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Polymorphisms in DNA Damage Response Genes and Head and Neck Cancer Risk

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Abstract

Context—Polymorphisms in DNA repair genes have been reported contributing factors in head and neck cancer risk but studies have shown conflicting results.

Objective—To clarify the impact of DNA repair gene polymorphisms in head and neck cancer risk.

Method—A meta-analysis including 30 case-control studies was performed.

Results—Marginally statistically significant association was found for *XRCC1 codon 399* (for Caucasians only), XPD Asp312Asn and *XRCC1 codon 194* variants and head and neck cancer.

Conclusion—Assessments of the effects of smoking, alcohol, HPV and race/ethnicity on the association between DNA repair gene polymorphisms and head and neck cancer are needed.

Keywords

DNA repair genes; *XP*; *ERCC1*; *XRCC1*; *XRCC3*

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the eighth most common cancer worldwide(Parkin et al., 2005), with approximately 48,010 new cases expected in the United States during 2009(Jemal et al., 2009) that varies in terms of incidence, mortality and survival by race. Among the documented risk factors associated with head and neck cancer, smoking and alcohol consumption are by far the main factors, followed by diet, poor oral health, exposure to human papillomavirus (HPV), exposure to environmental carcinogens, and genetic polymorphisms in carcinogen metabolizing enzymes, like alcohol dehydrogenases (ADH) and glutathione-S-transferase (GST) and DNA repair genes(Scully and Bagan, 2009).

Appropriate recognition and repair of DNA damage requires the integrity of the DNA damage response and repair machinery to maintain a normal cellular functionality. A defective DNA damage response can result in apoptosis or may lead to genomic instability,

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unregulated cell growth and an increased cancer risk(Hoeijmakers, 2001). There is considerable variation in the way an individual responds to DNA damage. While some individuals have proper DNA repair capacity (DRC), patients with a defective DNA damage response, such as those with Xeroderma Pigmentosum, are more susceptible to cancer. Phenotypically normal individuals with reduced DRC may also have increased cancer risk; these subjects if properly identified, could be targeted for intervention programs(Li et al., 2009).

There are three major pathways involved in DNA damage repair, depending on the type and magnitude of the damage, base excision repair (BER), nucleotide excision repair (NER) and double strand break (DSB) repair by the homologous recombination or nonhomologous endjoining pathways. Several molecular epidemiologic studies have evaluated the association of head and neck cancer with polymorphisms in DNA repair genes, such as *XPA*(An et al., 2007, Bau et al., 2007, Hall et al., 2007, Sugimura et al., 2006, Abbasi et al., 2009), *XPC*(Kietthubthew et al., 2006, Shen et al., 2001, Sugimura et al., 2006, Wang et al., 2007, Yang et al., 2005), *XPD*(An et al., 2007, Bau et al., 2007, Harth et al., 2008, Huang et al., 2005, Kietthubthew et al., 2006, Majumder et al., 2007, Ramachandran et al., 2006, Sturgis et al., 2002a, Sturgis et al., 2002b, Sturgis et al., 2000, Rydzanicz et al., 2005, Gajecka et al., 2005b), *XPF*(Sugimura et al., 2006), *ERCC1*(An et al., 2007, Sturgis et al., 2000, Sugimura et al., 2006), *XRCC1*(Demokan et al., 2005, Harth et al., 2008, Kietthubthew et al., 2006, Kowalski et al., 2009, Majumder et al., 2005, Olshan et al., 2002, Ramachandran et al., 2006, Sturgis et al., 1999, Tae et al., 2004, Varzim et al., 2003, Yen et al., 2008, Rydzanicz et al., 2005, Gajecka et al., 2005b, Csejtei et al., 2009) and *XRCC3*(Benhamou et al., 2004, Huang et al., 2005, Kietthubthew et al., 2006, Majumder et al., 2007, Werbrouck et al., 2008, Yen et al., 2008, Gajecka et al., 2005b, Rydzanicz et al., 2005). However, the results are conflicting rather than conclusive.

Given the large amount of data already published, it is important to perform a systematic review and meta-analysis of the current literature to assess the association of polymorphisms in DNA repair genes and head and neck cancer. A recent study by Vineis et al.(Vineis et al., 2009) provided a field synopsis of the association of variants in DNA repair genes and cancer risk. Although data for head and neck cancer were reported in this study, the focus of the study was to evaluate the associations between DNA repair gene variants in different types of cancers. Here, we present a meta-analysis with an updated literature review giving rise to a larger number of studies and additional data for a genetic polymorphism each in *XPC* and *ERCC1* that were not reported in the previous review. The association between the DNA damage repair genes, *XPA*, *XPC*, *XPD*, *XPF*, *ERCC1*, *XRCC1* and *XRCC3* with oral, pharyngeal and laryngeal cancer was evaluated. Associations according to race and head and neck sub-site were also evaluated when possible.

METHODS

Literature search and selection criteria

A bibliographical search was performed in both MEDLINE and EMBASE to identify studies that evaluated DNA repair gene polymorphisms and oral, pharyngeal and laryngeal cancer up to January 15, 2010. The search terms used were: (oral or buccal or mouth or “head and neck” or pharyngeal or pharynx or oropharyngeal or laryngeal or larynx) and (cancer or neoplasms or tumor or carcinoma or carcinogenesis) and (“xeroderma pigmentosum complementation group A” XPA or “xeroderma pigmentosum complementation group C” or XPC or “xeroderma pigmentosum complementary group D” or XPD or “xeroderma pigmentosum complementation group F” or XPF or ERCC1 or “X-ray repair cross complementing protein 1” or XRCC1 or “X-ray repair cross complementing protein 3” or XRCC3). The literature cited from the selected articles was manually reviewed

in order to detect articles that might have been missed in the search. The inclusion criteria for the selection of papers were the following: (1) the papers should be written in English or Spanish, (2) the papers should be case-control studies assessing the association between polymorphisms in DNA damage response genes and oral, pharyngeal and laryngeal cancer, including at least one of the following genes: *XPA, XPC, XPD, XPF, ERCC1, XRCC1* and *XRCC3*, (3) studies must provide data to calculate crude odds ratios for oral, pharyngeal and laryngeal cancer. The exclusion criteria were (1) studies on nasopharyngeal cancer, (2) studies that included only cases and no controls, (3) studies with overlapping patient populations, (4) studies that evaluated response to treatment, secondary tumors or recurrence. From each study, the following information was extracted and tabulated: author's last name, country where the study was conducted, year of publication, race/ethnicity of the study population, and genotyping information from cases and controls. The literature search yielded 58 publications. The following studies were excluded: two were published in Chinese(Yang et al., 2008b, Wen et al., 2007) and one in Polish(Rusin et al., 2008); three did not report gene polymorphisms(Cheng et al., 2002, Wei et al., 2005, Yang et al., 2006); two assessed the association between gene polymorphisms and survival(Grau et al., 2009, Handra-Luca et al., 2007); seven evaluated treatment efficacy(Bozec et al., 2007, Carles et al., 2006, Fountzilas et al., 2009, Jun et al., 2008, Kornguth et al., 2005, Quintela-Fandino et al., 2006, Werbrouck et al., 2009); one assessed the potential of gene polymorphisms as predictive and prognostic markers(Koh et al., 2009); two studies were conducted in patients only(Geisler et al., 2005, Hsieh et al., 2003); one study evaluated the potential of gene polymorphisms as risk modifiers of the association of oral contraceptives and oral cancer risk(Applebaum et al., 2009); one did not evaluate the genes of interest(Gajecka et al., 2005a); three studies evaluated the risk of oral leukoplakia(Majumder et al., 2009, Wang et al., 2007, Yang et al., 2008a); two studies evaluated the risk of secondary primary neoplasms(Gal et al., 2005); two reported on haplotypes only(Michiels et al., 2007, Majumder et al., 2009) and one included lung cancer under upper-aerodigestive tract (UADT) cancer(Buch et al., 2005). Therefore, 30 studies that included 19,343 individuals (7,291 cases and 12,052 controls) were considered for the meta-analysis.

