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Reduction of head and neck cancer risk following smoking cessation: a systematic review and meta-analysis

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ABSTRACT

Objective Head and neck (HN) cancer comprises the neoplasms originating from the oral cavity, pharynx and larynx. We aimed at reviewing the available literature on the effect of smoking cessation on HN cancer risk.

Method We conducted a systematic search in Medline, PubMed and Embase to June 2022. We abstracted or calculated relative risks (RR) and 95% CIs of HN cancer after cessation of tobacco smoking (both former smoking status and duration of quitting) and combined them using random effects meta-analyses. Papers included were case–control or cohort studies available in the English language. Studies investigating smoking cessation after cancer diagnosis, case reports, intervention studies or animal studies were excluded. Quality and susceptibility to bias of each included study were evaluated using the Newcastle-Ottawa Scale. Publication bias was assessed using funnel plot and Egger's test.

Results A total of 65 studies were included in the review, including 5 cohort and 60 case–control studies. The RR of HN cancer for former smokers compared with current smokers was 0.40 (95% CI 0.35 to 0.46). In an analysis by cancer site, the RR of oral cancer was 0.44 (95% CI 0.35 to 0.55), that of pharyngeal cancer 0.44 (95% CI 0.32 to 0.60) and that of laryngeal cancer 0.38 (95% CI 0.29 to 0.50). The dose-response meta-analysis was based on 37 studies. The RR per 10-year increase in smoking cessation was 0.47 (95% CI 0.43 to 0.52).

Conclusions The risk of HN cancer declines within the first 5 years of quitting smoking. Quitting smoking is an essential element of HN cancer prevention.

Trial registration number The protocol has been deposited in the PROSPERO repository (CRD42022338262).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large number of studies and participants provide high statistical power.
⇒ Effect of duration of smoking cessation was precisely estimated.
⇒ Publication bias did not appear to have influenced the results.
⇒ Heterogeneity between studies was observed which may be due to differences in design and quality of studies.
⇒ Some studies did not provide adjusted risk ratio and only crude risk ratios were calculated leading to a higher risk of residual confounding.

INTRODUCTION

Head and neck (HN) cancer, comprising neoplasms originating from the oral cavity, pharynx and larynx, is considered the sixth most common cancer in the world, with an estimated 660 740 new cases in 2020.[1] Smoking is one of the main factors associated with HN cancer.[2 3] HN cancer has the highest proportion of cases attributable to smoking after lung cancer.[4]

Quitting smoking is challenging and knowing the benefits of quitting can be one factor to aid the cessation process. Having high-quality evidence on the beneficial effect of smoking cessation can help patients, clinicians and policy-makers plan for and support smoking cessation efforts. Although former smokers may have higher risk of HN cancer than never smokers, they had lower risk than current smokers.[5–11]

Duration of smoking cessation was shown in some studies to reduce HN cancer risk with a dose–response relation.[12] These results, however, have not been subject to a systematic review and meta-analysis.

Therefore, we aimed to review the available literature investigating the effect of smoking cessation on HN cancer risk, with emphasis on the effect of duration of quitting. This study would contribute to quantify the importance of smoking cessation to prevent HN cancer.

METHOD

The systematic review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[13] The protocol has been deposited in the PROSPERO repository (CRD42022338262). The literature search was conducted in June 2022 on three databases: PubMed, Medline (Ovid) and Embase to identify studies that investigated

the association between smoking cessation and the risk of HN cancer. We used different keywords and controlled vocabularies related to smoking cessation including tobacco, cigarette, cigar and waterpipe and HN cancer (details included in online supplemental material); in addition, we reviewed the reference lists of the included articles.

Inclusion criteria comprised case–control or cohort studies that reported results on HN cancer risk associated with smoking cessation, including both former smoking status and duration of quitting for adults aged older than 18 years. Studies investigating smoking cessation after cancer diagnosis, case reports, intervention studies or animal studies were excluded. The search was restricted to articles published in English since most papers are available in the English language.

