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PPAR γ in Head and Neck Cancer Prevention

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Abstract

Head and neck cancer is a major source of morbidity and mortality worldwide. Intervention during the early phases of carcinogenesis represents a promising new strategy for curbing the devastating effects of this disease and its primary treatment modalities, surgery and radiation with or without concomitant chemotherapy. This review focuses on the peroxisome proliferator-activated receptor gamma (PPAR γ) as a target for chemoprevention of oral cancer. Accumulating data suggest that ligands of PPAR γ , which include the thiazolidinedione class of agents approved for the treatment of diabetes, inhibit cancer cell growth in vitro and in animal carcinogenesis models, providing the rationale for testing this approach in populations at risk for head and neck cancer.

Keywords

Head and Neck cancer; Oropharyngeal Carcinoma; PPAR γ (Peroxisome proliferator-activated receptor γ); pioglitazone

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) remains a major cause of morbidity and mortality worldwide, with approximately 550,000 new cases and 300,000 deaths reported in 2011.¹ Development of HNSCC is closely tied to chronic use of tobacco products and alcohol, with current smokers having a relative risk (RR) of 6.5 for the development of HNSCC compared to non-smokers.² In the United States and Europe, tobacco and alcohol together account for approximately 72% of cases.³ Preclinical studies support the synergistic effect of tobacco and alcohol. Autrup et al. demonstrated increased uptake of tobacco carcinogens by the oral epithelial cells after exposure to alcohol, as measured by the amount of DNA adducts produced.⁴ Clinically, the multiplicative effect of these factors has been demonstrated in several epidemiological studies. For instance,

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Hashibe et al. showed that the odds ratio (OR) for the combination of tobacco use (more than 20 cigarettes per day) and alcohol use (3 or more drinks per day) is 14.2 ($P < 0.01$).³

More recently, infection with high risk strains of human papillomavirus (HPV) has emerged as a major etiologic factor for oropharyngeal carcinoma. The prevalence of HPV in oropharyngeal cancer is approximately 70% in the United States.⁵ Although HPV 16, 18, 31 and 33 have all been associated with HNSCC, serotype 16 is implicated in more than 85% of cases.⁶ In the United States the prevalence of HPV infection in healthy men and women aged 14–69 years is 6.9%, being 2.8 times more common in men than women and associated with a previous history of sexual contact and number of sexual partners.⁷ Whereas the incidence of HPV-positive oropharyngeal cancers has increased by 225% between 1984 and 2004, the incidence of HPV-negative HNSCC declined by 50% during this same time frame.⁵ In contrast to oropharyngeal cancer, oral cancers are much less frequently associated with HPV infection. A recent analysis of high risk HPV E6/7 expression in 430 oral cancer samples found HPV in only 5.9% of the samples (95% CI, 3.6–8.2).⁸ Other less common risk factors that have been identified for oral cancer include hereditary syndromes such as Fanconi's anemia, dyskeratosis congenita and the DNA repair deficiency syndrome, ataxia telangiectasia.^{9–11}

Despite major advances in the understanding of HNSCC etiology and molecular pathogenesis, the long term survival for advanced disease, particularly when associated with tobacco and alcohol use, is poor. While 5-year survival for early stage disease is approximately 80%, it is only 30 to 50% for locally advanced disease.¹² The inability to cure many patients with loco-regional or metastatic disease and the huge morbidity associated with the primary curative treatment modalities provide the impetus for the development of preventive strategies.

Oral premalignant lesions and cancer progression

A variety of chronic lesions with variable association with cancer development have been described in the oral cavity. Oral leukoplakia is defined as a white mucosal patch that cannot be clinically or pathologically categorized as any other definable lesion.¹³ Leukoplakia is characterized by epithelial proliferation with variable amounts of dysplasia and/or hyperkeratosis. It represents a reactive process to insults such as tobacco and can regress spontaneously, remain unchanged for long periods of time, or evolve to cancer at rates of up to 5% per year in high risk populations.¹⁴ Leukoplakia is also associated with the development of cancer elsewhere in the head and neck region. Lee et al. reported that in individuals with oral leukoplakia who were followed for a median of 7 years, approximately half of the diagnosed cancers developed at sites of previous leukoplakia while the other half developed elsewhere in the head and neck anatomical region.¹⁴

