordinary salivary duct carcinoma is positive for AR [76]. In a study on small differentiated thyroid cancers (DTC), T1 cases according to the TNM Staging System, 2006 with AR-positive tumors showed more aggression as compared to the AR-negative tumors [77]. Taking into account, the relatively scarce previous data from the literature, further studies are required to determine the aggressive role of AR expression in different types of HNCs.

Clinical significance of ER and AR in HNC

According to their various biology functions, ERs play pivotal roles in the clinical disease progression of various HNC types. Accumulating evidence suggests that ERs are associated with shorter survival duration [78]. On the one hand, higher ERα expression significantly influences survival [39]. On the other hand, ERβ positive expression suggests improved survival rates in patients with oropharyngeal cancer [79]. Notably, the relationship between ER expression and other factors exerts essential effects in some cancer types, as well as exhibits a great impact on the development of HNC. However, this influence depends on the type of cancer, along with the correlation between the factor and ER expression. Several studies confirm that ER is associated with prolactin receptor (PRLR) [39], epidermal growth factor receptor (EGFR) [61], and the apolipoprotein B mRNA-editing catalytic polypeptide 3 A (APOBEC3A, A3A) [80]. The EGFR and ERα cross-talks are associated with poor prognoses because of enhanced tumor invasion [61]. This implies that ER can interact with another factor, thereby influencing the development and progression of HNC. Considering all these findings based on previous studies, ER may serve as a novel predictor for HNC, particularly as a prognosticator or biomarker [55, 61].

The relationship between levels of AR and HNC clinical progression cannot be overlooked. In several cases, the role of AR in the progression of other cancer types is consistent with HNC, that is, favorable for tumor growth [69, 81]. Empirical studies report that AR is closely associated with pathological classification, clinical stage, and lymph node metastasis, all of which can promote the growth of laryngeal carcinoma cells [73]. Some reports emphasize that intraprostatic/tumor AR heterogeneity is associated with unfavorable clinical prognoses [82], while for laryngeal squamous cell carcinoma, no significant differences in the survival curves between the low and high expression groups [39] have been observed. Overall, the correlation between AR expression and prognosis in HNC has been rarely documented and warrants further examination.

Application of ER and AR in HNC therapy

Increasing evidence demonstrates that ER and AR are involved in tumor initiation and progression. As described in previous sections, the expressions of ER and AR are high in HNC, indicating that they both are potential targets for HNC treatment. Some cases are amenable to anti-estrogen or anti-androgen therapy and are listed in Table 3 and Table 4, respectively.

Table 3. Application of anti-estrogen therapy in HNC

Receptor	ER level	HNC Type	Treatment	Response	Outcome	Ref.
ER	Positive	Laryngeal cancer	Tamoxifen citrate	Suppress the growth of cells	NA	[103]
ERβ	Positive	Tongue cancer	Fulvestrant	Promote apoptosis	NA	[41]
ER	Positive	Salivary gland cancer	Tamoxifen/ tore-mifene	Negative ER status after therapy	Long-term stability of disease	[84]

Abbreviations: NA, not available; Ref: reference.

Given the impact of ER, HNC treatment benefits from the advantageous effects of anti-estrogen drugs. Studies indicate growth inhibition of ER-positive OSCC cells upon treatment with an ER antagonist, tamoxifen. ER promotes the growth of OSCC cells, while tamoxifen suppresses cell growth [83]. Nonetheless, the mechanisms through which these anti-estrogen agents exert anti-proliferative effects on laryngeal carcinoma cell lines remain unclear. However, the anti-estrogen agents prevent both translocation and nuclear binding of the receptor, thereby blocking ER, resulting in the inhibition of transcriptional activation of estrogen-responsive genes; they also possess potential disease-stabilizing effects in other cancer types [41, 84]. Hence, we speculate that ER-positive patients may benefit from anti-estrogen treatment owing to the blockade of E_2 and ER-related signaling cascades. This may underlie the effects of anti-estrogen treatment in HNC.

Furthermore, ER is associated with unfavorable outcomes after chemoradiation in patients with HNC. Tamoxifen is favorable for overcoming resistance to cisplatin in HNC-squamous cell carcinoma cell lines by inducing G1 arrest and sensitizing the cells to cisplatin-induced apoptosis [85]. *In vitro* studies show that enhanced expression of human submaxillary gland androgen regulatory protein 3A (SMR3A) is accompanied by an upregulation in estrogen receptor 2 (ESR2) level after fractionated irradiation. ESR2-dependent regulation of SMR3A is supported by estradiol (E_2) stimulation of SMR3A, and the co-treatment of estradiol (E_2) with tamoxifen or fulvestrant, correspondingly, attenuate the regulation of SMR3A by ESR2. Both drugs significantly sensitize the HNC tumor cells to graded irradiation and accelerate apoptosis as evidenced by the results of the colony formation assay (CFA). These data suggest that ESR2 plays an important role in radioresistance [86]. In thyroid cancer, the estrogen-related receptor γ (ERRγ, a nuclear receptor with high sequence identity to ERs) inverse agonist contributes to enhanced sensitivity towards radioiodine therapy, suggesting that it may be beneficial in restoring the unresponsiveness of poorly differentiated thyroid cancer cells to radioiodine therapy [87]. On the contrary, ERα-positive oropharyngeal squamous carcinoma (OPSC) patients who underwent radiotherapy, show better overall, disease-free, progression-free, and relapse-free survival as compared to ERα-negative patients, suggesting that ERα may serve as a potential therapeutic target for OPSC [42]. Taken together, the role of ER in HNC chemoradiation therapy remains controversial and needs further validation.

