A systematic literature review of the HPV prevalence in locally-regionally advanced (LA) and recurrent/metastatic (RM) head and neck cancers through the last decade: The ‘ALARM’ study

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Abstract

**Background:** ‘ALARM’ is a systematic review of available literature aiming to provide updated information on the prevalence of Human Papillomavirus (HPV) in locally-regionally advanced (LA) and recurrent/metastatic (RM) head and neck cancer (HNC) worldwide.

**Methods:** Electronic searches were conducted on clinicaltrials.gov, MEDLINE (via Pubmed), Embase and ASCO/ESMO journals of congresses for interventional studies (IS; phase I-III trials) as well as MEDLINE and Embase for non-interventional studies (NIS) of LA/RM HNC published between 01Jan2010 and 31Dec2020. Criteria for study selection included: availability of HPV prevalence data for patients with LA/RM HNC, patient enrollment from 01Jan2010 onwards, and oropharyngeal cancer (OPC) included among HNC types. HPV prevalence per study was calculated as proportion of HPV-positive (HPV+) over total number of HNC enrolled patients. For overall HPV prevalence across studies, mean of reported HPV prevalence rates across studies and pooled estimate, i.e., sum of all HPV+ patients over sum of all HNC patients enrolled, were assessed.

**Results:** Eighty-one studies (62 IS; 19 NIS) were included in this evidence synthesis, representing 9607 LA/RM HNC cases, with an overall mean (pooled) HPV prevalence of 32.6% (25.1%). HPV prevalence was 44.7% (44.0%) in LA and 24.3% (18.6%) in RM. Among 2714 LA/RM OPC patients from 52 studies with available data, the mean (pooled) value was 55.8% (50.7%). The majority of published HPV prevalence data were derived from countries in Northern America and Europe, with overall HPV prevalence of 46.0% (42.1%) and 24.7% (25.3%) across studies conducted exclusively in these geographic regions, respectively. Mean (pooled) HPV prevalence in Northern Europe was 31.9% (63.1%), numerically higher than the European average. A “p16-based” assay was the most frequently reported HPV detection methodology (58.0%).

**Conclusion:** Over the last decade, at least one quarter of LA/RM HNC and half of OPC cases studied in IS and NIS were HPV+, with variation across disease stages and geographic regions. This alarming burden is consistent with a potential implication of HPV in the pathogenesis of at least a subgroup of HNC. The observed rates underscore the relevance of HPV testing and prophylaxis to the prevention and management of these cancers.

**PROSPERO Number:** CRD42021256876

**Background**

Head and neck cancer (HNC) accounted for approximately 5% of new cancer cases and cancer-related deaths worldwide in 2020, with an estimated annual burden of 931,931 incident cases and 467,125 deaths [1]. Most HNCs arise from the squamous epithelium of the oral cavity, oropharynx (OPX), larynx and hypopharynx, collectively referred to as head and neck squamous cell carcinoma (HNSCC) [2]. HNSCC incidence varies across regions, generally reflecting the diverse epidemiology of risk factors such as consumption of tobacco, alcohol, and areca nut [2]. Another cause of cancers developed in the head
and neck (HN) is Human papillomavirus (HPV) infection [3, 4]. Among HNC subtypes, HPV has been most frequently associated with oropharyngeal squamous cell carcinoma (OPSCC) [5-7] and is considered to account to a great extent for the increasing incidence of oropharyngeal cancer (OPC) in several high-income countries over the past decades [8-10].

Besides its etiological role, HPV is also recognized as a prognostic factor in HNC and has been correlated with better survival outcomes and response to treatment [11-13]. Consistently, differences in the underlying pathogenetic mechanisms between HPV-positive (HPV+) and HPV-unrelated HN tumors are also implied by their distinct clinical, immunological and molecular characteristics [14, 15]. This highlights the clinical utility of HPV testing in HNC, which, in the absence of diagnostic tests with regulatory approval for use in HNC, is performed by various methodologies [16]. Each of the available techniques has specific limitations; thus, a combined approach using multiple protein or nucleic acid-based methods has been suggested for optimal detection of potentially causative HPV [16, 17]. Testing of p16 is recommended by the European Head and Neck Society/European Society for Medical Oncology/European Society for Radiotherapy and Oncology, the National Comprehensive Cancer Network, the College of American Pathologists, and the American Society of Clinical Oncology guidelines as a surrogate HPV biomarker in OPSCC management [12, 13, 18-20]. Nevertheless, routine examination for HPV presence for other HNC types is not warranted [18].

Ongoing research examines HPV+ HNC patients as a special group for particular therapies, mainly immunotherapy, including immunomodulatory vaccines and auto-specific T-cell transfusion [12, 21, 22]. Current guidelines recommend HPV testing for all patients diagnosed with OPC, in order to determine clinical stage and subsequently make treatment decisions [23, 24]. In most other HNC subtypes, though, HPV status has not been incorporated in the therapeutic decision algorithm, and treatment selection is mainly guided by disease stage [12]. For patients with limited or early stage HNSCC, current treatment modalities are potentially curative, while for recurrent and/or metastatic (RM) HNSCC, treatment is complex, prognosis is poor and the burden on quality of life and productivity can be substantial [25, 26]. Importantly, more than 50% of HNSCC patients present with locally-regionally advanced (LA) or metastatic HNSCC at diagnosis, and recurrence rate for early stage and LA HNSCC is high [21, 26, 27]. The proportion of those patients who are HPV+ remains unknown, as available data are not only outdated, but also mainly refer to the totality of HNCs, not distinguishing the disease by stage [5, 28-31]. Besides therapeutic developments for HNC, available HPV prophylactic vaccines have shown preliminary efficacy against HN infections, opening an opportunity for primary prevention of the specific cancers [32-34], with this potential being investigated in ongoing Phase III clinical trials [35, 36].

Given the challenges in the management of LA and RM HNC, and the increasing incidence of HPV-associated HNC, updated information on the HPV prevalence is essential, with possible implications for preventive interventions. This systematic literature review (SLR) aimed to enhance understanding of the current HPV prevalence in LA and RM HNC based on evidence from the last decade (2010-2020). Additionally, HPV prevalence in LA and RM OPC, geographic distribution of HPV prevalence, and level of homogeneity between HPV testing methodologies were explored.
The primary objective of this SLR was to examine the prevalence of HPV in LA and/or RM HNC through the last decade as reported in IS and NIS and descriptively present our findings. The secondary objective of this study was to understand the prevalence HPV in OPC in the LA and RM setting, since OPX is the primary HN sub-site where HPV-related carcinomas develop. As exploratory objectives, the geographic distribution of HPV prevalence and level of homogeneity between HPV testing methodologies were examined.

