

Review

Naturally Occurring Feline Cancers in Comparative Oncology: Translational Insights from Oral Squamous Cell Carcinoma and Mammary Carcinoma

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Simple Summary

Comparative oncology studies naturally occurring cancers in pet animals to better understand similar cancers in people and improve treatment for both. Cats are becoming uniquely helpful because they develop cancers naturally, have intact immune systems, share many environmental exposures with humans, and often show aggressive disease patterns that resemble human cancers. In this review, we focus on two common feline cancers, oral squamous cell carcinoma and mammary (breast) carcinoma, which share important clinical and biological features with human head and neck cancer and an aggressive form of human breast cancer. These similarities suggest that studying cancer in cats can help researchers better understand how similar cancers develop in people and test new treatments in settings that more closely reflect real-world disease.

Abstract

Background: Comparative oncology uses naturally occurring cancers in companion animals to study tumor biology and therapeutic responses relevant to human cancer. Spontaneous feline tumors are increasingly recognized as useful comparative models because they arise in immunocompetent hosts, develop under shared environmental exposures, and can reproduce selected clinical, histopathologic, molecular, and therapeutic features of human malignancies. **Methods:** This review compares feline oral squamous cell carcinoma (FOSCC) with human head and neck squamous cell carcinoma (HNSCC), and feline mammary carcinoma (FMC) with human breast cancer, emphasizing shared pathologic, molecular, tumor microenvironment, and therapeutic features. **Results:** Recent immunohistochemical, genomic, transcriptomic, and biomarker studies have identified shared features between feline and human cancers. FOSCC resembles human HNSCC through aggressive local invasion, histologic features, therapeutic resistance, and recurrent alterations of *TP53*, *MYC*, and *PTEN*. FMC shows strong overlap with aggressive human triple-negative breast cancer, including reduced hormone receptor expression, recurrent *TP53*, *PIK3CA*, and *CXCL12/CXCR4* signaling alterations, and tumor microenvironment features involving immune-checkpoint, inflammatory, and angiogenic pathways. FOSCC clinical trials and emerging clinical investigations into FMC treatments further support the use of cats for translational therapy evaluation. **Conclusions:** FOSCC and FMC are promising comparative oncology models for human HNSCC and aggressive breast cancer, respectively. Future multicenter studies incorporating standardized tumor classification and grading, predefined stratification criteria, and clinically meaningful endpoints will be essential to strengthen their translational value.



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1. Introduction

In the United States, an estimated 89 million pet dogs and 62 million pet cats reside in households [1]. These companion animals share many environmental exposures with humans and often develop cancers that resemble human disease in genetic pathways, histology, clinical presentation, disease outcomes, and responses to treatment [2–4]. Comparative oncology uses biologic and clinical insights from naturally occurring cancers in companion animals to improve understanding of cancer biology, support biomarker discovery, and advance therapeutic development in humans [2,3]. This approach is closely aligned with the concept of “One Health” [5–7], which emphasizes the bidirectional exchange of knowledge between veterinary and human medicine to improve health outcomes across species [8].

Spontaneously arising feline tumors offer several advantages over in vitro systems and conventional rodent models (Figure 1). Unlike experimentally induced or implanted tumors, cancers in cats develop in an immunocompetent host and can better reflect the natural history and biologic heterogeneity of human cancers [9–14]. Moreover, because cats have shorter life spans than humans and many feline cancers progress rapidly, longitudinal clinical and biologic data can often be collected over a shorter time frame [4,15]. Complementing these features, advances in molecular characterization have enabled the evaluation of feline tumors with greater resolution, further strengthening their translational relevance [4,16]. Recent studies have shown that feline cancers share many genetic and molecular similarities with human cancers, including frequent alterations in cancer-associated genes and pathways [12,16–18]. For example, targeted sequencing of 493 feline tumor samples and matched normal tissues across 13 tumor types revealed strong similarities between the feline and human oncogenomes [16]. *TP53* was the most frequently mutated gene in feline tumors, with a prevalence similar to that reported in human cancer datasets [16,19–22]. Feline tumors also showed recurrent copy-number gains in *MYC* and losses in *PTEN* and *FAS*, alterations that are broadly consistent with patterns observed across human cancers [16,23,24]. Histologic evidence further supports the comparative value of feline cancers. Across several tumor types, including feline oral squamous cell carcinoma (FOSCC), feline mammary carcinoma (FMC), pulmonary carcinoma, and intestinal carcinoma, feline tumors show features similar to those observed in humans, including comparable tissue architecture, differentiation patterns, cytologic atypia, stromal responses, and invasive growth behavior [25–28]. Together, these genetic, molecular, and histologic parallels support the use of naturally occurring feline cancers as comparative oncology models.

Among feline cancers, FOSCC and FMC are particularly promising comparative models for HNSCC and human mammary carcinoma, respectively [4,13,26,29–31]. This review examines FOSCC and FMC within the context of comparative oncology, emphasizing their histopathologic and molecular parallels with human cancers and their potential value for biomarker discovery, therapeutic evaluation, and translational research. The goal is not to suggest a simple one-to-one correspondence between feline and human malignancies but to critically evaluate where the comparative evidence is strongest, where important biologic differences remain, and what additional studies are needed to strengthen the contribution of feline oncology to human cancer research.

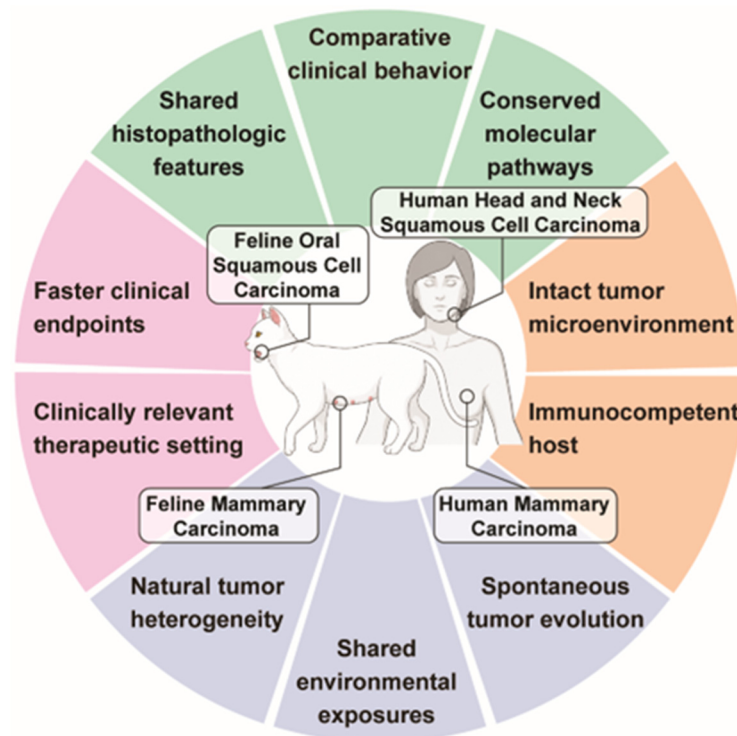


Figure 1. Key advantages of spontaneous feline cancers in comparative oncology. Spontaneous feline cancers develop in a real-world disease context, preserve host–tumor interactions, and often reach clinical endpoints more rapidly than comparable human cancers. FOSCC and FMC are highlighted as representative examples that recapitulate important aspects of human head and neck squamous cell carcinoma and mammary carcinoma, respectively, in their clinical behavior, histopathology, genomic alterations, and dysregulated signaling pathways. These features support the value of naturally occurring feline cancers as comparative oncology models for biomarker discovery, translational therapeutic studies, and evaluation of treatment response in spontaneous disease.

2. FOSCC and Human HNSCC

FOSCC is the most common oral malignancy in cats and the fourth most common feline cancer overall [30,32–35]. It arises from the squamous epithelium of the oral cavity and most commonly affects the gingiva, tongue, sublingual region, and tonsils [32,33]. Clinically, FOSCC is highly locally invasive and can cause extensive destruction of surrounding soft tissues and bones, leading to pain, difficulty swallowing, excessive salivation, weight loss, and reduced quality of life [33,36,37]. Although metastasis is generally uncommon at initial diagnosis, regional lymph node and pulmonary metastases can occur in advanced disease. This is particularly true for tonsillar FOSCC, which often shows more aggressive biologic behavior with a high metastatic rate [38,39]. Despite multimodal treatment approaches, including surgery, radiation therapy, chemotherapy, and immunotherapeutic strategies [40–42], the prognosis remains poor, with reported 1-year survival rates of less than 10% [32,37]. In humans, HNSCC is among the most common cancers worldwide and remains a major cause of cancer-related mortality [43,44]. Many patients present with locally advanced disease, and the overall 5-year survival rate is approximately 50% [44,45]. FOSCC shares several important clinical features with human HNSCC, including aggressive local invasion with destruction of surrounding tissues, relatively late metastatic progression, and limited response to conventional therapies [43]. In both species, tumors are often diagnosed at advanced stages, contributing to poor outcomes and highlighting the need for improved early detection and more effective therapeutic strategies [33,43].

2.1. Viral Etiology

Human HNSCC is commonly divided into two major etiologic subtypes: HPV-positive and HPV-negative disease. HPV-positive HNSCC is driven by infection with high-risk HPV strains, whereas HPV-negative HNSCC is more often associated with carcinogen exposure, particularly tobacco and alcohol usage [46,47]. These subtypes differ substantially in biology and clinical behavior. Compared with HPV-positive disease, HPV-negative HNSCC is generally associated with shorter survival, higher rates of local recurrence, and greater risk of distant metastasis [48,49]. Current evidence suggests that most FOSCC cases more closely resemble HPV-negative HNSCC than HPV-positive HNSCC [16,30,31,50,51]. Although *Felis catus* papillomavirus (FcaPV) DNA has been detected in some FOSCC cases, the reported detection rate varies widely across studies, from rare or absent detection to approximately 47% in selected cohorts [16,30,31,50–55]. This variation is difficult to interpret because studies differ in cohort size, geographic origin, tumor site, tissue preservation, and detection method. Earlier PCR-based studies, often using broad or non-type-specific primers on formalin-fixed paraffin-embedded tissue-derived DNA, reported rare or absent viral detection, and virome sequencing detected FcaPV in only a small minority of FOSCCs [31,52]. In contrast, studies using FcaPV type-specific PCR assays have reported higher detection rates [53–55]. One study detected FcaPV2 DNA in 46.9% of feline SCC cases from Taiwan but in only 8.6% of cases from Japan, suggesting possible geographic variation [54]. Overall, the wide range of reported FcaPV detection rates likely reflects biologic and geographic variation, as well as differences in assay sensitivity. However, detection of viral DNA alone does not prove that FcaPV drives tumor development. Stronger evidence of active viral involvement would require viral oncogene expression, a high viral load in tumor tissue, and viral localization within tumor cells [51,53–55]. Current evidence therefore supports FcaPV infection as a plausible contributor in a subset of FOSCCs, while most FOSCC cohorts not selected for viral positivity remain more consistent with HPV-negative human HNSCC biology [31,51]. At the molecular level, FOSCC also shares several alterations with HPV-negative HNSCC, including copy-number gains in *MYC* and copy-number losses in *PTEN* and *FAS* [12,16,20,21,56,57]. Together, virologic and molecular evidence support FOSCC as a closer comparative model for HPV-negative HNSCC than for HPV-positive disease [30,31,51,58,59].

2.2. Risk Factors

Risk factors for human HNSCC include chronic inflammation, HPV infection, periodontitis, and poor oral hygiene, with tobacco smoking and alcohol consumption representing the predominant drivers [43,60–62]. These factors create a sustained inflammatory and carcinogenic environment that promotes squamous epithelial transformation and tumor progression. In cats, exposure to environmental tobacco smoke has been associated with an increased risk of FOSCC, potentially because tobacco-derived carcinogens accumulate on the fur and are subsequently ingested during grooming [63,64]. This finding parallels the role of tobacco exposure in human HNSCC and supports the concept that shared carcinogens may contribute to oral squamous carcinogenesis across species. Additional environmental and lifestyle factors have also been associated with FOSCC, including ectoparasite-control products, flea-collar use, and dietary variables [35,63,64]. Flea-collar exposure has been associated with an approximately 5-fold increased risk of FOSCC, whereas high consumption of canned food and canned tuna has been associated with approximately 3.6-fold and 4.7-fold increased risks, respectively [63]. Collectively, these findings indicate that both human HNSCC and FOSCC arise in the context of chronic environmental exposures and sustained inflammatory stimuli.

2.3. Histopathologic Similarities Between Feline and Human Oral Squamous Cell Carcinoma (OSCC)

FOSCC closely resembles human OSCC histologically. In both species, the predominant histopathologic feature is invasive squamous differentiation, in which malignant epithelial cells form nests, islands, cords, or sheets that infiltrate the underlying stroma. FOSCC and human OSCC also show variable degrees of keratinization, cytologic atypia, nuclear pleomorphism, and mitotic activity. These epithelial changes are often accompanied by a stromal response characterized by desmoplasia, fibrosis, and mixed inflammatory cell infiltration [25,33,65,66]. In FOSCC, the invasive tumor component commonly consists of small clusters, cords, or trabeculae of neoplastic cells extending into the submucosa and deeper tissues, closely mirroring the infiltrative growth pattern described in human OSCC [25,33]. Both diseases are also characterized by marked local invasion, including extension into adjacent soft tissues and bone, consistent with their clinically aggressive behavior [33,37]. In addition to conventional histologic patterns, FOSCC may display variants such as verrucous and papillary forms, which correspond to recognized morphologic subtypes within the human head and neck cancer spectrum [33,67].

Despite these strong histopathologic similarities, feline-specific grading and classification systems for FOSCC remain incompletely standardized. Several studies have applied human-derived grading schemes, including Anneroth's and Bryne's systems, and have described histologic subtypes such as conventional, verrucous, papillary, acantholytic, and adenosquamous variants [68,69]. However, the prognostic relevance of these grading approaches and subtypes has not been consistently validated in cats. As a result, FOSCC currently lacks a universally accepted feline-specific histopathologic grading framework. Establishing standardized criteria that integrate histology with clinical outcomes, molecular features, and therapeutic response would improve case stratification, enhance reproducibility across studies, and strengthen the translational value of FOSCC as a comparative model for human OSCC/HNSCC.

2.4. Shared Molecular Pathways and Oncogenic Drivers in FOSCC and Human HNSCC

Genomic and transcriptomic profiling has revealed substantial overlap between FOSCC and human HNSCC at both the mutational and gene-expression levels [12,34,70], as summarized in Table 1. These shared alterations span several biological processes, including tumor suppressor disruption, invasion-associated transcriptional programs, inflammatory and receptor-mediated signaling, angiogenesis, and developmental pathway dysregulation. In HNSCC, *TP53* is the most consistently altered gene, with mutations reported in approximately 70% of cases and recognized as key events in tumor initiation and progression [71–73]. *TP53* alterations are also prominent in FOSCC, although reported frequencies vary across cohorts and sequencing platforms. Whole-exome sequencing identified *TP53* mutations in 12 of 42 FOSCC cases (29%), while a smaller cohort detected *TP53* mutations in 4 of 6 cases [16,34]. In a recent targeted sequencing study, 24 of 34 tumors (71%) contained predicted consequential *TP53* variants [12]. These genetic alterations are further supported by transcriptomic evidence of *TP53* pathway disruption in FOSCC, including reduced expression of the p53 target gene *CDKN1A* [34].

FOSCC and HNSCC share activation of epithelial–mesenchymal transition (EMT)-associated programs. EMT promotes tumor cell plasticity, local invasion, metastasis, and treatment resistance, making it highly relevant to the aggressive behavior of both diseases [74–77]. In human OSCC/HNSCC, EMT is associated with poor prognosis and treatment resistance and is marked by increased expression of transcriptional regulators such as *ZEB1*, *ZEB2*, and *TWIST1* [74,78]. Transcriptomic profiling of FOSCC has shown enrichment of a similar EMT-associated program, including increased expression of *ZEB1*,

ZEB2, and *TWIST1* [34,79,80]. This shared EMT signature suggests that FOSCC and HNSCC may use similar mechanisms to promote invasion, metastasis, and therapy resistance, supporting the relevance of FOSCC for studying tumor plasticity in a comparative oncology context.

Inflammation-associated signaling represents another shared feature that may contribute to invasion and treatment resistance in FOSCC and human HNSCC. Transcriptomic profiling of FOSCC has shown enrichment of IL-6/JAK/STAT, TNF/NF- κ B, hypoxia, and related inflammatory pathways [34]. Consistent with this pathway-level evidence, STAT3 activation has also been detected in FOSCC-derived cell lines [81]. Pharmacologic STAT3 inhibition in pet cats with FOSCC achieved a 35% disease control rate, further supporting the potential therapeutic relevance of this pathway [41]. In HNSCC, IL-6-mediated activation of JAK/STAT3 signaling promotes tumor growth, immune evasion, therapeutic resistance, and poor clinical outcomes [82–86]. EGFR signaling can activate the JAK/STAT3 signaling pathway [87], and EGFR overexpression has been reported in approximately 69–100% of FOSCC cases and 90% of HNSCC cases and is associated with increased proliferation, invasion, and treatment resistance [34,88–90].

FOSCC and HNSCC also share signaling pathways that regulate angiogenesis, tumor growth, and invasion. In HNSCC, COX-2 promotes tumor progression in part through prostaglandin-mediated signaling and regulation of angiogenic mediators such as VEGF [91–96]. A similar pattern has been reported in FOSCC, where COX-2 overexpression occurs in a subset of cases and is often associated with VEGF expression [97–100]. Aberrant WNT/ β -catenin signaling has also been described in both HNSCC and FOSCC [25,101–103]. Because WNT/ β -catenin regulates development, epithelial homeostasis, and cell fate, its dysregulation may contribute to tumor growth and invasion in both diseases [25,101–104].