Statistical analysis

The association between DNA damage response gene polymorphisms and oral, pharyngeal and laryngeal cancer risk was assessed by calculating odds ratios (OR) with 95% confidence intervals (CI). The combined ORs were calculated under the dominant, recessive, and additive genetic model for each polymorphism using the meta-analysis technique. Stratified combined ORs were calculated for each gene association according to race when data were provided by three or more studies. The majority of studies included more than one head and neck sub-site, and there were some studies conducted in Asian populations that included only oral cavity sub-site cases. Therefore, it was only possible to evaluate subsite-specific meta-ORs for the Asian studies. The between-study heterogeneity was determined by performing the X^2-basedQ statistics test, and it was considered significant for a $P<0.10$(Whitehead and Whitehead, 1991). When significant heterogeneity was observed (Q-test p-value<0.10), the meta-OR was not reported in the results. The fixed-effect model was used under the assumption of homogeneity between studies. The I^2 statistic was used as a confirmatory test for heterogeneity(Higgins et al., 2003, Ioannidis et al., 2007), with I^2 <25%, 25–50%, and >50% representing low, moderate and high degree of heterogeneity, respectively. To explore between-study heterogeneity, stratification by race and control source was conducted. When heterogeneity could not be resolved, meta-ORs were not reported. To detect potential publication bias the Harbord test was employed. The Harbord test is a modified linear regression test for funnel plot asymmetry and is a measurement of small-study effect, considering significance at $p< 0.10$(Harbord et al., 2006). Genotype frequencies in the control populations according to race were calculated and tests on the

equality of proportions was performed for Asian and Caucasian control populations in order to compare differences in genotype frequencies between the two groups. All of the statistical tests were performed using STATA SE (version 10) software (StataCorp LP, College Station, TX).

RESULTS

Thirty publications were included in this meta-analysis with a total of 19,343 subjects (7,291 cases and 12,052 controls). Some of the publications reported on multiple gene polymorphisms. There were five studies with results on the *XPA 5′-UTR (A23G)*, one on *XPD exon 8 C23047T*, one on *XPD exon 8 C23051T*, six on *XPD exon 6 codon 156 C22541A*, twelve on *XPD exon 23 codon 751 C35931A*, six on XPD Asp312Asn, four on *XPC-PAT*, one on XPC Ala499Val, three on *XPC exon 15* Lys939Gln, one on *XPF 5′-UTR T2063A*, four on *ERCC1 3′UTR C8092A*, fifteen on *XRCC1 codon 194*, sixteen on *XRCC1 codon 399*, four on *XRCC1 exon 9 codon 280* Arg280His, and eight on *XRCC3* Thr241Met. The study-specific OR, meta OR and heterogeneity statistics for each polymorphism are shown in Table 1.

XPA polymorphisms

XPA 5′-UTR A23G—Five publications reported data on *XPA 5′-UTR A23G*, for a total of 1,959 cancer cases and 4,279 controls. The source of controls was mostly from hospital populations (three out of five studies). Three of the studies were conducted in Caucasian populations while the other two studies were conducted in Asian populations. There was no significant difference in the frequency of the *XPA 5′-UTR A23G* heterozygous polymorphism between Caucasians and Asians (45.7% vs. 44.5%, p=0.667).

Overall, there was evidence of moderate between-study heterogeneity for the heterozygous variant (A/G) (Q statistics: 8.03 p= 0.090; I^2= 50%, 95% CI: 0–82). Stratification by control source did not resolve heterogeneity. For Caucasian populations moderate heterogeneity was observed (Q statistics: 2.74, p= 0.256; I^2= 26%, 95% CI: 0–92). There was no association between the heterozygous variant and oral, pharyngeal and laryngeal cancer risk and no evidence of small-study effect (p=0.858). For the homozygous and combined variants of *XPA 5′-UTR A23G*, overall there was no association with oral, pharyngeal and laryngeal cancer risk. No evidence of between study heterogeneity was observed for the homozygous variant (G/G) (Q statistics: 3.21; p= 0.523; I^2= 0%, 95% CI: 0–79), and low heterogeneity was observed for the combined variants (A/G and G/G alleles) (Q statistics: 5.28; p= 0.260; I^2= 24%, 95% CI: 0–69). There was no evidence of a small-study effect (homozygous: p=0.867; combined: p=0.546).

Race-specific analysis could only be performed for Caucasians, there was a marginal association between the homozygous variant and oral, pharyngeal and laryngeal cancer risk (meta-OR: 1.11, 95% CI: 0.91–1.34) and no heterogeneity was observed between the studies (Q statistics: 1.23; p= 0.541; I^2= 0%, 95% CI: 0–90). For the combined variant, no association was found for this population (meta-OR: 1.05, 95% CI: 0.88–1.26) and there was no heterogeneity between the studies (Q statistics: 0.90; p= 0.638; I^2= 0%, 95% CI: 0–90).

XPD polymorphisms

XPD Exon 6 C22541A Codon 156—For the *XPD exon 6 C22541A codon 156* polymorphism, six studies involved 1,337 cases and 2,283 controls. The source of controls was mostly healthy population (five out of six studies). Two of the studies were conducted in Asian populations and four studies were conducted in Caucasian populations. There was

no significant difference in the frequency of the *XPD exon 6 C22541A codon 156* heterozygous polymorphism between Caucasians and Asians (45.8% vs. 45.7%, p=0.967).

Large between-study heterogeneity was observed for the heterozygous and the combined variants and this was not resolved after stratification by race and control source. For the *XPD exon 6 C22541A* codon 156 homozygous variant, no association was observed and there was no evidence of between-study heterogeneity. No evidence of a small-study effect on any of the variants (p=0.467; p=0.841; p=0.495).

Race-specific analyses could only be performed for Caucasians. A significant inverse association was seen between the homozygous variant and oral, pharyngeal and laryngeal cancer risk (AA, meta-OR: 0.74, 95% CI: 0.57–0.95). There was no heterogeneity between these studies (Q statistics: 1.04; p= 0.791; I^2= 0%, 95% CI: 0–85).

XPD Exon 23 A35931C Codon 751—Twelve studies reporting the e*xon 23 A35931C* polymorphism of *XPD* were conducted to evaluate its association with oral, pharyngeal and laryngeal cancer risk, for a total of 3,289 cases and 5,135 controls. The source of controls was mostly from the healthy population (ten out of twelve studies). Seven studies were conducted in Caucasian populations, four studies were performed in Asian populations which included oral cavity cases only, and one study was conducted in a mixed population comprised of Caucasians, African-Americans and Hispanics. There was significant difference in the frequency of the *XPD* e*xon 23 A35931C codon 751* heterozygous polymorphism between Caucasians and Asians (31.3% vs. 44.7%, p<0.0001).

