Effects of metformin on head and neck cancer: A systematic review

Daniela Fortunato Rêgo a, Ludmila Madeira Cardoso Pavan a, Silvia Taveira Elias a, Grazia De Luca Canto b,c, Eliete Neves Silva Guerra a,*

a Oral Histopathology Laboratory, Health Sciences Faculty, University of Brasília, Brasília, Brazil
b Department of Dentistry, Federal University of Santa Catarina, Florianópolis, Brazil
c Department of Dentistry, University of Alberta, Edmonton, Canada

SUMMARY

Conventional therapeutic approaches for head and neck squamous cell carcinoma (HNSCC) are associated with many adverse effects that reduce quality of life. Therefore, identification of new less cytotoxic treatments is highly important. Metformin, which is commonly used for type 2 diabetes, may reduce cancer risk. A few clinical studies have examined the association between HNSCC and metformin. Therefore, the aim of this systematic review was to synthesize the available literature of the potential effect of metformin on HNSCC. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Studies were gathered by searching PubMed, MEDLINE, EMBASE, LILACS, and the Cochrane database before June 28, 2014, with no time or language restrictions. Studies that evaluated individuals of any age that underwent metformin and had HNSCC and compared with patients without treatment or patients that use other kind of treatment for HNSCC (drugs or radiotherapy) were considered. Selected articles were evaluated according to the Critical Appraisal Skills Programs. Of 313 identified citations, 3 studies met the inclusion criteria and were used for qualitative analysis. These studies demonstrated that individuals taking metformin had decreased rates of locoregional recurrence and metastasis and improved overall survival and disease-free survival rates. Individuals taking metformin had a lower incidence of HNSCC than those not taking metformin. Though there are only a few studies on the topic, currently available evidence suggests an association between HNSCC and metformin use. Metformin reportedly improves the overall survival of HNSCC patients.

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of the anticancer effects of metformin, though other mechanisms have also been described. Activation of AMPK has been proposed as the main direct mechanism by which metformin inhibits tumor growth. This enzyme influences cellular energy homeostasis, acting as a metabolic master switch that regulates several intracellular systems [24–26].

Oral and pharyngeal cancer, grouped together, are the sixth most common type of cancer in the world [27]. Moreover, the concept of using metformin as a chemopreventive agent to control head and neck carcinogenesis is promising [10,11,28]. Therefore, the aim of this systematic review was to synthesize the available literature of the potential effect of metformin on HNSCC.

Materials and methods

This systematic review was conducted following as closely as possible the PRISMA checklist [29]. We did not register a protocol.

Eligibility criteria

We selected articles that dealt primarily with the effect of metformin on HNSCC located in the lip and/or oral cavity, pharynx, larynx, nasal cavity, or paranasal sinuses [30]. Studies that evaluated individuals of any age that underwent metformin and had HNSCC and compared with patients without treatment or patients that use other kind of treatment for HNSCC (drugs or radiotherapy) were considered. The study design included randomized or non-randomized clinical trials, cohort studies, and case-control studies. Studies were excluded for the following reasons: (1) different target conditions, such as metformin was not used as a coadjuvant in cancer treatment; (2) reviews, letters, personal opinions, book chapters, and conference abstracts; and (3) associations between metformin and HNSCC treatment in experimental studies (in vivo or in vitro animal studies) and clinical trials (phase 1, 2, or 3).

Information sources and search strategy

Studies to be considered for inclusion were identified using a search strategy for each electronic bibliographic database: the Cochrane Library, EMBASE, MEDLINE, LILACS (Literatura Latino Americana em Ciências da Saúde), and PubMed (Appendix 1). The reference list will be checked at the end of search. We conducted all searches across all databases from the beginning dates through June 28, 2014. We managed the references manually and removed duplicate hits.

Study selection

We selected articles for inclusion in 2 phases. In phase 1, 2 authors (D.F.R. and S.T.E.) independently reviewed the titles and abstracts of all the references. These authors selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, 2 authors (D.F.R. and S.T.E.) read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. The same 2 authors independently reviewed all full text articles. Any disagreements in the first or second phases were resolved by discussion and mutual agreement between the 2 authors. If the 2 authors could not reach a consensus, a third author (E.N.S.G.) was involved to make a final decision.

Data collection process and items

One author (D.F.R.) collected the required information from the selected articles: authors, year of publication, country, main objective, study design, source population, setting, register or hospital, median age, samples, referenced group, adjusting variables, results and main conclusions. A second author (S.T.E.) crosschecked all the retrieved information. Again, any disagreements were resolved by discussion and mutual agreement between the 2 authors. The third author (E.N.S.G.) became involved, when required, to make a final decision.

