Review Article

Physical activity and laryngeal cancer

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Abstract: Although an active lifestyle physical has been convincingly associated with a decreased risk of developing many forms of cancers, including neck and head malignancies, uncertainty surrounds the relationship between physical activity (PA) and laryngeal carcinogenesis. Epidemiologic evidence, garnered from some well-conducted cross-sectional, prospective and retrospective studies, seemingly attests that the impact of PA may be not so straightforward in lowering laryngeal cancer risk as for other malignancies. Reasonable consensus has been reached that moderate-intensity PA may generate the larger potential benefits, whilst the effect of high-intensity PA appears more controversial and even contradictory. This is mainly attributable to the fact that moderate PA may have more favorable effects than high-intensity exercise in decreasing the impact of some risk factors of laryngeal cancer such as metabolic syndrome, cigarette smoking, inflammation, and gastroesophageal reflux disease. Significant biological and psychological benefits from moderate-intensity exercise have also been described in patients surviving from primary laryngeal cancers. This would hence lead us to conclude that promotion of an active lifestyle, characterized by performance of moderate-intensity PA (e.g., between 3 and 6 metabolic equivalents, equaling short distance running), may be beneficial for lowering the risk of developing laryngeal cancer and for improving the quality of life of larynx cancer survivors.

Keywords: Larynx; laryngeal cancer; physical activity (PA); prevention

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Introduction

Laryngeal cancer [International Classification of Diseases (ICD)-10 code C32; malignant neoplasms of larynx, including glottis, supraglottis, subglottis, and laryngeal cartilage], belongs to the specific category of head and neck malignancies and is a relatively rare condition. According to the Global Burden of Disease Cancer Collaboration, the currently estimated incidence of laryngeal cancer is 211 [95% confidence interval (95% CI), 206–216] per 1,000, with a 5:1 male to female ratio and approximately 10% of patients in metastatic or terminal phase (1). The estimated mortality for laryngeal cancer approximates 126 (95% CI, 123–130) per 1,000, again with a 5:1 male to female ratio. Notably, the burden of this malignancy, expressed as years lived with disability (YLDs), has increased by nearly 25% (25.1%; 95% CI, 21.7–28.5%) during the past 3 decades (2). The large majority of larynx cancers, approximating 98%, are represented by squamous cell carcinoma, whilst leiomyosarcomas, chondrosarcomas, lymphomas, and melanomas account for the remaining 2% (3).

According to the joint document of the World Cancer

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Research Fund (WCRF) and the American Institute for Cancer Research (AICR) (4), the most important factors associated with an enhanced risk of developing mouth, pharynx and larynx cancers include alcohol intake, tobacco (smoking, chewing and snuffing), human papillomavirus (HPV) infection, obesity (i.e., being overweight) and environmental exposure to asbestos, whilst some evidence exists that consuming non-starchy vegetables, choosing healthy dietary patterns, consuming coffee and avoiding mate may reduce the risk for this cancer. Notably, the WCRF and AICR also claim that limited evidence exists on the relationship between physical activity (PA) and mouth, pharynx and larynx cancers, so that no conclusions or recommendations can be made other than endorsing regular engagement in PA for preventing all other types of cancer. The American Cancer Society (ACS) clearly states that tobacco is the most important risk factor for larynx and hypopharynx cancers (5), followed by moderate or heavy alcohol use (i.e., >1 drink per day), HPV infection, exposure to asbestos or wood dust, paint fumes and chemicals used in petroleum, plastics, metalworking and textile industries, poor nutrition (i.e., vitamin deficiencies), intake of large amount of fried and processed foods, gastroesophageal reflux disease, inherited syndromes such as Fanconi anemia, and dyskeratosis congenita. Neither in this case, the ACS provides clear recommendations about favorable effects of PA on decreasing the risk of development and/or progression of laryngeal cancer.

Establishing whether PA recommendations are also valid for laryngeal cancer is pivotal, considering the accumulating evidence that PA may prevent the development of head and neck cancers, in general (6-8). Therefore, we aimed to review the current epidemiologic evidence on the effect of PA on larynx cancer risk to provide evidence-based, larynx cancer-specific indications.

