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Letter to the editor

A two-way relationship between the head and neck cancer and esophageal cancer

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Primary head and neck cancer (PHNC) affecting the oral cavity, pharynx and larynx ranks as the 5th most common cancer worldwide [1]. Although, locoregional control is imperative, improved survival is often dictated by second primaries (SPs) and distant metastasis (DM) [2]. Roughly, 33% of deaths in head and neck cancer (HNC) occur due to SPs, which is 3-fold higher than those due to DM [2]. With a 20 year follow-up, the cumulative risk of a SP developing after PHNC diagnosis stands at 36% [3]. The most common SPs are the second primary esophageal cancer (SPEC) and second primary lung cancer (SPLC) [1,3–7]. SPEC and SPLC harbour the worst prognosis among other second primary head and neck cancer (SPHNC) lower down the upper aero digestive tract (UADT) [1,7]. The Cox proportional hazards regression shows SPEC and SPLC to have a 31–105% higher risk of death compared to those without SP. Despite aggressive treatment, the median survival time of individuals suffering from SPEC and SPLC is 12 months, which is poorer than the primary cancer at these sites. Incidentally, the SPs in the head and neck region portend a better prognosis when compared to those in the non-head and neck regions [1].

While people in the older age group are at a higher risk of developing malignancy, SP's in HNC patients have shown to be associated with a younger age ($\leq$65 years) [7]. The proclivity of PHNC to induce SPs lower down in the UADT [4] are linked to its proximity to the site of SP [1–7]. Thus, in the oral cavity, floor of the mouth squamous cell carcinoma (SCC) have an increased proneness for SP esophageal SCC and hypopharyngeal SCC compared to tongue SCC or gingivobuccal SCC [5]. The odds ratio (OR) of SPEC is 18.41 in oral cancer, which increases to 40.49 in oropharyngeal cancer [3]. Furthermore, the anatomical location of PHNC with respect to SPEC dictates the survival rate with the larynx at 61%, the nasopharynx, 55% and the oral/pharynx at 47% [1].

Field cancerization of the entire UADT due to carcinogens might be the reason for these associations [2–4,7,8]. Alcohol consumption seems to be an independent risk factor for SPs in the hypopharynx and esophagus [3]. Besides, shared genetic alterations like TP53 mutations, ALDH-2 deficiency (resulting in hampered metabolism of acetaldehyde), and epigenetic alterations of HOX-9 explains the association of PHNC with SPEC [4,5,7]. The keystone periodontal pathogen P. *gingivalis* has been shown to promote carcinogenesis via receptor upregulation, EMT induction, MMP-9 activation, IL-8 secretion, non-canonical β-catenin activation and conversion of alcohol to the carcinogen acetaldehyde [9]. It appears to be a common agent in the induction of HNC and esophageal cancer downstream of UADT [9].

The surveillance of the hypopharynx and esophagus is recommended in patients with PHNC, so that treatment can be initiated early. Although visual inspection is the traditional and mainstay technique to detect SPs following PHNC, it does not allow the systematic check-up of the hypopharynx and esophagus [3]. Thus, a significant proportion of SPs is missed. Also, the conditions associated with the curative treatment of HNC such as anatomic alterations and trismus, further hinder the examination of these regions [3]. The newer techniques, like chromoendoscopy and narrowband imaging, might be helpful in the detection of SPEC and SP hypopharyngeal carcinomas. As they are labour intensive and unaffordable, routine endoscopy is recommended for screening SPEC [3]. Recently, Matsui et al. have developed a modified non-invasive esophagogastroduodenoscopy, which may be an effective alternative for early detection of SPs of the esophagus and hypopharynx [5].

Adjuvant chemotherapy (CT) with 5-flurouracil prodrugs (e.g. S-1), which have a longer half-life and reduced toxicity can reduce the death rate in HNC, through the reduction of SPs. Survival rate of the laryngeal cancer patients only on radiotherapy (RT) increased from 62 to 91% on addition of S-1 CT. Moreover, the 5-year incidence of DM + SP in these patients significantly decreased from 19 to 5% in RT + S-1 CT group [2]. Lin et al. reported a 35% reduction in SPEC and stomach cancer in HNC patients, on aspirin use for 1–3 years. Incidentally, these patients were risk-free even after three years of follow up. SPs decrease resulted from COX-2 and PGE inhibition [6].

Prominently, the primary esophageal cancer (PEC) also provokes SPHNC [4,8,10,11]. The predominant histological subtypes of PEC are ESCC and esophageal adenocarcinomas (EAC) that are restricted to the Eastern and Western populations respectively [4]. Notably, ESCC but not EAC is shown to be associated with SPHNC [4,7,8]. Chen et al. in their 15 year study on PEC cases, reported the highest standardized incidence ratios (SIR) for SPHNC (15.83) followed by stomach (3.30), lung and mediastinum (2.10) [10]. Among the pharyngeal sites, hypopharynx (12.6) was the most susceptible for SPs succeeding PEC,

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followed by the oropharynx (11.6) and nasopharynx (1.47) [8]. The age (greater than 60 years), male gender, liver cirrhosis, major surgery and chemotherapy were the risk factors for SP associated with PEC [10]. Moreover, the SIR of SPs in the head and neck region following PEC remained high even after 10 years follow-up. Thus, a longer monitoring than the standard five year surveillance is necessary to detect SPHNC developing post discovery PEC [10].

Hence, there exists a reciprocal/two-way relationship between the HNC and esophageal cancer [4,5,8]. Lee et al. in their population-based study spanning over 28 years confirmed this relationship [4]. They reported that individuals with PHNC stood a tenfold risk of acquiring SP ESCC, and individuals with primary ESCC were at a sevenfold risk of developing SPHNC [4]. Further confirmation of this relationship has a potential to change the treatment plan of the two malignancies. The scanning of cancer registries for the involvement of the entire UADT should be undertaken for this purpose. Upon validation of this relationship further molecular and/or bacteriological studies could be undertaken to untangle their relationship and revise the treatment paradigms of the two cancers.

Declaration of Competing Interest

All the authors of the manuscript hereby state that there is no financial implication or personal relationship with other people or organization that could inappropriately influence the outcome of this work.

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