Studies were screened and evaluated for their relevance to the research question and for their compliance with participants, interventions, comparisons and outcomes criteria. Participants were subjects at risk of HN cancer, intervention was smoking cessation (time since quitting), comparison was current smokers and outcome was HN cancer. Two reviewers independently conducted the initial screening based on title and abstract. The full text of articles retained after this initial screening was reviewed by two reviewers. All duplicates were excluded manually and by two screeners. The final list of articles selected for the review was agreed between all authors. The references of cited papers were added using EndNote V.20.

The following information was collected from the selected studies: author name and year of publication, country, study design (case–control or cohort study), the number of participants, patient characteristics (sex, age, ethnicity), site of HN cancer (oral, laryngeal or pharyngeal), period of the study and duration of follow-up, duration of smoking cessation, confounding variables included in the analysis and effect estimate (OR, risk ratio or HR, here thereafter referred to as relative risk (RR), with corresponding 95% CI). Current smokers were included as the reference category. If an effect measure with current smokers as the reference group was not reported, it was calculated whenever possible, based on the raw numbers reported in the original publications.

The quality and susceptibility to bias of each included study were evaluated using Newcastle-Ottawa Scale,[14] separately for case–control and cohort studies.

We excluded individual studies which were part of pooled studies. For reports based on the same database, we included only the most informative report, that is, which is based on the largest number of cases.

The meta-analysis was based on RR of HN cancer, overall and for specific subsites, associated with smoking cessation, using current smokers as reference category. If a study did not report results for HN cancer combined but only for a subsite, we nonetheless used those results in the analysis of overall HN. The RR from individual studies was combined using a meta-analysis based on random-effects model.[15] For the analysis of cessation of smoking,

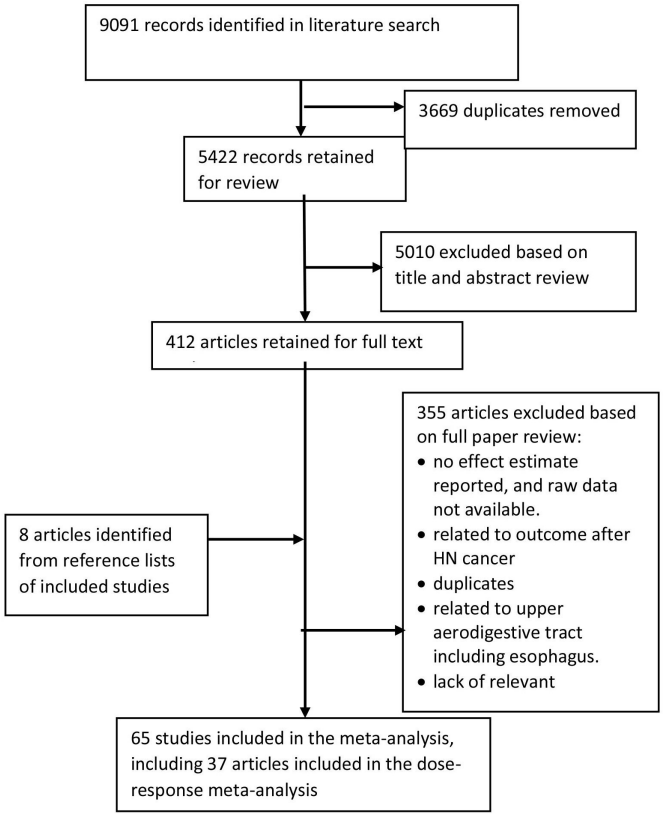

Figure 1 Flow chart of study selection. HN, head and neck.

we examined different periods including less than 5 years, 5–9 years, 10–20 years or more than 20 years. Heterogeneity was tested using Cochran's Q test and quantified by the I^2 statistics.[16] In addition, we conducted a meta-regression to estimate the study-specific RR for a 10-year increase in duration of quitting, using the midpoint of the categories of duration and conducted a random-effect meta-analysis (dose-response meta-analysis) of these results.