Other lesions with malignant potential that occur in the oral cavity include erythroplakia and lichen planus. Similar to leukoplakia, erythroplakia is defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable lesion.¹⁵ The risk of transformation of erythroplakia to cancer is much higher compared to other premalignant lesions in the oral cavity and thorough histologic evaluation of erythroplakia frequently

reveals areas of carcinoma in situ or high grade dysplasia. The rate of progression to invasive cancer is described to be as high as 50%.¹⁶ On the other hand, lichen planus is a chronic oral inflammatory lesion that usually presents with white plaques, ulceration or thick hyperkeratosis plaques. The risk of malignant transformation is substantially lower compared to leukoplakia and erythroplakia, with the risk variably described as ranging from 0.5% to 2%.^{17,18}

The clinical care of individuals with oral premalignant lesions is fraught with uncertainties regarding follow-up schedules (with and without biopsies), treatment strategies, and the utility of the histologic diagnosis in predicting long term outcomes. A meta-analysis of studies of individuals with dysplasia (922 cases in 14 studies) reported a malignant transformation rate of 12.1% with a mean time of 4.3 years to transformation.¹⁹ The development of cancer in non-leukoplakia sites as well as the tendency for lesions to recur (locally or elsewhere in the oral cavity) suggest that local surgical treatment alone is insufficient to protect against future cancer occurrence.

Several reports have examined various prognostic indicators associated with progression, concentrating on genetic markers such as loss of heterozygosity (LOH). Mao et al. found LOH in 51% of 37 patients with premalignant lesions and demonstrated progression to cancer in 37% of cases with LOH while cancer developed only in 6% of cases without LOH.²⁰ Similarly, Rosin et al. showed that 3p and/or 9p loss in leukoplakia arising at sites of previous oral cancer increase the rate of development of second oral cancer 26-fold.²¹ More recently, Zhang et al. validated the prognostic value of LOH at specific chromosomal loci (3p, 9p, 17p, 4q) in 296 histologic samples with mild or moderate dysplasia. Dividing the cohort into 3 groups, the highest risk group was found to have a 52-fold increase in the risk to progression to severe dysplasia or cancer.²² This type of molecular prognostication could potentially be incorporated in the future design of clinical prevention and screening trials as well as in determining the frequency and invasive nature of routine follow-up of individuals with oral premalignant lesions.

Chemoprevention

Carcinogenesis can be viewed as a multistep process culminating in the acquisition of mutations and microenvironment changes. The hallmarks of cancer, as proposed by Weinberg and Hanahan, point out the increasing complexity in the understanding of cancer, and at the same time, allow its organization into basic pathway aberrations.²³ As originally proposed in 2000, the major hallmarks of cancer are sustained proliferation, evasion of growth suppressors, resistance to apoptosis, replicative immortality, angiogenesis, and invasion and metastasis. Additional factors that support carcinogenic progression across a wide variety of tumor types have been identified – these include genomic instability, inflammation, deregulated cellular energetics and immune evasion.²⁴

The rationale for cancer prevention (chemoprevention, as it is usually called) is predicated on the concepts that the hallmarks of cancer evolve over a lengthy period of time in individuals exposed to carcinogenic influences such as tobacco and that the entire epithelial surface is subject to the carcinogenic damage.^{25,26} The genetic and epigenetic insults lead to

the accumulation of histologic and molecular changes that continue to evolve independently. This view of carcinogenesis is strongly supported by identification of multiple histologic and molecular changes at varying stages of progression in the lungs of smokers with and without lung cancer (another tobacco-related malignancy) and in the high incidence of second primary cancers after a first HNSCC.^{27–29}

The goal of chemoprevention, therefore, is to intervene at the early stages of carcinogenesis, possibly even before the beginning, by preventing the changes that eventually give rise to invasive tumor formation. Chemoprevention can be defined as the use of pharmacologic or natural agents that inhibit the development of invasive cancer, either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells to malignant cells.³⁰ The appeal of this approach has been tested in a limited number of clinical trials – however, to date, none have led to a clinically acceptable strategy for the prevention of HNSCC (table 1).

Complementary to chemoprevention is screening, which is the identification of unrecognized tumor in people without signs or symptoms.³¹ The goal of screening is to improve the chance of curing cancer at early stages. Therefore, optimal cancer preventive strategies on a population level would incorporate both chemopreventive and screening approaches targeted to the most high risk individuals to decrease cancer mortality.

PPAR gamma as a target for prevention of cancer of the head and neck

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors that belong to the nuclear receptor superfamily. This family has a structure and function that is similar to other steroid type receptors, with an N-terminal ligand-independent activation domain, a central DNA binding domain, and a large carboxy-terminal ligand binding domain that includes an activation domain responsible for ligand-dependent activation.³² Currently there are three known members of the PPAR family, designated as alpha, beta and gamma (γ); there are two PPAR γ isoforms, γ 1 and γ 2, with the former being expressed in many tissues while the latter is primarily expressed in adipocytes.