Epidemiological evidence between PA and laryngeal cancer

The very first study which explored the relationship between PA and the risk of developing larynx cancer was published in 1993 by Dosemeci *et al.* (9). In this hospital-based study population, the PA levels performed by 779 patients diagnosed with larynx cancer were compared with that of 2,371 controls. The level of PA was defined as sedentary (<8 kJ/min), or working in jobs with moderate (between 8–12 kJ/min) and high (>12 kJ/min) intensity. After adjustment for age, smoking and socioeconomic status, sedentary subjects exhibited a non-significant trend (P=0.09) towards enhanced risk of laryngeal cancer compared to highly active subjects (OR, 1.2; 95% CI, 0.9–1.9), whilst the risk of moderately highly active subjects was globally comparable to that of highly active subjects (OR, 1.0; 95% CI, 0.8–1.2). A similar trend was observed for physical inactivity, i.e., when subjects seated for <2 h/day were compared to those seated for 2–6 h/day (OR, 1.1; 95% CI, 0.9–1.4) or for >6 h/day (OR, 1.1; 95% CI, 0.8–1.8; P=0.07 for trend).

The largest study on the relationship between laryngeal cancer and PA has been published by Leitzmann, in 2008, who followed-up as many as 487,732 subjects (192,479 women and 295,253 men) for a mean period of 7.2 years (10). A questionnaire was disseminated to obtain information on PA, whose level was ranked according to the frequency, i.e., <1, 1–2, 3–4 or ≥5 times per week. A total number of 406 individuals developed laryngeal cancer during follow-up. In univariate analysis, increasing level of PA was found to be inversely associated with the risk of developing cancer. More specifically, compared to sedentary subjects, the risk of developing larynx cancer was non-significantly decreased [relative risk (RR), 0.81; 95% CI, 0.59–1.11] in subjects exercising <1 time per week, but was significantly reduced by ~40% (RR, 0.61; 95% CI, 0.45–0.82) in those exercising 1–2 times per week and by ~50% in those exercising 3–4 times per week (RR, 0.54, 95% CI, 0.41–0.72) and ≥5 times per week (RR, 0.52; 95% CI, 0.38–0.71; P<0.001 for trend). In the subsequent multivariable analysis, the favorable effect of PA on the risk of developing laryngeal cancer was almost lost (P=0.225 for trend), whereby the RR compared to sedentary people was 0.96 (95% CI, 0.69–1.32), 0.82 (95% CI, 0.60–1.10), 0.84 (95% CI, 0.63–1.12) and 0.82 (95% CI, 0.59–1.13) in subjects exercising <1, 1–2, 3–4 or ≥5 times per week, respectively.

In a subsequent investigation, Nicolotti *et al.* (11) pooled data from four case-control studies including 612 cases of laryngeal cancer and 4,947 controls. PA was ranked as none/low (≤3 h per week or ≤1 time per week), moderate (2–9 h per week or 1–4 times per week) and high (any value above moderate) according to the frequency of practice in the four different studies, despite levels occasionally overlap. Notably, a highly significant, graded and inverse relationship could be observed between the level of PA and the risk of developing pharyngeal cancer. Compared to those reporting none/low PA, the risk of those reporting moderate PA was 33% lower (OR, 0.67; 95% CI, 0.53–0.85), whilst that of those reporting high PA was 42% lower (OR, 95% CI, 95% CI, 0.38–0.89). Unlike these findings,

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no relationship could be observed between the level of PA and the risk of developing laryngeal cancer. Compared to those reporting none/low PA, the risk of those reporting moderate PA was slightly but not significantly lower (OR, 0.81; 95% CI, 0.60–1.11), whilst that of those reporting high PA was significantly higher (OR, 1.73; 95% CI, 1.04–2.88). This last finding was partially explained by the authors with a higher number of smokers in their high PA group.

Lin *et al.* (12) carried out another case-control study involving 74 patients with laryngeal cancer and 731 healthy controls. Recreational PA was ranked according to lifestyle habits (sedentary or performing regular PA), intensity (sedentary, light, moderate and vigorous) and frequency (sedentary, 3 days per week, 4–5 days per week, 6–7 days per week). Compared to sedentary subjects, the risk of laryngeal cancer was found to be virtually identical in people reporting PA habits (OR, 1.03; 95% CI, 0.58–1.85), in those performing moderate (OR, 0.93; 95% CI, 0.46–1.87) or high (OR, 1.01; 95% CI, 0.45–2.24) volumes of PA, as well as in those exercising 3 days per week (OR, 1.19; 95% CI, 0.36–3.96) , 4–5 days per week (OR, 0.32; 95% CI, 0.04–2.55) and even 6–7 days per week (OR, 1.14; 95% CI, 0.61–2.12).