There was no association between *XPD Exon 23 A35931C* heterozygous or homozygous variants with oral, pharyngeal and laryngeal cancer risk. Moderate between-studies heterogeneity was observed and there was no evidence of a small-study effect (p=0.976; p=0.684, respectively). For the combined variants, large heterogeneity was observed (A/C + C/C, Q statistics: 61.32; p= 0.000; I^2= 82%, 95% CI: 70–89) and stratification by race and control source did not resolve heterogeneity.

For the race-specific analysis, no independent associations were observed in Caucasians for the heterozygous (meta-OR: 1.00, 95% CI: 0.90–1.12) and homozygous (meta-OR: 0.94, 35% CI: 0.81–1.10) variants. There was low and moderate heterogeneity observed between studies, respectively. For Asians, large heterogeneity was seen for the heterozygous variant (Q statistics: 7.02; p= 0.071; I^2= 57%, 95% CI: 0–86). The meta-OR for the homozygous variant did not show an association with oral cavity cancer risk (meta-OR: 1.06, 95% CI: 0.68–1.66). There was moderate heterogeneity between these studies (Q statistics: 5.26; p= 0.154; I^2= 43%, 95% CI: 0–81).

***XPD* Asp312Asn—**Six studies reported data on the *XPD* Asp312Asn polymorphism for a total of 2,103 cases and 3,719 controls. Five studies were conducted in Caucasian populations and one in an Asian population. There was significant difference in the frequency of the *XPD* Asp312Asn heterozygous polymorphism between Caucasians and Asians (37.5% vs. 44.3%, p=0.010).

A marginally significant association was observed between the *XPD* Asp312Asn heterozygous and combined variants and oral, pharyngeal and laryngeal cancer risk (G/A, meta-OR: 1.14, 95% CI: 1.01–1.29 and G/A + A/A, meta-OR: 1.11, 95% CI: 0.99–1.25, respectively). There was no indication of between-studies heterogeneity for these studies (heterozygous, G/A, Q statistics: 2.53; p= 0.772; I^2= 0%, 95% CI: 0–75, combined variant, G/A + A/A, Q statistics: 2.89; p= 0.717; I^2= 0%, 95% CI: 0–75) and no evidence of a small-study effect (p=0.987 and p=0.350, respectively). For the homozygous variant (A/A),

moderate between-studies heterogeneity was observed (Q statistics: 10.01; p= 0.075; I^2= 50%, 95% CI: 0–80). Stratification by race and control source did not resolve the observed heterogeneity, and there was no evidence of a small-study effect (p=0.100).

Race-specific analyses could only be performed for Caucasians. There was no change in the marginally significant association between the heterozygous and combined variants and oral, pharyngeal and laryngeal cancer risk, and no heterogeneity was observed between the studies (data not shown).

XPD Exon 8 C23047G and C23051G—Only one study evaluated the association between both polymorphisms *XPD Exon 8 C23047G* and *C23051G* and oral, pharyngeal and laryngeal cancer risk. This study was conducted in a non-Hispanic White population including 180 cases and 400 controls. No significant association was evident when estimating the crude ORs for the combined variants.

XPC polymorphisms

XPC-PAT—Four publications reported data for *XPC-PAT*, for a total of 588 cases and 798 controls. The source of controls was mostly a hospital population (three out of four studies). Three studies were conducted in Asian populations and one study was performed in a mixed population comprised of non-Hispanic Whites, African-American, Hispanic-Americans and Asians. There was no significant difference in the frequency of the *XPC-PAT* heterozygous polymorphism between Caucasians and Asians (46.6% vs. 42.8%, p=0.293).

Overall, no significant association was reported for heterozygous or combined variants but a marginally significant association for the homozygous variant (−/−, meta-OR: 1.39, 95% CI: 0.99–1.97) was observed. There was no evidence of heterogeneity between the studies for the heterozygous and homozygous variants and for the combined variants, moderate heterogeneity was observed between the studies. No small-study effect was seen for any of the variants (homozygous: p=0.205; heterozygous: p=0.441; combined: p=0.134).

Similar to the overall population, no association was observed for the heterozygous and combined variants in Asians (−/+, meta-OR: 0.88, 95% CI: 0.65–1.21; −/+ and −/−, meta-OR: 0.92, 95% CI: 0.68–1.23). However, the marginally significant association no longer remained for the homozygous variant in the Asian population (−/−, meta-OR: 1.05, 95% CI: 0.65–1.71) and no heterogeneity observed between any of the Asian studies (data not shown).

XPC Exon 15 Lys939Gln—For the *XPC Exon 15* Lys939Gln polymorphism, three studies reported data for 1,192 cases and 1,787 controls. Most of the controls were drawn from a hospital population (two out of three studies). Two studies were performed in Caucasians, while one study was conducted in Asians. There was no significant difference in the frequency of the *XPD exon 6 C22541A codon 156* heterozygous polymorphism between Caucasians and Asians (40.9% vs. 46.5%, p=0.170).

Overall, no association of this polymorphism with oral, pharyngeal and laryngeal cancer was reported for heterozygous, homozygous or the combined variants. There was no evidence of heterogeneity between the studies for the any of the variants; nor was there a small-study effect (p=0.661; p=0.467; p=0.987, respectively)

XPC Exon 15 Ala499Val—One study reported data for *XPC Exon 15* Ala499Val for a total of 829 cases and 854 controls. This study was conducted in Caucasians, while using hospital population as a source for controls. It reported a significant association between the

homozygous variant and oral, pharyngeal and laryngeal cancer risk (OR: 1.56, 95% CI: 1.09–2.23).

XPF polymorphisms

XPF 5′-UTR T2063A—Only one study reported data on *XPF 5′-UTR T2063A* (122 cases and 241 controls). It was conducted in Asians and used hospital population as a source of controls. No association with the risk of oral, pharyngeal and laryngeal cancer was reported. No other *XPF* gene polymorphisms were reported in the studies reviewed.

ERCC1 polymorphisms

ERCC1 3′UTR C8092A—Four studies were reported for a total of 1,521 cases and 2,177 controls. Three studies were conducted in Caucasians, and one in an Asian population. Regarding the source of controls, two studies used hospital-based controls, while the remaining two used a healthy population. There was no significant difference in the frequency of the *ERCC1 3′UTR C8092A* heterozygous polymorphism between Caucasians and Asians (39.0% vs. 34.1%, p=0.132).

Overall, large heterogeneity between studies was detected for the heterozygous variant, and there was no evidence of a small-study effect (p=0.112). After stratification by race, homogeneity was obtained for the Caucasian population but no association was observed (C/A, meta-OR: 1.04, 95% CI: 0.89–1.21; Q statistics: 1.69; p= 0.429, I^2= 0%, 95% CI: 0–90). For the homozygous and combined variants, no association was reported. There was no between-studies heterogeneity detected for these variants, and no evidence of a small-study effect (p=0.420; p=0.144, respectively). For Caucasians, no association was observed for the homozygous or combined variants (A/A, meta-OR: 0.98, 95% CI: 0.72–1.34; and C/A + A/A, meta-OR: 1.03, 95% CI: 0.98–1.19), and no heterogeneity was observed between studies (data not shown).