Risk of bias in individual studies

The authors methodologically appraised all of the selected studies according to a modified check list based on the Critical Appraisal Skills Programs (CASP) [31]. No attempt was made to validate the selected criteria. Two reviewers (D.F.R and E.N.S.G.) answered 12 questions that were able to assess the quality of the included studies. In the end, the articles were categorized as “high,” “low,” or “moderate” according to the analysis of each study. Disagreements between the 2 reviewers were resolved by a third reviewer (S.T.E).

Summary measures

Any outcome measurements were considered in this review (risk ratios, odds ratios [OR], or risk differences for dichotomous outcomes; mean differences or standardized mean differences for continuous outcomes).

Synthesis of results

A meta-analysis was planned since the data from the included studies was considered relatively homogeneous.

Risk of bias across studies

Only to be applied if meta-analysis was possible.

Results

Study selection

In phase 1 of study selection, 313 citations were identified across the five electronic databases. After the duplicate articles were removed, only 262 citations reminded. Comprehensive evaluation of the abstracts was completed and 238 articles were excluded, so 24 articles remained after phase 1. No additional studies from the reference lists of the identified studies. From the 24 articles retrieved to conduct a full text review. This process led to exclusion of 21 studies (Appendix 2). In the end, only 3 articles [9,20,21] were selected. A flow chart detailing the process of identification, inclusion, and exclusion of studies is shown in Fig. 1.

Study characteristics

The studies were conducted in 2 different countries: the United States of America [9,20] and Taiwan [21]. All 3 studies were published recently (1 article in 2012 and 2 articles in 2014) and were written in English. All selected articles were prospective cohort studies. A summary of descriptive characteristics for the studies is given in Table 1.

Risk of bias within studies

The reported methodological quality of the 3 included studies is outlined in Table 2. Included studies ranged from moderate to high risk of potential bias. Common weaknesses identified were: failure
to calculate or justify sample sizes, failure to identify and account for exposure variability between control and test groups, failure to identify and account for all confounding variables, insufficient statistical reporting and analysis. The selected studies did not represent the best level of evidence available to answer the clinical question presented in this systematic review, however, as they were retrospective cohorts in design, there is inherently a large risk of bias as certain measures of potential bias were irrelevant to the studies or impossible to fulfill. (Table 2)

**Synthesis of results**

A study by Skinner et al. [20], published in 2012, found a significantly decreased locoregional recurrence rate and improved overall survival in patients treated with metformin compared to controls ($p = 0.04$ and $0.01$, respectively). The 5-year overall survival rate was 87% in patients treated with metformin, compared to 41% in the remaining patients ($p = 0.04$).