Taken together, these findings indicate that FOSCC and HNSCC share alterations in TP53-mediated tumor suppression, EMT-associated invasion, STAT3-mediated inflammatory signaling, COX-2/VEGF-associated angiogenesis, and WNT/ β -catenin developmental signaling. This molecular similarity provides a mechanistic rationale for using FOSCC as a spontaneous comparative model of selected pathway-driven mechanisms in HNSCC, particularly invasion, metastasis, and therapeutic resistance.

Table 1. Shared molecular features between FOSCC and human HNSCC.

Molecular Feature	Human HNSCC	FOSCC
<i>TP53</i>	Loss-of-function mutation of <i>TP53</i> is associated with loss of genome surveillance, impaired apoptosis and cell-cycle arrest, with mutations reported in approximately 70% of cases [71–73,105,106].	<i>TP53</i> mutations have been reported in up to 71% of FOSCC tumors [12,16,34].
<i>MYC</i>	<i>MYC</i> overexpression, with an estimated prevalence of 12% in HNSCC, is linked to aggressive behavior, poorer survival, and therapeutic resistance, particularly in HPV-negative tumors [107,108].	<i>MYC</i> expression is increased in FOSCC tissue, and recent whole-exome sequencing identified <i>MYC</i> copy-number gain in 31% of FOSCCs [16,25,34].
<i>PTEN</i>	In HNSCC, <i>PTEN</i> loss or inactivation promotes cell proliferation, migration, and survival, with mutations detected in ~10% of patients [109–112].	<i>PTEN</i> copy-number loss was identified in 24% of FOSCCs [16].

Table 1. Cont.

Molecular Feature	Human HNSCC	FOSCC
<i>FAS</i>	<i>FAS</i> pathway dysregulation contributes to apoptosis resistance and immune escape in HNSCC [113–115].	<i>FAS</i> copy-number loss was identified in 21% of FOSCCs [16].
<i>CDKN2A</i>	Loss-of-function mutation of <i>CDKN2A</i> has been identified as a prognostic biomarker in HNSCC, associated with poor overall survival and increased risk of metastasis [116–118].	<i>CDKN2A</i> inactivation has been reported in FOSCC [50,119].
EMT-related pathways	In HNSCC, upregulated EMT contributes to invasion, metastasis, poor prognosis, and treatment resistance [77,78].	FOSCC RNA-seq shows enrichment of EMT-related pathways [34,79,80].
IL-6/JAK/STAT3	In HNSCC, hyperactivated IL-6/JAK/STAT3 signaling promotes tumor growth, immune evasion, invasion, treatment resistance, and poor prognosis [82–86].	The IL-6/JAK/STAT pathway is enriched in FOSCC [41,81].
EGFR signaling	<i>EGFR</i> is up to 90% overexpressed in human HNSCC and is associated with proliferation, invasion, and treatment resistance [89,90,120].	<i>EGFR</i> is overexpressed in 69–100% of FOSCC cases and is associated with tumor aggressiveness [34,39,88].
COX-2 and <i>VEGF</i>	In HNSCC, upregulation of <i>COX-2</i> and <i>VEGF</i> is linked to angiogenesis, lymph node metastasis, tumor progression, and poorer survival outcomes [93–96,121,122].	<i>COX-2</i> overexpression has been reported in approximately 33% of FOSCC cases, with <i>VEGF</i> colocalization [97–100,123].
WNT/ β -catenin	WNT/ β -catenin signaling is upregulated in HNSCC and contributes to tumor progression, invasion, and treatment resistance [101–104].	Upregulation of WNT pathway components has been reported in FOSCC [25].

FOSCC, feline oral squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; HPV, human papillomavirus; EMT, epithelial–mesenchymal transition.

2.5. Translational and Clinical Trial Insights of FOSCC

FOSCC is highly aggressive and progresses rapidly after diagnosis. The median survival time after diagnosis of FOSCC is approximately 66 days, reflecting the highly aggressive nature of the disease [38,124,125]. This short clinical course allows treatment response and tumor-associated biologic changes to be evaluated relatively quickly, facilitating translational studies that are difficult to conduct over comparable time frames in human patients [30,42,59].

Targeted therapeutic clinical trials in FOSCC have demonstrated the feasibility of using this disease for translational treatment studies. In a phase I clinical trial of systemic cyclic STAT3 decoy oligonucleotide (CS3D) in 20 pet cats with FOSCC, treatment was well tolerated, with no dose-limiting toxicity observed at 10 mg/kg, and 7 of 20 cats showed either partial response or stable disease [41]. Notably, tumors from responding cats showed distinct immunologic features, including increased intratumoral PD-1 expression, suggesting that STAT3 inhibition may be associated with tumor immune environment responses [41]. Additional studies have evaluated FOSCC in the context of therapeutic approaches relevant to human HNSCC. In human HNSCC, cisplatin-based chemoradiotherapy is commonly used, although systemic toxicity can limit completion of planned treatment regimens, highlighting the need for better-tolerated therapeutic strategies [126,127]. In a retrospective study, cats with FOSCC treated with accelerated radiation and concurrent carboplatin, follow-up treatment with toceranib phosphate, a multi-target

tyrosine kinase inhibitor, did not significantly improve overall survival or progression-free interval [40]. This finding suggests that empiric multi-kinase inhibition with toceranib may have limited benefit in biologically unselected cats with FOSCC and highlights the need for biomarker-guided patient selection. Another prospective feasibility study evaluated ultrasound- and microbubble-mediated bleomycin delivery in six cats with FOSCC as a site-specific drug-delivery strategy [128]. In this approach, bleomycin is given systemically, followed by intravenously administered microbubbles that circulate through the tumor vasculature and are activated locally by ultrasound [128]. This ultrasound–microbubble interaction can increase vascular permeability and temporarily permeabilize tumor-cell membranes, potentially improving bleomycin uptake within the tumor without increasing the systemic drug dose [129–132]. Although antitumor responses were limited, the study demonstrated technical feasibility and acceptable tolerability, supporting further optimization of this delivery strategy before broader translational application.

Metabolic targeting strategies have also been evaluated in FOSCC. In HNSCC, polyamine metabolism is an active therapeutic target because squamous carcinoma cells require polyamines for proliferation and tumor regrowth during radiotherapy [133,134]. Difluoromethylornithine (DFMO) inhibits polyamine synthesis and suppresses tumor growth in mouse models, but its efficacy can be limited when tumor cells compensate by increasing polyamine uptake from outside the cell [135–137]. To address this limitation, a phase I/II feline study combined DFMO with the polyamine transport inhibitor MQT 1426 in cats with FOSCC, thereby targeting both polyamine synthesis and uptake [138–140]. Serial tumor biopsies showed reduced intratumoral polyamine levels, confirming that the treatment affected its intended metabolic pathway [138]. Although clinical responses were limited, with partial responses in two cats and stable disease in six cats, the combination was feasible and provided important safety and proof-of-mechanism data [138]. These findings support further investigation of dual polyamine blockade as a translational strategy relevant to HNSCC.

Collectively, these studies support FOSCC as a clinically relevant comparative model for aggressive HNSCC. FOSCC shares important features with human HNSCC, including advanced-stage presentation, marked local invasion, limited response to standard therapies, p53 dysfunction, EMT activation, and inflammatory signaling [34,42,43,81,85,86,96–100,123]. Because FOSCC arises spontaneously, progresses rapidly, and has limited standard treatment options, it provides a practical setting for evaluating new therapeutic strategies relevant to both feline OSCC and human HNSCC. These features support FOSCC as a translational model for studying HNSCC biology and treatment response.

3. FMC and Human Mammary Carcinoma

FMC is the third most common neoplasm in cats, accounting for approximately 11–35.5% of all feline tumors [141,142]. The annual incidence has been estimated at approximately 230 cases per 100,000 cats in Sweden [143]. Unlike canine mammary tumors, most feline mammary tumors are malignant at diagnosis, and FMC is commonly characterized by high-grade histology and aggressive clinical behavior, with frequent relapse after surgery and early metastasis to regional lymph nodes, lungs, and pleura [4,142,144,145]. An important anatomical distinction is that humans have one pair of breasts, whereas cats typically have four pairs of mammary glands arranged in two longitudinal chains with drainage to the axillary and superficial inguinal lymph nodes [146–149]. Although multifocal disease also occurs in human breast cancer (HBC), cats commonly present with synchronous tumors involving multiple mammary glands; one series reported multiple masses in approximately 60% of affected cats [150,151]. Tumors within the same cat may differ in histologic type or surrogate molecular subtype, providing opportunities for within-cat comparisons but also

requiring each lesion to be evaluated separately [152,153]. The comparative relevance of FMC is strongest for aggressive HBC subtypes. In human breast carcinoma, high-grade tumors are typically characterized by reduced tubule formation, marked nuclear pleomorphism, and high mitotic activity, and they may also show lymphovascular invasion and desmoplastic stroma [153–156]. FMC shares many of these aggressive histologic features, including poor differentiation, nuclear atypia, high mitotic activity, lymphovascular invasion, and stromal desmoplasia [14,28,29,142,157–160]. FMCs are also frequently hormone receptor-negative, and a substantial subset shows a triple-negative immunophenotype resembling human triple-negative breast cancer (TNBC) [28,142,153,159]. Molecular studies further support the relevance of FMC as a comparative model for aggressive HBC subtypes. Conserved oncogenic pathways are dysregulated in both FMC and human TNBC, including alterations involving *TP53*, *PTEN*/*AKT*/*mTOR* signaling, *CXCR4*-mediated metastatic pathways, and EMT programs [16,22,161,162]. These subtype-specific molecular features are discussed further in Section 3.2. Together, these clinical, histologic, and molecular similarities suggest that FMC may be useful for studying aggressive HBC subtypes, especially TNBC-like disease, rather than serving as a broad model for all forms of HBC. This comparative framework supports the use of FMC to investigate tumor progression, metastatic biology, therapeutic resistance, and emerging targeted therapeutic strategies.

3.1. Risk Factors

Several risk factors associated with HBC, including aging, lifetime hormonal exposure, and environmental toxicants, have also been implicated in FMC development [142,163–167]. In cats, the incidence of FMC increases markedly with age, with most tumors diagnosed in middle-aged to older animals, particularly between 10 and 14 years of age [168,169]. Lifetime hormonal exposure is a major risk factor for FMC, and early ovariohysterectomy markedly reduces this risk. Cats spayed before 6 months of age have an approximately 91% lower risk of developing FMC, while those spayed before 1 year of age have an approximately 86% lower risk [142,164,170]. This protective effect is thought to result primarily from reduced lifetime exposure to endogenous ovarian hormones, particularly estrogen and progesterone [142,164]. Consistently, exposure to exogenous progestogens has been associated with an increased risk of feline mammary hyperplasia and neoplasia, including in male cats [171,172]. Environmental factors may also contribute to FMC development. Heavy metals and environmental pollutants have been proposed as potential risk factors, possibly through endocrine disruption, oxidative stress, chronic inflammation, and genomic instability [173].

Breed-associated susceptibility to FMC is less consistently defined than age and hormonal risk factors [174,175]. Earlier North American studies reported an approximately two-fold increased risk of mammary carcinoma in Siamese cats [163], whereas other studies have reported different breed distributions among affected cats [174,176,177]. More recent UK primary-care data suggest an increased risk in purebred cats overall, whereas Brazilian cohorts have not identified a clear breed predisposition [174,178]. These differences likely reflect regional variation in breed distribution and the proportion of mixed-breed cats within each study population. Therefore, breed should be considered a possible population-dependent risk factor rather than a consistently established predictor of FMC risk.

Several FMC risk factors parallel epidemiological patterns observed in HBC. In women, advancing age is one of the strongest risk factors, with the highest incidence occurring after 50 years of age, and risk continues to increase with increased age [165–167,179,180]. Prolonged lifetime exposure to estrogen and progesterone also contributes substantially to breast cancer risk. Reproductive and hormonal factors that increase cumulative hormonal exposure are associated with increased breast cancer susceptibility, including nullipar-

ity, late age at first pregnancy, early menarche, late menopause, and shorter duration of breastfeeding [167,179,180]. Environmental exposures may also contribute to mammary carcinogenesis. Volatile organic compounds, particulate matter, and heavy metals have been linked to endocrine disruption, chronic inflammation, oxidative stress, epigenetic changes, and altered gene-expression pathways involved in breast cancer development and progression [181–184]. Collectively, the shared influences of aging, hormonal exposure, and environmental toxicants across both species support the value of FMC as a spontaneous comparative model for investigating hormone-associated and environmentally influenced mammary carcinogenesis.

3.2. Molecular and Biomarker Parallels

In HBC, tumors are commonly classified using the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [185,186]. Combined assessment of these biomarkers allows classification into clinically relevant subtypes, including hormone receptor-positive/HER2-negative (ER+/HER2−), HER2-positive, triple-positive (ER+/PR+/HER2+), and TNBC (ER−/PR−/HER2−) [185–188]. Within hormone receptor-positive disease, luminal A-like and luminal B-like tumors are further distinguished by proliferative activity, commonly assessed by Ki-67 expression, together with PR expression and HER2 status [185–189]. Luminal A tumors are typically ER+/PR+/HER2− with low Ki-67 expression and are generally associated with the most favorable clinical outcomes [185,186]. In contrast, luminal B-like tumors usually show higher proliferative activity, lower PR expression, and are associated with more aggressive clinical behavior [189]. TNBC lacks ER, PR, and HER2 expression and is characterized by poorly differentiated, highly proliferative, high-grade tumors. Triple-negative breast cancer comprises distinct molecular subtypes, including a basal-like subtype defined by high gene expression of basal cytokeratins such as CK5/6, CK14 and CK17 [186,190–192]. It remains one of the most aggressive breast cancer subtypes because of its marked biologic heterogeneity and limited availability of targeted hormonal or HER2-directed therapies [193–197].

Similar to HBC classification systems, feline mammary adenocarcinomas have been stratified using ER, PR, and HER2 expression into luminal-like, HER2-positive, and triple-negative subtypes. Immunohistochemistry-based studies identified six surrogate molecular subtypes analogous to HBC categories: luminal A, luminal B/HER2-negative, luminal B/HER2-positive, HER2-positive, triple-negative basal-like, and triple-negative non-basal-like [28,153,159]. Notably, FMCs are predominantly hormone receptor-negative and share important clinicopathologic, immunophenotypic, and molecular similarities with aggressive human TNBC [14,28,29,142,157–160]. One study reported that 58% of feline mammary adenocarcinomas were triple-negative [28], while another found that 85% of FMCs displayed a triple-negative phenotype [159]. Consistent with the aggressive behavior of human TNBC, triple-negative FMCs have been associated with larger tumor size, poor differentiation, necrosis, high mitotic activity, increased invasive behavior, and shorter overall survival [28,142,153,159]. Although luminal A-like and luminal B-like subtypes have been described in FMC, FMC is not yet well established as a model of hormone-responsive luminal breast cancer [175,198]. HER2-positive FMCs have also been reported, but the estimated prevalence varies by assay, antibody, and scoring criteria, with some studies reporting approximately 30% of cases with HER2 overexpression [199,200]. Overall, current evidence most strongly supports FMC as a spontaneous model of aggressive TNBC-like breast cancer rather than as a broad model for all HBC subtypes.

Integrative molecular analyses also indicate that FMC most closely resembles aggressive human TNBC rather than the full spectrum of human breast carcinoma subtypes

(Table 2) [13,29]. RNA-seq profiling of FMC tumors and derived cell lines has shown dysregulation of cell-cycle, metabolic, heat-shock, p53-associated, and centrosome-regulatory programs [201]. These alterations overlap with key molecular features of aggressive TNBC, including high proliferative activity, TP53 pathway disruption, metabolic reprogramming, HSP90-associated proteostasis, and FOXM1/E2F-driven mitotic programs, all of which contribute to genomic instability, therapeutic resistance, and poor clinical outcome [202–206]. Copy-number and genomic sequencing studies further support this comparison. In FMC, copy-number losses in tumor-suppressor loci and gains in oncogenic loci such as *MYC* have been reported [156]. This pattern resembles human TNBC, which is characterized by extensive genomic instability, frequent copy-number alterations, gains in oncogenic regions such as *MYC*, and copy-number losses in tumor-suppressor loci [207–210]. Large-scale feline cancer sequencing studies have also identified recurrent driver-gene alterations in FMC, including *PIK3CA*, *TP53*, and *PTEN* alterations [16,22,161,162]. *PIK3CA* mutations have been reported in 22 of 47 FMCs, whereas *PTEN* alterations primarily occur through copy-number loss [16,157,211]. These alterations are biologically relevant because *PIK3CA* activation and *PTEN* loss can activate PI3K/AKT/mTOR signaling, promoting tumor-cell proliferation, survival, angiogenesis, metastatic progression, and therapeutic resistance in human TNBC [161,162,212,213]. *TP53* alterations further contribute to impaired DNA-damage responses, genomic instability, and aggressive clinical behavior, particularly in TNBC [212,214]. Together, these transcriptomic, copy-number, and genomic data support FMC as a spontaneous comparative model for studying molecular mechanisms in aggressive TNBC-like breast cancer.

Immune-checkpoint and prognostic biomarkers show several similarities between FMC and HBC. PD-1, PD-L1, and PD-L2 expression have been reported in FMC [10,215,216], similar to aggressive HBC subtypes such as TNBC, where immune-checkpoint signaling contributes to immune evasion and therapeutic response [217,218]. Bcl-2 expression also appears to have similar prognostic associations in both species. In FMC, Bcl-2 expression has been linked to longer disease-free interval and overall survival [219]. Similarly, in HBC, high Bcl-2 expression is associated with lower tumor grade, hormone receptor positivity, improved survival, and reduced tumor aggressiveness [220,221].