Stratified analyses were conducted according to site within the HN, sex, geographical region, period of publication and quality score. We also conducted a sensitivity analysis in which one study at a time was excluded from the meta-analysis. Publication bias was assessed using funnel plot and Egger's test.[17] The package Stata V.17 was used for data analysis.

Patient and public involvement

No patient involved.

RESULTS

The selection of studies is reported in figure 1. A total of 65 studies were included in the meta-analysis of smoking status, of which 35 were included also in the dose-response meta-analysis. Of the 65 studies, 5 were cohort and 60 case–control studies. 24 studies reported data on oral cancer, 11 studies on pharyngeal cancer and 23 studies on laryngeal cancer. Selected characteristics of the studies are reported in online supplemental table 1. Most

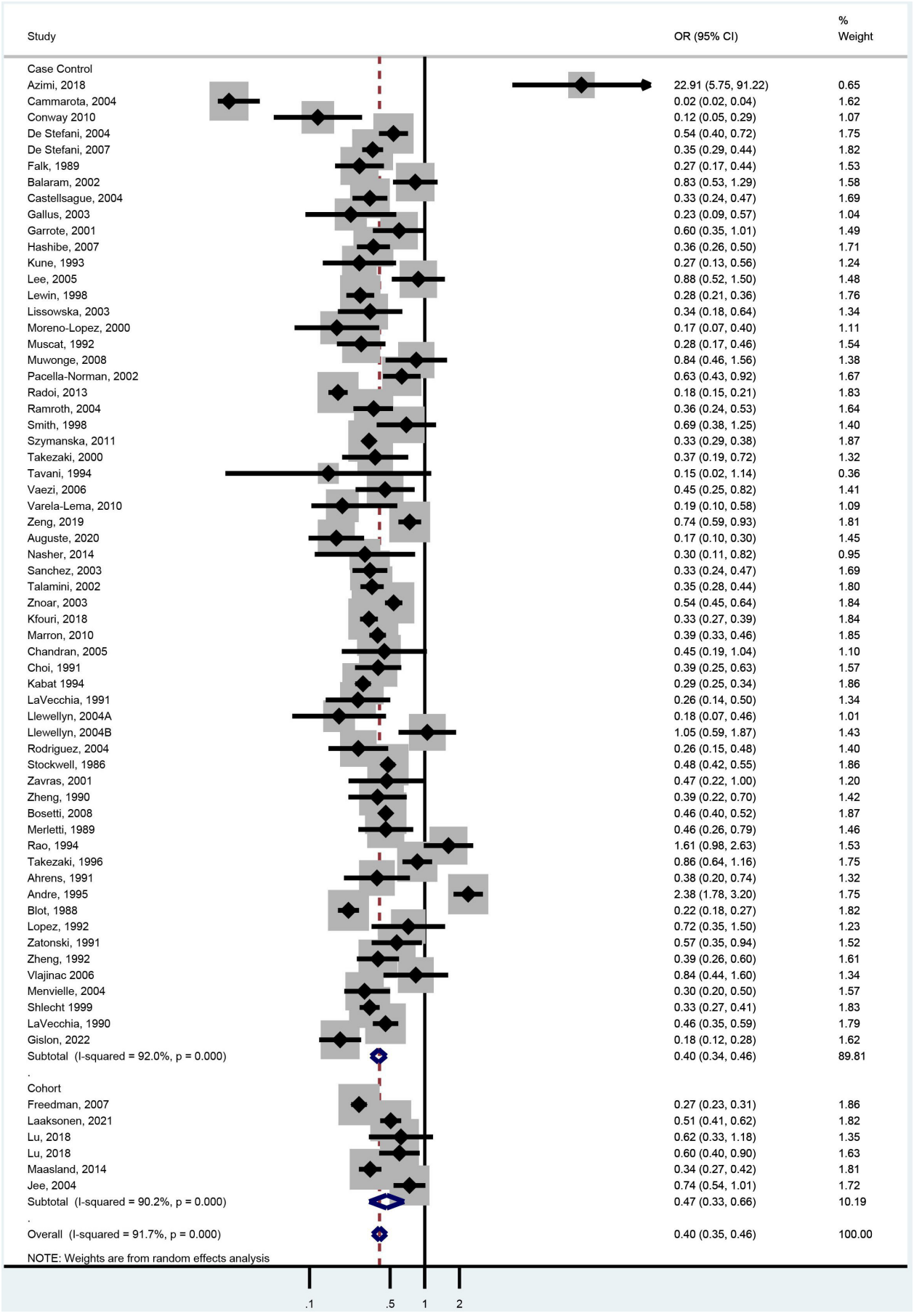

Figure 2 Forest plot for head and neck cancer stratified by study design. The error bars represent the corresponding 95% CIs.

Table 1 Relative risk of head and neck cancer in former smokers*

Risk of former smoker	Number of studies	RR	95% CI	Heterogeneity test (I^2) %	P value
Head and neck cancer	65	0.40	0.35 to 0.46	91.8	
Cancer site:					
Oral cancer	24	0.44	0.35 to 0.55	89.6	0.38
Pharyngeal cancer	11	0.44	0.32 to 0.6	85.7	
Laryngeal cancer	23	0.38	0.29 to 0.5	91.3	
Gender:					
Men	33	0.45	0.38 to 0.54	90.2	0.78
Women	9	0.49	0.28 to 0.87	85	
Newcastle-Ottawa quality score:					
High quality (score ≥7	23	0.44	0.34 to 0.57	92.3	0.35