XRCC1 polymorphisms

XRCC1 Exon 6 Codon 194—Fifteen studies were reviewed on the association of *XRCC1 exon 6 codon 194*, for a total of 2,330 cases and 3,834 controls. Six studies were performed in Asians (four of these included oral cavity cases only), seven studies were performed in Caucasians, one study was performed in a mixed population of non-Hispanic whites, African-Americans and Mexican-Americans, and one study was conducted in a mixed population of White and non-Whites. Nine studies used healthy population controls and the remaining six studies used hospital population controls. There was significant difference in the frequency of the *XRCC1 exon 6 codon 194* heterozygous polymorphism between Caucasians and Asians (22.8% vs. 13.0%, p<0.0001).

Moderate heterogeneity was seen between the studies that reported data for the heterozygous variant, (C/T, Q statistics: 27.21; p= 0.018; I^2= 49%, 95% CI: 7–72), while large between-study heterogeneity was observed for the combined variant and there was no small-study effect (heterozygous: p=0.621; combined: p=0.535). For the heterozygous variant, stratification by control source did not resolve heterogeneity. There were differences in association of the C/T variant according to race. An increased association for the C/T variant and oral, pharyngeal and laryngeal cancer risk was observed only for the Asian population (Asians, meta-OR: 1.59, 95% CI: 1.27–1.99; Caucasians, meta-OR: 0.92, 95% CI: 0.74–1.14). Moderate heterogeneity was still observed for the Asian population (C/T, Q statistics: 7.44; p= 0.190; I^2= 33%, 95% CI: 0–73), while homogeneity was obtained for the Caucasian population (C/T, Q statistics: 7.83; p= 0.451; I^2= 0%, 95% CI: 0–65). Race stratification was also performed to evaluate the source of heterogeneity for the combined variants. No association was found for Caucasians (C/T + TT variants: meta-OR: 0.92, 95% CI: 0.74–

1.14) and the studies were homogeneous (C/T + TT, Q statistics: 7.71; p= 0.462; I^2= 0%, 95% CI: 0–65). For Asians, large heterogeneity remained and this was not resolved when the Asian studies were limited to oral cavity cases only. For the homozygous variants, overall, a significant increased risk of oral, pharyngeal and laryngeal cancer was observed (meta-OR: 1.69, 95% CI: 1.10–2.58). There was no between-study heterogeneity (T/T, Q statistics: 7.38; p= 0.496; I^2= 0%, 95% CI: 0–64) and no small-study effect (p=0.902).

Tumor site-specific analysis was possible for oral cavity studies, and all of these studies were conducted in Asian populations. Similar to the overall results for the heterozygous variant in Asian populations irrespective of tumor site, a significantly increased association was still observed (meta-OR: 1.50, 95% CI: 1.14–1.97) for oral cavity studies and moderate between-study heterogeneity remained (Q statistics: 4.96; p= 0.175; I^2= 40%, 95% CI: 0–79) (Figure 1).

Race-specific analyses revealed no association of the homozygous variant and cancer risk for Caucasians and there was no heterogeneity between the studies (T/T, Q statistics: 1.21; p= 0.876; I^2= 0%, 95% CI: 0–79) (Figure 2a). In contrast, the meta-OR was significantly associated between the homozygous variant and oral, pharyngeal and laryngeal cancer in Asians (meta-OR: 1.78, 95% CI: 1.13–2.82), and there was no between-study heterogeneity (TT, Q statistics: 6.00, p= 0.306; I^2= 17%, 95% CI: 0–79) (Figure 2b). When the Asian studies were limited to oral cavity cases, there was in increased, but non-significant association between the homozygous variant and oral cavity cancer risk (Asian, oral cavity, meta-OR: 1.50, 95% CI: 0.82–2.74) with moderate heterogeneity between these studies (Q statistics: 4.78; p= 0.189; I^2= 37%, 95% CI: 0–78).

XRCC1 Exon 10 Codon 399—Sixteen studies reported the association of *XRCC1 exon 10 codon 399* and oral, pharyngeal and laryngeal cancer for a total of 3,582 cases and 5,347 controls. Five studies were conducted in Asians (four of these included oral cavity cases only); seven studies were conducted in Caucasians, one study was conducted in non-Hispanic whites, one study was performed in a mix population of non-Hispanic whites, African-Americans and Mexican-Americans, and one study were conducted in a mix population of whites and nonwhites. The majority of the studies used healthy control populations (ten out of fifteen studies). There was no significant difference in the frequency of the *XRCC1 exon 10 codon 399* heterozygous polymorphism between Caucasians and Asians (42.8% vs. 44.5%, p=0.340).

For all of the studies, moderate between-study heterogeneity was observed in the heterozygous variant, while large heterogeneity was observed in the homozygous and combined variants. There was no small-study effect observed for any of these variants (heterozygous: p=0.360; homozygous: p=0.868; combined: p=0.355). Race and tumor-site stratification did not resolve the observed heterogeneity for the heterozygous variant but homogeneity was obtained after stratification by controls source. For the studies that used hospital controls no association between G/A variant and oral, pharyngeal and laryngeal cancer risk was observed [Hospital (G/A, meta-OR: 0.95, 95% CI: 0.82–1.11; Q statistics: 3.56; p= 0.469; I^2= 0%, 95% CI: 0–79)] but there was large heterogeneity for the studies that used healthy controls. For the homozygous variant, stratification by race, control source, and limiting to oral cavity cases, did not resolve heterogeneity. For the combined variants G/A + AA, race-specific analyses revealed large between-study heterogeneity for Asians (G/A + AA, Q statistics: 16.27; p= 0.003; I^2= 75%, 95% CI: 40–90) which was not resolved when the analysis was limited to oral cavity Asian cases only (data not shown). In contrast, a marginal association between G/A + AA variant and oral, pharyngeal and laryngeal cancer risk was observed for Caucasians (meta-OR: 1.14, 95% CI: 1.01–1.27) and homogeneity was observed (Q statistics: 7.63; p= 0.470; I^2= 0%, 95% CI: 0–65).

XRCC1 Exon 9 Codon 280—Four publications reported data on *XRCC1 exon 9 codon 280*, for a total of 879 cases and 926 controls. The source of controls was mostly a healthy population (three out of four studies). Three studies were conducted in Asian populations, while one study was conducted in a Caucasian population. There was significant difference in the frequency of the *XRCC1 exon 6 codon 194* heterozygous polymorphism between Caucasians and Asians (21.7% vs. 10.0%, $p<0.0001$).

Overall, there was no association between *XRCC1 exon 9 codon 280* and the risk of oral, pharyngeal and laryngeal cancer. There was no evidence of between-study heterogeneity for any of the variants. No evidence of a small-study effect was observed for heterozygous and combined variants ($p=0.634$ and $p=0.749$, respectively) but a small study-effect was observed for the homozygous variant ($p=0.003$).

Similarly, no association was observed for *XRCC1 exon 9 codon 280* and the risk of oral, pharyngeal and laryngeal cancer, after limiting the analysis to the Asian population (G/A, meta-OR: 1.11, 95% CI: 0.84–1.46; A/A, meta-OR: 1.62, 95% CI: 0.47–5.57; and G/A + A/A, meta-OR: 1.12, 95% CI: 0.86–1.47) and there was no heterogeneity between studies for any of the variants (data not shown).