In addition to established molecular and immunologic markers (Table 2), tissue proteomic studies in FMC have identified discovery-stage biomarker candidates, including dermatopontin (*DPT*) and sorting nexin 5 (*SNX5*) [14,222]. Reduced *DPT* expression is associated with poorer overall survival and linked to predicted drug-response patterns involving doxorubicin, lapatinib, and neratinib, although the translational relevance of these findings requires further validation [14,222]. Collectively, these molecular and biomarker parallels support the value of FMC as a spontaneous comparative model for aggressive HBC, particularly TNBC, and provide opportunities for cross-species biomarker discovery, prognostic modeling, and development of targeted therapeutic strategies.

Table 2. Shared molecular features between FMC and HBC.

Molecular Feature	HBC	FMC
<i>TP53</i>	<i>TP53</i> is frequently altered in aggressive breast cancer, with mutations reported in approximately 80% of TNBC cases [223]. Loss or alteration of p53 function is associated with high-grade, poor-prognosis tumors and increased metastatic potential [224].	<i>TP53</i> mutations have been recurrently reported in FMC [16,160,225,226].

Table 2. Cont.

Molecular Feature	HBC	FMC
<i>PIK3CA</i>	<i>PIK3CA</i> is one of the most frequently mutated genes in breast cancer [227]. The PI3K/AKT/mTOR pathway promotes tumor-cell growth, survival, and therapeutic vulnerability [227–230]. Activating mutations are reported in ~26% of invasive breast carcinomas overall and 13–22.1% of TNBC [231,232].	<i>PIK3CA</i> has been identified as an FMC driver, with mutations reported in approximately 45% of FMCs [16,233].
<i>PTEN</i>	<i>PTEN</i> loss promotes proliferation, invasion, metastatic competence, and treatment resistance, and has been detected in approximately 48.6% of TNBC cases in some cohorts [234,235].	<i>PTEN</i> is a recurrent FMC driver. Loss of <i>PTEN</i> expression is reported in ~77% of cases and has been associated with poorer prognosis and shorter survival [16,157,211].
<i>FBXW7</i>	<i>FBXW7</i> is a tumor suppressor, and low <i>FBXW7</i> expression has been associated with poorer prognosis in breast cancer patients [236–238].	<i>FBXW7</i> has been identified as an FMC driver, with mutations reported in approximately 72% of cases [16].
CXCL12/CXCR4	Overexpression of the CXCL12/CXCR4 axis promotes tumor growth, metastasis, and chemotherapy resistance, particularly in aggressive breast cancer, including TNBC [239–241].	Serum SDF-1/CXCL12 has been proposed as a diagnostic biomarker in FMC; CXCR4 overexpression was detected in 86% of tumors [242].
Leptin/ObR	In HBC, leptin–ObR signaling promotes tumor-cell survival, angiogenesis, inflammation, and disease progression, particularly in obesity-associated breast cancer biology [243,244]. Leptin and ObR expression were detected in 83% and 33.7% of breast cancer tissues, respectively [245].	ObR is overexpressed in FMC tissues, and serum ObR levels have been correlated with immune downregulation and tumor development [10,29,246].
Immune checkpoint	In HBC, especially TNBC, the PD-1/PD-L1 immune-checkpoint pathway can suppress antitumor immune responses [217,218]. Tumoral PD-L1 staining was reported in 12% of breast cancers overall and 32% of triple-negative cases [247].	PD-1 and PD-L1 are detectable in FMC, with enrichment reported in aggressive subtypes, including HER2-positive and triple-negative tumors [10,215,216,248].
<i>Bcl-2</i>	In HBC, high <i>Bcl-2</i> expression is associated with a favorable prognosis, improved survival, and less aggressive disease [220,221].	<i>Bcl-2</i> expression has been associated with longer disease-free interval and overall survival in FMC [219].

FMC, feline mammary carcinoma; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; ObR, leptin receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

3.3. Tumor Microenvironment Parallels

The tumor microenvironment plays an important role in breast cancer progression, therapeutic resistance, and immune evasion in both humans and cats. In HBC, particularly in TNBC, extracellular matrix remodeling, cancer-associated fibroblasts (CAFs), regulatory T-cell enrichment, leptin signaling, and reduced cytotoxic T-cell infiltration have been associated with invasion, metastatic progression, immune suppression, and poor clinical outcome [249,250]. Similar features have been reported in FMC, including collagen remodeling, CAF enrichment, increased regulatory T-cell infiltration, and enhanced leptin signaling, all of which correlate with more aggressive tumor behavior and reduced survival [10,246,251–254].

Recent spatial immunohistochemical analyses further support similarities in immune and stromal organization between FMC and aggressive HBC. One immunohistochemical study found that high-grade FMC is characterized by an immunosuppressed, highly vascularized, and highly proliferative tumor microenvironment [9]. In high-grade FMC, macrophages, neutrophils, and antigen-presenting cells were predominantly localized within the tumor-associated stroma surrounding neoplastic cell nests, whereas intratumoral T cells demonstrated limited activation [9,10]. This stromal immune architecture may support tumor progression by promoting angiogenesis, extracellular matrix remodeling, invasion, and suppressing effective antitumor immune responses [9]. Similar features are observed in aggressive HBC, particularly TNBC, where stromal immune exclusion, tumor-associated macrophage enrichment, and limited CD8+ T-cell infiltration into tumor-cell clusters are associated with invasion, immune evasion, and adverse clinical behavior [255,256].

Several pathways involved in tumor–stromal communication also appear to be shared between FMC and HBC. For example, CXCL12–CXCR4 signaling axis promotes tumor-cell migration, metastatic spread, angiogenesis, and formation of a supportive tumor microenvironment in HBC [257]. This pathway has also been implicated in FMC, where serum CXCL12 has been proposed as a potential diagnostic biomarker in HER2-overexpressing feline mammary tumors [241,242]. Leptin signaling represents another shared pathway. In HBC, leptin–leptin receptor (ObR) signaling promotes tumor-cell survival, angiogenesis, proliferation, inflammation, and disease progression, particularly in obesity-associated breast cancer biology [243,244]. Overexpression of ObR has also been reported in FMC [10,29].

A recent review summarized emerging evidence that immune-checkpoint expression, inflammatory and adipokine signaling, chemokine alterations, and angiogenic pathways contribute to tumor–microenvironment interactions in FMC [258]. These mechanisms are also relevant to aggressive HBC, including TNBC, where immune infiltration, PD-1/PD-L1 signaling, macrophage polarization, stromal remodeling, and angiogenesis influence prognosis and treatment response [259–261]. Together, these findings suggest that FMC shares several stromal and immune features with aggressive HBC, particularly TNBC. This supports the use of FMC as a comparative model for studying tumor–stromal interactions, immune escape, and microenvironment-targeted therapeutic strategies in an immunocompetent host.

3.4. Patient-Derived FMC Organoids

The comparative value of spontaneous FMC can be further strengthened by emerging patient-derived experimental platforms. A large-scale feline oncogenomics study used patient-derived FMC tumoroids to test whether genomic alterations could predict drug sensitivity [16]. *FBXW7* was identified as a frequent candidate driver in FMC, with mutations reported in approximately 53–72% of cases across sequencing cohorts [16]. Because *FBXW7* functions as a tumor suppressor that promotes degradation of cell-cycle and mitotic regulators, its mutation may create vulnerability to drugs that disrupt mitosis [237,238]. Consistent with this hypothesis, *FBXW7*-mutant feline mammary tumoroids were significantly more sensitive than *FBXW7*-wild-type tumoroids to microtubule-disrupting chemotherapies [16]. Notably, recurrent *FBXW7* driver alterations in FMC overlap with genomic alterations reported for patient selection in human precision oncology trials [262], suggesting that feline genomic profiling can identify human-relevant therapeutic hypotheses for functional testing in patient-derived tumoroids. A separate organoid study further supported the translational value of FMC organoids by establishing patient-derived models that recapitulated tumor morphology, receptor heterogeneity, tumorigenic poten-

tial, and variable drug sensitivity [14]. Using this platform, the authors identified the LMTK3/FADS2 axis as a candidate pathway involved in FMC proliferation, invasion, and apoptosis resistance [14]. LMTK3 inhibition reduced FMC organoid viability, inhibited invasion, induced apoptosis, and suppressed tumor growth in xenograft models [14]. Importantly, LMTK3 inhibition also reduced the viability of HBC organoids, supporting the LMTK3/FADS2 axis as a potentially conserved progression pathway across feline and HBC [14]. Together, these studies show that patient-derived FMC organoids can connect genomic alterations with functional drug response, identify candidate therapeutic vulnerabilities, and prioritize conserved targets for further validation in HBC models.

3.5. FMC Therapeutic Studies

Therapeutic studies in FMC have evaluated conventional cytotoxic chemotherapy, targeted therapies, and emerging molecular approaches, providing translational insights relevant to HBC, particularly TNBC. Most clinical studies of cytotoxic chemotherapy in cats have focused on adjuvant doxorubicin after surgical resection. In one study, cats treated with surgery followed by doxorubicin had a disease-free interval of 255 days and a median survival time of 448 days [263]. However, a subsequent multi-institutional comparison of adjuvant doxorubicin, metronomic cyclophosphamide plus meloxicam, and surgery alone found no significant survival benefit for either chemotherapy regimen over surgery alone in unselected cats with FMC [264,265]. These findings highlight the need for biomarker-driven treatment stratification.

Targeted therapy studies in FMC have primarily focused on HER2- and PI3K/AKT/mTOR-related pathways. In vitro studies of anti-HER2 monoclonal antibodies and HER2-targeted tyrosine kinase inhibitors, including lapatinib and neratinib, have demonstrated dose-dependent antiproliferative effects across FMC cell lines [266]. Synergistic activity has also been observed when these tyrosine kinase inhibitors were combined with the mTOR inhibitor rapamycin [266]. Together, these findings support further investigation of HER2- and PI3K/AKT/mTOR-directed strategies in cats with spontaneous FMC.

To date, no published studies have evaluated PD-1/PD-L1 checkpoint blockade as a therapeutic intervention in cats with spontaneous FMC. However, the PD-1/PD-L1 pathway has emerged as a promising immunotherapeutic target based on studies demonstrating its expression and biologic relevance in FMC [216,258]. A more directly translational example comes from a case report evaluating an iron oxide nanoparticle-delivered miR-10b inhibitor in a cat with spontaneous metastatic FMC [267]. Magnetic resonance imaging confirmed tumor delivery, and molecular analyses demonstrated on-target engagement, providing proof-of-concept evidence to support progression toward human clinical trials [267]. Nevertheless, no prospective phase I or II clinical trials in cats with spontaneous FMC have yet been completed with the mechanistic rigor typical of comparative oncology trial design. As a result, the current therapeutic evidence base for FMC remains largely retrospective, preclinical, or limited to small translational studies.

4. Current Challenges and Future Directions

Spontaneous feline cancers are increasingly recognized as valuable comparative oncology models because they share biologic and clinical features with human cancers that are difficult to reproduce faithfully in ex vivo systems and conventional rodent models [2,3,16]. Previous reviews have established the broader value of cats in comparative oncology and have summarized key clinical, pathologic, and molecular features of FOSCC and FMC [32,35,142]. Building on this foundation, this review compares FOSCC and FMC with their corresponding human cancers across epidemiology, histology, molecular pathways, tumor microenvironment features, therapeutic studies, and emerging model systems. Recent

genomic, transcriptomic, and tumor microenvironment studies support the translational relevance of FOSCC for HNSCC and FMC for aggressive TNBC [4,16,26,34]. These shared features provide opportunities for biomarker discovery, therapeutic testing, and improved cancer care in both cats and humans.

Although spontaneous feline tumors offer important strengths for comparative oncology, they also have limitations. Compared with laboratory models, studies of spontaneous feline tumors have less control over genetic background, environmental exposures, reproductive history, prior treatment, biospecimen handling, and longitudinal follow-up. Therefore, spontaneous feline tumors should be viewed as complementary to, rather than replacements for, laboratory models. A major limitation of the current feline comparative oncology literature is heterogeneity across study populations and methods. Differences in cohort composition, tumor type, breed distribution, reproductive status, clinical management, sample processing, and follow-up can make direct comparisons across studies difficult and may weaken cross-species conclusions. Variation in classification and grading systems is another important challenge. Some studies use traditional veterinary histopathologic criteria, whereas others adapt human cancer classification frameworks. For example, p16, pRb, and p53 staining patterns in FOSCC may differ from those typically described in human HNSCC, highlighting the need to validate human-derived biomarker frameworks before applying them to feline disease [119]. Similarly, FMC studies use inconsistent grading systems. Some rely on traditional veterinary histologic grading systems, such as the World Health Organization-based approach used by Millanta et al. [268], whereas others apply HBC-inspired molecular subtyping based on markers such as ER, PR, HER2, Ki-67, and EGFR [215]. This lack of standardization may affect subtype assignment, prognostic interpretation, and comparisons between feline and human mammary tumors. These limitations do not diminish the value of spontaneous feline tumors, but they highlight the need for more standardized study designs.

Future studies should prioritize larger multicenter cohorts, prospective enrollment, and appropriately matched tumor and control groups. Key clinical, demographic, and biospecimen variables should be recorded systematically, including age, breed, sex, reproductive status, age at neutering, geographic region, tumor site, stage, prior treatment, biospecimen type, and clinical outcome. Careful documentation of these variables is essential because uncontrolled variation can obscure true biologic associations and limit comparisons across studies. Standardized biospecimen collection, centralized pathology review, harmonized grading and classification criteria, validated feline-specific or cross-reactive antibodies, and consistent molecular workflows are particularly important for genomic, transcriptomic, immune, and tumor microenvironment studies. Prospective feline clinical trials should further incorporate molecular stratification, standardized response criteria, toxicity assessment, quality-of-life measures, disease-free interval, and overall survival. Together, these approaches would improve reproducibility, strengthen cross-species interpretation, and help define which feline tumors are most suitable as translational models for specific human cancer subtypes.

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Abbreviations

The following abbreviations are used in this manuscript:

AKT	Protein kinase B
Bcl-2	B-cell lymphoma 2
CAF	Cancer-associated fibroblast
CDKN1A	Cyclin-dependent kinase inhibitor 1A
COX-2	Cyclooxygenase-2
CS3D	Cyclic STAT3 decoy oligonucleotide
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	C-X-C chemokine receptor type 4
DFMO	Difluoromethylornithine
DNA	Deoxyribonucleic acid
DPT	Dermatopontin
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
ER	Estrogen receptor
FADS2	Fatty acid desaturase 2
FAS	Fas cell surface death receptor
FBXW7	F-box and WD repeat domain containing 7
FcaPV	<i>Felis catus</i> papillomavirus
FMC	Feline mammary carcinoma
FOSCC	Feline oral squamous cell carcinoma
FOXM1	Forkhead box M1
HBC	Human breast cancer
HER2	Human epidermal growth factor receptor 2
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
IL-6	Interleukin-6
JAK	Janus kinase
LMTK3	Lemur tyrosine kinase 3
mTOR	Mechanistic target of rapamycin
MYC	MYC proto-oncogene, bHLH transcription factor
NF- κ B	Nuclear factor kappa B
ObR	Leptin receptor
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog
SCC	Squamous cell carcinoma
SDF-1	Stromal cell-derived factor 1

SNX5	Sorting nexin 5
STAT3	Signal transducer and activator of transcription 3
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TP53	Tumor protein p53
TWIST1	Twist family bHLH transcription factor 1
VEGF	Vascular endothelial growth factor
WNT	Wingless/Int-1 signaling pathway
ZEB1	Zinc finger E-box binding homeobox 1