Low quality (score <7)	42	0.38	0.32 to 0.45	91.7	
Publication year:					
≤1999	22	0.45	0.35 to 0.58	92.4	0.18
2000–2009	29	0.39	0.32 to 0.49	91.2	
≥2010	14	0.35	0.27 to 0.46	92.4	
Geographic region:					
Europe	30	0.32	0.24 to 0.43	93.8	<0.001
USA	7	0.31	0.24 to 0.4	88.6	
Latin America	8	0.37	0.31 to 0.44	74.9	
Asia	9	0.59	0.47 to 0.74	64.3	
Others	10	0.71	0.5 to 1	83.9	
Reported versus calculated RR:					
Reported	4	0.43	0.29 to 0.65	88.2	0.74
Calculated	61	0.40	0.35 to 0.46	92	

*Reference category: current smokers.
.CI, Confidence Interval; RR, relative risk.

of the studies were conducted in Italy (n=9),[18–26] the USA (n=7),[27–33] France (n=4),[11 34–36] Spain (n=5),[37–41] Brazil (n=4),[10 12 42 43] India (n=4),[44–47] China (n=3),[48–50] the UK (n=3)[51–53] and Japan (n=3).[54–56] Two studies each were conducted in Switzerland,[18 21] Uruguay,[7 57] Australia,[6 58] Korea,[59 60] Germany,[61 62] Poland[63 64] and South Africa,[65 66] and one study each in the Netherlands,[8] Iran,[67] Cuba,[68] Taiwan,[69] Sweden,[70] Greece,[71] Serbia[72] Latin America[73] and Yemen.[74]

Most of the studies were assigned either moderate quality (score=6, n=25) or high-quality score (score ≥7, n=25) while 15 studies were assigned low quality score (score <6). In all cohort studies, cases were identified through record linkages, and the longest duration of follow-up was 17.3 years.[8] Among cases control studies, 12 included controls from the community while others used hospital controls. When the RR was calculated from raw data, it was not possible to adjust for potential confounders.