A study by Sandulache et al. [9], published in 2014, found that patients taking metformin presented with a greater percentage of early stage tumors (T1 tumors: 48% of patients taking metformin vs. 27% of patients not taking metformin) and less metastasis (N0: 81% of patients taking metformin vs. 50% of patients not taking metformin). Furthermore, 76% of patients taking metformin were alive, compared to 41% for diabetics not on metformin and 51% of non-diabetics. Patients taking metformin had a significantly higher overall survival rate compared to diabetic patients not taking metformin (OR = 3, 95% confidence interval [CI] = 1.04–8.4;
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Main objective</th>
<th>Study design</th>
<th>Source population: setting, register or hospital</th>
<th>Age – years (median age)</th>
<th>Samples</th>
<th>Reference group</th>
<th>Adjusting variables</th>
<th>Results</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Sandulache et al., 2014 [9]</td>
<td>USA</td>
<td>To determine the impact of metformin on the survival of patients with laryngeal cancer</td>
<td>Retrospective cohort study</td>
<td>Patients with diabetes randomized to metformin or usual care in Veterans Affairs Medical Center. Two years of follow-up</td>
<td>63</td>
<td>21/43</td>
<td>Non-metformin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Age, mean, race, smoker, drinker, tumor and nodal stage</td>
<td>Met&lt;sup&gt;+&lt;/sup&gt; presented with a greater percentage of early tumors (T1: 48% met&lt;sup&gt;+&lt;/sup&gt; vs. 27% met/C0) and less regional metastasis (N0: 81% met&lt;sup&gt;+&lt;/sup&gt; vs. 50% met/C0). Met&lt;sup&gt;+&lt;/sup&gt; exhibited a trend toward improved OS compared to non-diabetics ([OR], 2.23; [CI], 0.9–5.6; p = .04)</td>
<td>Patients taking metformin during treatment for laryngeal cancer exhibited improved clinical outcome compared to non-metformin user and even compared to patients that are not diabetic. The clinical data regarding the benefit of metformin is compelling, only a small number of patients were treated with the drug at the time of radiation.</td>
</tr>
<tr>
<td>Skinner et al., 2012 [20]</td>
<td>USA</td>
<td>To investigate the clinical use of metformin for HNSCC and identified and the impact of concurrent metformin (LRR rate, OS rate, TP53 status)</td>
<td>Cohort study</td>
<td>All clinical studies have been approved by the Institutional Review Board of the University of Texas. Patients were evaluated every 2–3 months for 1 year following treatment, every 3–4 months the following year, and every 6 months thereafter</td>
<td>–</td>
<td>10/30</td>
<td>Non-metformin&lt;sup&gt;b&lt;/sup&gt; (Radiation alone)</td>
<td>Tumor and nodal stage, surgical margin status or extracapsular extension, site, gender, smoking history, and TP53 status</td>
<td>Metformin use was significantly associated with decreased LRR (p = 0.04) as well as improved OS (p = 0.01)</td>
<td>The clinical data regarding the benefit of metformin is compelling, only a small number of patients were treated with the drug at the time of radiation.</td>
</tr>
<tr>
<td>Yen et al., 2014 [21]</td>
<td>Taiwan</td>
<td>To identify the potential effects of preventing or suppressing the growth of head and neck cancer tumors in patients with diabetes</td>
<td>Prospective cohort study</td>
<td>Patients with diabetes enrolled in National Health Insurance Program of Taiwan. Follow up: 1996–2011</td>
<td>&lt;40 = 4452, 40–65 = 18,321, &gt;65 = 10,527</td>
<td>195/33,300</td>
<td>Non-metformin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Sex, Age, Average age, Comorbidities, geographic distribution, monthly income, new head and neck cancer</td>
<td>Incidence of head and neck cancer that was 0.64 times lower in Met&lt;sup&gt;+&lt;/sup&gt; and the most prevalent site was the oral cavity (53.6% of all head and neck cancers). Met&lt;sup&gt;+&lt;/sup&gt; patients &gt; 65 had the most prominent cancer-risk reduction benefits (IRR = 0.53; p &lt; 0.01)</td>
<td>Patients with newly diagnosed diabetes and treated with metformin had a 0.66 times lower incidence of developing head and neck cancer.</td>
</tr>
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</table>

Abbreviation: IRR = incidence rate ratio, LRR = locoregional recurrence, OS = overall survival, TP53 = tumor protein 53.

<sup>a</sup> A retrospectively reviewed patients with diagnosis of laryngeal squamous cell carcinoma were checked for the impact of metformin on the disease-free survival and overall survival.

<sup>b</sup> A cohort of patients treated with postoperative radiation therapy (PORT) for head and neck squamous cell carcinoma was identified and the impact of concurrent metformin use was investigated.

<sup>c</sup> This cohort study, involving two control groups: metformin and the other insulin-based therapies (non-metformin). The effect of metformin on the overall risk and the specific types and sites of head and neck cancer in patients with diabetes.
significant associations were found between disease-free survival and disease subsite, and patients who were taking metformin showed trends toward improved survival compared to non-diabetics and diabetics not taking metformin (OR = 1.77 and 1.99, respectively). A study by Yen et al. [21], published in 2014, found that the incidence of head and neck cancer was 0.64 times lower in a cohort of patients taking metformin compared to patients not taking metformin ($p < 0.01$). There were significantly lower incidence rates of head and neck cancer in subgroups of patients taking metformin who were 40–65 years old or >65 years old compared to patients not taking metformin in the same age subgroups (incidence ratio rate = 0.70 and 0.53, respectively; $p < 0.01$ for both). In the cohort of patients taking metformin, the incidence of nasopharyngeal cancer was 0.08% (adjusted hazard ratio = 0.50, 95% CI = 0.31–0.80) and the incidence of oropharyngeal cancer was 0.03% (hazard ratio = 0.36, 95% CI = 0.17–0.74). The disease-free survival of patients without head and neck cancer was significantly higher in the metformin cohort vs. the cohort of patients not taking metformin. Patients with diabetes who did or did not take metformin who subsequently developed head and neck cancer did not have significantly different overall survival.

Risk of bias across studies

The selected studies used similar methods, which reduced the possibility of misinterpretation. The studies selected for this analysis were considered to be relatively homogeneous, but they did not have compatible data that would allow a meta-analysis.