References

1. Tu, A.Y.; Springer, C.M.; Albright, J.D. Evaluation of Characteristics Associated with Self-Identified Cat or Dog Preference in Pet Owners and Correlation of Preference with Pet Interactions and Care: An Exploratory Study. *Animals* **2024**, *14*, 2534. [\[CrossRef\]](#)
2. MacEwen, E.G. Spontaneous tumors in dogs and cats: Models for the study of cancer biology and treatment. *Cancer Metastasis Rev.* **1990**, *9*, 125–136. [\[CrossRef\]](#)
3. Vail, D.M.; MacEwen, E.G. Spontaneously occurring tumors of companion animals as models for human cancer. *Cancer Investig.* **2000**, *18*, 781–792. [\[CrossRef\]](#)
4. Cannon, C.M. Cats, Cancer and Comparative Oncology. *Vet. Sci.* **2015**, *2*, 111–126. [\[CrossRef\]](#)
5. Oh, J.H.; Cho, J.Y. Comparative oncology: Overcoming human cancer through companion animal studies. *Exp. Mol. Med.* **2023**, *55*, 725–734. [\[CrossRef\]](#)
6. Nance, R.L.; Sajib, A.M.; Smith, B.F. Canine models of human cancer: Bridging the gap to improve precision medicine. *Prog. Mol. Biol. Transl. Sci.* **2022**, *189*, 67–99. [\[CrossRef\]](#)
7. Cardiff, R.D.; Ward, J.M.; Barthold, S.W. ‘One medicine—One pathology’: Are veterinary and human pathology prepared? *Lab. Invest.* **2008**, *88*, 18–26. [\[CrossRef\]](#)
8. King, T.A. The One Medicine concept: Its emergence from history as a systematic approach to re-integrate human and veterinary medicine. *Emerg. Top. Life Sci.* **2021**, *5*, 643–654. [\[CrossRef\]](#)
9. De Haes, C.; de Rooster, H.; Demeyere, K.; Van de Vijver, K.; De Cock, H.; Meyer, E.; Steenbrugge, J. Grade III canine and feline mammary carcinomas are associated with an immunosuppressed, vascularized and proliferative microenvironment. *BMC Vet. Res.* **2026**, *22*, 247. [\[CrossRef\]](#)
10. Rodrigues-Jesus, J.; Canadas-Sousa, A.; Vilhena, H.; Dias-Pereira, P. Inside the Tumor: Decoding the Feline Mammary Tumor Microenvironment and Its Prognostic Value—A Review. *Vet. Sci.* **2025**, *12*, 959. [\[CrossRef\]](#)
11. Alkayyal, A.A. Insights from veterinary models for advancing oncolytic virotherapy through comparative oncology. *Front. Mol. Biosci.* **2025**, *12*, 1615393. [\[CrossRef\]](#)
12. Chu, S.; Skidmore, Z.L.; Warren, W.; Fisk, B.; Kim, D.Y.; Peralta, S.; Rodney, A.; Bryant, J.; Fronick, C.; Skinner, O.; et al. Whole Exome Sequencing of Feline Oral Squamous Cell Carcinoma Reveals Genomic Parallels With Human Head and Neck Squamous Cell Carcinoma. *Vet. Comp. Oncol.* **2026**, *24*, 300–312. [\[CrossRef\]](#)
13. Sommerville, L.; Howard, J.; Evans, S.; Kelly, P.; McCann, A. Comparative gene expression study highlights molecular similarities between triple negative breast cancer tumours and feline mammary carcinomas. *Vet. Comp. Oncol.* **2022**, *20*, 535–538. [\[CrossRef\]](#)
14. Yamamoto, H.; Elbadawy, M.; Tsunedomi, R.; Maeda, N.; Nagano, H.; Ishihara, Y.; Abugomaa, A.; Shiota, Y.; Yu, T.W.; Liu, Y.; et al. Novel organoid-based exploration reveals the role of LMTK3/FADS2 signaling in metastatic breast cancer progression in felines and humans. *Sci. Rep.* **2025**, *15*, 45016. [\[CrossRef\]](#)
15. Alshammari, A.H.; Oshiro, T.; Ungkulpasvich, U.; Yamaguchi, J.; Morishita, M.; Khadair, S.A.; Hatakeyama, H.; Hirotsu, T.; di Luccio, E. Advancing Veterinary Oncology: Next-Generation Diagnostics for Early Cancer Detection and Clinical Implementation. *Animals* **2025**, *15*, 389. [\[CrossRef\]](#)
16. Francis, B.A.; Ludwig, L.; He, C.; Dobromylskyj, M.; Bertram, C.A.; Aupperle-Lellbach, H.; Wong, H.; Foster, A.P.; Arends, M.J.; Suarez-Bonnet, A.; et al. The oncogenome of the domestic cat. *Science* **2026**, *391*, 793–799. [\[CrossRef\]](#)
17. Ahn, S.; Yun, J.H. Comparative Cancer Genetics and Veterinary Therapeutics in Dogs and Cats: A Species-Aware Framework for Comparative Oncology. *Life* **2026**, *16*, 430. [\[CrossRef\]](#)
18. Wong, K.; Ludwig, L.; Krijgsman, O.; Adams, D.J.; Wood, G.A.; van der Weyden, L. Comparison of the oncogenomic landscape of canine and feline hemangiosarcoma shows novel parallels with human angiosarcoma. *Dis. Models Mech.* **2021**, *14*, dmm049044. [\[CrossRef\]](#)
19. The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. *Nature* **2020**, *578*, 82–93. [\[CrossRef\]](#)

20. Deneka, A.Y.; Baca, Y.; Serebriiskii, I.G.; Nicolas, E.; Parker, M.I.; Nguyen, T.T.; Xiu, J.; Korn, W.M.; Demeure, M.J.; Wise-Draper, T.; et al. Association of TP53 and CDKN2A Mutation Profile with Tumor Mutation Burden in Head and Neck Cancer. *Clin. Cancer Res.* **2022**, *28*, 1925–1937. [\[CrossRef\]](#)
21. Brown, N.A.; Plouffe, K.R.; Yilmaz, O.; Weindorf, S.C.; Betz, B.L.; Carey, T.E.; Seethala, R.R.; McHugh, J.B.; Tomlins, S.A.; Udager, A.M. TP53 mutations and CDKN2A mutations/deletions are highly recurrent molecular alterations in the malignant progression of sinonasal papillomas. *Mod. Pathol.* **2021**, *34*, 1133–1142. [\[CrossRef\]](#)
22. Shahbandi, A.; Nguyen, H.D.; Jackson, J.G. TP53 Mutations and Outcomes in Breast Cancer: Reading beyond the Headlines. *Trends Cancer* **2020**, *6*, 98–110. [\[CrossRef\]](#)
23. Schaub, F.X.; Dhankani, V.; Berger, A.C.; Trivedi, M.; Richardson, A.B.; Shaw, R.; Zhao, W.; Zhang, X.; Ventura, A.; Liu, Y.; et al. Pan-cancer Alterations of the MYC Oncogene and Its Proximal Network across the Cancer Genome Atlas. *Cell Syst.* **2018**, *6*, 282–300.e2. [\[CrossRef\]](#)
24. Vidotto, T.; Melo, C.M.; Lautert-Dutra, W.; Chaves, L.P.; Reis, R.B.; Squire, J.A. Pan-cancer genomic analysis shows hemizygous PTEN loss tumors are associated with immune evasion and poor outcome. *Sci. Rep.* **2023**, *13*, 5049. [\[CrossRef\]](#)
25. Giuliano, A.; Swift, R.; Arthurs, C.; Marote, G.; Abramo, F.; McKay, J.; Thomson, C.; Beltran, M.; Millar, M.; Priestnall, S.; et al. Quantitative Expression and Co-Localization of Wnt Signalling Related Proteins in Feline Squamous Cell Carcinoma. *PLoS ONE* **2016**, *11*, e0161103. Correction in *PLoS ONE* **2016**, *11*, e0163838. <https://doi.org/10.1371/journal.pone.0163838>. [\[CrossRef\]](#)
26. Groll, T.; Schopf, F.; Denk, D.; Mogler, C.; Schwittlick, U.; Aupperle-Lellbach, H.; Sarker, S.R.J.; Pfarr, N.; Weichert, W.; Matiassek, K.; et al. Bridging the Species Gap: Morphological and Molecular Comparison of Feline and Human Intestinal Carcinomas. *Cancers* **2021**, *13*, 5941. [\[CrossRef\]](#)
27. Thrift, E.; Greenwell, C.; Turner, A.L.; Harvey, A.M.; Maher, D.; Malik, R. Metastatic pulmonary carcinomas in cats ('feline lung-digit syndrome'): Further variations on a theme. *JFMS Open Rep.* **2017**, *3*, 2055116917691069. [\[CrossRef\]](#)
28. Wiese, D.A.; Thaiwong, T.; Yuzbasiyan-Gurkan, V.; Kiupel, M. Feline mammary basal-like adenocarcinomas: A potential model for human triple-negative breast cancer (TNBC) with basal-like subtype. *BMC Cancer* **2013**, *13*, 403. [\[CrossRef\]](#)
29. Gameiro, A.; Urbano, A.C.; Ferreira, F. Emerging Biomarkers and Targeted Therapies in Feline Mammary Carcinoma. *Vet. Sci.* **2021**, *8*, 164. [\[CrossRef\]](#)
30. Wypij, J.M. A naturally occurring feline model of head and neck squamous cell carcinoma. *Pathol. Res. Int.* **2013**, *2013*, 502197. [\[CrossRef\]](#)
31. Chu, S.; Wylie, T.N.; Wylie, K.M.; Johnson, G.C.; Skidmore, Z.L.; Fleer, M.; Griffith, O.L.; Bryan, J.N. A virome sequencing approach to feline oral squamous cell carcinoma to evaluate viral causative factors. *Vet. Microbiol.* **2020**, *240*, 108491. [\[CrossRef\]](#)
32. Bilgic, O.; Duda, L.; Sanchez, M.D.; Lewis, J.R. Feline Oral Squamous Cell Carcinoma: Clinical Manifestations and Literature Review. *J. Vet. Dent.* **2015**, *32*, 30–40. [\[CrossRef\]](#)
33. Tutu, P.; Daraban Bocaneti, F.; Altamura, G.; Dascalu, M.A.; Horodincu, L.; Soreanu, O.D.; Tanase, O.I.; Borzacchiello, G.; Mares, M. Feline oral squamous cell carcinoma: Recent advances and future perspectives. *Front. Vet. Sci.* **2025**, *12*, 1663990. [\[CrossRef\]](#)
34. Rodney, A.R.; Skidmore, Z.L.; Grenier, J.K.; Griffith, O.L.; Miller, A.D.; Chu, S.; Ahmed, F.; Bryan, J.N.; Peralta, S.; Warren, W.C. Genomic landscape and gene expression profiles of feline oral squamous cell carcinoma. *Front. Vet. Sci.* **2023**, *10*, 1079019. [\[CrossRef\]](#)
35. Sequeira, I.; Pires, M.D.A.; Leitao, J.; Henriques, J.; Viegas, C.; Requicha, J. Feline Oral Squamous Cell Carcinoma: A Critical Review of Etiologic Factors. *Vet. Sci.* **2022**, *9*, 558. [\[CrossRef\]](#)
36. Sparger, E.E.; Murphy, B.G.; Kamal, F.M.; Arzi, B.; Naydan, D.; Skouritakis, C.T.; Cox, D.P.; Skorupski, K. Investigation of immune cell markers in feline oral squamous cell carcinoma. *Vet. Immunol. Immunopathol.* **2018**, *202*, 52–62. [\[CrossRef\]](#)
37. Martin, C.K.; Tannehill-Gregg, S.H.; Wolfe, T.D.; Rosol, T.J. Bone-invasive oral squamous cell carcinoma in cats: Pathology and expression of parathyroid hormone-related protein. *Vet. Pathol.* **2011**, *48*, 302–312. [\[CrossRef\]](#)
38. Soltero-Rivera, M.M.; Krick, E.L.; Reiter, A.M.; Brown, D.C.; Lewis, J.R. Prevalence of regional and distant metastasis in cats with advanced oral squamous cell carcinoma: 49 cases (2005–2011). *J. Feline Med. Surg.* **2014**, *16*, 164–169. [\[CrossRef\]](#)
39. Bergkvist, G.T.; Argyle, D.J.; Morrison, L.; MacIntyre, N.; Hayes, A.; Yool, D.A. Expression of epidermal growth factor receptor (EGFR) and Ki67 in feline oral squamous cell carcinomas (FOSCC). *Vet. Comp. Oncol.* **2011**, *9*, 106–117. [\[CrossRef\]](#)
40. Schlueter, A.; Hanot, C.; Sellon, R.; Fidel, J. Treatment of feline oral squamous cell carcinoma with accelerated radiation and carboplatin with and without follow-up toceranib phosphate. *J. Feline Med. Surg.* **2025**, *27*, 1098612X251314343. [\[CrossRef\]](#)
41. Grandis, J.R.; Skorupski, K.A.; Cheng, N.; Cui, Z.; Li, H.; Woerner, L.C.; Gencel-Augusto, J.; Zeng, Y.; Shiah, J.V.; Bhola, N.E.; et al. Safety and efficacy of a STAT3-targeted cyclic oligonucleotide: From murine models to a phase 1 clinical trial in pet cats with oral cancer. *Cancer Cell* **2025**, *43*, 2051–2068.e9. [\[CrossRef\]](#)
42. Hayes, A.M.; Adams, V.J.; Scase, T.J.; Murphy, S. Survival of 54 cats with oral squamous cell carcinoma in United Kingdom general practice. *J. Small Anim. Pract.* **2007**, *48*, 394–399. [\[CrossRef\]](#)
43. Johnson, D.E.; Burtness, B.; Leemans, C.R.; Lui, V.W.Y.; Bauman, J.E.; Grandis, J.R. Head and neck squamous cell carcinoma. *Nat. Rev. Dis. Primers* **2020**, *6*, 92. [\[CrossRef\]](#)

44. Veeramachaneni, R.; Walker, T.; Revil, T.; Weck, A.; Badescu, D.; O'Sullivan, J.; Higgins, C.; Elliott, L.; Liloglou, T.; Risk, J.M.; et al. Analysis of head and neck carcinoma progression reveals novel and relevant stage-specific changes associated with immortalisation and malignancy. *Sci. Rep.* **2019**, *9*, 11992. [\[CrossRef\]](#)
45. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **2015**, *136*, E359–E386. [\[CrossRef\]](#)
46. Powell, S.F.; Vu, L.; Spanos, W.C.; Pyeon, D. The Key Differences between Human Papillomavirus-Positive and -Negative Head and Neck Cancers: Biological and Clinical Implications. *Cancers* **2021**, *13*, 5206. [\[CrossRef\]](#)
47. Park, R.; Chung, C.H. Advanced Human Papillomavirus-Negative Head and Neck Squamous Cell Carcinoma: Unmet Need and Emerging Therapies. *Mol. Cancer Ther.* **2024**, *23*, 1717–1730. [\[CrossRef\]](#)
48. Qian, X.; Nguyen, D.T.; Dong, Y.; Sinikovic, B.; Kaufmann, A.M.; Myers, J.N.; Albers, A.E.; Graviss, E.A. Prognostic Score Predicts Survival in HPV-Negative Head and Neck Squamous Cell Cancer Patients. *Int. J. Biol. Sci.* **2019**, *15*, 1336–1344. [\[CrossRef\]](#)
49. Mittal, K.; Choi, D.H.; Wei, G.; Kaur, J.; Klimov, S.; Arora, K.; Griffith, C.C.; Kumar, M.; Imhansi-Jacob, P.; Melton, B.D.; et al. Hypoxia-Induced Centrosome Amplification Underlies Aggressive Disease Course in HPV-Negative Oropharyngeal Squamous Cell Carcinomas. *Cancers* **2020**, *12*, 517. [\[CrossRef\]](#)
50. Munday, J.S.; He, Y.; Aberdein, D.; Klobukowska, H.J. Increased p16(CDKN2A), but not p53, immunostaining is predictive of longer survival time in cats with oral squamous cell carcinomas. *Vet. J.* **2019**, *248*, 64–70. [\[CrossRef\]](#)
51. Altamura, G.; Borzacchiello, G. Feline oral squamous cell carcinoma and *Felis catus* papillomavirus: Is it time to walk the path of human oncology? *Front. Vet. Sci.* **2023**, *10*, 1148673. [\[CrossRef\]](#)
52. Munday, J.S.; Knight, C.G.; French, A.F. Evaluation of feline oral squamous cell carcinomas for p16CDKN2A protein immunoreactivity and the presence of papillomaviral DNA. *Res. Vet. Sci.* **2011**, *90*, 280–283. [\[CrossRef\]](#)
53. Altamura, G.; Cuccaro, B.; Eleni, C.; Strohmayer, C.; Brandt, S.; Borzacchiello, G. Investigation of multiple *Felis catus* papillomavirus types (-1/-2/-3/-4/-5/-6) DNAs in feline oral squamous cell carcinoma: A multicentric study. *J. Vet. Med. Sci.* **2022**, *84*, 881–884. [\[CrossRef\]](#)
54. Yamashita-Kawanishi, N.; Chang, C.Y.; Chambers, J.K.; Uchida, K.; Sugiura, K.; Kukimoto, I.; Chang, H.W.; Haga, T. Comparison of prevalence of *Felis catus* papillomavirus type 2 in squamous cell carcinomas in cats between Taiwan and Japan. *J. Vet. Med. Sci.* **2021**, *83*, 1229–1233. [\[CrossRef\]](#)
55. Altamura, G.; Cardeti, G.; Cersini, A.; Eleni, C.; Cocumelli, C.; Bartolome Del Pino, L.E.; Razzuoli, E.; Martano, M.; Maiolino, P.; Borzacchiello, G. Detection of *Felis catus* papillomavirus type-2 DNA and viral gene expression suggest active infection in feline oral squamous cell carcinoma. *Vet. Comp. Oncol.* **2020**, *18*, 494–501. [\[CrossRef\]](#)
56. Liu, S.; Qin, Z.; Mao, Y.; Zhang, W.; Wang, Y.; Jia, L.; Peng, X. Therapeutic Targeting of MYC in Head and Neck Squamous Cell Carcinoma. *Oncoimmunology* **2022**, *11*, 2130583. [\[CrossRef\]](#)
57. Borgato, G.B.; Borges, G.A.; Souza, A.P.; Squarize, C.H.; Castilho, R.M. Loss of PTEN sensitizes head and neck squamous cell carcinoma to 5-AZA-2'-deoxycytidine. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2020**, *130*, 181–190. [\[CrossRef\]](#)
58. Hsieh, J.C.; Wang, H.M.; Wu, M.H.; Chang, K.P.; Chang, P.H.; Liao, C.T.; Liao, C.T. Review of emerging biomarkers in head and neck squamous cell carcinoma in the era of immunotherapy and targeted therapy. *Head Neck* **2019**, *41*, 19–45. [\[CrossRef\]](#)
59. Supsavhad, W.; Dirksen, W.P.; Martin, C.K.; Rosol, T.J. Animal models of head and neck squamous cell carcinoma. *Vet. J.* **2016**, *210*, 7–16. [\[CrossRef\]](#)
60. Galati, L.; Chiocca, S.; Duca, D.; Tagliabue, M.; Simoens, C.; Gheit, T.; Arbyn, M.; Tommasino, M. HPV and head and neck cancers: Towards early diagnosis and prevention. *Tumour Virus Res.* **2022**, *14*, 200245. [\[CrossRef\]](#)
61. Frank, D.N.; Qiu, Y.; Cao, Y.; Zhang, S.; Lu, L.; Kofonow, J.M.; Robertson, C.E.; Liu, Y.; Wang, H.; Levens, C.L.; et al. A dysbiotic microbiome promotes head and neck squamous cell carcinoma. *Oncogene* **2022**, *41*, 1269–1280. [\[CrossRef\]](#)
62. Miranda-Galvis, M.; Loveless, R.; Kowalski, L.P.; Teng, Y. Impacts of Environmental Factors on Head and Neck Cancer Pathogenesis and Progression. *Cells* **2021**, *10*, 389. [\[CrossRef\]](#)
63. Bertone, E.R.; Snyder, L.A.; Moore, A.S. Environmental and lifestyle risk factors for oral squamous cell carcinoma in domestic cats. *J. Vet. Intern. Med.* **2003**, *17*, 557–562.
64. Snyder, L.A.; Bertone, E.R.; Jakowski, R.M.; Dooner, M.S.; Jennings-Ritchie, J.; Moore, A.S. p53 expression and environmental tobacco smoke exposure in feline oral squamous cell carcinoma. *Vet. Pathol.* **2004**, *41*, 209–214. [\[CrossRef\]](#)
65. Pai, S.I.; Westra, W.H. Molecular pathology of head and neck cancer: Implications for diagnosis, prognosis, and treatment. *Annu. Rev. Pathol.* **2009**, *4*, 49–70. [\[CrossRef\]](#)
66. Atarbashi-Moghadam, S.; Lotfi, A.; Roghanizadeh, L.; Mirebeigi Jamasbi, S.S.; Akbarzadeh Fathabadi, Z. Infrequent Histopathologic Subtypes of Oral Squamous Cell Carcinoma: A Case Series with Emphasis on Histopathologic Characteristics. *J. Dent.* **2025**, *26*, 186–193. [\[CrossRef\]](#)
67. Goncalves, M.W.A.; de Lima-Souza, R.A.; Ribeiro-de-Assis, M.C.F.; Cattani, M.E.S.; Egal, E.S.A.; Altemani, A.; Mariano, F.V. Prognostic implications across histological subtypes of head and neck squamous cell carcinoma: An update. *J. Stomatol. Oral Maxillofac. Surg.* **2025**, *126*, 102149. [\[CrossRef\]](#)