Bravi *et al.* (13) pooled data from two Italian case-control studies including 689 patients with larynx cancer and 1,605 matched controls. Information on the level of PA was garnered by using a structured questionnaire, where participants self-reported occupational PA (i.e., very heavy, heavy, intermediate, standing and sedentary job) and leisure-time PA (hours of sports practice per week). Regarding the overall amount of PA, 1 point was attributed to people meeting the minimum amount (i.e., 150 min of moderate PA per week or 75 min of vigorous PA per week), 0.5 points to those who partially met the minimum amount, and a score of 0 when the minimum amount was largely unmet. Compared to subjects scoring 0 points, those with a score of 0.5 (OR, 0.58; 95% CI, 0.43–0.78; P=0.005) and 1 (OR, 0.61; 95% CI, 0.46–0.82; P=0.005) had nearly 40% lower risk of developing laryngeal cancer. Interestingly, a similar beneficial effect of PA was found also on the risk of developing overall head and neck cancers (between 26–30% reduction; P=0.001).

More recently, Kim *et al.* (14) performed a population-based retrospective study in South Korea including as many as 23.2 million people, 5,322 of whom were diagnosed with laryngeal cancer during a 7-year follow-up period. Notably, sedentary status (i.e., no routine PA) was reported by 54.9% of laryngeal cancer patients compared to 50.4% controls, so that PA was found to be associated with 16% decreased risk of larynx cancer (OR, 0.84; 95% CI, 0.79–0.88; P<0.001).

Another case-control study has been published (in Chinese) by Wang *et al.* (15). Although the contents of this article are not accessible, the authors concluded that PA may decrease the risk of laryngeal cancer by approximately 60% (OR, 0.41).

Discussion

Both PA and inactivity are believed to positively or negatively affect cellular processes and tumor growth. Briefly, PA reduces the risk of recurrence and improves survival throughout eliciting changes in adiposity, circulating levels of both adipokines and sex hormones, metabolic dysregulation, oxidative stress causing DNA damage and gene mutations, inflammation, and immune function (16-18). Moreover, PA might decrease the risk of cancer through epigenetic mechanisms (19).

Several biological mechanisms are implicated in the beneficial effects of exercise in cancer prevention and/or as adjuvant therapy (20). PA may prevent certain types of cancer as well as improve the quality of life among cancer survivors and/or those diagnosed with several malignancies, especially breast, gastrointestinal, colorectal, prostate, and lung cancers (21-23). This is also confirmed by the evidence that high-level athletes have a reduced risk of developing certain types of cancer (24). We previously suggested the combination of obesity, physical inactivity, and low fitness as a toxic triad highly implicated in cancer incidence and mortality (25), whilst physical inactivity itself is also related with an increased incidence of colorectal and breast cancer (26,27).

Taken together, the currently available scientific evidence seemingly attests that the impact of PA may be not so straightforward in lowering the laryngeal cancer risk as for other malignancies. In particular, reasonable consensus has been reached that moderate-intensity PA may generate the larger potential benefits on the risk of developing laryngeal cancer, whilst the effect of high-intensity PA is more contradictory, as shown in *Table 1*. In this regard, Nicolotti *et al.* (11) reported that high levels of PA might even be associated with an enhanced risk of developing this type of cancer. This finding is in keeping with the association between laryngeal malignancies and leanness. In particular, Garavello *et al.* (28) reported that subjects (especially men) with lower abdominal fat display a significantly enhanced risk of laryngeal cancer. This evidence has then been confirmed

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Table 1 Summary of studies exploring the association between physical activity and risk of laryngeal cancer