PPAR γ heterodimerizes with retinoic acid receptors and controls the expression of several genes involved in metabolic pathways, including lipid biosynthesis and glucose metabolism.³³ The retinoic acid receptors comprise 2 main groups with 6 subtypes, of which retinoid X receptor (RXR) is thought to be PPAR γ 's primary partner.³⁴ The heterodimer binds to target gene promoters in a sequence specific manner with associated nuclear corepressors, often functioning as transcriptional repressors in the absence of ligand binding.³⁵ Upon ligand binding, the corepressors are replaced by coactivators that result in transcriptional activation. In some circumstances, such as with regard to anti-inflammatory effects in macrophages, PPAR γ represses gene transcriptional responses that are mediated by other classes of signal-dependent transcription factors via a process called transrepression.³⁶ In contrast to direct DNA binding in a sequence specific manner, this occurs via indirect association of the receptor with target genes. Endogenous ligands that have been found to activate PPAR γ include fatty acids and their derivatives, such as the

eicosanoid, 15-deoxy-^{12,14}-prostaglandin J₂, while synthetic ligands include the thiazolidinedione class of anti-diabetic agents.³⁷

Accumulating data over the past 15 years indicate that PPAR γ is involved in differentiation and induction of apoptosis, working as a tumor suppressor gene (figure 1).³⁸ The ligands of this transcription factor have shown anti-proliferative properties in vitro and have induced differentiation in a variety of transformed cell lines, as discussed below.³⁴

Pioglitazone and the thiazolidinedione class of anti-diabetic agents

Pioglitazone is a synthetic PPAR γ ligand used clinically to treat type II diabetes. It belongs to the thiazolidinedione class of drugs that include rosiglitazone and troglitazone. These agents were developed for the treatment of type II diabetes mellitus because they increase insulin sensitivity of normal tissues involved in metabolism, such as the liver, muscle and fat.³⁹ Pioglitazone and its related compounds improve insulin action in muscle by increasing glucose transport. Consequently the rates of glycogen synthesis and glucose oxidation are augmented. Other actions of these types of drugs are mediated in an indirect manner and include the redistribution of intracellular lipid storage from liver and muscle to white adipose tissue, augmentation of adiponectin and other adipokine secretion, and anti-inflammatory effects on macrophages.^{40–43}

Although three thiazolidinediones were initially approved for use, only pioglitazone remains in active use in the US. The first drug of this class, troglitazone, was withdrawn from the market due to idiosyncratic hepatotoxicity, although this has not been an issue for pioglitazone and rosiglitazone.³⁹ However, adverse cardiovascular events have surfaced as a potential problem with thiazolidinediones, despite beneficial effects on intermediate outcomes such as dyslipidemia, atherosclerosis and inflammation.^{44–46} Both rosiglitazone and pioglitazone cause fluid retention that can result in congestive heart failure. However, unlike pioglitazone, rosiglitazone has been associated with increased risk of myocardial infarction (MI) and cardiovascular events. Nissen et al. performed a meta-analysis of 42 trials that included rosiglitazone in the intervention arm. The odds ratio (OR) for MI was 1.43 (95% CI, 1.03 to 1.98; P=0.03) and for risk of death due to cardiovascular causes it was 1.64 (95% CI, 0.98 to 2.74; P=0.06).⁴⁶ Thus rosiglitazone use has been severely curbed by the US FDA and is not recommended by the American Diabetes Association and the European Association for the Study of Diabetes. In contrast, a meta-analysis evaluating the safety of pioglitazone, which included 16,390 patients in 19 trials, showed that the hazard ratio (HR) for the composite outcome of death, myocardial infarction or stroke of pioglitazone compare to placebo or other anti-diabetic drug was 0.82 (95% CI, 0.72–0.94; P = 0.005).⁴⁷ Similarly, a phase III randomized trial of 5,238 high risk diabetic patients evaluated pioglitazone versus placebo and showed a reduced rate of myocardial infarction in the intervention arm, 28% (P=0.045) risk reduction of nonfatal MI and 37% (P=0.035) in acute coronary syndrome.⁴⁸ In both of these studies pioglitazone increased the risk of congestive heart failure but not associated mortality.

More recently, extended pioglitazone use has also been associated with increased incidence of bladder cancer. Lewis et al. used the Kaiser Permanente diabetes registry data and found

that 2 years or more of pioglitazone use compared with non-use increased the risk of development of bladder cancer 1.4-fold (95% CI 1.03–2.0), with 95% of the cases presenting with early stage disease.⁴⁹ Ferrara et al., using the same cohort registry of 252,467 patients, showed no significant increase in 10 other common tumors.⁵⁰ On the other hand, use of pioglitazone in the metabolic syndrome has been associated with decreased progression to overt diabetes.⁵¹ Thus the risk-benefit calculation for pioglitazone use is complex, with potential beneficial effects with regard to some chronic conditions and potential risks of harm with regard to others.