68. Ozturk-Gurgen, H.; Almilli, O.; Sennazli, G.; Majzoub-Altweck, M. Histopathological Investigation of Feline Oral Squamous Cell Carcinoma and the Possible Role of Papillomavirus Infection. *Pak. Vet. J.* **2022**, *42*, 95–101. [\[CrossRef\]](#)
69. Klobukowska, H.J.; Munday, J.S. High Numbers of Stromal Cancer-Associated Fibroblasts Are Associated With a Shorter Survival Time in Cats With Oral Squamous Cell Carcinoma. *Vet. Pathol.* **2016**, *53*, 1124–1130. [\[CrossRef\]](#)
70. Onken, M.D.; Winkler, A.E.; Kanchi, K.L.; Chalivendra, V.; Law, J.H.; Rickert, C.G.; Kallogjeri, D.; Judd, N.P.; Dunn, G.P.; Piccirillo, J.F.; et al. A surprising cross-species conservation in the genomic landscape of mouse and human oral cancer identifies a transcriptional signature predicting metastatic disease. *Clin. Cancer Res.* **2014**, *20*, 2873–2884. [\[CrossRef\]](#)
71. Miniuk, M.; Reszec-Gielazyn, J.; Bortnik, P.; Borsukiewicz, A.; Mroczek, A. Novel Predictive Biomarkers in the Head and Neck Squamous Cell Carcinoma (HNSCC). *J. Clin. Med.* **2024**, *13*, 5876. [\[CrossRef\]](#)
72. The Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* **2015**, *517*, 576–582. [\[CrossRef\]](#)
73. Mahmoud, A.A.; Raih, M.F.; Sage, E.E.; Ali, Q.M.; Suliman, O.H.; Ibrahim, S.A.E.; Mohamed, O.; Abdelrazeg, S.; Mohamed, S.B. The impact of mutations on TP53 protein and MicroRNA expression in HNSCC: Novel insights for diagnostic and therapeutic strategies. *PLoS ONE* **2025**, *20*, e0307859. [\[CrossRef\]](#)
74. Gonzalez-Gonzalez, R.; Ortiz-Sarabia, G.; Molina-Frechero, N.; Salas-Pacheco, J.M.; Salas-Pacheco, S.M.; Lavallo-Carrasco, J.; Lopez-Verdin, S.; Tremillo-Maldonado, O.; Bologna-Molina, R. Epithelial-Mesenchymal Transition Associated with Head and Neck Squamous Cell Carcinomas: A Review. *Cancers* **2021**, *13*, 3027. [\[CrossRef\]](#)
75. Mani, S.A.; Guo, W.; Liao, M.J.; Eaton, E.N.; Ayyanan, A.; Zhou, A.Y.; Brooks, M.; Reinhard, F.; Zhang, C.C.; Shipitsin, M.; et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell* **2008**, *133*, 704–715. [\[CrossRef\]](#)
76. Ai, J.; Tan, Y.; Liu, B.; Song, Y.; Wang, Y.; Xia, X.; Fu, Q. Systematic establishment and verification of an epithelial-mesenchymal transition gene signature for predicting prognosis of oral squamous cell carcinoma. *Front. Genet.* **2023**, *14*, 1113137. [\[CrossRef\]](#)
77. Pawlicka, M.; Gumbarewicz, E.; Blaszcak, E.; Stepulak, A. Transcription Factors and Markers Related to Epithelial-Mesenchymal Transition and Their Role in Resistance to Therapies in Head and Neck Cancers. *Cancers* **2024**, *16*, 1354. [\[CrossRef\]](#)
78. de Moraes, E.F.; de Oliveira, L.Q.R.; Marques, C.E.; Teo, F.H.; Rocha, G.V.; Rodini, C.O.; Gurgel, C.A.; Salo, T.; Graner, E.; Coletta, R.D. Generation and Characterization of Cisplatin-Resistant Oral Squamous Cell Carcinoma Cells Displaying an Epithelial-Mesenchymal Transition Signature. *Cells* **2025**, *14*, 1311. [\[CrossRef\]](#)
79. Harris, K.; Gelberg, H.B.; Kiupel, M.; Helfand, S.C. Immunohistochemical Features of Epithelial-Mesenchymal Transition in Feline Oral Squamous Cell Carcinoma. *Vet. Pathol.* **2019**, *56*, 826–839. [\[CrossRef\]](#)
80. Nasry, W.H.S.; Wang, H.; Jones, K.; Dirksen, W.P.; Rosol, T.J.; Rodriguez-Lecompte, J.C.; Martin, C.K. CD147 and Cyclooxygenase Expression in Feline Oral Squamous Cell Carcinoma. *Vet. Sci.* **2018**, *5*, 72. [\[CrossRef\]](#)
81. Brown, M.E.; Bear, M.D.; Rosol, T.J.; Premanandan, C.; Kisseberth, W.C.; London, C.A. Characterization of STAT3 expression, signaling and inhibition in feline oral squamous cell carcinoma. *BMC Vet. Res.* **2015**, *11*, 206. [\[CrossRef\]](#)
82. Ao, J.; Fei, J.; Wang, G.; Zhang, W.; Yu, S.; Guo, R.; Niu, M.; Chen, H.; Cao, Y.; Xiao, Z.J.; et al. pSTAT3 transactivates EGFR in maintaining EGFR protein homeostasis and EGFR-TKI resistance. *Acta Biochim. Biophys. Sin.* **2024**, *57*, 310–316. [\[CrossRef\]](#)
83. Xiao, L.; Li, X.; Cao, P.; Fei, W.; Zhou, H.; Tang, N.; Liu, Y. Interleukin-6 mediated inflammasome activation promotes oral squamous cell carcinoma progression via JAK2/STAT3/Sox4/NLRP3 signaling pathway. *J. Exp. Clin. Cancer Res.* **2022**, *41*, 166. [\[CrossRef\]](#)
84. Paschold, L.; Schultheiss, C.; Schmidt-Barbo, P.; Klinghammer, K.; Hahn, D.; Tometten, M.; Schafhausen, P.; Blaurock, M.; Brandt, A.; Westgaard, I.; et al. Inflammation and limited adaptive immunity predict worse outcomes on immunotherapy in head and neck cancer. *npj Precis. Oncol.* **2025**, *9*, 272. [\[CrossRef\]](#)
85. Macha, M.A.; Matta, A.; Kaur, J.; Chauhan, S.S.; Thakar, A.; Shukla, N.K.; Gupta, S.D.; Ralhan, R. Prognostic significance of nuclear pSTAT3 in oral cancer. *Head Neck* **2011**, *33*, 482–489. [\[CrossRef\]](#)
86. Sun, Y.; Sang, Z.; Jiang, Q.; Ding, X.; Yu, Y. Transcriptomic characterization of differential gene expression in oral squamous cell carcinoma: A meta-analysis of publicly available microarray data sets. *Tumour Biol.* **2016**, *37*, 15913–15924. [\[CrossRef\]](#)
87. Sriuranpong, V.; Park, J.I.; Amornphimoltham, P.; Patel, V.; Nelkin, B.D.; Gutkind, J.S. Epidermal growth factor receptor-independent constitutive activation of STAT3 in head and neck squamous cell carcinoma is mediated by the autocrine/paracrine stimulation of the interleukin 6/gp130 cytokine system. *Cancer Res.* **2003**, *63*, 2948–2956.
88. Looper, J.S.; Malarkey, D.E.; Ruslander, D.; Proulx, D.; Thrall, D.E. Epidermal growth factor receptor expression in feline oral squamous cell carcinomas. *Vet. Comp. Oncol.* **2006**, *4*, 33–40. [\[CrossRef\]](#)
89. Aggarwal, S.; Devaraja, K.; Sharma, S.C.; Das, S.N. Expression of vascular endothelial growth factor (VEGF) in patients with oral squamous cell carcinoma and its clinical significance. *Clin. Chim. Acta* **2014**, *436*, 35–40. [\[CrossRef\]](#)
90. Marcu, L.G.; Yeoh, E. A review of risk factors and genetic alterations in head and neck carcinogenesis and implications for current and future approaches to treatment. *J. Cancer Res. Clin. Oncol.* **2009**, *135*, 1303–1314. [\[CrossRef\]](#)
91. Wu, G.; Luo, J.; Rana, J.S.; Laham, R.; Sellke, F.W.; Li, J. Involvement of COX-2 in VEGF-induced angiogenesis via P38 and JNK pathways in vascular endothelial cells. *Cardiovasc. Res.* **2006**, *69*, 512–519. [\[CrossRef\]](#)

92. Gallo, O.; Franchi, A.; Magnelli, L.; Sardi, I.; Vannacci, A.; Boddi, V.; Chiarugi, V.; Masini, E. Cyclooxygenase-2 pathway correlates with VEGF expression in head and neck cancer. Implications for tumor angiogenesis and metastasis. *Neoplasia* **2001**, *3*, 53–61. [\[CrossRef\]](#)
93. Kamal, M.V.; Damerla, R.R.; Dikhit, P.S.; Kumar, N.A. Prostaglandin-endoperoxide synthase 2 (PTGS2) gene expression and its association with genes regulating the VEGF signaling pathway in head and neck squamous cell carcinoma. *J. Oral Biol. Craniofac. Res.* **2023**, *13*, 567–574. [\[CrossRef\]](#)
94. Guo, Z.; Li, K.; Liu, P.; Zhang, X.; Lv, J.; Zeng, X.; Zhang, P. Targeted therapy for head and neck squamous cell carcinoma microenvironment. *Front. Med.* **2023**, *10*, 1257898. [\[CrossRef\]](#)
95. Nasry, W.H.S.; Rodriguez-Lecompte, J.C.; Martin, C.K. Role of COX-2/PGE2 Mediated Inflammation in Oral Squamous Cell Carcinoma. *Cancers* **2018**, *10*, 348. [\[CrossRef\]](#)
96. Gallo, O.; Masini, E.; Bianchi, B.; Bruschini, L.; Paglierani, M.; Franchi, A. Prognostic significance of cyclooxygenase-2 pathway and angiogenesis in head and neck squamous cell carcinoma. *Hum. Pathol.* **2002**, *33*, 708–714. [\[CrossRef\]](#)
97. Beam, S.L.; Rassnick, K.M.; Moore, A.S.; McDonough, S.P. An immunohistochemical study of cyclooxygenase-2 expression in various feline neoplasms. *Vet. Pathol.* **2003**, *40*, 496–500. [\[CrossRef\]](#)
98. DiBernardi, L.; Dore, M.; Davis, J.A.; Owens, J.G.; Mohammed, S.I.; Guptill, C.F.; Knapp, D.W. Study of feline oral squamous cell carcinoma: Potential target for cyclooxygenase inhibitor treatment. *Prostaglandins Leukot. Essent. Fat. Acids* **2007**, *76*, 245–250. [\[CrossRef\]](#)
99. Kabak, Y.B.; Sozmen, M.; Devrim, A.K.; Sudagidan, M.; Yildirim, F.; Guvenc, T.; Yarim, M.; Gulbahar, Y.M.; Ahmed, I.; Karaca, E.; et al. Expression levels of angiogenic growth factors in feline squamous cell carcinoma. *Acta Vet. Hung.* **2020**, *68*, 37–48. [\[CrossRef\]](#)
100. Millanta, F.; Andreani, G.; Rocchigiani, G.; Lorenzi, D.; Poli, A. Correlation Between Cyclo-oxygenase-2 and Vascular Endothelial Growth Factor Expression in Canine and Feline Squamous Cell Carcinomas. *J. Comp. Pathol.* **2016**, *154*, 297–303. [\[CrossRef\]](#)
101. Leethanakul, C.; Patel, V.; Gillespie, J.; Pallente, M.; Ensley, J.F.; Koontongkaew, S.; Liotta, L.A.; Emmert-Buck, M.; Gutkind, J.S. Distinct pattern of expression of differentiation and growth-related genes in squamous cell carcinomas of the head and neck revealed by the use of laser capture microdissection and cDNA arrays. *Oncogene* **2000**, *19*, 3220–3224. [\[CrossRef\]](#)
102. Uraguchi, M.; Morikawa, M.; Shirakawa, M.; Sanada, K.; Imai, K. Activation of WNT family expression and signaling in squamous cell carcinomas of the oral cavity. *J. Dent. Res.* **2004**, *83*, 327–332. [\[CrossRef\]](#)
103. Abalkhail, K.A.; Kukuruzinska, M.A. Emerging Insights into Wnt/beta-catenin Signaling in Head and Neck Cancer. *J. Dent. Res.* **2018**, *97*, 665–673. [\[CrossRef\]](#)
104. Polakis, P. The many ways of Wnt in cancer. *Curr. Opin. Genet. Dev.* **2007**, *17*, 45–51. [\[CrossRef\]](#)
105. Hsu, P.C.; Huang, J.H.; Tsai, C.C.; Lin, Y.H.; Kuo, C.Y. Early Molecular Diagnosis and Comprehensive Treatment of Oral Cancer. *Curr. Issues Mol. Biol.* **2025**, *47*, 452. [\[CrossRef\]](#)
106. Li, C.; Fang, Y.; Xu, S.; Zhao, J.; Dong, D.; Li, S. Nanomedicine in HNSCC therapy-a challenge to conventional therapy. *Front. Pharmacol.* **2024**, *15*, 1434994. [\[CrossRef\]](#)
107. Yang, C.; Pang, X.; Teng, S.; Wilson, S.; Gu, X.; Xie, G. MYC Overexpression Enhances Sensitivity to MEK Inhibition in Head and Neck Squamous Cell Carcinoma. *Int. J. Mol. Sci.* **2025**, *26*, 588. [\[CrossRef\]](#)
108. Cyberski, T.F.; Singh, A.; Korzinkin, M.; Mishra, V.; Pun, F.; Shen, L.; Wing, C.; Cheng, X.; Baird, B.; Miao, Y.; et al. Acquired resistance to immunotherapy and chemoradiation in MYC amplified head and neck cancer. *npj Precis. Oncol.* **2024**, *8*, 114. [\[CrossRef\]](#)
109. Wang, R.; Li, S.; Ma, Y.; Da, D.; Zhang, Q.; Dang, C.; Zhao, X.; Liang, S.; Li, H. HPV16-miR-H1 promotes proliferation, migration, and glycolysis in head and neck squamous cell carcinoma cells via the PTEN/AKT pathway. *Sci. Rep.* **2025**, *15*, 45047. [\[CrossRef\]](#)
110. Xu, Q.; Ma, H.; Chang, H.; Feng, Z.; Zhang, C.; Yang, X. The interaction of interleukin-8 and PTEN inactivation promotes the malignant progression of head and neck squamous cell carcinoma via the STAT3 pathway. *Cell Death Dis.* **2020**, *11*, 405. [\[CrossRef\]](#)
111. Izumi, H.; Wang, Z.; Goto, Y.; Ando, T.; Wu, X.; Zhang, X.; Li, H.; Johnson, D.E.; Grandis, J.R.; Gutkind, J.S. Pathway-Specific Genome Editing of PI3K/mTOR Tumor Suppressor Genes Reveals that PTEN Loss Contributes to Cetuximab Resistance in Head and Neck Cancer. *Mol. Cancer Ther.* **2020**, *19*, 1562–1571. [\[CrossRef\]](#)
112. Squarize, C.H.; Castilho, R.M.; Abrahao, A.C.; Molinolo, A.; Lingen, M.W.; Gutkind, J.S. PTEN deficiency contributes to the development and progression of head and neck cancer. *Neoplasia* **2013**, *15*, 461–471. [\[CrossRef\]](#)
113. Fesharaki, S.A.H.; Abari, S.K.; Yazdani, B.; Farajollahi, H.; Kalashami, F.P.; Zadsar, A.; Sirous, H. A comprehensive bioinformatics analysis of fatty acid metabolism-associated genes in the diagnosis and prognosis of head and neck squamous cell carcinoma. *Res. Pharm. Sci.* **2025**, *20*, 356–372. [\[CrossRef\]](#)
114. Costa, E.F.D.; Lima, T.R.P.; Lopes-Aguiar, L.; Nogueira, G.A.S.; Visacri, M.B.; Quintanilha, J.C.F.; Pincinato, E.C.; Calonga, L.; Mariano, F.V.; Altemani, A.; et al. FAS and FASL variations in outcomes of tobacco- and alcohol-related head and neck squamous cell carcinoma patients. *Tumour Biol.* **2020**, *42*, 1010428320938494. [\[CrossRef\]](#)
115. Reichert, T.E.; Strauss, L.; Wagner, E.M.; Gooding, W.; Whiteside, T.L. Signaling abnormalities, apoptosis, and reduced proliferation of circulating and tumor-infiltrating lymphocytes in patients with oral carcinoma. *Clin. Cancer Res.* **2002**, *8*, 3137–3145.