Discussion

Summary of evidence

Oral and pharyngeal cancer is a serious and growing problem in many parts of the globe [27]. There is a wide geographical variation in the incidence of this cancer. The areas characterized by high incidence rates for oral cancer are found in the South and Southeast Asia (e.g. Sri Lanka, India, Pakistan and Taiwan), parts of Western (e.g. France) and Eastern Europe (e.g. Hungary, Slovakia and Slovenia), parts of Latin America and the Caribbean (e.g. Brazil, Uruguay and Puerto Rico) and in Pacific regions [32]. The most important etiological factors for these cancers are cigarette smoking and alcohol consumption [33]. Although high-risk human papillomavirus (HPV), particularly HPV-16, is an independent risk factor for a subset of HNSCC patients, and there is a strong association between HPV infection and tonsil carcinoma [34]. Advanced stage cancers are often treated with combination therapy, which includes surgical resection followed by adjuvant radiation with or without chemotherapy [35]. All therapeutics are associated with many adverse effects that reduce quality of life. Therefore, identification of new effective therapies that are less cytotoxic is very important.

Metformin, which is widely used for patients with type 2 diabetes, may reduce cancer risk [36]. A comprehensive systematic review and meta-analysis performed by Decensi et al. [3] in 2010 showed that metformin was associated with a 30% reduction in cancer incidence in individuals with type 2 diabetes compared to patients receiving other diabetic treatments. The authors also observed promising trends in overall cancer mortality for pancreatic and hepatocellular cancer patients and, to a lesser extent, for colon, breast, and prostate cancer patients. Metformin is an old drug that is now gaining increasing attention as an anticancer agent [37].

It is thought that metformin exerts anticancer effects through inhibition of insulin and mammalian target of rapamycin (mTOR) pathways [38]. Studies have found that mTOR plays a key role in the control of cell growth, proliferation, and metabolism and mediates the phosphoinositide 3-kinase/Akt signaling pathway, which is frequently deregulated in human cancers [39]. AMPK activation results in downregulation of mTOR complex 1 (mTORC1), which is 1 of the 2 signaling complexes formed by mTOR and the insulin-like growth factor 1/Akt pathway [40]. Metformin primarily works by blocking a step in the aerobic production of the cellular energy molecule adenosine triphosphate, which activates a signaling pathway that involves sensing of cellular energetic stress by the enzyme AMPK. Though metformin activates AMPK, it has been shown to work independently of this enzyme [41,42].

Recent discoveries involving 2 tumor suppressor proteins, liver kinase B1 (LKB1) and ataxia telangiectasia mutated (ATM), help explain the mechanism by which metformin mediates activation of AMPK [43,44]. LKB1 is a well-recognized tumor suppressor that functions as an upstream regulator of AMPK. Its ability to activate AMPK might explain, at least in part, the ability of LKB1 to act as a tumor suppressor. LKB1 may also be an upstream kinase for other members of the AMPK-like subfamily of protein kinases [45]. Similarly to LKB1, ATM is also a tumor suppressor protein. ATM is involved in DNA repair and cell cycle control. In response to metformin, ATM may phosphorylate LKB1, therefore mediating the phosphorylation that activates AMPK. Alternatively, ATM might activate AMPK independently of LKB1, or reduce blood glucose levels through pathways entirely independent of AMPK [43].

In this systematic review, we investigated the effects and the potential association of metformin with HNSCC. Several studies have provided evidence about this relationship, but most of them

Table 2

<table>
<thead>
<tr>
<th>Methodological appraisal of selected studies based on a modified critical appraisal skills program checklist for cohort studies.</th>
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<tr>
<td>1. Did the study address a clearly focused question?</td>
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<tr>
<td>2. Did the authors use an appropriate method to answer the question?</td>
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<td>3. Was the cohort recruited in an acceptable way?</td>
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<td>4. Was the exposure accurately measured to minimize bias?</td>
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<tr>
<td>5. Was the outcome accurately measured to minimize bias?</td>
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<tr>
<td>6. A. Have the authors identified all important confounding factors?</td>
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<tr>
<td>B. Have they taken account of the confounding factors in the design and/or analysis?</td>
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<tr>
<td>7. A. Was the follow up of subjects complete enough?</td>
</tr>
<tr>
<td>B. Was the follow up of subjects long enough?</td>
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<tr>
<td>8. Is there a clearly defined result of the study?</td>
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<td>9. How precise are the results?</td>
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<td>10. Do you believe the results?</td>
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<tr>
<td>11. Can the results be applied to the local population?</td>
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<tr>
<td>12. Do the results of this study fit with other available evidence?</td>
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<tr>
<td>13. Associated risk of potential bias</td>
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</table>

Abbreviations: Y = Yes; N = No; CT = Cannot tell; P = Precise; NP = Not Precise; SP = Somewhat Precise; L = Low; M = Moderate; H = High.