Preclinical evidence for PPAR γ ligands as chemopreventive agents

Although initially identified as a key driver of adipogenic differentiation, activation of PPAR γ has been found to be associated with antiproliferative, pro-apoptotic, pro-differentiation, anti-inflammatory, and anti-metastatic properties in a variety of cancer cell lines and rodent carcinogenesis model systems.^{37,38,52} The following discussion will focus primarily on HNSCC and to a lesser extent on lung and esophageal tumors, since these cancers have shared etiology with respect to tobacco exposure.

Multiple lines of evidence suggest a role for PPAR γ in cancer prevention and in HNSCC prevention in particular. Theocharis et al. evaluated PPAR γ expression by immunohistochemistry in 49 patients with squamous cell carcinoma (SCC) of the tongue.⁵³ Moderate or intense expression was found in approximately 60% of cancers, while minimal expression was found in the adjacent histologically normal epithelium. PPAR γ expression was also associated with reduced depth of invasion. The expression of PPAR γ was associated with a longer overall survival in a univariate analysis, with a HR of 4.24 (95% CI 1.17–15.30; P=0.02) when PPAR γ low-expressing tumors were compared with high expressors. However, in the multivariable analysis the expression of PPAR γ was not independently correlated with disease-free survival or overall survival.⁵³ In an analogous fashion, Kourelis et al. examined PPAR γ expression in 89 laryngeal tumors and premalignancies.⁵⁴ PPAR γ expression correlated with degree of differentiation across the spectrum of laryngeal abnormalities, with strongest expression in the suprabasal well differentiated epithelium as compared with basal undifferentiated epithelium. No statistically significant differences were seen between the various histologic categories. Curiously, there is little description of PPAR γ expression in human premalignant lesions in the oral cavity.

Several studies indicate that PPAR γ ligands inhibit growth of aerodigestive cancer cell lines. In human esophageal squamous cell carcinoma cell lines, pioglitazone and troglitazone caused dose-dependent growth inhibition, cell cycle arrest and induction of interleukin-1 α , which has antitumor activity.⁵⁵ In NSCLC cell lines, we previously showed that treatment with ciglitazone (another thiazolidinedione that is not used clinically) causes growth arrest and induction of differentiation, as demonstrated through up-regulation of general differentiation markers and down-regulation of progenitor cell lineage-specific differentiation markers (e.g., type II pneumocytes and Clara cell markers). This study also showed that PPAR γ activation decreases expression of matrix metalloproteinase 2, a known marker of invasion and metastasis.⁵⁶ Similar data were reported by Bren-Mattison et al.,

who showed that overexpression of PPAR γ in a lung adenocarcinoma cell line inhibited tumor growth and metastasis and promoted a more differentiated epithelial phenotype.⁵⁷

A number of animal models of head and neck or lung carcinogenesis have examined the anti-tumorigenic properties of PPAR γ activation. Yoshida et al., using the carcinogen 4-nitroquinoline 1-oxide (4-NQO) to induce tongue tumors, showed that increasing doses of troglitazone decreased the incidence of tumors compared with controls (45.8% vs. 5%, $P < 0.005$) and severe dysplasia (65.3% vs. 15%, $P < 0.001$).⁵⁸ Wang et al., using pioglitazone in a carcinogen-induced lung squamous cell carcinoma (SCC) model, showed that treated mice had 35% less tumor burden than controls ($P < 0.05$).⁵⁹ The same group reported that pioglitazone significantly decreased the adenocarcinoma load by 64% and 50% in wild type or p53 mutant mice, respectively, after exposure by the carcinogen vinyl carbamate. Pioglitazone induced apoptosis in both model systems, but had minimal effect on proliferation. Similarly, Lyon et al., using the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to induce lung tumors in A/J mice, demonstrated that rosiglitazone inhibits progression of pre-invasive lesions as reflected by an increase in hyperplasia with a concomitant decrease in adenoma formation and a decrease in the Ki67 proliferation marker.⁶⁰ Bren-Mattison et al. examined the mechanisms responsible for suppression of carcinogenesis by activation of PPAR γ by overexpressing PPAR γ in the alveolar epithelial type II cells. These investigators found that increased PPAR γ resulted in a proportional decrease in COX-2 expression and protection from urethane-induced tumor formation.⁶¹