116. Xue, L.; Tang, W.; Zhou, J.; Xue, J.; Li, Q.; Ge, X.; Lin, F.; Zhao, W.; Guo, Y. Next-generation sequencing identifies CDKN2A alterations as prognostic biomarkers in recurrent or metastatic head and neck squamous cell carcinoma predominantly receiving immune checkpoint inhibitors. *Front. Oncol.* **2023**, *13*, 1276009. [\[CrossRef\]](#)
117. Jiang, X.; Ye, J.; Dong, Z.; Hu, S.; Xiao, M. Novel genetic alterations and their impact on target therapy response in head and neck squamous cell carcinoma. *Cancer Manag. Res.* **2019**, *11*, 1321–1336. [\[CrossRef\]](#)
118. Zhou, C.; Shen, Z.; Ye, D.; Li, Q.; Deng, H.; Liu, H.; Li, J. The Association and Clinical Significance of CDKN2A Promoter Methylation in Head and Neck Squamous Cell Carcinoma: A Meta-Analysis. *Cell. Physiol. Biochem.* **2018**, *50*, 868–882. [\[CrossRef\]](#)
119. Supsavhad, W.; Dirksen, W.P.; Hildreth, B.E.; Rosol, T.J. p16, pRb, and p53 in Feline Oral Squamous Cell Carcinoma. *Vet. Sci.* **2016**, *3*, 18. [\[CrossRef\]](#)
120. Kalyankrishna, S.; Grandis, J.R. Epidermal growth factor receptor biology in head and neck cancer. *J. Clin. Oncol.* **2006**, *24*, 2666–2672. [\[CrossRef\]](#)
121. Chen, Y.H.; Chien, C.Y.; Wang, Y.M.; Li, S.H. Serum Levels of Stromal Cell-Derived Factor-1alpha and Vascular Endothelial Growth Factor Predict Clinical Outcomes in Head and Neck Squamous Cell Carcinoma Patients Receiving TPF Induction Chemotherapy. *Biomedicines* **2022**, *10*, 803. [\[CrossRef\]](#)
122. Sridharan, V.; Margalit, D.N.; Lynch, S.A.; Severgnini, M.; Hodi, F.S.; Haddad, R.I.; Tishler, R.B.; Schoenfeld, J.D. Effects of definitive chemoradiation on circulating immunologic angiogenic cytokines in head and neck cancer patients. *J. Immunother. Cancer* **2016**, *4*, 32. [\[CrossRef\]](#)
123. Sugiura, T.; Inoue, Y.; Matsuki, R.; Ishii, K.; Takahashi, M.; Abe, M.; Shirasuna, K. VEGF-C and VEGF-D expression is correlated with lymphatic vessel density and lymph node metastasis in oral squamous cell carcinoma: Implications for use as a prognostic marker. *Int. J. Oncol.* **2009**, *34*, 673–680. [\[CrossRef\]](#)
124. Gendler, A.; Lewis, J.R.; Reetz, J.A.; Schwarz, T. Computed tomographic features of oral squamous cell carcinoma in cats: 18 cases (2002–2008). *J. Am. Vet. Med. Assoc.* **2010**, *236*, 319–325. [\[CrossRef\]](#)
125. Strohmayer, C.; Klang, A.; Kneissl, S. Computed Tomographic and Histopathological Characteristics of 13 Equine and 10 Feline Oral and Sinonasal Squamous Cell Carcinomas. *Front. Vet. Sci.* **2020**, *7*, 591437. [\[CrossRef\]](#)
126. Szturz, P.; Wouters, K.; Kiyota, N.; Tahara, M.; Prabhash, K.; Noronha, V.; Adelstein, D.; Van Gestel, D.; Vermorken, J.B. Low-Dose vs. High-Dose Cisplatin: Lessons Learned From 59 Chemoradiotherapy Trials in Head and Neck Cancer. *Front. Oncol.* **2019**, *9*, 86. [\[CrossRef\]](#)
127. Buglione, M.; Alterio, D.; Maddalo, M.; Greco, D.; Gerardi, M.A.; Tomasini, D.; Pegurri, L.; Augugliaro, M.; Marvaso, G.; Turturici, I.; et al. Three weekly versus weekly concurrent cisplatin: Safety propensity score analysis on 166 head and neck cancer patients. *Radiat. Oncol.* **2021**, *16*, 239. [\[CrossRef\]](#)
128. de Maar, J.S.; Zandvliet, M.; Veraa, S.; Tobon Restrepo, M.; Moonen, C.T.W.; Deckers, R. Ultrasound and Microbubbles Mediated Bleomycin Delivery in Feline Oral Squamous Cell Carcinoma—An In Vivo Veterinary Study. *Pharmaceutics* **2023**, *15*, 1166. [\[CrossRef\]](#)
129. Deprez, J.; Lajoinie, G.; Engelen, Y.; De Smedt, S.C.; Lentacker, I. Opening doors with ultrasound and microbubbles: Beating biological barriers to promote drug delivery. *Adv. Drug Deliv. Rev.* **2021**, *172*, 9–36. [\[CrossRef\]](#)
130. Frinking, P.; Segers, T.; Luan, Y.; Tranquart, F. Three Decades of Ultrasound Contrast Agents: A Review of the Past, Present and Future Improvements. *Ultrasound Med. Biol.* **2020**, *46*, 892–908. [\[CrossRef\]](#)
131. Snipstad, S.; Sulheim, E.; de Lange Davies, C.; Moonen, C.; Storm, G.; Kiessling, F.; Schmid, R.; Lammers, T. Sonopermeation to improve drug delivery to tumors: From fundamental understanding to clinical translation. *Expert Opin. Drug Deliv.* **2018**, *15*, 1249–1261. [\[CrossRef\]](#)
132. Chong, W.K.; Papadopoulou, V.; Dayton, P.A. Imaging with ultrasound contrast agents: Current status and future. *Abdom. Radiol.* **2018**, *43*, 762–772. [\[CrossRef\]](#)
133. Shantz, L.M.; Levin, V.A. Regulation of ornithine decarboxylase during oncogenic transformation: Mechanisms and therapeutic potential. *Amino Acids* **2007**, *33*, 213–223. [\[CrossRef\]](#)
134. Casero, R.A., Jr.; Marton, L.J. Targeting polyamine metabolism and function in cancer and other hyperproliferative diseases. *Nat. Rev. Drug Discov.* **2007**, *6*, 373–390. [\[CrossRef\]](#)
135. Levin, V.A.; Uhm, J.H.; Jaecle, K.A.; Choucair, A.; Flynn, P.J.; Yung, W.K.A.; Prados, M.D.; Bruner, J.M.; Chang, S.M.; Kyritsis, A.P.; et al. Phase III randomized study of postradiotherapy chemotherapy with alpha-difluoromethylornithine-procarbazine, N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosurea, vincristine (DFMO-PCV) versus PCV for glioblastoma multiforme. *Clin. Cancer Res.* **2000**, *6*, 3878–3884.
136. O'Shaughnessy, J.A.; Demers, L.M.; Jones, S.E.; Arseneau, J.; Khandelwal, P.; George, T.; Gersh, R.; Mauger, D.; Manni, A. Alpha-difluoromethylornithine as treatment for metastatic breast cancer patients. *Clin. Cancer Res.* **1999**, *5*, 3438–3444.
137. Chen, Y.; Weeks, R.S.; Burns, M.R.; Boorman, D.W.; Klein-Szanto, A.; O'Brien, T.G. Combination therapy with 2-difluoromethylornithine and a polyamine transport inhibitor against murine squamous cell carcinoma. *Int. J. Cancer* **2006**, *118*, 2344–2349. [\[CrossRef\]](#)

138. Skorupski, K.A.; O'Brien, T.G.; Guerrero, T.; Rodriguez, C.O.; Burns, M.R. Phase I/II clinical trial of 2-difluoromethyl-ornithine (DFMO) and a novel polyamine transport inhibitor (MQT 1426) for feline oral squamous cell carcinoma. *Vet. Comp. Oncol.* **2011**, *9*, 275–282. [\[CrossRef\]](#)
139. Liu, T.A.; Stewart, T.M.; Casero, R., Jr. The Synergistic Benefit of Combination Strategies Targeting Tumor Cell Polyamine Homeostasis. *Int. J. Mol. Sci.* **2024**, *25*, 8173. [\[CrossRef\]](#)
140. Lewis, J.R.; O'Brien, T.G.; Skorupski, K.A.; Krick, E.L.; Reiter, A.M.; Jennings, M.W.; Journey, C.H.; Shofer, F.S. Polyamine inhibitors for treatment of feline oral squamous cell carcinoma: A proof-of-concept study. *J. Vet. Dent.* **2013**, *30*, 140–145. [\[CrossRef\]](#)
141. Pinello, K.; Pires, I.; Castro, A.F.; Carvalho, P.T.; Santos, A.; de Matos, A.; Queiroga, F.; Niza-Ribeiro, J. Vet-OncoNet: Developing a Network of Veterinary Oncology and Reporting a Pioneering Portuguese Experience. *Vet. Sci.* **2022**, *9*, 72. [\[CrossRef\]](#)
142. Rodrigues-Jesus, J.; Vilhena, H.; Canadas-Sousa, A.; Dias-Pereira, P. Feline Mammary Tumors: A Comprehensive Review of Histological Classification Schemes, Grading Systems, and Prognostic Factors. *Vet. Sci.* **2025**, *12*, 736. [\[CrossRef\]](#)
143. Egenvall, A.; Bonnett, B.N.; Haggstrom, J.; Strom Holst, B.; Moller, L.; Nodtvedt, A. Morbidity of insured Swedish cats during 1999–2006 by age, breed, sex, and diagnosis. *J. Feline Med. Surg.* **2010**, *12*, 948–959. [\[CrossRef\]](#)
144. Souza, F.R.; Balabram, D.; Moreira, I.S.; Flecher, M.C.; Nakagaki, K.Y.R.; Abreu, C.C.; Ferreira, E.; Cassali, G.D. Lymph node status of felines affected by mammary gland neoplasms: A look beyond the presence or absence of metastasis. *Res. Vet. Sci.* **2025**, *193*, 105789. [\[CrossRef\]](#)
145. Petrucci, G.; Henriques, J.; Gregorio, H.; Vicente, G.; Prada, J.; Pires, I.; Lobo, L.; Medeiros, R.; Queiroga, F. Metastatic feline mammary cancer: Prognostic factors, outcome and comparison of different treatment modalities—A retrospective multicentre study. *J. Feline Med. Surg.* **2021**, *23*, 549–556. Correction in *J. Feline Med. Surg.* **2021**, *23*, NP1. <https://doi.org/10.1177/1098612X20979892>. [\[CrossRef\]](#)
146. Hughes, K. Comparative mammary gland postnatal development and tumourigenesis in the sheep, cow, cat and rabbit: Exploring the menagerie. *Semin. Cell Dev. Biol.* **2021**, *114*, 186–195. [\[CrossRef\]](#)
147. Papadopoulou, P.L.; Patsikas, M.N.; Charitanti, A.; Kazakos, G.M.; Papazoglou, L.G.; Karayannopoulou, M.; Chrisogonidis, I.; Tziris, N.; Dimitriadis, A. The lymph drainage pattern of the mammary glands in the cat: A lymphographic and computerized tomography lymphographic study. *Anat. Histol. Embryol.* **2009**, *38*, 292–299. [\[CrossRef\]](#)
148. Raharison, F.; Sautet, J. Lymph drainage of the mammary glands in female cats. *J. Morphol.* **2006**, *267*, 292–299. [\[CrossRef\]](#)
149. Silver, I.A. The anatomy of the mammary gland of the dog and cat. *J. Small Anim. Pract.* **1966**, *7*, 689–696. [\[CrossRef\]](#)
150. Avera, E.; Valentic, L.; Bui, L. Current understanding and distinct features of multifocal and multicentric breast cancers. *Cancer Rep.* **2023**, *6*, e1851. [\[CrossRef\]](#)
151. Morris, J. Mammary tumours in the cat: Size matters, so early intervention saves lives. *J. Feline Med. Surg.* **2013**, *15*, 391–400. [\[CrossRef\]](#)
152. Rodrigues-Jesus, J.; Canadas-Sousa, A.; Oliveira, P.; Figueira, A.C.; Marrinhas, C.; Petrucci, G.N.; Gregorio, H.; Tinoco, F.; Goulart, A.; Felga, H.; et al. Distribution of Inflammatory Infiltrate in Feline Mammary Lesions: Relationship With Clinicopathological Features. *Vet. Comp. Oncol.* **2024**, *22*, 398–409. [\[CrossRef\]](#)
153. Soares, M.; Madeira, S.; Correia, J.; Peleteiro, M.; Cardoso, F.; Ferreira, F. Molecular based subtyping of feline mammary carcinomas and clinicopathological characterization. *Breast* **2016**, *27*, 44–51. [\[CrossRef\]](#)
154. Kuhn, E.; Gambini, D.; Despini, L.; Asnaghi, D.; Runza, L.; Ferrero, S. Updates on Lymphovascular Invasion in Breast Cancer. *Biomedicines* **2023**, *11*, 968. [\[CrossRef\]](#)
155. van Dooijeweert, C.; van Diest, P.J.; Ellis, I.O. Grading of invasive breast carcinoma: The way forward. *Virchows Arch.* **2022**, *480*, 33–43. [\[CrossRef\]](#)
156. Granados-Soler, J.L.; Bornemann-Kolatzki, K.; Beck, J.; Brenig, B.; Schutz, E.; Betz, D.; Junginger, J.; Hewicker-Trautwein, M.; Murua Escobar, H.; Nolte, I. Analysis of Copy-Number Variations and Feline Mammary Carcinoma Survival. *Sci. Rep.* **2020**, *10*, 1003. Correction in *Sci. Rep.* **2020**, *10*, 5482. <https://doi.org/10.1038/s41598-020-62222-5>. [\[CrossRef\]](#)
157. Adeg, F.; Borges, A.; Chaves, R. Cat Mammary Tumors: Genetic Models for the Human Counterpart. *Vet. Sci.* **2016**, *3*, 17. [\[CrossRef\]](#)
158. Maniscalco, L.; Millan, Y.; Iussich, S.; Denina, M.; Sanchez-Céspedes, R.; Gattino, F.; Biolatti, B.; Sasaki, N.; Nakagawa, T.; Di Renzo, M.F.; et al. Activation of mammalian target of rapamycin (mTOR) in triple negative feline mammary carcinomas. *BMC Vet. Res.* **2013**, *9*, 80. [\[CrossRef\]](#)
159. Caliar, D.; Zappulli, V.; Rasotto, R.; Cardazzo, B.; Frassinetti, F.; Goldschmidt, M.H.; Castagnaro, M. Triple-negative vimentin-positive heterogeneous feline mammary carcinomas as a potential comparative model for breast cancer. *BMC Vet. Res.* **2014**, *10*, 185. [\[CrossRef\]](#)
160. Ludwig, L.; Dobromylskyj, M.; Wood, G.A.; van der Weyden, L. Feline Oncogenomics: What Do We Know about the Genetics of Cancer in Domestic Cats? *Vet. Sci.* **2022**, *9*, 547. [\[CrossRef\]](#)
161. Lebok, P.; Kopperschmidt, V.; Kluth, M.; Hube-Magg, C.; Ozden, C.; B, T.; Hussein, K.; Mittenzwei, A.; Lebeau, A.; Witzel, I.; et al. Partial PTEN deletion is linked to poor prognosis in breast cancer. *BMC Cancer* **2015**, *15*, 963. [\[CrossRef\]](#)