**Methods**

This SLR was conducted and outcomes were reported in accordance with PRISMA guidelines (see Additional file 1). The study protocol was registered with PROSPERO, the international prospective register of systematic reviews (registration number: CRD42021256876) and is publicly available.

**Information sources and search strategy**

Identification of studies in LA and RM HNC was performed separately for IS (i.e., Phase I-III trials) and NIS. For IS, electronic searches were conducted on Clinicaltrials.gov using the keywords "Head and Neck" in combination with “Local”, “Regional”, “Advanced”, “Recurrent”, or “Metastatic” for Phase 1, 2 and 3 studies starting on or after 01 January 2010 until 31 December 2020. The corresponding National Clinical Trial (NCT) numbers were used to search PubMed and Embase databases as well as ASCO/ESMO journals of congresses for related articles and/or abstracts with available results. For NIS, MEDLINE via Pubmed and Embase databases were searched for related publications using Medical subject heading terms and keywords developed for disease (HNC), outcome of interest (HPV), relevant cancer type (OPC) to expand search results, disease stage (local, regional, recurrent, metastatic, advanced), and study design (epidemiology, real-life, non-interventional, observational). The searches were restricted using embedded filters to publications from the last 10 years (January 01, 2010 – December 31, 2020). They were also restricted to articles published in English language and to studies conducted in 'humans', while congress abstracts and reviews were excluded. The detailed search strategy including search strings and resulting number of hits is provided in Additional file 2. Electronic searches for both IS and NIS were completed on March 19, 2021.

**Study selection**

Studies were selected based on prespecified eligibility criteria designed according to the PICOTS (population, intervention, comparisons, outcome, time, study design) framework. Specifically, studies were selected if patients with RM and/or LA HNC had participated, OPX was included among the HN sub-sites and HPV status of cancer was available, even if only the OPC subpopulation had been tested for HPV (Population). There were no restrictions as to the intervention and comparator of the study, as long as they were intended for disease treatment and not management of safety events of previous therapies (Intervention; Comparator). Only studies with available results on HPV prevalence (i.e., prevalence of HPV related HNC), and/or on the number of HPV+ HNC patients, allowing the calculation of corresponding prevalence were selected (Outcome). Studies initiating enrollment of participants prior to 01 January
2010 were excluded (Time). IS of any design were included as long as there was no prerequisite regarding the proportion of patients per HN sub-site that needed to be enrolled and NIS of any design and direction of temporal observation (Study design). Articles published in a language other than English were excluded. Finally, only original, peer reviewed articles published in scientific journals were selected, with the exception of abstracts published in ASCO/ESMO congress abstract books for IS which were also included. Non-original studies such as literature reviews were excluded. For IS for which full manuscripts were pending and corresponding abstracts in ASCO/ESMO congress abstract books were available, selection was based on information included in those abstracts. Study design and results captured in Clinicaltrials.gov were utilized cumulatively with manuscripts and/or abstracts available in ASCO/ESMO journals of congresses for selecting IS.

For study selection, an initial screening of titles/abstracts was performed against each eligibility criterion followed by examination of the full-text article if a definite decision could not be made. Study review and selection was performed by two reviewers working independently. The decisions of the reviewers were compared and any conflicts were resolved by a third reviewer.

**Data extraction and analysis**

Data from each of the studies that met the pre-defined eligibility criteria were extracted and cross-checked by two independent reviewers with respect to the following variables: study design, country, study period, study population including disease stage, age, HPV status detection methodology, sub-sites where HPV status was assessed (any included site or only OPX), number of LA and/or RM HNC patients enrolled ("N\text{\textsubscript{HNC enrolled}}"), number of HPV+ LA and/or RM HNC patients ("N\text{\textsubscript{HNC HPV+}}") and/or HPV prevalence (%) in LA and/or RM HNC as defined by the author, number of HPV- LA and/or RM HNC patients ("N\text{\textsubscript{HNC HPV-}}") to reflect missing HPV status data, number of LA and/or RM OPC patients enrolled ("N\text{\textsubscript{OPC enrolled}}"), number of HPV+ LA and/or RM OPC patients ("N\text{\textsubscript{OPC HPV+}}") and/or HPV prevalence (%) in LA and/or RM OPC as defined by the author.

The primary outcome of HPV prevalence in LA and RM HNC was calculated as the proportion (%) of "N\text{\textsubscript{HNC HPV+}}" over "N\text{\textsubscript{HNC enrolled}}". Similarly, OPC fraction among LA and/or RM HNC patients was calculated as the proportion (%) of "N\text{\textsubscript{OPC enrolled}}" over "N\text{\textsubscript{HNC enrolled}}", as available. For the secondary outcome of HPV prevalence in LA and/or RM OPC, HPV prevalence among selected HNC studies was calculated as the proportion (%) of "N\text{\textsubscript{OPC HPV+}}" over "N\text{\textsubscript{OPC enrolled}}", as available. Hence, the estimated prevalence of HPV in HNC and OPC represented the minimum number of HPV+ patients in the pool of HNC or OPC patients enrolled in each study, respectively, since patients with no available data on HPV status were also included in the denominators ("N\text{\textsubscript{HNC enrolled}}" and "N\text{\textsubscript{OPC enrolled}}").

Data extracted from selected studies was organized in summary tables and figures using standard Microsoft Excel\textsuperscript{\textregistered} functions and descriptively analyzed. No inferential statistical analysis was conducted. Studies were categorized by design in the subgroups of IS or NIS and by HNC disease stage as either LA, RM or Other, the latter of which included LA and/or RM stage as defined by the author with no further
specification or both LA and RM. Studies were also grouped based on geographic region as defined by the International Agency for Research on Cancer [37]. In estimating the prevalence of HPV or OPC fraction across HNC studies overall and per the above-described subgroups, mean and median proportion (%) of HPV+ or OPC patients across studies in each subgroup were calculated. HPV prevalence and OPC fraction overall and per subgroup were also estimated as pooled prevalence, i.e., as proportion (%) of the sum of “N_{HNC or OPC} HPV+” or “N_{OPC} enrolled” across studies, respectively, over the sum of “N_{HNC or OPC} enrolled” across studies.