Authors	Study design	Population	Impact of physical activity
Dosemeci *et al.*, 1993 (9)	Case-control	779 cases and 2,371 controls	Non-significant trend towards lower larynx cancer risk (~20% reduction)
Leitzmann *et al.*, 2008 (10)	Prospective	406 cases and 487,732 controls	Lower larynx cancer risk in univariate analysis (20-50% reduction), no effect in multivariate analysis
Nicolotti *et al.*, 2011 (11)	Case-control	612 cases and 4,947 controls	No effect
Lin *et al.*, 2017 (12)	Case-control	74 cases and 731 controls	No effect
Bravi *et al.*, 2017 (13)	Case-control	689 cases and 1,605 controls	Lower larynx cancer risk (~40%)
Kim *et al.*, 2019 (14)	Population-based retrospective study	5,322 cases and 23,247,948 controls	Lower larynx cancer risk (~16%)

in subsequent studies (29,30). It is hence conceivable that part of the benefits conferred by high-regimen PA on lowering the general risk of cancers may be attenuated in the setting of laryngeal malignancies, whereby frequent, vigorous and strenuous exercise is inherently associated with leanness (31).

Despite the still controversial epidemiologic evidence, some plausible biological grounds would make it reasonable to expand PA and exercise recommendations to also embrace the prevention and care of laryngeal cancer. In the nationwide cohort study of Kim *et al.* (14), patients with metabolic syndrome had 13% enhanced risk of larynx cancer than those without metabolic syndrome. The role of PA for preventing and managing metabolic syndrome is extensively known (32). Even more importantly, current evidence advocates that adults should be engaged in 60 min of daily moderate-intensity PA for preventing unhealthy weight gain, thus reducing the risk of obesity and metabolic syndrome (33). This would hence contribute to explain the favorable association of moderate PA in lowering the larynx cancer risk.

The synergistic effect between low PA and smoking may provide an alternative explanation. In a large study including more than one hundred thousand individuals, O'Donovan *et al.* (34) showed that the combined risk of mortality in current cigarette smokers was indeed higher in sedentary people (OR, 3.38; 95% CI, 2.76–4.13) than in physically active individuals, and that same risk was very similar in those engaged in moderate (<60 min/week; OR, 2.35; 95% CI, 1.74–3.19) or high (>60 min/week; OR, 2.27; 95% CI, 1.64–2.1) levels of PA. Notably, cardiovascular mortality was paradoxically higher in subjects engaged in high (OR, 2.58; 95% CI, 1.33–5.03) than in those reporting moderate PA (OR, 2.45; 95% CI, 1.30–4.64). When the intensity of PA was expressed in terms of relative intensity, subjects engaged in middle-intensity exercise [6.63–23.8 metabolic equivalent (MET)/h per week; OR 0.87; 95% CI, 0.73–1.03] had a lower risk of cancer mortality than those engaged in high-intensity exercise (>23.8 MET/h per week; OR, 0.97; 95% CI, 0.81–1.16).

Another plausible mechanism encompasses the link between PA and inflammation. Vigorous, high-intensity physical exercise is always accompanied by an acute phase response, which is directly proportional to the intensity and duration of the physical effort, according to an exercise-dose-dependent manner (35-37). Since some pro-inflammatory conditions are associated with enhanced risk and faster progression of laryngeal cancer (38-41), it is hence reasonable to envision that moderate PA would produce large benefits than high-intensity exercise. Finally, emerging evidence attests that recreational PA may reduce the risk of gastroesophageal reflux disease (42), which is, in turn, a risk factor for laryngeal carcinogenesis (43).

Besides these important effects, recent literature data reveal that PA may play an important role in improving the quality of life, functional wellbeing, cardiorespiratory fitness, and self-esteem of patients with laryngeal cancer (44-47), thus further strengthening the inverse relationship between active lifestyle and laryngeal malignancies. Avoidance of sedentary behaviors may also be a relatively easy and important healthcare intervention for prolonging life expectancy in patients surviving from larynx cancer, whereby the 5-, 10- and 20-year cumulative risk of second primary laryngeal malignancies is as high as 4.6%, 9.9% and 19.0%, respectively (48).

Conclusions

In conclusion, the available clinical and biological evidence

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would lead us to conclude that promotion of an active lifestyle, characterized by performance of moderate-intensity PA (e.g., between 3 and 6 MET, equaling short distance running) may be beneficial for lowering the risk of developing laryngeal cancer as well as for improving the quality of life of cancer survivors. This specific training regimen seems to be even more effective than high-intensity exercise in individuals at a particularly higher risk of this type of malignancy (49).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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