162. Thorpe, L.M.; Yuzugullu, H.; Zhao, J.J. PI3K in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat. Rev. Cancer* **2015**, *15*, 7–24. [\[CrossRef\]](#)
163. Hayes, H.M., Jr.; Milne, K.L.; Mandell, C.P. Epidemiological features of feline mammary carcinoma. *Vet. Rec.* **1981**, *108*, 476–479. [\[CrossRef\]](#)
164. Overley, B.; Shofer, F.S.; Goldschmidt, M.H.; Sherer, D.; Sorenmo, K.U. Association between ovariectomy and feline mammary carcinoma. *J. Vet. Intern. Med.* **2005**, *19*, 560–563. [\[CrossRef\]](#)
165. Schoemaker, M.J.; Folkert, E.J.; Jones, M.E.; Rae, M.; Allen, S.; Ashworth, A.; Dowsett, M.; Swerdlow, A.J. Combined effects of endogenous sex hormone levels and mammographic density on postmenopausal breast cancer risk: Results from the Breakthrough Generations Study. *Br. J. Cancer* **2014**, *110*, 1898–1907. [\[CrossRef\]](#)
166. Bravi, F.; Decarli, A.; Russo, A.G. Risk factors for breast cancer in a cohort of mammographic screening program: A nested case-control study within the FRiCaM study. *Cancer Med.* **2018**, *7*, 2145–2152. [\[CrossRef\]](#)
167. Ahi, S.; Ayata, M.K.; Seyhan, M. Evaluation of breast cancer symptoms and risk factors in women: The case of Türkiye. *Rev. Esc. Enferm. USP* **2025**, *59*, e20250240. [\[CrossRef\]](#)
168. Pinello, K.; Pires, I.; Castro, A.F.; Carvalho, P.T.; Santos, A.; de Matos, A.; Queiroga, F.; Canadas-Sousa, A.; Dias-Pereira, P.; Catarino, J.; et al. Cross Species Analysis and Comparison of Tumors in Dogs and Cats, by Age, Sex, Topography and Main Morphologies. Data from Vet-OncoNet. *Vet. Sci.* **2022**, *9*, 167. [\[CrossRef\]](#)
169. Manuali, E.; Forte, C.; Vichi, G.; Genovese, D.A.; Mancini, D.; De Leo, A.A.P.; Cavicchioli, L.; Pierucci, P.; Zappulli, V. Tumours in European Shorthair cats: A retrospective study of 680 cases. *J. Feline Med. Surg.* **2020**, *22*, 1095–1102. [\[CrossRef\]](#)
170. Marshall, T.; Chen, J.; Vilorio-Petit, A.M. Adipocyte-Derived Adipokines and Other Obesity-Associated Molecules in Feline Mammary Cancer. *Biomedicines* **2023**, *11*, 2309. [\[CrossRef\]](#)
171. Jacobs, T.M.; Hoppe, B.R.; Poehlmann, C.E.; Ferracane, J.D.; Sorenmo, K.U. Mammary adenocarcinomas in three male cats exposed to medroxyprogesterone acetate (1990–2006). *J. Feline Med. Surg.* **2010**, *12*, 169–174. [\[CrossRef\]](#)
172. Skorupski, K.A.; Overley, B.; Shofer, F.S.; Goldschmidt, M.H.; Miller, C.A.; Sorenmo, K.U. Clinical characteristics of mammary carcinoma in male cats. *J. Vet. Intern. Med.* **2005**, *19*, 52–55. [\[CrossRef\]](#)
173. Giugliano, R.; Dell’Anno, F.; De Paolis, L.; Crescio, M.I.; Ciccotelli, V.; Vivaldi, B.; Razzuoli, E. Mammary gland, skin and soft tissue tumors in pet cats: Findings of the feline tumors collected from 2002 to 2022. *Front. Vet. Sci.* **2024**, *11*, 1320696. [\[CrossRef\]](#)
174. Pickard Price, P.; Stell, A.; O’Neill, D.; Church, D.; Brodbelt, D. Epidemiology and risk factors for mammary tumours in female cats. *J. Small Anim. Pract.* **2023**, *64*, 313–320. [\[CrossRef\]](#)
175. Zappulli, V.; Rasotto, R.; Caliri, D.; Mainenti, M.; Pena, L.; Goldschmidt, M.H.; Kiupel, M. Prognostic evaluation of feline mammary carcinomas: A review of the literature. *Vet. Pathol.* **2015**, *52*, 46–60. [\[CrossRef\]](#)
176. Amorim, F.V.; Souza, H.J.; Ferreira, A.M.; Fonseca, A.B. Clinical, cytological and histopathological evaluation of mammary masses in cats from Rio de Janeiro, Brazil. *J. Feline Med. Surg.* **2006**, *8*, 379–388. [\[CrossRef\]](#)
177. Ito, T.; Kadosawa, T.; Mochizuki, M.; Matsunaga, S.; Nishimura, R.; Sasaki, N. Prognosis of malignant mammary tumor in 53 cats. *J. Vet. Med. Sci.* **1996**, *58*, 723–726. [\[CrossRef\]](#)
178. Souza, F.R.; Moreira, I.S.; Dariva, A.A.; Nakagaki, K.Y.R.; Abreu, C.C.; Balabram, D.; Cassali, G.D. Epidemiologic and Clinicopathological Characterization of Feline Mammary Lesions. *Vet. Sci.* **2024**, *11*, 549. [\[CrossRef\]](#)
179. Travis, R.C.; Key, T.J. Oestrogen exposure and breast cancer risk. *Breast Cancer Res.* **2003**, *5*, 239–247. [\[CrossRef\]](#)
180. Hankinson, S.E.; Colditz, G.A.; Willett, W.C. Towards an integrated model for breast cancer etiology: The lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Res.* **2004**, *6*, 213–218. [\[CrossRef\]](#)
181. Mahasa, P.S.; Milambo, M.J.P.; Nkosi, S.F.; Mukwada, G.; Nyaga, M.M.; Tesfamichael, S.G. The Relationship Between Climate Change and Breast Cancer and Its Management and Preventative Implications in South Africa. *Int. J. Environ. Res. Public Health* **2025**, *22*, 1486. [\[CrossRef\]](#)
182. Fiore, M.; Palella, M.; Ferroni, E.; Miligi, L.; Portaluri, M.; Marchese, C.A.; Mensi, C.; Civitelli, S.; Tanturri, G.; Mangia, C. Air Pollution and Breast Cancer Risk: An Umbrella Review. *Environments* **2025**, *12*, 153. [\[CrossRef\]](#)
183. Ponce, E.; Louie, M.C.; Sevigny, M.B. Acute and chronic cadmium exposure promotes E-cadherin degradation in MCF7 breast cancer cells. *Mol. Carcinog.* **2015**, *54*, 1014–1025. [\[CrossRef\]](#)
184. Aquino, N.B.; Sevigny, M.B.; Sabangan, J.; Louie, M.C. The role of cadmium and nickel in estrogen receptor signaling and breast cancer: Metalloestrogens or not? *J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev.* **2012**, *30*, 189–224. [\[CrossRef\]](#)
185. Franco Jones, C.; Dias, D.; Moreira, A.C.; Goncalves, G.; Cinti, S.; Djamgoz, M.B.A.; Castelo Ferreira, F.; Sanjuan-Alberte, P.; Moreddu, R. Multilevel classification framework for breast cancer cell selection and its integration with advanced disease models. *iScience* **2025**, *28*, 113579. [\[CrossRef\]](#)
186. Carvalho, E.; Canberk, S.; Schmitt, F.; Vale, N. Molecular Subtypes and Mechanisms of Breast Cancer: Precision Medicine Approaches for Targeted Therapies. *Cancers* **2025**, *17*, 1102. [\[CrossRef\]](#)
187. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* **2012**, *490*, 61–70. [\[CrossRef\]](#)

188. Perou, C.M.; Sorlie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; Rees, C.A.; Pollack, J.R.; Ross, D.T.; Johnsen, H.; Akslen, L.A.; et al. Molecular portraits of human breast tumours. *Nature* **2000**, *406*, 747–752. [\[CrossRef\]](#)
189. Santos, I.P.; Martins, C.B.; Batista de Carvalho, L.A.E.; Marques, M.P.M.; Batista de Carvalho, A.L.M. Who's Who? Discrimination of Human Breast Cancer Cell Lines by Raman and FTIR Microspectroscopy. *Cancers* **2022**, *14*, 452. [\[CrossRef\]](#)
190. Rios-Hoyo, A.; Shan, N.L.; Karn, P.L.; Pusztai, L. Clinical Implications of Breast Cancer Intrinsic Subtypes. *Adv. Exp. Med. Biol.* **2025**, *1464*, 435–448. [\[CrossRef\]](#)
191. Sinn, H.P.; Varga, Z. Triple-negative breast cancer: Classification, current concepts, and therapy-related factors. *Pathologie* **2023**, *44*, 32–38. [\[CrossRef\]](#)
192. Botti, G.; Cantile, M.; Collina, F.; Cerrone, M.; Sarno, S.; Anniciello, A.; Di Bonito, M. Morphological and pathological features of basal-like breast cancer. *Transl. Cancer Res.* **2019**, *8*, S503–S509. [\[CrossRef\]](#)
193. Geyer, F.C.; Pareja, F.; Weigelt, B.; Rakha, E.; Ellis, I.O.; Schnitt, S.J.; Reis-Filho, J.S. The Spectrum of Triple-Negative Breast Disease: High- and Low-Grade Lesions. *Am. J. Pathol.* **2017**, *187*, 2139–2151. [\[CrossRef\]](#)
194. Pareja, F.; Geyer, F.C.; Marchio, C.; Burke, K.A.; Weigelt, B.; Reis-Filho, J.S. Triple-negative breast cancer: The importance of molecular and histologic subtyping, and recognition of low-grade variants. *npj Breast Cancer* **2016**, *2*, 16036. [\[CrossRef\]](#)
195. Xiong, N.; Wu, H.; Yu, Z. Advancements and challenges in triple-negative breast cancer: A comprehensive review of therapeutic and diagnostic strategies. *Front. Oncol.* **2024**, *14*, 1405491. [\[CrossRef\]](#)
196. Fan, Y.; Wang, H.; Zhang, H.; Ma, T.; Zhao, Y. Integrating molecular targeting and immune modulation in triple-negative breast cancer: From mechanistic insights to therapeutic innovation. *Front. Immunol.* **2025**, *16*, 1711415. [\[CrossRef\]](#)
197. Pont, M.; Marques, M.; Sorolla, A. Latest Therapeutical Approaches for Triple-Negative Breast Cancer: From Preclinical to Clinical Research. *Int. J. Mol. Sci.* **2024**, *25*, 13518. [\[CrossRef\]](#)
198. Millanta, F.; Calandrella, M.; Bari, G.; Niccolini, M.; Vannozzi, I.; Poli, A. Comparison of steroid receptor expression in normal, dysplastic, and neoplastic canine and feline mammary tissues. *Res. Vet. Sci.* **2005**, *79*, 225–232. [\[CrossRef\]](#)
199. Muscatello, L.V.; Di Oto, E.; Sarli, G.; Monti, V.; Foschini, M.P.; Benazzi, C.; Brunetti, B. HER2 Amplification Status in Feline Mammary Carcinoma: A Tissue Microarray-Fluorescence In Situ Hybridization-Based Study. *Vet. Pathol.* **2019**, *56*, 230–238. [\[CrossRef\]](#)
200. Soares, M.; Ribeiro, R.; Najmudin, S.; Gameiro, A.; Rodrigues, R.; Cardoso, F.; Ferreira, F. Serum HER2 levels are increased in cats with mammary carcinomas and predict tissue HER2 status. *Oncotarget* **2016**, *7*, 17314–17326. [\[CrossRef\]](#)
201. Granados-Soler, J.L.; Taher, L.; Beck, J.; Bornemann-Kolatzki, K.; Brenig, B.; Nerschbach, V.; Ferreira, F.; Junginger, J.; Hewicker-Trautwein, M.; Murua Escobar, H.; et al. Transcription profiling of feline mammary carcinomas and derived cell lines reveals biomarkers and drug targets associated with metabolic and cell cycle pathways. *Sci. Rep.* **2022**, *12*, 17025. [\[CrossRef\]](#)
202. Rida, P.; Andrae, R.; Bikhazi, N.; Jackson, B.; Wang, I.; Jinna, N. FOXM1 Signaling Network Transcriptionally Upregulates Expression of Proteins Involved in Mitotic Progression to Induce High Proliferation and Chromosomal Instability in Androgen Receptor-Low Triple-Negative Breast Cancer. *Int. J. Mol. Sci.* **2026**, *27*, 1823. [\[CrossRef\]](#)
203. Dibra, D.; Moyer, S.M.; El-Naggat, A.K.; Qi, Y.; Su, X.; Lozano, G. Triple-negative breast tumors are dependent on mutant p53 for growth and survival. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2308807120. [\[CrossRef\]](#)
204. Gong, Y.; Ji, P.; Yang, Y.S.; Xie, S.; Yu, T.J.; Xiao, Y.; Jin, M.L.; Ma, D.; Guo, L.W.; Pei, Y.C.; et al. Metabolic-Pathway-Based Subtyping of Triple-Negative Breast Cancer Reveals Potential Therapeutic Targets. *Cell Metab.* **2021**, *33*, 51–64.e9. [\[CrossRef\]](#)
205. Munkacsy, G.; Santarpia, L.; Gyorffy, B. Therapeutic Potential of Tumor Metabolic Reprogramming in Triple-Negative Breast Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 6945. [\[CrossRef\]](#)
206. Reynolds, T.S.; Hu, D.D.; Weaver, S.D.; Ronck, E.C.; Mishra, S.J.; Champion, M.M.; Blagg, B.S.J. Proteomic Analysis of Hsp90beta-Selective Inhibitors Against Triple-Negative Breast Cancer to Gain a Mechanistic Insight. *Mol. Cell. Proteom.* **2025**, *24*, 101043. [\[CrossRef\]](#)
207. Guo, M.; Wang, Y.J.; Shi, J.; Cao, L.X.; Ou, Y.; Jia, X.; Qi, C.C.; Li, Z.X.; Liu, Y.X.; Zuo, S.Y.; et al. Oxidative stress-induced ZEB1 acetylation drives a hybrid epithelial-mesenchymal phenotype and promotes lung metastasis in triple-negative breast cancer. *Redox Biol.* **2025**, *86*, 103834. [\[CrossRef\]](#)
208. Felsheim, B.M.; Fernandez-Martinez, A.; Fan, C.; Pfefferle, A.D.; Hayward, M.C.; Hoadley, K.A.; Rashid, N.U.; Tolaney, S.M.; Somlo, G.; Carey, L.A.; et al. Prognostic and molecular multi-platform analysis of CALGB 40603 (Alliance) and public triple-negative breast cancer datasets. *npj Breast Cancer* **2025**, *11*, 24. [\[CrossRef\]](#)
209. Varzaru, V.B.; Vlad, T.; Popescu, R.; Vlad, C.S.; Moatar, A.E.; Cobec, I.M. Triple-Negative Breast Cancer: Molecular Particularities Still a Challenge. *Diagnostics* **2024**, *14*, 1875. [\[CrossRef\]](#)
210. Nagahashi, M.; Ling, Y.; Toshikawa, C.; Hayashida, T.; Kitagawa, Y.; Futamura, M.; Kuwayama, T.; Nakamura, S.; Yamauchi, H.; Yamauchi, T.; et al. Copy number alteration is an independent prognostic biomarker in triple-negative breast cancer patients. *Breast Cancer* **2023**, *30*, 584–595. [\[CrossRef\]](#)
211. Asproni, P.; Millanta, F.; Ressel, L.; Podesta, F.; Parisi, F.; Vannozzi, I.; Poli, A. An Immunohistochemical Study of the PTEN/AKT Pathway Involvement in Canine and Feline Mammary Tumors. *Animals* **2021**, *11*, 365. [\[CrossRef\]](#)