**Risk of bias**

Taking into account the narrative nature of this SLR and that prevalence of HPV pertains to a baseline patient characteristic, study outcomes are not expected to be affected by the design, conduct, or the statistical power in the results of each included study. To reduce bias with respect to generalizability of HPV prevalence outcomes, during the study selection process, studies with a prespecified patient eligibility criterion regarding HPV status (e.g. HPV+ patients only) or associated with HPV status (e.g. OPC patients only) were excluded. No restrictions were applied with respect to HPV detection methodologies as distribution of different methodologies was an exploratory outcome of interest. Last, the effect of sample size on the primary outcome was examined by visual inspection of the distribution of studies around the overall prevalence of HPV (mean, median, pooled) in a plot of sample size (“N_{HNC enrolled}” against HPV prevalence.

**Results**

**Literature search results and characteristics of included studies**

The search strategy identified a total of 2618 records, of which 855 corresponded to IS and 1763 to NIS. Following removal of duplicate records, records with lack of published articles and/or congress abstracts, and studies not fulfilling the PICOTS criteria, a total of 62 IS and 19 NIS were included in the evidence synthesis (Fig. 1).

*Figure 1 to be inserted here*

All included studies (N=81) provided an HPV prevalence of LA and/or RM HNC captured between 1st of January 2010 and 31st of December 2020 and were used for addressing the primary study objective. Of the included studies, 43 IS and 9 NIS reported data on prevalence of HPV specifically for OPC, and were thus used to address the secondary outcome of interest.

Characteristics of the studies included in the evidence synthesis and outcomes of interest derived from each study are presented in Table 1 and Additional file 3. Of the IS, 42 (67.7%) were single-arm and 20 (32.3%) were multi-arm; of the latter 17 (27.5%) were randomized. Of the NIS, 13 (68.4%) were retrospective, two (10.5%) were prospective cohort studies, another two (10.5%) were cross-sectional studies, and the remaining two were of a mixed cohort study design (10.5%). Sixty-one (75.3%) of the
included studies were single-country studies conducted in Northern America, Europe and Asia, five (6.2%) were multi-country, single-continent studies and the remaining 15 (18.5%) were multi-country, multi-continent studies. Overall, the selected studies were conducted in 51 countries distributed in all continents (Table 1).

[Table 1 to be inserted here]

According to the disease stage of the included population, 31 (38.3%) studies were classified as LA HNC, 45 (55.6%) as RM HNC, and the remaining five (6.2%) as Other. The selected studies cumulatively included 9607 LA and/or RM HNC patients. Median patient age ranged from 47 to 78 years across studies (Table 1).

**Prevalence of HPV in HNC**

The proportion of HPV+ patients over HNC patients enrolled in each study, i.e., HPV prevalence per study, and overall HPV prevalence are presented in Fig. 2 and Table 2. The prevalence of HPV in HNC varied considerably across studies, ranging from 2.9% to 100.0%, with a mean value of 32.6%. To account for variations in sample size of each included study, the pooled HPV prevalence was also calculated across studies and was found to be 25.1%. In the IS (n=62), the prevalence of HPV ranged from 2.9% to 100.0%, with a mean value of 34.5% and a pooled HPV prevalence of 27.1%; while in NIS (n=19) the prevalence of HPV ranged from 3.3% to 47.6%, with a mean value of 26.5% and a pooled HPV prevalence of 19.4%. In a further analysis by disease stage and regardless of study design, prevalence of HPV was examined in the subgroups of patients with LA and RM, as these represent distinct disease phenotypes with different management approaches and survival outcomes. In LA HNC studies (n=31) HPV prevalence ranged from 10.3% to 100.0% (mean 44.7%), with a pooled fraction of 44.0%, while in RM HNC studies (n=45), HPV prevalence ranged from 2.9% to 55.6% (mean 24.3%), with a pooled fraction of 18.6%. Interestingly, in about one sixth of the studies, the prevalence of HPV exceeded 50.0%, indicating that the infection can account for a substantial proportion of HNC in certain patient populations.

[Figure 2 to be inserted here]

Table 2

<table>
<thead>
<tr>
<th>Study Type</th>
<th>HPV Prevalence in LA and RM HNC and OPC, and OPC Fraction, per Design and Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV prevalence in LA and RM HNC and OPC, and OPC fraction, per design and stage</td>
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</table>
### HPV prevalence in HNC

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<th></th>
<th>n_{studies}</th>
<th>Mean</th>
<th>Median</th>
<th>Range (min, max)</th>
<th>N_{HNC pts enrolled}</th>
<th>N_{HPV+ HNC pts}</th>
<th>Pooled</th>
</tr>
</thead>
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<td><strong>Interventional Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>26</td>
<td>47.6%</td>
<td>43.6%</td>
<td>10.3% - 100.0%</td>
<td>1624</td>
<td>812</td>
<td>50.0%</td>
</tr>
<tr>
<td>RM</td>
<td>34</td>
<td>25.2%</td>
<td>23.7%</td>
<td>2.9% - 55.6%</td>
<td>5484</td>
<td>1119</td>
<td>20.4%</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>3.1% - 40.0%</td>
<td>42</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>62</strong></td>
<td><strong>34.5%</strong></td>
<td><strong>30.4%</strong></td>
<td><strong>2.9% - 100.0%</strong></td>
<td><strong>7150</strong></td>
<td><strong>1936</strong></td>
<td><strong>27.1%</strong></td>
</tr>
<tr>
<td><strong>Non-interventional Studies</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>5</td>
<td>29.5%</td>
<td>32.7%</td>
<td>16.0% - 37.4%</td>
<td>615</td>
<td>173</td>
<td>28.1%</td>
</tr>
<tr>
<td>RM</td>
<td>11</td>
<td>21.4%</td>
<td>21.5%</td>
<td>3.3% - 44.4%</td>
<td>1551</td>
<td>189</td>
<td>12.2%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>30.3% - 47.6%</td>
<td>291</td>
<td>114</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>19</strong></td>
<td><strong>26.5%</strong></td>
<td><strong>28.6%</strong></td>
<td><strong>3.3% - 47.6%</strong></td>
<td><strong>2457</strong></td>
<td><strong>476</strong></td>
<td><strong>19.4%</strong></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LA</td>
<td>31</td>
<td>44.7%</td>
<td>37.4%</td>
<td>10.3% - 100.0%</td>
<td>2239</td>
<td>985</td>
<td>44.0%</td>
</tr>
<tr>
<td>RM</td>
<td>45</td>
<td>24.3%</td>
<td>23.4%</td>
<td>2.9% - 55.6%</td>
<td>7035</td>
<td>1308</td>
<td>18.6%</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>3.1% - 47.6%</td>
<td>333</td>
<td>119</td>
<td>NA</td>
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<tr>
<td><strong>Overall</strong></td>
<td><strong>81</strong></td>
<td><strong>32.6%</strong></td>
<td><strong>29.6%</strong></td>
<td><strong>2.9% - 100.0%</strong></td>
<td><strong>9607</strong></td>
<td><strong>2412</strong></td>
<td><strong>25.1%</strong></td>
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</table>

