Oral Oncology 85 (2018) 68–81

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Protective effects of metformin, statins and anti-inflammatory drugs on head and neck cancer: A systematic review

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ARTICLE INFO

Keywords:
Oral cancer
Head and neck cancer
Mouth neoplasm
Hydroxymethylglutaryl-CoA reductase inhibitors
Metformin
Anti-inflammatory agents
Non-steroidal
Statins

ABSTRACT

The main objective of this study was to evaluate the effect of metformin, statins and anti-inflammatory drugs (NSAIDs) on head and neck cancer (HNC). Specifically, the potential beneficial effects on risk, survival and recurrence based on epidemiological studies.

PRISMA guidelines were followed. After searching MEDLINE (PubMed), IBECS, LILACS and the Cochrane Central Register for Controlled Trials, 13 studies met the inclusion criteria and so underwent qualitative synthesis (six studies for metformin and seven for NSAIDs). No studies were found for statins. Studies varied in their methodological quality. Meta-analyses showed that metformin exerts significant beneficial effects on HNC risk (RR = 0.71 95% CI 0.61–0.84) and overall survival (RR = 1.71 95% CI 1.20–2.42). Qualitative synthesis also suggests an apparently dose-response relationship and increased benefit when administered alone. The pooled-analyses yielded an almost significant effect of NSAIDs on HNC risk (RR = 0.86 95% CI 0.74–1.01). No associations were found between aspirin use and the risk of HNC (RR = 0.98 95% CI 0.77–1.24) and overall survival (RR = 1.10 95% CI 0.89–1.36).

Metformin appears to have beneficial effects on HNC risk and overall survival, with an apparently dose-response relationship and increased benefit when administered alone. NSAIDs also seem to have a modest beneficial effect on HNC risk. No definitive conclusions can be reached for aspirin as the evidence available was proved inconsistent. Further research by means of well designed and conducted studies are needed to determine firm clinical implications. Standardized assessment methods for HNC outcomes should be established and account for known confounding factors such as smoking and alcohol consumption.

Introduction

Epidemiology of oral and pharyngeal cancer

Oral and pharyngeal cancers are the sixth most common type of cancer worldwide and the seventh in the European Union, with estimates reaching 300,400 and 86,700 new cases in 2012, respectively [1]. In Spain, oral cancer (OC) incidence occupies an intermediate position in Europe, with 12–15 cases/100,000 inhabitants/year in men, and 2–4 cases/100,000 inhabitants/year in women [2]. Among Spanish women, incidence trends for OC increased significantly during the period 1983–2002, although this did not occur for men or for oropharyngeal cancer [3]. The five-year survival rate is 65%, which has increased slightly over the past three decades [4].

Etiological factors

Oral squamous cell carcinoma (OSCC) represents 95% of OC [5]. Tobacco smoking, betel quid chewing, and alcohol consumption are its main etiological factors, acting separately or synergistically [6]. Denture-related trauma has also been identified as an etiological factor although with inconsistent results [7,8]. Infection by human

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https://doi.org/10.1016/j.oraloncology.2018.08.015
Received 17 May 2018; Received in revised form 14 August 2018; Accepted 25 August 2018

papillomavirus (HPV16) has been related with oropharyngeal cancer in 56% of cases, compared with only 2% of cancers in the oral cavity [9]. Positive HPV16 tumors have been associated with improved overall survival rates of patients with oropharyngeal cancers, but not with OSCC [9].

Periodontal disease (PD) and type-2 diabetes mellitus (DM-2) are non-classic factors related with an increased risk of OSCC. Mechanisms involved in the association between PD and cancer are mainly related to the alteration of oral microbiome due to infection by periodontopathogenic bacteria and subsequent chronic systemic inflammation. Moreover, epithelial integrity loss implies the activation of inflammatory cells and the consequent penetration of carcinogens such as tobacco and alcohol [10,11]. Inflammatory cells and mediators [tumor necrosis factor-alpha (TNF-α), metalloproteinase (MMP), interleukins 1 and 6 (IL-1, -6), and proteases] are significant markers in the progression of cancer [11]. Associations between PD and an increased risk of lung [12,13] and pancreatic cancer [14] have been demonstrated. One systematic review reported an increased risk of OC in individuals with PD [11]. Likewise, 2 meta-analyses have shown that subjects with periodontitis run a significantly higher risk of OSCC (OR = 2.6 for both of them) [15,16].

The relation between cancer and DM-2 are mainly explained by hyperinsulinemia and hyperglycemia. The direct mitogenic effects of insulin are mediated by insulin receptors that are expressed in tumor cells [17]. Insulin facilitates the production of insulin growth factors and increases the mitogenic activity of these products [18], stimulating tumor growth through cell proliferation, inhibition of apoptosis, and increased mitosis in the cell-lines of several epithelial tumors, including OC. Furthermore, insulin resistance leads to the increased release of multiple pro-inflammatory cytokines, which favors inflammation and subsequent malignant transformation [19]. Due to oxidative balance failure in hyperglycemia, advanced glycation end products (AGEs) accumulate, generating the release of free radicals, cytokines and growth factors, which produce extracellular matrix damage and increase the permeability of the basal membrane, thus promoting the spread of cancers [18]. AGEs enhance the expression of their receptor, RAGE, which is one of the main regulatory factors underlying tumor cell invasion [18]. Several systematic reviews have shown that DM-2 is a risk factor for diverse cancers [20–26] and OC [19]. Meta-analyses based on the latter study have reported that individuals with DM-2 had significantly increased risk of OC (RR = 1.15 95% CI 1.02–1.29) and increased OC mortality (RR = 1.41 95% CI 1.16–1.72).