The meta-analysis on smoking status, based on 65 studies, resulted in an RR of 0.40 (95% CI 0.35 to 0.46; I^2=91.8%) for former smokers compared with current smokers (figure 2). The results of the stratified analyses are reported in table 1. The RR among former smokers was similar in men (RR 0.45; 95% CI 0.38 to 0.54) and women (RR 0.49; 95% CI 0.28 to 0.87). In the analysis by cancer type, the RR of oral cancer was 0.44 (95% CI 0.35 to 0.55), that of pharyngeal cancer 0.44 (95% CI 0.32 to 0.6), and that of laryngeal cancer 0.38 (95% CI 0.29 to 0.5) (figure 3). High-quality studies (≥7) resulted in a similar summary RR (0.44, 95% CI 0.34 to 0.57) compared with moderate-quality and low-quality studies (score <7, risk ratio=0.38, 95% CI 0.32 to 0.45) (table 1).

The summary RR for former smokers remained comparable for studies published up to 1999 (RR 0.45, 95% CI 0.35 to 0.58), between 2000 and 2009 (RR 0.39, 95% CI 0.32 to 0.49) and in 2010 or later (RR 0.35, 95% CI 0.27 to 0.46). The RR among former smokers was similar in studies conducted in Europe (RR 0.32, 95% CI 0.24 to 0.43), Latin America (RR 0.37, 95% CI 0.31 to 0.44) and the USA (RR 0.31, 95% CI 0.24 to 0.4) while the reduction was less marked in studies from Asia (RR 0.59, 95% CI 0.47 to 0.74, p=0.001 compared with European studies) and other countries (RR 0.71, 95% CI 0.50 to 1.00, p<0.001)