### OPC fraction in HNC

<table>
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<tr>
<th></th>
<th>n_{studies}</th>
<th>Mean</th>
<th>Median</th>
<th>Range (min, max)</th>
<th>N_{HNC pts enrolled}</th>
<th>N_{OPC pts enrolled}</th>
<th>Pooled</th>
</tr>
</thead>
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<td><strong>Interventional Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>25</td>
<td>65.8%</td>
<td>67.8%</td>
<td>37.9% -</td>
<td>1585</td>
<td>1090</td>
<td>68.8%</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Range (min, max)</td>
<td>N&lt;sub&gt;OPC pts&lt;/sub&gt; enrolled</td>
<td>N&lt;sub&gt;HPV+ OPC pts&lt;/sub&gt;</td>
<td>Pooled</td>
<td></td>
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<tr>
<td><strong>Overall</strong></td>
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<tr>
<td><strong>Interventional Studies</strong></td>
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<td></td>
</tr>
<tr>
<td>LA</td>
<td>64.9%</td>
<td>70.0%</td>
<td>24.0% - 100.0%</td>
<td>829</td>
<td>557</td>
<td>67.2%</td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>50.4%</td>
<td>52.8%</td>
<td>18.9% - 88.9%</td>
<td>1436</td>
<td>643</td>
<td>44.8%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
<td>4</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>57.8%</td>
<td>59.2%</td>
<td>18.9% - 100.0%</td>
<td>2273</td>
<td>1204</td>
<td>53.0%</td>
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<td><strong>Non-interventional Studies</strong></td>
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<td></td>
</tr>
<tr>
<td>LA</td>
<td>62.5%</td>
<td>72.0%</td>
<td>35.7% -</td>
<td>98</td>
<td>70</td>
<td>71.4%</td>
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</table>
Prevalence of HPV in OPC

Given the increasing incidence of OPC reported previously, and the proposed contribution of HPV to this increase, the proportion of HPV+ patients was also assessed among the subgroup of patients with LA and/or RM OPC in the studies of the evidence synthesis. The proportion of patients with OPC among those with LA and/or RM HNC, referred to as the OPC fraction, is presented in Fig. 2 and summarized in Table 2. The OPC fraction among studies with available HN sub-site proportions (n=69) ranged from 4.3% to 100.0%, with a mean of 51.4%. Based on pooled data, of the 8213 LA and/or RM HNC patients, 3904 had OPC, resulting in a pooled fraction of 47.5%. The mean (and pooled) fractions in IS (n=53; range 4.3% to 100.0%) and NIS (n=16; range 23.0% to 76.8%) were 52.0% (47.2%) and 49.4% (48.3%), respectively. Upon analysis by disease stage, the mean (and pooled) OPC fraction was 64.9% (67.1%) in LA HNC studies (n=30; range 37.9% to 100.0%) and 38.5% (39.5%) in RM HNC studies (n=35; ranging from 4.3% to 75.0%) (Table 2).

HPV prevalence in LA and/or RM OPC was available for 52 studies and ranged from 14.3% to 100.0%, with a mean value of 55.8% and a pooled fraction of 50.7%. HPV prevalence in LA and/or RM OPC ranged from 18.9% to 100.0% in IS, and from 14.3% to 82.4% in NIS with available data, with respective mean (and pooled) rates of 57.8% (53.0%) and 46.2% (39.0%). Upon analysis by disease stage, the mean (and pooled) HPV prevalence in LA OPC studies was 64.6% (67.6%), ranging from 24.0% to 100.0%, while in RM OPC studies it was 46.1% (40.7%), ranging from 14.3% to 88.9% (Table 2).
Geographic distribution of HPV prevalence

To gain insight into the availability of published data on the prevalence of HPV across geographical regions, as well as to qualitatively assess potential variations among countries or regions, the geographic distribution of HPV prevalence was addressed as an exploratory objective. Of the 53 countries where the studies included in the analysis of the present review were conducted, 29 were located in Europe, 13 in Asia (including Taiwan and Hong Kong and Taiwan as territories of China), 5 in Southern America, 2 countries each in Northern America and Africa, and 1 country each in Central America and Oceania. The following were included in more than ten studies each: United States of America (USA) (44 studies), Germany (16), France (15), Spain (13), Italy (12), Belgium (11), Canada (11), and the United Kingdom (11) (Table 1). Thus, although studies with published data on HPV prevalence in LA and RM HNC through the last decade display a wide geographic distribution, several geographic regions are underrepresented in the literature and further studies would be needed to more accurately capture the global epidemiological picture.

The prevalence of HPV in LA and RM HNC and OPC is summarized per geographical region in Table 3 and in Additional file 4, while it is also presented per disease stage in Additional file 5. Based on the geographic regions included, studies can be broadly divided into those conducted in a single continent and those conducted in multiple continents. In single-continent HNC studies conducted in Northern America (n=34), the prevalence of HPV ranged from 8.3% to 100.0%; in Europe (n=29) from 3.1% to 75.9%; in Eastern Asia (n=3) from 10.3% to 33.3%. The mean (and pooled) prevalence of HPV among single-continent studies conducted in Northern America was 46.0% (42.1%), followed by 24.7% (25.3%) in Europe, and 20.1% (15.7%) in Eastern Asia. Studies conducted in Europe were also grouped into those conducted in Northern Europe, Southern Europe, Western Europe, or Multiple European regions (including Western, Central/Eastern, and Southern Europe) based on data availability. The respective mean (and pooled) HPV prevalence was 31.9% (63.1%), 23.2% (26.4%), 24.3% (23.5%), and 17.2% (9.4%). In studies conducted in multiple continents (n=15) the prevalence of HPV ranged from 2.9% to 30.4%, and the mean (and pooled) prevalence of HPV was 19.8% (18.4%).