Beneficial effects of drugs on cancer

Metformin, statins, and non-steroidal anti-inflammatory drugs (NSAIDs), could have a beneficial effect on cancer.

The activation of cyclic adenosine monophosphate-dependent-protein-kinase (AMPK), a protein involved in the regulation of cellular metabolism, constitutes the main direct mechanism by which metformin exerts its antineoplastic activity [27,28]. Activation of AMPK inhibits the mammalian target of the rapamycin (mTOR) pathway, specifically mTOR complex-1 (mTORC1), which plays a key role in the control of cell growth, proliferation and metabolism, which becomes deregulated in cancer [27]. Consequently, mTORC1 does not respond to the growth factor signals leading to inhibition of gluconeogenesis, protein synthesis, cell proliferation [17], tumor reduction and neovascularization [28]. Indirect metformin effects are mediated through its blood glucose lowering ability and subsequent reduction in levels of circulating insulin [17]. Henderson et al. [29] showed that diabetic metformin-users with colorectal and lung cancer showed improved survival by up to 5 years compared with not-metformin users. Meireles et al. [30] reported that women with endometrial cancer, treated with metformin, presented improved survival rates (HR = 0.82 95% CI 0.70–0.95). Diabetic metformin-users had a decreased risk of developing colon cancer (RR = 0.79 95% CI 0.69–0.95) [31] and patients with prostate cancer showed decreased mortality and recurrence rates (HR = 0.88 95% CI 0.86–0.90, HR = 0.79 95% CI 0.63–1.00, respectively) [32]. Recently, Rego et al. [33] have reported the anti-tumor effects of metformin on head and neck cancer (HNC) cell-lines, showing that metformin reduces cell viability by > 50% in a dose-dependent manner, induced G0/G1 cell cycle arrest and apoptosis, and regulates proteins related with carcinogenesis pathways, such as mTORC1 inhibition.

The beneficial effects of statins on cancer are mainly related to the inhibition of the mevalonate pathway. Mevalonate is synthesized from 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase, a crucial enzyme in the synthesis of cholesterol, which is inhibited by statins [34]. Mevalonate is further metabolized to farnesyl-pyrophosphate and to geranylgeranyl-pyrophosphate [35], which are used for post-translational modification of the proteins involved in diverse aspects of tumor development and progression [35]. Inhibition of protein prenylation affects a variety of key cellular functions, including membrane integrity, cell signaling, protein synthesis, and cell cycle progression [34,36]. Through mevalonate pathway inhibition, statins inhibit the function of epidermal growth factor receptor (EGFR), which inhibits the mTOR cascade and the phosphoinositide-3-kinase pathway involved in angiogenesis induction. Furthermore, they regulate the translation of mRNA, which encodes proto-oncogene proteins, and so inhibits the proliferation and survival of malignant cells [37]. Several studies have reported that the mevalonate pathway is up-regulated in different cancers: breast, hepatic, pancreatic, oesophageal and prostate cancer [35]. Statins reduce the incidence of oesophageal cancer in general [38]. Nayan et al. [39] reported a 33% specific-mortality reduction from kidney cancer among statin-users. Other authors have shown an improved survival from colorectal cancer among statin-users before diagnosis (HR = 0.82 95% CI 0.79–0.86) [40]. Statins have been associated with improved recurrence-free survival in women with breast cancer (HR = 0.64 95% CI 0.53–0.79) [41]. Results by Pavan et al. on HNC [37] demonstrated that statins reduce cellular viability by < 50% in a dose-dependent manner, influence the accumulation of cells in G0/G1 phase, cell death and protein expression involved in carcinogenesis; these findings corroborate the potential in vitro anti-tumor effects of statins on HNC, pointing to their potential benefit as an adjuvant to HNC treatment.

The principal characteristic of the etiopathogenesis of cancer is inflammation. Inflammatory mediators such as nuclear factor-kappa (NF-κB), vascular endothelial growth factor (VEGF), cytokines, prostaglandins, p53, nitric oxide (NO), reactive oxygen species (ROS), and specific mRNA, are the main mediators involved in the pathogenesis of oral cancer. Their expression is mostly responsible for a pro-tumorigenic or anti-tumorigenic inflammatory response through changes in cell proliferation, cell death, cell senescence, DNA mutation and methylation, and angiogenesis [42]. The inducible form of cyclooxygenase, COX2, is expressed in neoplastic and inflamed tissues, and is induced by pro-inflammatory and mitogenic stimuli. Some mediators such as NF-κB, nuclear factor, IL-6, VEGF, TNF-α, NO and increased stability of COX2 mRNA may up-regulate COX2 over-expression [43]. Research suggests that COX2 has a role in neoplasia through several mechanisms: stimulating angiogenesis by inducing endothelial cell proliferation, increasing the synthesis of VEGF, suppressing apoptosis and stimulating cell adhesion and migration, as well as promoting tumor cell invasion through the activation of MMP [43,44]. It has been shown that COX2 is over-expressed in colon, breast, prostate and pancreas cancers [45], and in about 80% of malignant or premalignant HNC [43]. Therefore, COX inhibitors – specifically, COX2 inhibitors –