XRCC3 polymorphisms

***XRCC3* Thr241Met—**Ten studies reported on *XRCC3* Thr241Met, for a total of 2,235 cases and 3,601 controls. Six studies were conducted in Caucasian populations, three studies were conducted in Asian populations, and one study was conducted in a mixed population of Whites and non-Whites. The source of controls was primarily healthy populations (seven out of nine studies). There was significant difference in the frequency of the *XRCC3* Thr241Met heterozygous polymorphism between Caucasians and Asians (24.9% vs. 48.4%, $p<0.0001$).

Overall, there was no association between *XRCC3* Thr241Met heterozygous, homozygous and combined variants and the risk of oral, pharyngeal and laryngeal cancer, no evidence of between-study heterogeneity for any of the variants and no evidence of a small-study effect (heterozygous: $p=0.457$; homozygous: $p=0.641$; combined: $p=486$). No independent associations were observed for Caucasians or Asians (data not shown). For the Caucasian studies, there was no to low heterogeneity between studies for all of the variants; and for the Asian studies, moderate between-study heterogeneity was observed (data not shown).

DISCUSSION

This meta-analysis of 30 case-control studies assessed the association of polymorphisms in DNA damage response genes with oral, pharyngeal and laryngeal cancer risk. A previous review by Vineis et al.(Vineis et al., 2009), evaluated the association of variants in DNA repair genes and cancer susceptibility in general, without in-depth analysis of head and neck cancer, given the broad scope of their paper. Here, we provide an updated systematic revision of the literature analyzing a larger number of studies and genetic polymorphisms. We have also reported results according to race and head and neck subsite, when possible.

There are three major pathways involved in DNA repair, depending on the type and magnitude of the damage. First, the base excision repair (BER) pathway repairs small base modifications, including oxidatively-induced lesions and single-strand breaks (SSBs), through exposure of the cells to reactive oxygen species (ROS), an endogenous toxic agent. For this pathway, we report results for three polymorphisms in the *XRCC1* gene. The nucleotide excision repair (NER) pathway removes a broader spectrum of genomic damage, including bulky adducts induced by large polycyclic aromatic hydrocarbons, such as those present in benzo[α]pyrene in cigarette smoke, and crosslinks caused by UV-light

photoproducts and chemotherapeutic agents. We have evaluated eleven polymorphisms in nucleotide excision repair genes *XPA, XPC, XPD, XPF* and *ERCC1*. Finally, single (SSBs) and double strand breaks (DSBs), endogenously produced by reactive oxygen species among other factors, can undergo either an error-prone (by non-homologous DNA end joining) or an error-free (by homologous recombination) repair process(Hakem, 2008). For this pathway, we have evaluated one polymorphism in the *XRCC3* gene.

Although there is little evidence about the direct influence of genetic polymorphisms on the functionality of the BER pathway, recent publications with conflicting results have addressed the association between various polymorphisms in BER genes, such as *XRCC1*, and the risk of oral, pharyngeal and laryngeal cancer. Similar to Vineis et al.(Vineis et al., 2009), our meta-analysis revealed an almost two-fold statistically significant increased association between the *XRCC1* codon 194 homozygous T/T variant and oral, pharyngeal and laryngeal cancer. We also report that this statistically significant two-fold increased risk was observed for Asian populations and for Asian oral cavity cancer cases. Comparison of the meta-ORs between Asians and Caucasians was not possible, since the Caucasian studies included more than one head and neck subsite, while the Asian studies were more homogeneous and included oral cavity cancer cases only. Therefore, studies that investigate this association between *XRCC1* and cancer according to race and head and neck subsite are warranted.

XRCC1 is an important component in the BER, because it has the ability to interact with and serves as a scaffold for other key proteins that are responsible for strand incision at the DNA damage site, as well as DNA polymerase β and DNA ligase III, responsible for synthesis and re-joining of the DNA strand break, respectively(Altieri et al., 2008). Although the functional impact of the *XRCC1* codon 194 polymorphisms remains unknown since it was first reported(Shen et al., 1998), it is plausible that changes in amino acid sequence at conserved sites may alter the functionality of the protein. This eventually could lead to a defective BER pathway, increased genomic instability and cancer risk.

XPC, XPA and XPD play important roles the nucleotide excision repair pathway. We observed marginal significant increased associations between XPD Asp312Asn heterozygotes and combined variants, as well as the XPC-PAT homozygous variant and the risk of oral, pharyngeal and laryngeal cancer. Our findings contrast with those reported by Vineis et al.(Vineis et al., 2009) and Manuguerra et al.(Manuguerra et al., 2006), who found no association. However, our meta-analysis included twice as many studies for each of these polymorphisms. Although no associations were seen between the *XPA* 5′-UTR homozygous and *XPD* codon 156 variants, for Caucasians, a marginally increased association and a significantly inverse association were observed, respectively. XPC is responsible for the detection of the DNA damage lesion, while XPA and XPD, along with other proteins are responsible for the local unwinding of the DNA helix and the demarcation of the lesion. The formation of the open complex enables incorporation of endonucleases to excise the damaged site and further gap filling and sealing by DNA polymerase δ and ligase I, respectively(Altieri et al., 2008). It has been reported that the XPD Asp312Asn variant in smokers is significantly correlated with increased aromatic DNA adduct levels(Hou et al., 2002), while another study found decreased DNA damage-induced apoptosis in lymphoblastoid cells(Seker et al., 2001). Although the effect of the *XPD* codon 156 variant on this pathway is unknown, based on our findings, it would be interesting to determine whether this polymorphism provides a gain of function on the XPD protein activity. The functional implication of the *XPA* 5′-UTR (A23G) and *XPC-PAT* variants are unknown. The NER pathway is responsible for removing bulky adducts generated from cigarette smoke, among other environmental carcinogens(Altieri et al., 2008). Cigarette smoke is one of the primary risk factors for head and neck cancer, leading to chromosomal instability(Reshmi

and Gollin, 2005). Thus, further investigation of these polymorphisms in the context of tobacco dose is needed.

It is also important to consider our findings in the context of Human Papillomavirus (HPV), an additional independent risk factor for head and neck cancer. HPV distribution in head and neck cancer seems to be subsite-specific and associated with improved outcome. It has been reported that HPV is mainly distributed in the oropharynx, with the highest distribution in the tonsils(Ragin and Taioli, 2007). Patients with HPV-positive tumors are less likely to have subsequent tumors, recurrences, metastases and new primary tumors, which contrast with what is observed in patients with HPV-negative tumors(Ragin et al., 2004), and distinct molecular profiles are observed between HPV-positive and HPV-negative tumors(Ragin et al., 2006). Therefore, we were interested in exploring whether there was an association between DNA repair gene polymorphisms by anatomic sub-site and HPV status. This analysis could not be performed due to the lack of the studies reporting on gene polymorphisms by anatomic sub-site or HPV status. Further studies are needed to address this interesting question.

A recent report describes an unequal burden of head and neck cancer in the US, in which the disparities were greater in African-American males, who showed a higher incidence and mortality rate for head and neck cancer compared to Caucasians(Goodwin et al., 2008). Also, African-Americans have been reported to have a younger age of onset compared to Caucasians(Gourin and Podolsky, 2006), and a greater likelihood to be smokers(Arbes et al., 1999). Therefore, it is important to have a better understanding of health disparities in minority populations by knowing whether genetic polymorphisms can identify high-risk individuals in the population who could be targeted with chemoprevention strategies. Surprisingly, in our meta-analysis, just one study by Shen et al.(Shen et al., 2001) reported genetic polymorphisms by race (non-Hispanic Whites, African-Americans, Hispanic-Americans, and native Chinese) without finding significant ethnic differences among the four groups. We have also observed a lack of publications concerning African-Americans or individuals of African descent while evaluating other gene polymorphisms(Ragin et al., 2010). Future assessments of genetic polymorphisms in the DNA repair pathway in minority populations are needed.