Table 3 HPV prevalence in LA and RM HNC and OPC, and OPC fraction, per geographic region
### HPV prevalence in HNC

<table>
<thead>
<tr>
<th>Region</th>
<th>n\textsubscript{studies}</th>
<th>Mean (%)</th>
<th>Median (%)</th>
<th>Range (min, max)</th>
<th>N\textsubscript{HNC pts enrolled}</th>
<th>N\textsubscript{HPV+ HNC pts}</th>
<th>Pooled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern America</td>
<td>34</td>
<td>46.0%</td>
<td>43.6%</td>
<td>8.3% - 100.0%</td>
<td>1923</td>
<td>809</td>
<td>42.1%</td>
</tr>
<tr>
<td>Europe</td>
<td>29</td>
<td>24.7%</td>
<td>22.7%</td>
<td>3.1% - 75.9%</td>
<td>2804</td>
<td>710</td>
<td>25.3%</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>5</td>
<td>31.9%</td>
<td>20.7%</td>
<td>11.5% - 75.9%</td>
<td>377</td>
<td>238</td>
<td>63.1%</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>4</td>
<td>23.2%</td>
<td>26.6%</td>
<td>3.3% - 36.4%</td>
<td>284</td>
<td>75</td>
<td>26.4%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>17</td>
<td>24.3%</td>
<td>25.0%</td>
<td>3.1% - 47.6%</td>
<td>1381</td>
<td>325</td>
<td>23.5%</td>
</tr>
<tr>
<td>Multiple European regions\textdagger</td>
<td>3</td>
<td>17.2%</td>
<td>13.3%</td>
<td>6.8% - 31.6%</td>
<td>762</td>
<td>72</td>
<td>9.4%</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>3</td>
<td>20.1%</td>
<td>16.7%</td>
<td>10.3% - 33.3%</td>
<td>121</td>
<td>19</td>
<td>15.7%</td>
</tr>
<tr>
<td>Multiple continents</td>
<td>15</td>
<td>19.8%</td>
<td>21.6%</td>
<td>2.9% - 30.4%</td>
<td>4759</td>
<td>874</td>
<td>18.4%</td>
</tr>
</tbody>
</table>

### OPC fraction in HNC

<table>
<thead>
<tr>
<th>Region</th>
<th>n\textsubscript{studies}</th>
<th>Mean (%)</th>
<th>Median (%)</th>
<th>Range (min, max)</th>
<th>N\textsubscript{HNC pts enrolled}</th>
<th>N\textsubscript{OPC pts enrolled}</th>
<th>Pooled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern America</td>
<td>31</td>
<td>56.9%</td>
<td>57.8%</td>
<td>4.3% - 100.0%</td>
<td>1797</td>
<td>1051</td>
<td>58.5%</td>
</tr>
<tr>
<td>Europe</td>
<td>24</td>
<td>53.7%</td>
<td>51.9%</td>
<td>15.4% - 85.2%</td>
<td>2462</td>
<td>1371</td>
<td>55.7%</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>5</td>
<td>41.7%</td>
<td>33.3%</td>
<td>15.4% - 85.2%</td>
<td>377</td>
<td>273</td>
<td>72.4%</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>4</td>
<td>47.8%</td>
<td>45.6%</td>
<td>23.0% - 76.9%</td>
<td>284</td>
<td>128</td>
<td>45.1%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>13</td>
<td>60.3%</td>
<td>60.2%</td>
<td>37.5% - 80.0%</td>
<td>1279</td>
<td>777</td>
<td>60.8%</td>
</tr>
<tr>
<td>Multiple European regions\textdagger</td>
<td>2</td>
<td>52.1%</td>
<td>52.1%</td>
<td>35.8% - 68.4%</td>
<td>522</td>
<td>193</td>
<td>37.0%</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>2</td>
<td>33.0%</td>
<td>33.0%</td>
<td>22.9% - 43.1%</td>
<td>106</td>
<td>36</td>
<td>34.0%</td>
</tr>
<tr>
<td>Multiple continents</td>
<td>12</td>
<td>36.0%</td>
<td>36.5%</td>
<td>13.8% -</td>
<td>3848</td>
<td>1446</td>
<td>37.6%</td>
</tr>
</tbody>
</table>
HPV prevalence in OPC

<table>
<thead>
<tr>
<th></th>
<th>n_{studies}</th>
<th>Mean</th>
<th>Median</th>
<th>Range (min, max)</th>
<th>N_{OPC pts enrolled}</th>
<th>N_{HPV+ OPC pts}</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern America</td>
<td>25</td>
<td>70.0%</td>
<td>75.0%</td>
<td>21.4% - 100.0%</td>
<td>577</td>
<td>423</td>
<td>73.3%</td>
</tr>
<tr>
<td>Europe</td>
<td>17</td>
<td>44.1%</td>
<td>44.4%</td>
<td>14.3% - 89.1%</td>
<td>829</td>
<td>426</td>
<td>51.4%</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>4</td>
<td>61.4%</td>
<td>65.7%</td>
<td>25.0% - 89.1%</td>
<td>264</td>
<td>230</td>
<td>87.1%</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>4</td>
<td>48.2%</td>
<td>49.3%</td>
<td>14.3% - 79.7%</td>
<td>128</td>
<td>75</td>
<td>58.6%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>7</td>
<td>35.3%</td>
<td>35.7%</td>
<td>20.0% - 50.0%</td>
<td>244</td>
<td>81</td>
<td>33.2%</td>
</tr>
<tr>
<td>Multiple European regions†</td>
<td>2</td>
<td>32.5%</td>
<td>32.5%</td>
<td>18.9% - 46.2%</td>
<td>193</td>
<td>40</td>
<td>20.7%</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>25</td>
<td>6</td>
<td>24.0%</td>
</tr>
<tr>
<td>Multiple continents</td>
<td>9</td>
<td>41.6%</td>
<td>38.9%</td>
<td>15.8% - 59.2%</td>
<td>1283</td>
<td>521</td>
<td>40.6%</td>
</tr>
</tbody>
</table>

Abbreviations: HNC, head and neck cancer; HPV, human papilloma virus; N_{pts}, number of patients; n, number of studies; NA, not applicable; OPC, oropharyngeal cancer.

† The category of Multiple European regions includes multi-country studies conducted in Europe. These studies were conducted in Western, Central/Eastern, and Southern Europe for HNC, and Southern and Western Europe for OPC.