Given the high expression of AR in most HNC cases, patients undergo treatment through androgen deprivation therapy (ADT), using bicalutamide (an androgen receptor antagonist with a non-steroidal structure) [18], abiraterone [88], and flutamide [89]. As first-line therapy for certain tumors, like the AR-positive salivary gland cancer [90], many patients benefit from ADT as it yields a higher response rate and better prognosis. Remarkably, 17 AR-positive salivary gland cancer patients who received ADT showed a 64.7% overall response rate, of which three showed a complete remission [91]. Patients treated with first-line ADT exhibited a higher response rate of 45% (9/20) as compared with those who received first-line chemotherapy (14% (2/14)) [90]. Additionally, relative to conventional chemo-therapy, ADT has equivalent efficacy and less toxicity for unresectable locally advanced salivary gland carcinoma (SGC) [17]. However, the emergence of ADT resistance has reduced its efficiency [92]. The mechanisms underlying ADT resistance are linked to the low expression of androgen synthesis enzyme-encoding gene (SRD5A1) and low activity of the AR pathway. Thus, SRD5A1 may be a promising factor for enhancing responses to ADT in recurrent/ metastatic SDC [92]. Moreover, the benefits of ADT in HNC patients may depend on the level of AR expression.

Table 4. Application of anti-androgen therapy in HNC

HNC Types	AR level	Treatment	Response	Outcome	Ref.
Salivary gland cancer	Positive	Bicalutamide and leuprorelin acetate	Clinical benefit rate (75%)	Favorable prognosis	[17]
Salivary duct carcinoma	Positive	Bicalutamide/combination with Goserelin (LHRH analog)	Stable disease for 32% patients and 50% patients with clinical benefit	Favorable prognosis	[18]
Salivary duct carcinoma	Positive	Bicalutamide with external beam radiotherapy	NA	Favorable prognosis	[93]
Parotid gland adenocarcinoma	Positive	Bicalutamide and Triptorelin (LHRH analog)	A complete remission	Favorable prognosis	[104]
Salivary gland cancer	Positive	Cyproaterone acetate and triptorelin	Overall response rate 64.7%	Favorable prognosis	[91]
Salivary Duct Carcinoma	Positive	Leuprolide and bicalutamide	Good partial response after 3 and 6 months	Favorable prognosis	[105]

Abbreviations: NA, not available; Ref: reference; LHRH: luteinizing hormone-releasing hormone.

Studies show that the combination of chemotherapy or radiotherapy with ADT is more effective for HNC treatment. In a case report, the ADT plus radiation regime was used to definitively treat androgen receptor-positive SDC. The patient showed a good clinical outcome with no clinical evidence of disease after 24 months post-treatment completion [93]. In addition, AR positively correlates with overall survival in patients undergoing radiotherapy and chemotherapy after surgery for head and neck squamous cell carcinoma [94]. Reports show that AR expression is an independent prognostic factor for overall survival and metastases-free survival [94], however, the relationship between AR expression and chemoradiation is ambiguous. In the future, clinical trials are expected to address whether combined androgen blockade is better than chemotherapy or radiotherapy alone as a first-line treatment for metastatic cancers, along with its correlation with AR.

Conclusions and perspectives

This review summarized the potential roles of ER and AR in the progression of HNC. Based on the findings from several studies, further investigations are required to evaluate the functional roles and mechanisms underlying ER and AR involvement in the development of HNC and the putative benefits by alleviating negative effects on tumor growth and progression using antagonists of ER or AR. Differential levels of ER and AR elicit controversial effects in HNC progression, indicating a complexity in their status and roles, which requires further confirmation in certain cancer types.

FOXA1 and fatty acid synthase (FASN) may be associated with ADT resistance in prostate cancer [37, 95-99]. Similarly, FOXA1 and FASN are also present in patients with AR-positive salivary gland cancer [100], and therefore, may be also associated with other HNC types. Targeting ERα36 can reduce the detrimental effects of E_2 in laryngeal cancer, suggesting the importance of the identification of novel drugs that specifically target the ERα36 [31]. Overall, all findings indicate the importance of anti-estrogen and anti-androgen therapies or the production of novel drugs targeting AR and ER in HNC.

Going forward, the possible effects of ER and AR, such as their involvement in oncogenesis and mediating cellular proliferation, make them prime candidates of novel and potential biomarkers or/and targets for cancer diagnosis and treatment. Given that the levels of expression of AR or ER are regulated by their upstream signaling pathways or transcription factors, for instance, tamoxifen interrupts MAPK and PI3K signaling cascades to reduce E_2-induced proliferation by decreasing ER expression [101], targeting the upstream pathways or transcription factors of ER and AR maybe a novel approach for the treatment of HNC.

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Author Contributions

YYW, WG and SXW conceived the study. CHQ, YL, and HMZ wrote the first version of the manuscript. CHQ, HMZ and ZZ organized the figures. CHQ, YL, HMZ, WX, SXW, YYW, and WG revised the manuscript. All of the authors approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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