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have been in vitro or in vivo animal studies [45,46]. We found only 3 prospective cohort studies for inclusion in this review, and all of them supported an association between metformin and decreased risk of HNSCC [9,20,21]. These studies demonstrated the effects of metformin on the treatment of head and neck cancer. The main analysis based on these 3 cohort studies showed that individuals taking metformin had decreased rates of locoregional recurrence and neck metastasis and improved overall survival and disease-free survival rates compared to individuals not taking metformin (control group). Furthermore, the incidence of HNSCC was lower in individuals taking metformin vs. those not taking metformin.

Overall survival (OS) was defined by three cohort studies included in this review, but with some different peculiarities. Skinner et al. [20] have reported the improvement in OS and 5 years-OS rate in the patients who took metformin. This cohort study was made in patients with head and neck cancer treated with postoperative radiation therapy who used metformin at the time of radiation. No information was reported if they were diabetic or not. The study published by Sandulache et al. [9] examined the OS in three groups: the first group demonstrated the percentage of OS at 2 years in glottic or supraglottic tumors (p = 0.01). The second group examined the OS in the proportion of diabetic patients survivors who were taking metformin or not (p = 0.05). Finally, at the group 3, the OS was measured through the odds ratio of diabetic patients taking metformin or not (p = 0.09 and 0.04, respectively). Yen et al. [21] built a large retrospective cohort study, the incidence of head and neck cancer was 0.64 times lower in the metformin user than in the metformin non-user (p < 0.01). There was no significant difference in overall survival between patients with diabetes in the metformin user and metformin non-user who subsequently developed head and neck cancer (p = 0.11). However, the overall survival for patients with diabetes but without head and neck cancer was significantly higher in the metformin user than those in the metformin non-user (p < 0.01).

Two other clinical studies of the association between metformin and HNSCC were not included in this review: a phase 1 clinical trial and a retrospective case-control study [47,48]. The phase 1 study included an analysis of temsirolimus and metformin in advanced solid tumors. That study included only 1 HNSCC patient, and that patient experienced a partial response [47]. The case-control study, which was performed in the United Kingdom, analyzed the relationship between antidiabetic drugs and the risk of head and neck cancer [48]. The authors concluded that antidiabetic drugs were not associated with HNSCC risk, but their data suggested that long-term metformin use had a protective effect against laryngeal cancer.

We identified 11 articles with experimental studies that were in vitro and in vivo animal studies that analyzed the effect of metformin in HNSCC [20,28,45,46,49–55] 2 of these studies presented the most important and complete results. Vitale-Cross et al. [46] showed that metformin reduced the growth of HNSCC cells and diminished their mTORC1 activity by both AMPK-dependent and AMPK-independent mechanisms. They also found that metformin specifically inhibited mTORC1 in the basal proliferating epithelial layer of oral premalignant lesions. Remarkably, the authors found that metformin prevented the development of HNSCC. In the same year (2012), Sandulache et al. [52] demonstrated that inhibition of respiration by metformin increased glycolytic dependence in wild-type TP53 expressing cells and potentiated the effects of glycolytic inhibition on radiation toxicity. These two works showed the potential clinical benefits of using metformin as a targeted chemopreventive and chemotherapy agent in the control of HNSCC developing and treatment.

In summary, this is the first systematic review of the effects of metformin on HNSCC treatment, and the first review to present evidence of a positive association between decrease of HNSCC and metformin use. Although Decensi et al. [3] (2010) performed a systematic review and meta-analysis of metformin and cancer risk in diabetic patients, they did not analyze head and neck cancer patients.

Currently available evidence suggests an association between metformin and HNSCC, although there are only a few studies that confirm that statement. Metformin appears to improve the overall survival of HNSCC patients.

**Limitations**

Some methodological limitations of this review should be considered. First, only 3 articles met the inclusion criteria, maybe because the subject of this review is very new. Of 313 identified citations, only 3 studies met the inclusion criteria and were used in the qualitative analysis. Furthermore, all of the included studies were very recent (from 2012 and 2014) demonstrating that use of metformin in HNSCC is a new concept.

It should be noted that, according to the CASP [31], the authors have not identified all important confounding factors. This systematic error can compromise the internal validity of the study. The failure to not include in the study the variables most relevant to the analysis and association in question leads to a bias of confounding. Another limitation is an insufficient reporting of losses of individuals throughout the research to permit judgment. We suggest that strong future research could eliminate these risks of bias.

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**Conflict of interest statement**

None declared.

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**Appendix A. Supplementary material**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2015.01.007.

**References**