Among studies with available HN sub-site proportions (regardless of HPV status), mean (and pooled) OPC fraction was 56.9% (58.5%), 53.7% (55.7%), 33.0% (34.0%), and 36.0% (37.6%) in studies conducted in Northern America (n=31), Europe (n=24), Eastern Asia (n=2) and multiple continents (n=12), respectively (Table 3). Moreover, based on the proportion of HPV+ OPC patients in studies with available data, the mean (and pooled) prevalence of HPV in LA and RM OPC was 70.0% (73.3%) in studies conducted in Northern America (n=25); 44.1% (51.4%) in studies conducted in Europe (n=17), and 41.6% (40.6%) in studies conducted in multiple continents (n=9). In the only single-country study conducted in Eastern Asia, the prevalence of HPV in LA and RM OPC was 24.0% (Table 3). Within Europe, the mean (and pooled) prevalence of HPV in LA and RM OPC was 61.4% (87.1%) in Northern Europe, 48.2% (58.6%) in Southern Europe, 35.3% (33.2%) in Western Europe, and 32.5% (20.7%) in multiple European regions (including Southern and Western Europe). Taken together, the above data illustrate high rates of HPV prevalence in LA and RM HNC and OPC across different geographical regions.
**HPV detection techniques**

In the absence of HPV diagnostic tests with regulatory approval for HNC over the examined period, and given that HPV testing is generally recommended for all newly diagnosed OPSCC but is not warranted for the other HNC types, the present review aimed to capture HPV detection techniques utilized in the included studies. HPV detection techniques are retrieved and analyzed as reported by the authors in the publications. Information on reported HPV detection assays across the included HNC studies are presented in Additional file 6. In total, HPV status was assessed in any HN anatomical site in 37 studies (45.7%), in OPX only in 38 studies (46.9%) while six studies (7.4%) did not provide information on the site examined. With respect to specific methodologies, of the 81 studies, 47 (58.0%) reported using a p16\(^{\text{INK4a}}\)-based method, two studies (2.5%) employed quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR), two studies (2.5%) employed *in situ* hybridization (ISH), while in one study each the detection method was referred to as DNA testing, quantitative Reverse Transcription-PCR (qRT-PCR), and immunohistochemistry (IHC). Seven studies (8.6%) reported using multiple detection techniques to determine HPV status at a cohort level, even though at a patient level HPV status could also have been derived solely based on a single technique. For the remaining 20 (24.7%) studies the authors did not provide any relevant information. HPV detection methods are also presented for IS and NIS, by disease stage, and site examined in Additional file 6. Irrespective of grouping, “p16-based” detection methodologies were the most frequently reported across studies.

**HPV prevalence in OPC using solely a p16-based method**

Considering that p16 overexpression is generally used as a surrogate marker for the presence of HPV in OPSCC and the recommendation for p16 testing in OPSCC clinical management [38, 39], a supplementary analysis was performed by isolating the studies reporting solely a p16-based method for HPV testing and having available results in OPC. In total, 30 studies were included in this analysis (26 IS and 4 NIS; 16 LA and 14 RM), with prevalence of HPV ranging from 15.8% to 100.0% and a mean (and pooled) HPV prevalence of 57.2% (52.6%) (Additional file 7), further supporting the main outcomes of this evidence synthesis.

**Distribution of HPV prevalence by number of enrolled HNC patients**

As a means to evaluate the potential effect of variations across individual sample sizes on the primary outcome of overall prevalence of HPV in LA and RM HNC, the prevalence of HPV reported for each included study was plotted against the respective sample size (Fig. 3). No obvious asymmetry was observed around the calculated overall mean HPV prevalence. Based on this distribution, no apparent bias in the estimation of the study primary outcome arising from sample size can be inferred.

*[Figure 3 to be inserted here]*

**Discussion**
The present SLR aimed to systematically review published data on the prevalence of HPV in the LA and RM setting of HNC captured over the last decade. Using specific selection criteria, 81 studies were identified, reporting data from numerous countries and covering available literature from the last decade (2010-2020). The results revealed a considerable HPV prevalence in LA and RM HNC and OPC across different regions. Numerically highest rates were reported in the LA setting, as well as in the regions of Northern America and Northern Europe. In addition, the data uncover substantial variation in HPV prevalence among studies, as well as in HPV testing methodologies.

The primary outcome of ‘ALARM’, prevalence of HPV in LA and RM HNC, was first retrieved from each study as the minimum proportion of HPV+ cases, unadjusted for HPV status data availability. In this manner, selection bias which would otherwise arise from increased testing of a certain type of cases as per the investigator’s clinical judgement was minimized to the extent possible. The average HPV prevalence in the LA and RM setting of HNC across studies was estimated at 32.6%, while the pooled HPV prevalence, derived from the sum of HPV+ patients over the sum of enrolled HNC patients in all studies was 25.1%. Other reviews have estimated HPV prevalence in HNC at 22-35%, though based on literature data preceding 2008 [28-31]. A more recent review of studies published between 2003 and 2014 estimated the mean percentage of HPV+ HNSCC patients at 32.9% [5], which was however derived from patients with available HPV status data only, regardless of disease stage. When we plotted reported HPV prevalence against the size of the population in each study, an apparently even distribution around the mean was observed, suggesting there was no significant bias due to outliers representing very small or very large sample sizes. On the other hand, data are slightly skewed in relation to the pooled estimate, which could derive from the large proportion of patients with unknown HPV status in some studies. Indeed, the top ten studies with highest sample size contributed data for 51% of the total number of patients included in this SLR (4933/9607) but more than half of those patients had unknown HPV status. This indicates that the estimated pooled prevalence of HPV is most likely underestimated, and also explains why the pooled estimate is smaller than the mean. As the latter doesn’t account for missing data either, and given that previous literature suggests that more than 70% of HPV+ HNC patients have LA and/or RM HNC [5, 28], the mean HPV prevalence of 32.6% estimated here is probably lower than the actual proportion of HPV+ HNC fraction, further highlighting the important contributing role of HPV in LA and RM HNC.