There are some limitations to this meta-analysis. First, the majority of the studies did not report gene polymorphism by sub-site and smoking status. Therefore, we were unable to perform stratification by those variables, which may explain some negative results. Second, heterogeneity due to ethnic ancestry (mostly Caucasians and Asians) and the small number of studies per ethnic group for the majority of the gene polymorphisms may have limited the ability of this meta-analysis to find true associations. Nevertheless, while performing a summary estimate, an average of each OR is weighted for the precision of each study, thus reducing the possibility of a biased estimate. Furthermore, despite performing stratification by race, when possible, to further assess heterogeneity, at times heterogeneity could not be resolved possibly due to the variation in the PCR methodology (PCR-RFLP, sequencing, melting curve analysis, 5′-exonuclease assay, MALDITOF-MS) employed in some of the studies in the same subgroups. In addition, subsite-specific analyses could only be performed for oral cavity cases, but these studies were only found in Asian populations. Therefore, the level of heterogeneity according to head and neck subsite in each racial group was not comparable. Third, despite conducting a meta-analysis with an almost overall absence of publication bias, it was only observed for the *XRCC1* exon 9 codon 280 homozygous variant. We have not included any unpublished data, which may lead to false-positive results and/or bias. The source of publication bias for that particular variant remains unknown. Despite these limitations, the current meta-analysis has also some advantages. First the overall number of studies and genetic polymorphisms included were consistently

large, compared to previously conducted meta-analysis, which significantly increased the statistical power of the analysis. Second, each of the studies included in the meta-analysis met our inclusion criteria. Third, we did not detect publication bias in the overall estimate that yielded statistically significant associations; which indicates that the pooled results should be unbiased.

CONCLUSION

In conclusion, our meta-analysis supports the idea that polymorphisms in DNA repair genes, *XRCC1* codon 194 and *XPD* codon 156 (in Caucasians), XPD Asp312Asn, may be associated with oral, pharyngeal and laryngeal cancer risk while borderline associations have been suggested for other DNA repair genes. The current meta-analysis also reflects the need for larger studies including minority populations like African-Americans and Hispanics, who happen to experience higher incidence, and worse survival rates for head and neck cancer compared to Caucasians. These larger studies should also include analysis of not only environmental risk factors, such as HPV infection and exposure to cigarette smoke, but also the possible role of gene-gene interactions. Based on our results, plausible candidates like XRCC1 and XPD gene polymorphisms should be included in future large-scale epidemiological studies that eventually will provide a better understanding of the contributions of environmental risk factors and genetic polymorphisms to the development of head and neck cancer and racial disparities in incidence and survival.

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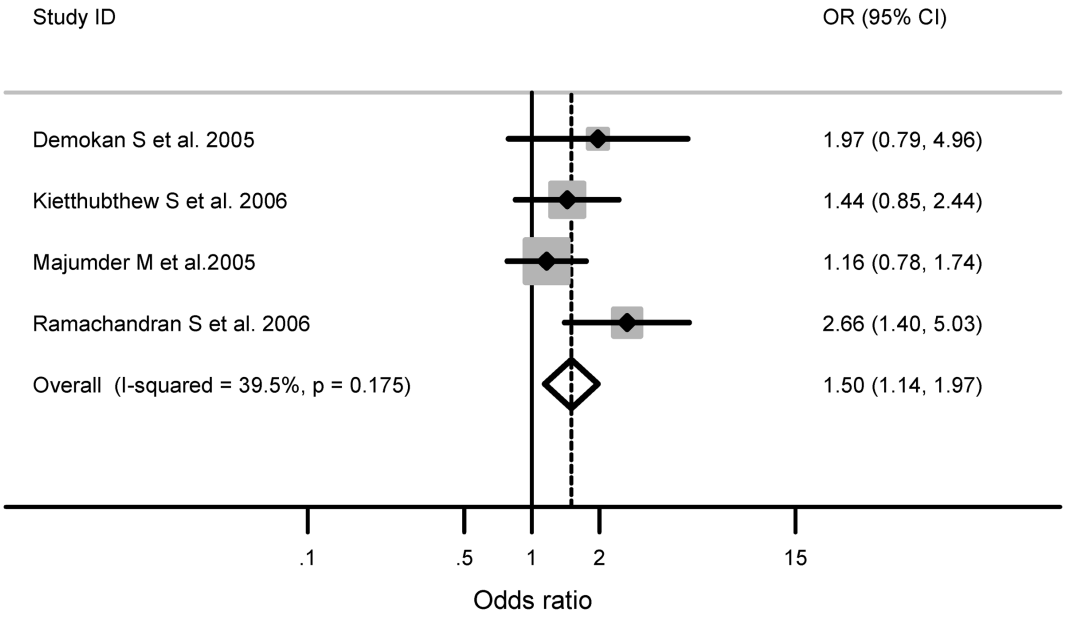

Figure 1.

Published case-control studies that included only oral cavity cases in Asian populations show a significant association of the *XRCC1 exon 6 codon 194 (C/T)* heterozygous variant and the risk of oral cavity cancer. The shaded boxes represent the study-specific odds ratio, and the horizontal lines represent the confidence intervals; the size of each box depict how each study is weighted in the analysis, the diamond represents the meta-OR and its width represents the CI for the meta-OR.