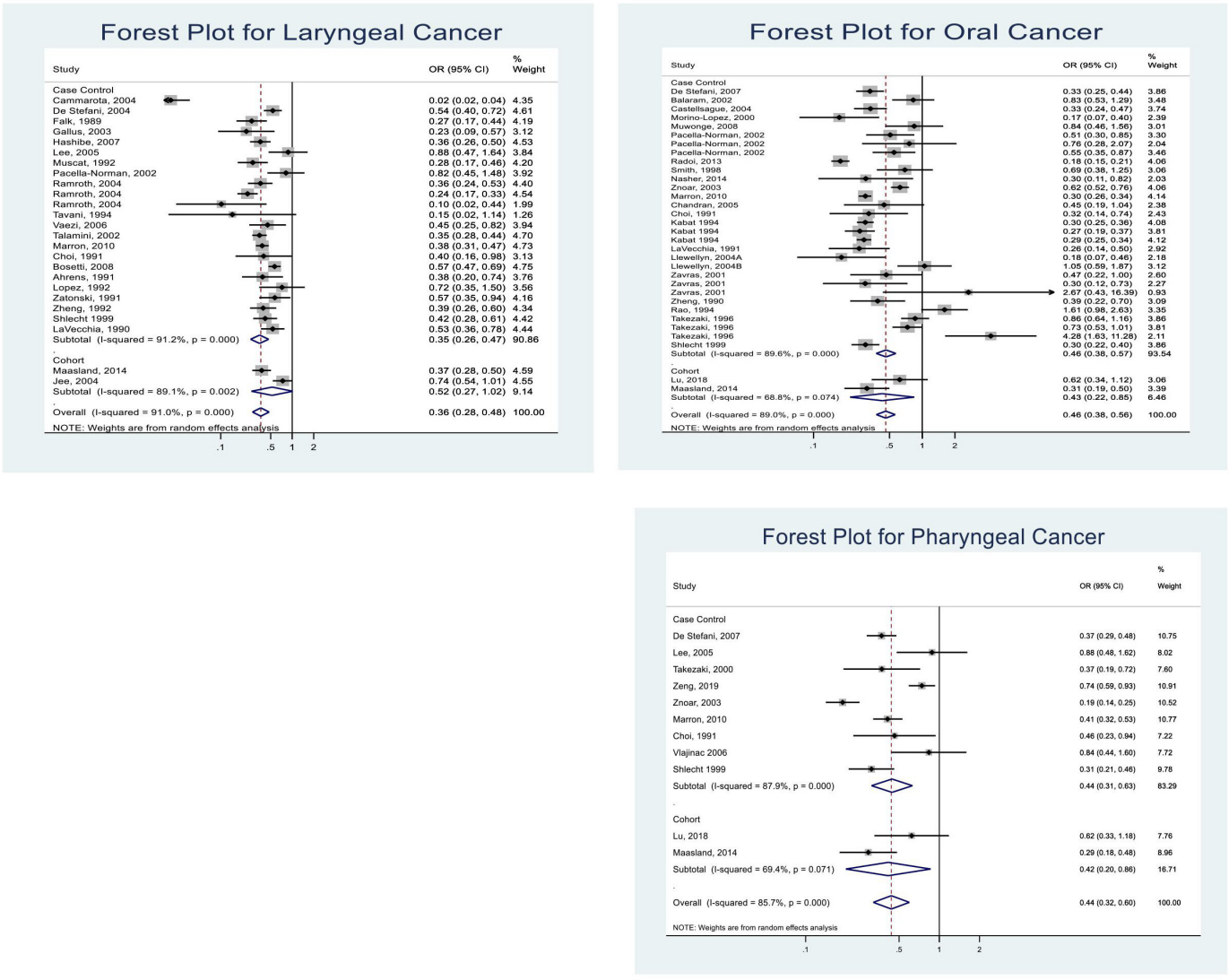

Figure 3 Forest plot for oral cavity, pharyngeal and laryngeal cancer stratified by study design. The error bars represent the corresponding 95% CIs.

(table 1). In the sensitivity analysis in which we excluded one study at a time, the RR for former smokers ranged between 0.39 and 0.42 (online supplemental table 2).

The dose-response meta-analysis was based on 37 studies. The RR per 10-year increase smoking cessation, compared with current smokers, was 0.47 (95% CI 0.43 to 0.52). A similar result was obtained for men, whereas the RR for women was 0.70 (95% CI 0.54 to 0.92) every 10 years (table 2). Similar findings were found for each site within HN.

Table 2 shows the reduction of RR of HN cancer compared with current smoker every 5 years. The RR decreased from 0.67 (95% CI 0.54 to 0.82) in quitters for less than 5 years to 0.20 (95% CI 0.16 to 0.25) for those who quit for more than 20 years. Results were too sparse to estimate the effect of quitting for a longer duration.

No publication bias was detected in the meta-analysis of risk of HN cancer overall for former versus current smokers, either by visual inspection of funnel plot or by Egger's test (p=0.54). Similarly, there was no evidence of publication bias in meta-analysis of results of specific cancer sites (results are not shown in detail).

DISCUSSION

This study showed that smoking cessation leads to a significant decrease in the risk of HN cancer compared with continuing smoking. The effect of quitting on HN cancer was similar across different HN cancer sites, sexes and period of publication. European and American populations seemed to benefit more from smoking cessation compared with Asian populations. Important and novel results of our study include (1) the risk of HN cancer appears to be reduced by half for each 10 years of smoking cessation; (2) a beneficial effect is shown even in the first 5 years since cessation and (3) the risk in long-term (more than 20 years) quitters approaches that of never smokers since the RR of never smokers have a risk of HN cancer which is about one-fifth of that of current smokers.[75]

Table 2 Relative risk of head and neck cancer using dose response meta-analysis for 10-year duration of cessation* and risk since years of quitting smoking*

	Number of studies	RR	95% CI
Risk in 10 years			
Head and neck cancer	37	0.47	0.43 to 0.52
Cancer site			
Oral cancer	12	0.50	0.44 to 0.57
Pharyngeal cancer	7	0.50	0.45 to 0.55
Laryngeal cancer	15	0.49	0.46 to 0.53
Gender			
Men	23	0.48	0.42 to 0.55
Women	3	0.70	0.54 to 0.92
Risk since years of smoking cessation			
<5 years	17	0.67	0.54 to 0.82
5 to <10 years	33	0.50	0.44 to 0.57
10 to <15 years	13	0.37	0.28 to 0.51
15 to <20 years	25	0.29	0.25 to 0.33
≥20 years	19	0.20	0.16 to 0.25

*Reference category: current smokers.
CI, Confidence Interval; RR, relative risk.