As the variable most strongly associated with HPV prevalence is the anatomic cancer site of OPX [40], findings of HPV prevalence should be interpreted in the context of the contribution of OPC. Irrespective of HPV status, almost half of the overall population in ‘ALARM’ had OPC. The etiological role of HPV in oropharyngeal carcinogenesis is widely recognized [4] and p16 testing is recommended for OPSCC management [12, 18, 38], hence HPV testing is expected to be more frequent among OPC patients. Indeed, in ‘ALARM’ in almost half of the studies (47%) HPV status was assessed in OPX only, reflecting current clinical practice. Though the study has not been designed to make any such comparisons, the prevalence of HPV is numerically higher in OPC than in HNC also including other sub-sites, which is consistent with published literature showing that HPV prevalence is greater in OPC than in not site-specific HNC [5-7, 30]. Specifically in LA and RM OPC, our data report the mean HPV prevalence at 55.8%,
with a pooled prevalence of 50.7%, which is almost double than the overall rate in LA and RM HNC. The prevalence of HPV in LA and RM OPC is close to that reported in a previous review, which showed a mean of 49.9% HPV-positive OPSCC, most of which comprised of stage III/IV disease (85.7%) [5]. Furthermore, in our supplementary analysis of HPV status in OPC tested using solely a p16-based method, the mean prevalence of HPV was 57.2%, further supporting the robustness of the main study outcomes. As OPSCC has been increasing worldwide over the past years [9, 40-43], our results reinforce the substantial contribution of HPV+ OPC to the overall burden especially in LA and RM HNC.

In ‘ALARM’, HPV prevalence was also investigated in IS and NIS by disease stage. Overall, both in IS and in NIS, approximately half of patients had OPC and approximately half of patients had available HPV status data. However, LA studies accounted for 42% of IS and only 26% of NIS. In the overall LA and RM HNC, estimates of HPV prevalence in LA HNC were numerically higher than in RM HNC (mean: 44.7% versus 24.3%; pooled: 44.0% versus 18.6%). This should also be interpreted taking into account the OPC fraction and HPV status availability, both of which were higher among LA than in RM patients (65% versus 39% and at least 70% versus 48%, respectively). Nevertheless, a numerically higher HPV prevalence was noted in LA than in RM OPC patients (mean: 64.6% versus 46.1%; pooled: 67.6% versus 40.7%), which might be worth investigating further, especially considering that a large proportion of HNC cases are either diagnosed at LA stage or experience disease recurrence from LA to RM stage, and that HPV+ cancers are considered to have better prognosis [21, 26, 27].

Previous literature has shown that the incidence of HNC anatomical subsites classified as a proxy for HPV infection, including the oropharynx, has been rising [44] and an increased OPSCC HPV prevalence has been observed over the years especially in Northern America and Northern Europe [9, 40-43]. Moreover, HPV prevalence in OPC was higher in more developed regions than in developing countries [6, 31, 42]. This is also reflected by the outcomes of the present review in terms of the heterogeneous geographic distribution of HPV prevalence being highest in studies conducted in Northern America and Northern Europe. The observed patterns could be attributable to several factors, such as HPV epidemiology which shows variation by ethnicity and gender, and is linked to lifestyle behaviors [40, 45-50]. Nevertheless, regardless of the regional variations in HPV prevalence and the factors that could contribute to the observed patterns, the results of the present study demonstrate that, though ranking lower in terms of prevalence than Northern America and Northern Europe, other parts of Europe and the globe, in general, have substantial rates of HPV+ HNC. These findings suggest that the need to implement preventive measures against HPV is imperative worldwide, and not only in the countries with the highest HPV burden.

The results of ‘ALARM’ reveal a considerable inconsistency in the availability of HPV prevalence data across countries and continents, with many parts of the world being underrepresented. In particular, countries in continents other than Northern America or Europe were mainly represented by the group of multi-continent studies, which could not be stratified further as relevant publications did not contain the required level of detail. Thus, there is a dearth of information on the HPV burden in those countries. This is in line with previous literature on specific ethnic groups which seems to be lacking in
terms of population-based studies [44]. Altogether these observations suggest a need for further investigation, in order to represent all geographical regions in the literature and better assess the burden of this disease.

Another factor that could be contributing to the variation in reported HPV prevalence across studies is the heterogeneity in HPV detection assays. Many of the studies included in the present SLR reported p16-based detection as the main assay (63% of studies, including four studies which used multiple techniques) but differences in the exact methodology, including specimen storage methods, p16-positivity threshold used to define HPV status, and source of result (e.g., medical records archived or freshly collected samples) cannot be excluded. Furthermore, methodology was not specified for one fourth of the studies of the evidence synthesis, uncovering significant literature gaps. As depicted in the present review, clinical practice usually relies on a single technique for HPV status assessment, even though each technique has its limitations. In OPC, p16 testing is generally the preferred method of HPV detection, yet for other HNC sites there is no clear guidance on the HPV testing methodology [24]. Novel diagnostic algorithms for the detection of HPV-driven HNC are being examined, with the combined use of HPV-DNA testing followed by p16 IHC having shown high concordance rates with E6*I mRNA detection and proposed to be helpful in OPC and oral cavity cancers [51]. To improve the precision of HPV burden estimates, standardization of HPV detection is necessary.

Methodological limitations are presumably also a source of bias in the present analysis, as in non-OPC HNC cases where HPV prevalence has been derived solely based on p16 overexpression, the estimates may not be accurate. Along this line, in the context of the primary outcome, the HPV prevalence, is possibly underestimated, as a result of the large proportion of patients with unknown HPV status. In any case, such limitations of the present review mainly derive from limitations of the individual studies included. In addition, certain limitations are due to the selection criteria applied in the present literature search, such as the exclusion of studies written in languages other than English, studies published in report format, for example on government websites, or studies that did not specify any study period or cancer stage. The above criteria may impact on the representativeness of the outcomes, but were employed as a method to ensure quality of included data. It should also be noted this SLR was designed to provide descriptive insight into the relevant literature from a qualitative point of view, including all studies that met a minimum set of criteria, with no restrictions in geographic location or patient eligibility (i.e., target indication, line of therapy, histology, or HN sub-site) increase generalizability of the present findings. The latter is further enhanced by the fact that overlapping data have been avoided to the extent feasible based on geographic location, site, period of enrollment and eligibility criteria in order to represent unique cases of HNC.

The results of the present literature search indicate a substantial proportion of HPV+ patients among LA and RM HNC patients in the last decade, which merits consideration particularly in light of increased awareness campaigns and preventive measures availability. HPV vaccines are effective in protecting against high-risk HPV types in women and men [52-57]. In Europe, most countries recommend HPV vaccination, with many of them having introduced gender-neutral HPV vaccination [58-60]. HPV
prevalence estimates can inform policy decisions and justify strategies to aim for higher levels of HPV vaccination coverage as well as ensure gender neutral vaccination for adolescents, timely catch-up programs, and the possibility to vaccinate adults. Such measures are anticipated to prevent a significant proportion of LA and/or RM HNC especially in regions with a very high burden of HPV-attributable HNC.