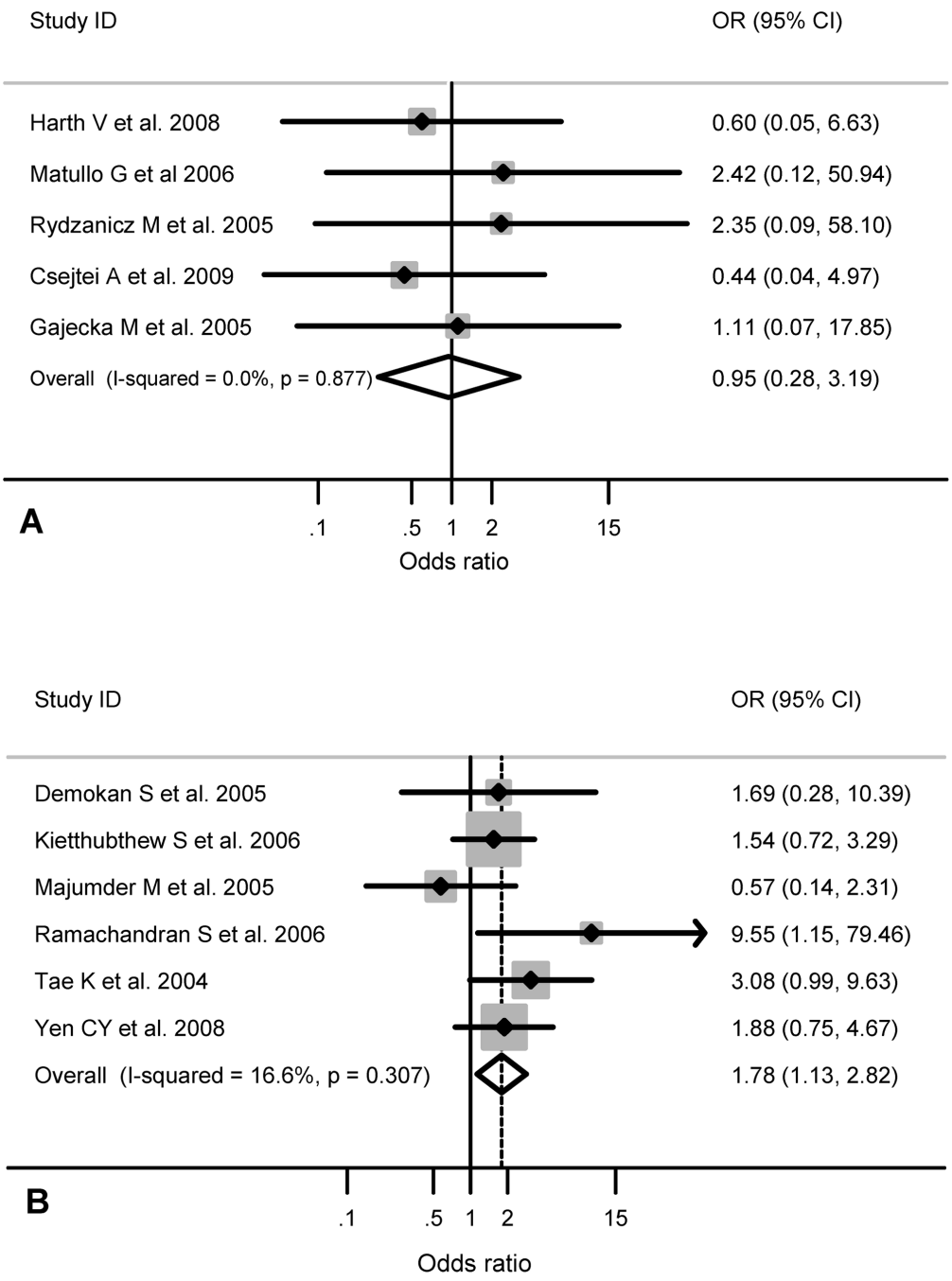

Figure 2.

(A) Published case-control studies show non-significant association of the *XRCC1 exon 6 codon 194 (T/T)* homozygous variant and the risk of head and neck cancer Caucasian populations. The shaded boxes represent the study-specific odds ratio, and the horizontal lines represent the confidence intervals; the size of the boxes depict how each study is weighted in the analysis, the diamond represents the meta-OR and its width represents the CI for the meta-OR. (B) Published case-control studies show a significant association of the *XRCC1 exon 6 codon 194 (T/T)* homozygous variant and the risk of head and neck cancer Asian populations. The shaded boxes represent the study-specific odds ratio, and the horizontal lines represent the confidence intervals; the size of the boxes depict how each

study is weighted in the analysis, the diamond represents the meta-OR and its width represents the CI for the meta-OR.

Table 1

Publications reporting DNA damage response gene polymorphisms and the risk of oral, pharyngeal and laryngeal cancer.

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
XPA 5′-UTR (A23G)					A/A	A/G	G/G	A/A	A/G	G/G	A/G vs. A/A	G/G vs. A/A	A/G + G/G vs. A/A
An J (2007)(An et al., 2007) USA	C (829)	1995–2005	Hospital	Oral cavity, pharynx, larynx	110	360	359	128	346	380	1.21 (0.90–1.62)	1.09 (0.82–1.47)	1.15 (0.88–1.52)
Bau DT (2007)(Bau et al., 2007) Taiwan	A (259)	1997–2005	Healthy	Oral Cavity	38	84	32	29	53	23	1.20 (0.66–2.18)	1.06 (0.51–2.18)	1.16 (0.66–2.05)
Hall J (2007)(Hall et al., 2007) Romania, Poland, Russia, Slovakia and Czeck Republic	C (1690)	2000–2002	Hospital	Oral cavity, pharynx, larynx	75	247	275	294	1125	891	0.86 (0.33–1.69)	1.20 (0.90–1.61)	1.01 (0.77–1.33)
Sugimura T (2006) (Sugimura et al., 2006) Japan	A (363)	1988–2004	Hospital	Oral cavity	23	65	34	74	105	62	1.99 (1.13–3.49)	1.76 (0.94–3.30)	1.91 (1.12–3.24)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	30	109	107	72	281	291	0.93 (0.59–1.50)	0.88 (0.55–1.43)	0.91 (0.58–1.43)
META												1.15 (0.96–1.36)	1.12 (0.95–1.32)
P, Q test											0.090	0.523	0.260
P, Eggers test											0.441	0.867	0.546
XPD Exon 6 C22541A Codon 156					C/C	C/A	A/A	C/C	C/A	A/A	C/A vs. C/C	A/A vs. C/C	C/A + AA vs. C/C
Majumder M (2007) (Majumder et al., 2007) India	A (699)	1999–2005	Healthy	Oral cavity	88	156	64	124	191	73	1.52 (0.91–2.56)	0.82 (0.34–1.95)	1.36 (0.82–2.22)
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	45	52	9	82	62	20	1.15 (0.81–1.62)	1.23 (0.80–1.90)	1.17 (0.85–1.63)
Sturgis EM (2000)(Sturgis et al., 2000)	NHW(685)	1995–1999	Healthy	Oral cavity, pharynx, hypopharynx	62	97	30	154	241	101	0.99 (0.68–1.45)	0.73 (0.44–1.22)	0.92 (0.64–1.32)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	79	28	41	199	309	139	1.04 (0.74–1.45)	0.74 (0.48–1.14)	0.95 (0.69–1.30)
Rydzanicz M (2005) (Rydzanicz et al., 2005)	C (325)	---	Healthy	Oral cavity and larynx	73	82	26	54	69	20	0.88 (0.55–1.41)	0.96 (0.49–1.90)	0.90 (0.57–1.41)

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
Poland													
Gajecka M (2005)(Gajecka et al., 2005b) Poland	C (615)	---	Healthy	Larynx	127	127	32	105	171	43	0.61 (0.43–0.87)	0.62 (0.36–1.04)	0.61 (0.44–0.85)
META												0.84 (0.68–1.04)	
P, Q test											0.052	0.402	0.067
P, Eggers test											0.467	0.841	0.495
XPD Exon 23 A35931C Codon 751					A/A	A/C	C/C	A/A	A/C	C/C	A/C vs. A/A	C/C vs. A/A	A/C + C/C vs. A/A
An J (2007)(An et al., 2007) USA	C (829)	1995–2005	Hospital	Oral cavity, pharynx, larynx	330	394	105	358	386	110	1.10 (0.90–1.35)	1.03 (0.76–1.40)	1.09 (0.90–1.33)
Bau DT (2007)(Bau et al., 2007) Taiwan	A (259)	1997–2005	Healthy	Oral cavity	134	18	2	89	15	1	0.79 (0.38–1.66)	1.32 (0.11–14.86)	0.83 (0.41–1.69)
Hart V (2008)(Harth et al., 2008) Germany	C (612)	1996–1998	Healthy	Oral cavity, pharynx, larynx	111	154	47	108	149	43	1.00 (0.71–1.42)	1.06 (0.65–1.73)	1.02 (0.73–1.42)
Huang WY (2005)(Huang et al., 2005)	W (2,250) B (258) O (186)	1997–2006	Healthy	Oral cavity, pharynx, larynx	240	235	69	345	325	105	1.03 (0.82–1.31)	0.94 (0.66–1.33)	1.02 (0.82–1.27)
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	83	21	1	126	36	2	0.88 (0.48–1.62)	0.75 (0.06–8.5)	0.88 (0.49–1.59)
Majumder M (2007) (Majumder et al., 2007) India	A (699)	1999–2005	Healthy	Oral cavity	158	125	26	190	158	40	0.95 (0.69–1.30)	0.78 (0.45–1.33)	0.92 (0.68–1.24)
Ramachandran S((2006)Ramachandran et al., 2006) India	A (220)	---	Healthy	Oral cavity	49	46	15	71	31	8	2.15 (1.20–3.85)	2.71 (1.06–6.90)	2.27 (1.32–3.90)
Sturgis EM (2000)(Sturgis et al., 2000) USA	NHW (685)	1995–1999	Healthy	Oral cavity, pharynx, hypopharynx	75	83	31	218	221	57	1.09 (0.75–1.57)	1.58 (0.94–2.63)	1.19 (0.85–1.68)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	95	117	34	250	280	114	1.09 (0.79–1.51)	0.78 (0.50–1.23)	1.01 (0.75–1.36)
Matullo G (2006)(Matullo et al., 2006)	C (1176)	1993–1998	Healthy	Oral cavity, pharynx, larynx	34	29	9	397	504	193	0.90 (0.56–1.45)	0.54 (0.25–1.15)	0.80 (0.51–1.27)