Clinical evidence for PPAR γ ligands as chemopreventive agents and ongoing trials

A retrospective analysis of a database from 10 Veteran Affairs medical centers was performed by Govindarajan and colleagues to examine the effect of thiazolidinediones on cancer risk in diabetic patients. These investigators showed that TZD use decreased the incidence of lung cancer by 33%, RR, 0.67 (95% CI, 0.51 to 0.87; $P=0.0033$), while no effect could be found on colon or prostate cancer.⁶² Similarly, the risk of HNSCC decreased by 41–55% with the use of TZDs, either alone or with other anti-diabetic agents.⁶³ More recently, a population-based cohort study from France examined the association between pioglitazone and cancer risk at a variety of target organ sites. In a cohort of 1,491,060 diabetic patients, the risk of head and neck cancer was reduced by 15% ($p=0.04$).⁶⁴ It is important to emphasize that these studies focused on diabetic subjects only, as this is the main population that uses thiazolidinediones. Whether these results are generalizable to a non-diabetic population is not at all clear.

One relevant clinical trial has been performed to date, although the results have not yet been reported in the literature ([NCT00099021](#)). Twenty-two individuals with oral leukoplakia were treated with pioglitazone for 3 months in a phase IIa clinical trial. The primary endpoints were clinical and histologic response. As reported in a preliminary fashion at the American Association of Cancer Research Frontiers in Cancer Prevention meeting in 2007, a substantial enough clinical response was seen to provide the rationale for a currently ongoing phase IIB randomized, placebo-controlled trial of pioglitazone given for 6 months

to individuals with oral premalignant lesions exhibiting either dysplasia or hyperplasia in high risk oral cavity sites (NCT00951379). An additional clinical trial is examining the use of pioglitazone in the chemoprevention of lung cancer (NCT00780234). Of note, all of these early phase clinical trials focus on non-diabetic populations at risk for aerodigestive malignancies.

Conclusion

Despite an ever increasing understanding of the complex biology of head and neck carcinogenesis, the development of invasive disease still portends significant risk of death and tremendous morbidity due to treatment. While prevention of invasive disease is an appealing strategy to reduce the morbidity and mortality due to HNSCC, thus far no agents have been conclusively shown to prevent any upper aerodigestive malignancy. The identification of PPAR γ as a target for chemoprevention is based on consistent data across multiple lines of evidence that include investigations of human tumors across a spectrum of histologies, cell line studies, animal carcinogenesis models, and epidemiological analysis. The availability of an approved well characterized drug, pioglitazone, for clinical trials allows the hypothesis that PPAR γ activation can prevent the progression of oral carcinogenesis to be tested. The results of these clinical trials, as well as further work to identify the highest risk individuals who would be most likely to benefit from early interventions, are eagerly awaited.

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Figure 1.

Effects of PPAR γ activation on head and neck carcinogenesis. Pioglitazone activates the PPAR γ -RXR complex to modulate the expression of genes involved in apoptosis, cellular differentiation, proliferation and inflammation, all of which are involved in head and neck carcinogenesis.

Table 1

Prevention Randomized Placebo Controlled Clinical Trials in HNSCC

Study Year	Number of participants	Intervention/control	Main Results
Hong ⁶⁵ 1986	44	13-cis-retinoic acid (13-cRA) Placebo	Response rates among patients with dysplasia: 54% (13- cRA) versus 10% (placebo)
* Hong ⁶⁶ 1990	103	13-cis-retinoic acid (13-cRA) placebo	Decreased 2 nd primary tumors (4% vs. 24%)
Sankaranarayanan ⁶⁷ 1997	160	Vitamin A BC Placebo	Complete regression: Vitamin A 52%, BC 33%, placebo 10%
* van Zandwijk ⁶⁸ 2000	2592	retinyl palmitate RP) N-acetyl cysteine (NAC) RP + NAC placebo	No effect on second primary tumors
* Mayne ⁶⁹ 2001	264	BC Placebo	BC does not have pro-oxidant effects
* Bairati ⁷⁰ 2005	540	Alpha-tocopherol + BC (terminated after 156 participants randomized) Placebo	No effect overall; increased second primary tumors in first 3.5 yrs., decreased second primary tumors afterwards
* Khuri ²⁹ 2006	1190	Isotretinoin Placebo	No effect on second primary tumors
Papadimitrakopoulou ⁷¹ 2008	50	Celecoxib Placebo	No significant effect

* endpoint was second primary tumors

OPL, oral premalignant lesions, BC, Beta carotene, RP, retinyl palmitate, NAC, N-acetyl cysteine