Conclusion

This SLR is the first review on HPV burden which focused on LA and RM HNC and reported results from the last decade (2010-2020). More than 80 studies provided information on HPV status demonstrating that a substantial HPV burden exists with at least one in four HNC cases being HPV+ and at least half of OPC cases contributing to this proportion. The proportion of HPV+ cases was considerable in most regions examined, and highest in Northern America and Northern Europe, with at least one in three LA and/or RM HNC cases being HPV+. More quality data are however needed for a better representation of geographic diversity, and implementation of homogeneous HPV detection methodologies is necessary to allow for more precise HPV burden estimation. Nevertheless, the results of this evidence synthesis come to reinforce the significant role of HPV in LA and RM HNC disease with a considerable proportion of LA and RM HNC cases being potentially preventable, highlighting the potential benefit from increasing HPV immunization coverage.

Abbreviations

HN: Head and neck; HNC: Head and neck cancer; HNSCC: Head and neck squamous cell carcinoma; HPV: Human Papillomavirus; IHC: immunohistochemistry; IS: Interventional studies; ISH: in situ hybridization; LA: Locally-regionally advanced; NIS: Non-interventional studies; OPC: Oropharyngeal cancer; OPSCC: Oropharyngeal squamous cell carcinoma; OPX: Oropharynx; qRT-PCR: quantitative Reverse Transcription-Polymerase Chain Reaction; RM: Recurrent and/or metastatic; SLR: Systematic Literature Review.

Declarations

Acknowledgements

The authors wish to thank Qualitis SA, a member of Optimapharm, for their support in data acquisition, data analysis, and medical writing undertaken as part of the project work performed for MSD Greece.

Authors’ contributions

GT and AC: conceptualized and designed the study. GT and AC: acquired, analyzed and interpreted the data, and drafted the manuscript. SA, IB, IA, ID, LP, EM, SU, and GB: contributed to interpretation of the results reviewed and substantively revised the manuscript. All authors read and approved the final manuscript.

Funding
Availability of data and materials

Data collection and review forms are available upon reasonable request. Data extracted from included studies and used for the analysis of outcomes of this study are included in this article and its additional supporting files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

SA is a member of the executive board of the Hellenic Society of Medical Oncology, has served as an investigator in clinical studies for MSD, Greece, has received consulting fees for participating in Expert Input Forums for MSD, Greece, and has received lecture honoraria by MSD, Greece. IB, former president of the Hellenic Society of Medical Oncology, has served as an investigator in clinical studies for MSD, Greece, has received consulting fees for participating in Advisory Boards for MSD, Greece, has received lecture honoraria by MSD, Greece, and has received support for attending international congress from MSD, Greece. IA has served as an investigator in clinical studies for MSD, Greece, has received consulting fees for participating in Advisory Boards for MSD, Greece, has received lecture honoraria by MSD, Greece, and has received support for attending international congress from MSD, Greece. GT, ID, LP, and AC are employees of MSD Greece and own stock in Merck & Co., Inc., Rahway, NJ, US. EM is an employee of MSD France and owns stock in Merck & Co., Inc., Rahway, NJ, US. SU is an employee of MSD Sweden and owns stock in Merck & Co., Inc., Rahway, NJ, US. GB is an employee of MSD Spain and owns stock in Merck & Co., Inc., Rahway, NJ, US.

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Table

Table 1 is available in the Supplementary Files section.

Figures
(a) **Interventional Studies**

Records identified through database searching: n = 855

Studies screened and assessed for eligibility: n = 620

Studies included in evidence synthesis:
HPV prevalence in HNC: n = 62
HPV prevalence in OPC: n = 43

Records excluded based on lack of published article and/or congress abstract corresponding to the identified NCT number: n = 235

Studies excluded (n = 558), with main reasons:
- Specific subpopulation/ not relevant (n = 388)
- HPV status not available (n = 137)
- HPV prevalence not available (n = 24)
- Stage not clear (n = 8)
- No OPX among HN sub-sites (n = 1)

(b) **Non-Interventional Studies**

Records identified through database searching: n = 1763

Records screened: n = 1327

Records excluded based on initial assessment of titles/abstracts: n = 1043

Full-text articles assessed for eligibility: n = 284

Full-text articles excluded (n=265), with reasons:
- Study initiation before 01Jan2010 (n = 178)
- HPV status not available (n = 128)
- HPV prevalence not available (n = 26)
- Disease stage or study period not clear (n = 17)
- Study design (n = 11)
- No OPX among HN sub-sites (n = 6)
- Language (n = 2)

Studies included in evidence synthesis:
HPV prevalence in HNC: n = 19
HPV prevalence in OPC: n = 9

**Figure 1**

PRISMA diagrams for selection of (a) interventional studies and (b) non-interventional studies

**Abbreviations:** HN, head and neck; HNC, head and neck cancer; HPV, human papilloma virus; n, number of studies; OPC, oropharyngeal cancer; OPX, oropharynx.
† Number of excluded articles per reason does not add up to total number of excluded articles since many cases were excluded for more than one reason.

Figure 2

HPV prevalence in LA and RM HNC, OPC fraction, and HPV prevalence in LA and RM OPC
**Abbreviations:** HNC, head and neck cancer; HPV, human papilloma virus; IS, interventional studies; LA, locally-regionally advanced; N, number of patients; NA, not applicable; n/a, not available; NIS, non-interventional studies; OPC, oropharyngeal cancer; RM, recurrent and/or metastatic.

Circle size corresponds to number of patients included in the study indicated, ranging from 6 to 882 patients across 81 studies in HNC, and from 3 to 447 patients across 52 studies in OPC. Overall HPV prevalence is provided as mean and pooled HPV prevalence across studies and depicted as a black and red diamond, respectively. Overall OPC fraction is provided as mean and pooled OPC fraction across studies as a black and red bar, respectively.

**Figure 3**

HPV prevalence by number of HNC cases in each study

**Abbreviations:** HPV, human papilloma virus; N, number of enrolled HNC patients.

HPV prevalence from studies included in the evidence synthesis is plotted against each study’s size. To visualize distribution of studies around the overall HPV prevalence and potential effect of sample size, estimated mean, median and pooled HPV prevalence across studies are provided in dotted lines.
Supplementary Files

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