Several meta-analyses addressed the effect of smoking on HN cancer risk, but this is the first estimating the effect of smoking cessation on this groups of neoplasms. Previous meta-analysis showed that former smokers had lower RR of HN cancer than current smokers compared with never smokers.[76] Koyanagi *et al* study is a meta-analysis reported that the summary RR for current smokers was 2.68 (95% CI 2.08 to 3.44) was higher than that of former smokers (RR 1.49, 95% CI 1.05 to 2.11).[76] Similarly, in Gandini *et al*'s study, the RR for former smoker was lower than that for current smoker.[75] However, these studies did not aim at directly estimate the effect of quitting compared with continuing smoking.

The rapid decline of HN cancer risk following smoking cessation suggests that smoking acts on late stages of the carcinogenic process on the HN; however, the fact that the effect is still apparent 20 years after cessation suggests that it also acts on early stages of the process.

The incidence of HN cancer remains higher in Europe and North America compared with other countries.[77] Therefore, smoking cessation would be highly beneficial in these countries. The apparently weaker effect of smoking cessation in Asia and other countries could be attributed to different intensity or duration of smoking before quitting, or to the concomitant effect of other risk factors such as dietary factors, alcohol drinking, air pollution or genetic factors, rather than to a shorter duration of quitting among smokers from these countries. In fact, in analyses stratified by duration of quitting, the effect of quitting was less pronounced in studies from Asia than in those from Europe and the USA for comparable categories of duration (results are not shown in detail).

Our study has several strengths, it included a large number of studies and participants that provide high statistical power resulting in stable risk estimates. Separate analysis for sites within the HN and other potential effect modifiers were conducted, and the effect of duration of smoking cessation was precisely estimated. Furthermore, despite heterogeneity in results between studies, publication bias did not appear to have influenced the results.

This study had also some limitations. Heterogeneity between studies was observed which may be due to differences in quality of studies, characteristics of participants, circumstances of tobacco smoking, the presence of residual confounding or other forms of bias. For this reason, we used random effects models in the meta-analysis; in addition, the results did not vary according to methodological quality. Although cohort studies are in general less prone to bias than case–control studies; however, the estimate of quitting in cohort studies might be subject to misclassification because smoking history is often not updated after enrolment of subjects. The fact that our results were comparable between cohort studies and case–control studies suggests that this was not likely to represent a major source of bias. Our search was limited to studies available in English language which means that some studies in different language were not included in our study. Furthermore, some studies did not provide adjusted risk ratio and only crude risk ratios were calculated based on the raw numbers reported in the original publications, leading to higher risk of residual confounding. However, the results of the meta-analysis were similar in studies with original (adjusted) results and in studies with calculated (crude) results.

Conclusion

In conclusion, this meta-analysis of 65 studies from different countries showed that smoking cessation reduces the risk of HN cancer by about half, with a strong effect on the duration of cessation. A protective effect is apparent within the first 5 years of cessation, and the risk is comparable to that of never smokers after 20 years of cessation. Quitting smoking is an essential element of HN cancer prevention.

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Contributors PB is the guarantor and is responsible for the overall content and communication. PB and MK conceived and designed the study; MK and PG selected the studies and extracted the data, with assistance by PB; MK and PB conducted the statistical analysis; MK drafted the manuscript; PB provided substantial comments to the manuscript and is responsible for the overall content and communication.

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