212. Zhou, Z.; Zhou, Q. Immunotherapy resistance in triple-negative breast cancer: Molecular mechanisms, tumor microenvironment, and therapeutic implications. *Front. Oncol.* **2025**, *15*, 1630464. [\[CrossRef\]](#)
213. Mallick, S.; Duttaroy, A.K.; Dutta, S. The PIK3CA gene and its pivotal role in tumor tropism of triple-negative breast cancer. *Transl. Oncol.* **2024**, *50*, 102140. [\[CrossRef\]](#)
214. Dibra, D.; Xiong, S.; Moyer, S.M.; El-Naggar, A.K.; Qi, Y.; Su, X.; Kong, E.K.; Korkut, A.; Lozano, G. Mutant p53 protects triple-negative breast adenocarcinomas from ferroptosis in vivo. *Sci. Adv.* **2024**, *10*, eadk1835. [\[CrossRef\]](#)
215. Joao, V.S.; Pereira, G.; Vicente, G.; Urbano, A.C.; Correia, J.; Ferreira, J.; Ferreira, F. Serum programmed death ligand 2 is elevated in cats with mammary carcinoma. *Sci. Rep.* **2026**, *16*, 8863. [\[CrossRef\]](#)
216. Franco, M.; Seixas, F.; Pires, M.D.; Alves, A.; Santos, A.; Marrinhas, C.; Vilhena, H.; Santos, J.; Faísca, P.; Dias-Pereira, P.; et al. PD-1, PD-L1, and PD-L2 Expression as Predictive Markers in Rare Feline Mammary Tumors. *Vet. Sci.* **2025**, *12*, 731. [\[CrossRef\]](#)
217. Jin, M.; Fang, J.; Peng, J.; Wang, X.; Xing, P.; Jia, K.; Hu, J.; Wang, D.; Ding, Y.; Wang, X.; et al. PD-1/PD-L1 immune checkpoint blockade in breast cancer: Research insights and sensitization strategies. *Mol. Cancer* **2024**, *23*, 266. [\[CrossRef\]](#)
218. Alkaabi, D.; Arafat, K.; Sulaiman, S.; Al-Azawi, A.M.; Attoub, S. PD-1 Independent Role of PD-L1 in Triple-Negative Breast Cancer Progression. *Int. J. Mol. Sci.* **2023**, *24*, 6420. [\[CrossRef\]](#)
219. Dagher, E.; Abadie, J.; Loussouarn, D.; Fanuel, D.; Campone, M.; Nguyen, F. Bcl-2 expression and prognostic significance in feline invasive mammary carcinomas: A retrospective observational study. *BMC Vet. Res.* **2019**, *15*, 25. [\[CrossRef\]](#)
220. Kedzierska, M.; Bankosz, M. Role of Proteins in Oncology: Advances in Cancer Diagnosis, Prognosis, and Targeted Therapy—A Narrative Review. *J. Clin. Med.* **2024**, *13*, 7131. [\[CrossRef\]](#)
221. Honma, N.; Horii, R.; Ito, Y.; Saji, S.; Younes, M.; Iwase, T.; Akiyama, F. Differences in clinical importance of Bcl-2 in breast cancer according to hormone receptors status or adjuvant endocrine therapy. *BMC Cancer* **2015**, *15*, 698. [\[CrossRef\]](#)
222. Aruvornlop, P.; Ploypetch, S.; Sakcamduang, W.; Sirivisoot, S.; Kasantikul, T.; Roytrakul, S.; Phaonakrop, N.; Arya, N. Tissue Proteomics of Feline Mammary Carcinoma: Differences in Protein Profiles Among Histological Grades Using Liquid Chromatography-Tandem Mass Spectrometry. *Vet. Comp. Oncol.* **2026**, *24*, 128–139. [\[CrossRef\]](#)
223. Darb-Esfahani, S.; Denkert, C.; Stenzinger, A.; Salat, C.; Sinn, B.; Schem, C.; Endris, V.; Klare, P.; Schmitt, W.; Blohmer, J.U.; et al. Role of TP53 mutations in triple negative and HER2-positive breast cancer treated with neoadjuvant anthracycline/taxane-based chemotherapy. *Oncotarget* **2016**, *7*, 67686–67698. [\[CrossRef\]](#)
224. Andrikopoulou, A.; Terpos, E.; Chatzinikolaou, S.; Apostolidou, K.; Ntanasis-Stathopoulos, I.; Gavriatopoulou, M.; Dimopoulos, M.A.; Zagouri, F. TP53 mutations determined by targeted NGS in breast cancer: A case-control study. *Oncotarget* **2021**, *12*, 2206–2214. [\[CrossRef\]](#)
225. Saif, R.; Awan, A.R.; Lyons, L.; Gandolfi, B.; Tayyab, M.; Ellahi Babar, M.; Khalid Mehmood, A.; Ullah, Z.; Wasim, M. Hspb1 and Tp53 Mutation and Expression Analysis in Cat Mammary Tumors. *Iran. J. Biotechnol.* **2016**, *14*, 202–212. [\[CrossRef\]](#)
226. Pang, L.Y.; Blacking, T.M.; Else, R.W.; Sherman, A.; Sang, H.M.; Whitelaw, B.A.; Hupp, T.R.; Argyle, D.J. Feline mammary carcinoma stem cells are tumorigenic, radioresistant, chemoresistant and defective in activation of the ATM/p53 DNA damage pathway. *Vet. J.* **2013**, *196*, 414–423. Corrigendum in *Vet. J.* **2021**, *276*, 105744. <https://doi.org/10.1016/j.tvjl.2021.105744>. [\[CrossRef\]](#)
227. Takeshita, T.; Yamamoto, Y.; Yamamoto-Ibusuki, M.; Inao, T.; Sueta, A.; Fujiwara, S.; Omoto, Y.; Iwase, H. Prognostic role of PIK3CA mutations of cell-free DNA in early-stage triple negative breast cancer. *Cancer Sci.* **2015**, *106*, 1582–1589. [\[CrossRef\]](#)
228. Miricescu, D.; Totan, A.; Stanescu, S., II; Badoiu, S.C.; Stefani, C.; Greabu, M. PI3K/AKT/mTOR Signaling Pathway in Breast Cancer: From Molecular Landscape to Clinical Aspects. *Int. J. Mol. Sci.* **2020**, *22*, 173. [\[CrossRef\]](#)
229. Cossu-Rocca, P.; Orru, S.; Muroi, M.R.; Sanges, F.; Sotgiu, G.; Ena, S.; Pira, G.; Murgia, L.; Manca, A.; Uras, M.G.; et al. Analysis of PIK3CA Mutations and Activation Pathways in Triple Negative Breast Cancer. *PLoS ONE* **2015**, *10*, e0141763. [\[CrossRef\]](#)
230. Guo, S.; Loibl, S.; von Minckwitz, G.; Darb-Esfahani, S.; Lederer, B.; Denkert, C. PIK3CA H1047R Mutation Associated with a Lower Pathological Complete Response Rate in Triple-Negative Breast Cancer Patients Treated with Anthracycline-Taxane-Based Neoadjuvant Chemotherapy. *Cancer Res. Treat.* **2020**, *52*, 689–696. [\[CrossRef\]](#)
231. Kriegsmann, M.; Endris, V.; Wolf, T.; Pfarr, N.; Stenzinger, A.; Loibl, S.; Denkert, C.; Schneeweiss, A.; Budczies, J.; Sinn, P.; et al. Mutational profiles in triple-negative breast cancer defined by ultradeep multigene sequencing show high rates of PI3K pathway alterations and clinically relevant entity subgroup specific differences. *Oncotarget* **2014**, *5*, 9952–9965. [\[CrossRef\]](#)
232. Lai, Y.L.; Mau, B.L.; Cheng, W.H.; Chen, H.M.; Chiu, H.H.; Tzen, C.Y. PIK3CA exon 20 mutation is independently associated with a poor prognosis in breast cancer patients. *Ann. Surg. Oncol.* **2008**, *15*, 1064–1069. [\[CrossRef\]](#)
233. Maniscalco, L.; Iussich, S.; de Las Mulas, J.M.; Millan, Y.; Biolatti, B.; Sasaki, N.; Nakagawa, T.; De Maria, R. Activation of AKT in feline mammary carcinoma: A new prognostic factor for feline mammary tumours. *Vet. J.* **2012**, *191*, 65–71. [\[CrossRef\]](#)
234. Prvanovic, M.; Nedeljkovic, M.; Tanic, N.; Tomic, T.; Terzic, T.; Milovanovic, Z.; Maksimovic, Z.; Tanic, N. Role of PTEN, PI3K, and mTOR in Triple-Negative Breast Cancer. *Life* **2021**, *11*, 1247. [\[CrossRef\]](#)

235. Dean, S.J.; Perks, C.M.; Holly, J.M.; Bhoo-Pathy, N.; Looi, L.M.; Mohammed, N.A.; Mun, K.S.; Teo, S.H.; Koobotse, M.O.; Yip, C.H.; et al. Loss of PTEN expression is associated with IGFBP2 expression, younger age, and late stage in triple-negative breast cancer. *Am. J. Clin. Pathol.* **2014**, *141*, 323–333. [\[CrossRef\]](#)
236. Chen, S.; Leng, P.; Guo, J.; Zhou, H. FBXW7 in breast cancer: Mechanism of action and therapeutic potential. *J. Exp. Clin. Cancer Res.* **2023**, *42*, 226. [\[CrossRef\]](#)
237. Hänle-Kreidler, S.; Richter, K.T.; Hoffmann, I. The SCF-FBXW7 E3 ubiquitin ligase triggers degradation of histone 3 lysine 4 methyltransferase complex component WDR5 to prevent mitotic slippage. *J. Biol. Chem.* **2022**, *298*, 102703. [\[CrossRef\]](#)
238. Sailo, B.L.; Banik, K.; Girisa, S.; Bordoloi, D.; Fan, L.; Halim, C.E.; Wang, H.; Kumar, A.P.; Zheng, D.L.; Mao, X.L.; et al. FBXW7 in Cancer: What Has Been Unraveled Thus Far? *Cancers* **2019**, *11*, 246. [\[CrossRef\]](#)
239. Bao, G.; Wang, Z.; Liu, L.; Zhang, B.; Song, S.; Wang, D.; Cheng, S.; Moon, E.S.; Roesch, F.; Zhao, J.; et al. Targeting CXCR4/CXCL12 axis via [(177)Lu]Lu-DOTAGA.(SA.FAPi)(2) with CXCR4 antagonist in triple-negative breast cancer. *Eur. J. Nucl. Med. Mol. Imaging* **2024**, *51*, 2744–2757. [\[CrossRef\]](#)
240. Hayasaka, H.; Yoshida, J.; Kuroda, Y.; Nishiguchi, A.; Matsusaki, M.; Kishimoto, K.; Nishimura, H.; Okada, M.; Shimomura, Y.; Kobayashi, D.; et al. CXCL12 promotes CCR7 ligand-mediated breast cancer cell invasion and migration toward lymphatic vessels. *Cancer Sci.* **2022**, *113*, 1338–1351. [\[CrossRef\]](#)
241. Zielinska, K.A.; Katanaev, V.L. The Signaling Duo CXCL12 and CXCR4: Chemokine Fuel for Breast Cancer Tumorigenesis. *Cancers* **2020**, *12*, 3071. [\[CrossRef\]](#)
242. Marques, C.S.; Soares, M.; Santos, A.; Correia, J.; Ferreira, F. Serum SDF-1 levels are a reliable diagnostic marker of feline mammary carcinoma, discriminating HER2-overexpressing tumors from other subtypes. *Oncotarget* **2017**, *8*, 105775–105789. [\[CrossRef\]](#)
243. Atoum, M.F.; Alzoughool, F.; Al-Hourani, H. Linkage Between Obesity Leptin and Breast Cancer. *Breast Cancer* **2020**, *14*, 1178223419898458. [\[CrossRef\]](#)
244. Linares, R.L.; Benitez, J.G.S.; Reynoso, M.O.; Romero, C.G.; Sandoval-Cabrera, A. Modulation of the leptin receptors expression in breast cancer cell lines exposed to leptin and tamoxifen. *Sci. Rep.* **2019**, *9*, 19189. [\[CrossRef\]](#)
245. Kim, Y.; Kim, S.Y.; Lee, J.J.; Seo, J.; Kim, Y.W.; Koh, S.H.; Yoon, H.J.; Cho, K.S. Effects of the expression of leptin and leptin receptor (OBR) on the prognosis of early-stage breast cancers. *Cancer Res. Treat.* **2006**, *38*, 126–132. [\[CrossRef\]](#)
246. Gameiro, A.; Nascimento, C.; Urbano, A.C.; Correia, J.; Ferreira, F. Serum and Tissue Expression Levels of Leptin and Leptin Receptor Are Putative Markers of Specific Feline Mammary Carcinoma Subtypes. *Front. Vet. Sci.* **2021**, *8*, 625147. [\[CrossRef\]](#)
247. Mills, A.M.; Dill, E.A.; Moskaluk, C.A.; Dziegielewski, J.; Bullock, T.N.; Dillon, P.M. The Relationship Between Mismatch Repair Deficiency and PD-L1 Expression in Breast Carcinoma. *Am. J. Surg. Pathol.* **2018**, *42*, 183–191. [\[CrossRef\]](#)
248. Nascimento, C.; Urbano, A.C.; Gameiro, A.; Ferreira, J.; Correia, J.; Ferreira, F. Serum PD-1/PD-L1 Levels, Tumor Expression and PD-L1 Somatic Mutations in HER2-Positive and Triple Negative Normal-Like Feline Mammary Carcinoma Subtypes. *Cancers* **2020**, *12*, 1386. [\[CrossRef\]](#)
249. Xu, A.; Ayoub, S.; Zhang, H.; Wu, Y.; Rau, M.; Ma, X. Regulatory T Cells in Invasive Breast Cancer: Prognosis, Mechanisms and Therapy. *Cancers* **2025**, *17*, 3172. [\[CrossRef\]](#)
250. Das, B.; Winterbottom, C.W.; Sikandar, S.S. The Trojan Horse Within: Mechanisms of Immune Evasion in Breast Cancer. *Cancer Heterog. Plast.* **2025**, *3*, 0001. [\[CrossRef\]](#)
251. Guimaraes, J.C.M.; Petrucci, G.; Prada, J.; Pires, I.; Queiroga, F.L. Immunohistochemical Expression and Prognostic Value of COX-2 and Alpha-Smooth Muscle Actin-positive Cancer-associated Fibroblasts in Feline Mammary Cancer. *In Vivo* **2024**, *38*, 598–605. [\[CrossRef\]](#)
252. Nascimento, C.; Gameiro, A.; Correia, J.; Ferreira, J.; Ferreira, F. The Landscape of Tumor-Infiltrating Immune Cells in Feline Mammary Carcinoma: Pathological and Clinical Implications. *Cells* **2022**, *11*, 2578. [\[CrossRef\]](#)
253. Rosen, S.; Brisson, B.K.; Durham, A.C.; Munroe, C.M.; McNeill, C.J.; Stefanovski, D.; Sorenmo, K.U.; Volk, S.W. Intratumoral collagen signatures predict clinical outcomes in feline mammary carcinoma. *PLoS ONE* **2020**, *15*, e0236516. [\[CrossRef\]](#)
254. Dagher, E.; Simbault, L.; Abadie, J.; Loussouarn, D.; Campone, M.; Nguyen, F. Identification of an immune-suppressed subtype of feline triple-negative basal-like invasive mammary carcinomas, spontaneous models of breast cancer. *Tumour Biol.* **2020**, *42*, 1010428319901052. [\[CrossRef\]](#)
255. Maller, O.; Drain, A.P.; Barrett, A.S.; Borgquist, S.; Ruffell, B.; Zakharevich, I.; Pham, T.T.; Gruosso, T.; Kuasne, H.; Lakins, J.N.; et al. Tumour-associated macrophages drive stromal cell-dependent collagen crosslinking and stiffening to promote breast cancer aggression. *Nat. Mater.* **2021**, *20*, 548–559. [\[CrossRef\]](#)
256. Zheng, S.; Zou, Y.; Xie, X.; Liang, J.Y.; Yang, A.; Yu, K.; Wang, J.; Tang, H.; Xie, X. Development and validation of a stromal immune phenotype classifier for predicting immune activity and prognosis in triple-negative breast cancer. *Int. J. Cancer* **2020**, *147*, 542–553. [\[CrossRef\]](#)
257. Singh, D.D.; Yadav, D.K.; Shin, D. Targeting the CXCR4/CXCL12 Axis to Overcome Drug Resistance in Triple-Negative Breast Cancer. *Cells* **2025**, *14*, 1482. [\[CrossRef\]](#)

258. Vilela, T.; Valente, S.; Correia, J.; Ferreira, F. Advances in immunotherapy for breast cancer and feline mammary carcinoma: From molecular basis to novel therapeutic targets. *Biochim. Biophys. Acta Rev. Cancer* **2024**, 1879, 189144. [\[CrossRef\]](#)
259. Pe, K.C.S.; Saetung, R.; Yodsurang, V.; Chaotham, C.; Suppipat, K.; Chanvorachote, P.; Tawinwung, S. Triple-negative breast cancer influences a mixed M1/M2 macrophage phenotype associated with tumor aggressiveness. *PLoS ONE* **2022**, 17, e0273044. [\[CrossRef\]](#)
260. Madu, C.O.; Wang, S.; Madu, C.O.; Lu, Y. Angiogenesis in Breast Cancer Progression, Diagnosis, and Treatment. *J. Cancer* **2020**, 11, 4474–4494. [\[CrossRef\]](#)
261. Cortes, J.; Cescon, D.W.; Rugo, H.S.; Nowecki, Z.; Im, S.A.; Yusof, M.M.; Gallardo, C.; Lipatov, O.; Barrios, C.H.; Holgado, E.; et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): A randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* **2020**, 396, 1817–1828. [\[CrossRef\]](#)
262. Schram, A.M.; Lee, E.K.; Hojgaard, M.; Simpkins, F.; LoRusso, P.; Duska, L.R.; Garrido-Laguna, I.; Weiss, M.C.; Mandilaras, V.; Carneiro, B.A.; et al. Efficacy and safety of the combination PKMYT1-inhibitor lunresertib and ATR-inhibitor camonsertib in patients with ovarian and endometrial cancers: Phase I MYTHIC study (NCT04855656) Free. *Cancer Res.* **2025**, 85, CT262. [\[CrossRef\]](#)
263. Novosad, C.A.; Bergman, P.J.; O'Brien, M.G.; McKnight, J.A.; Charney, S.C.; Selting, K.A.; Graham, J.C.; Correa, S.S.; Rosenberg, M.P.; Gieger, T.L. Retrospective evaluation of adjunctive doxorubicin for the treatment of feline mammary gland adenocarcinoma: 67 cases. *J. Am. Anim. Hosp. Assoc.* **2006**, 42, 110–120. [\[CrossRef\]](#)
264. McNeill, C.J.; Sorenmo, K.U.; Shofer, F.S.; Gibeon, L.; Durham, A.C.; Barber, L.G.; Baez, J.L.; Overley, B. Evaluation of adjuvant doxorubicin-based chemotherapy for the treatment of feline mammary carcinoma. *J. Vet. Intern. Med.* **2009**, 23, 123–129. [\[CrossRef\]](#)
265. Petrucci, G.N.; Henriques, J.; Lobo, L.; Vilhena, H.; Figueira, A.C.; Canadas-Sousa, A.; Dias-Pereira, P.; Prada, J.; Pires, I.; Queiroga, F.L. Adjuvant doxorubicin vs metronomic cyclophosphamide and meloxicam vs surgery alone for cats with mammary carcinomas: A retrospective study of 137 cases. *Vet. Comp. Oncol.* **2021**, 19, 714–723. [\[CrossRef\]](#)
266. Gameiro, A.; Nascimento, C.; Correia, J.; Ferreira, F. HER2-Targeted Immunotherapy and Combined Protocols Showed Promising Antiproliferative Effects in Feline Mammary Carcinoma Cell-Based Models. *Cancers* **2021**, 13, 2007. [\[CrossRef\]](#)
267. Savan, N.A.; Saavedra, P.V.; Halim, A.; Yuzbasiyan-Gurkan, V.; Wang, P.; Yoo, B.; Kiupel, M.; Sempere, L.; Medarova, Z.; Moore, A. Case report: MicroRNA-10b as a therapeutic target in feline metastatic mammary carcinoma and its implications for human clinical trials. *Front. Oncol.* **2022**, 12, 959630. [\[CrossRef\]](#)
268. Millanta, F.; Lazzeri, G.; Mazzei, M.; Vannozzi, I.; Poli, A. MIB-1 labeling index in feline dysplastic and neoplastic mammary lesions and its relationship with postsurgical prognosis. *Vet. Pathol.* **2002**, 39, 120–126. [\[CrossRef\]](#)

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