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
France, Italy, Spain, United Kingdom, The Nederlands, Greece, Germany, Denmark													
Rydzanicz M (2005) (Rydzanicz et al., 2005) Poland	C (325)	---	Healthy	Oral cavity, larynx							0.89 (0.55–1.46)	0.94 (0.50–1.78)	0.91 (0.57–1.43)
Gajecka M (2005)(Gajecka et al., 2005b) Poland	C (615)	---	Healthy	Larynx							0.61 (0.43–0.87)	0.65 (0.41–1.05)	0.62 (0.44–0.87)
META											1.01 (0.91–1.12)	0.96 (0.82–1.11)	
P, Q test											0.126	0.184	0.000
P, Eggers test											0.719	0.720	0.446
XPD Asp312Asn					G/G	G/A	A/A	G/G	G/A	A/A	G/A vs. G/G	A/A vs. G/G	G/A + A/A vs. G/G
An J (2007)(An et al., 2007) USA	C (771)	1995–2005	Hospital	Oral cavity, pharynx, larynx	330	395	104	370	386	98	1.14 (0.93–1.40)	1.18 (0.86–1.62)	1.16 (0.95–1.40)
Hart V (2008)(Harth et al., 2008) Germany	C (612)	1996–1998	Healthy	Oral cavity, pharynx, larynx	113	158	40	101	145	52	0.97 (0.68–1.38)	0.68 (0.42–1.12)	0.90 (0.64–1.25)
Majumder M (2007) (Majumder et al., 2007) India	A (699)	1999–2005	Healthy	Oral cavity	152	119	34	205	146	36	1.09 (0.79–1.51)	1.27 (0.76–2.12)	1.13 (0.84–1.53)
Sturgis EM (2002a)(Sturgis et al., 2002b) USA	NHW (626)	1995–2001	Healthy	Oral cavity, pharynx, larynx	123	165	25	142	135	36	1.41 (1.01–1.96)	0.80 (0.45–1.40)	1.28 (0.93–1.76)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	93	119	34	258	304	82	1.08 (0.79–1.49)	1.15 (0.72–1.83)	1.10 (0.81–1.49)
Matullo G (2006)(Matullo et al., 2006) France, Italy, Spain, United Kingdom, The Nederlands, Greece, Germany, Denmark	C (1176)	1993–1998	Healthy	Oral, pharyngeal, laryngeal	32	46	4	418	506	170	1.18 (0.74–1.89)	0.30 (0.10–0.88)	0.97 (0.61–1.53)
META											1.14 (1.01–1.29)		1.11 (0.99–1.25)
P, Q test											0.772	0.075	0.717
P, Eggers test											0.987	0.100	0.350
XPD Exon 8 C23047G					C/C	C/G	G/G	C/C	C/G	G/G	C/G vs. C/C	G/G vs. C/C	C/G + G/G vs. C/C

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
Sturgis EM (2002b)(Sturgis et al., 2002a) USA	NHW (580)	1995–1998	Hospital	Oral cavity, oro/hypopharynx, larynx	179	0	1	393	7	0	---	---	0.31 (0.03–2.57)
XPD Exon 8 C23051G					C/C	C/G	G/G	C/C	C/G	G/G	C/G vs. C/C	C/G vs. C/C	C/G + G/G vs. C/C
Sturgis EM (2002b)(Sturgis et al., 2002a) USA	NHW (580)	1995–1998	Hospital	Oral cavity, oro/hypopharynx, larynx	24	2	0	110	5	0	---	---	6.70 (0.27–165.11)
XPC PAT					+/+	+/−	−/−	+/+	+/−	−/−	+/− vs. +/+	−/− vs. +/+	(+/−) + (−/−) vs. +/+
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	60	36	10	89	66	9	0.80 (0.48–1.36)	1.64 (0.63–4.29)	0.91 (0.56–1.49)
Shen H (2001)(Shen et al., 2001) USA	NHW (294) AA (178) HA (103) NCh (109)	1995–1999	Healthy	Oral cavity, pharynx, larynx	102	135	50	141	133	37	1.40 (0.98–1.99)	1.86 (1.13–3.06)	1.50 (1.08–2.09)
Sugimura T (2006) (Sugimura et al., 2006) Japan	A (363)	1988–2004	Hospital	Oral cavity	42	63	17	78	128	35	0.91 (0.56–1.47)	0.90 (0.45–1.79)	0.91 (0.57–1.44)
Yang M (2005)(Yang et al., 2005) South Korea	A (155)	---	Hospital	Oral cavity, oro/hypopharynx, larynx	35	29	9	38	33	11	0.95 (0.48–1.87)	0.88 (0.32–2.39)	0.94 (0.50–1.76)
META											1.09 (0.86–1.37)	1.39 (0.99–1.97)	1.14 (0.92–1.43)
P, Q test											0.270	0.287	0.186
P, Eggers test											0.205	0.441	0.134
XPC Exon 15 Lys939Gln					Lys/Lys	Lys/Gln	Gln/Gln	Lys/Lys	Lys/Gln	Gln/Gln	Lys/Gln vs. Lys/Lys	Gln/Gln vs. Lys/Lys	Lys/Gln + Gln/Gln vs. Lys/Lys
An J (2007)(An et al., 2007) USA	C (771)	1995–2005	Hospital	Oral cavity, pharynx, larynx	312	339	118	315	425	114	0.94 (0.77–1.16)	1.10 (0.90–1.34)	0.97 (0.79–1.18)
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	59	37	10	87	67	10	0.81 (0.48–1.36)	0.85 (0.61–1.19)	0.90 (0.55–1.47)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	83	120	45	230	329	88	1.01 (0.73–1.40)	1.41 (0.91–2.19)	1.10 (0.81–1.49)
META											0.94 (0.80–1.12)	1.17 (0.92–1.49)	0.99 (0.85–1.16)
P, Q test											0.787	0.470	0.737

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
P, Eggers test											0.661	0.467	0.987
XPC Exon 15 Ala499Val					Ala/Ala	Ala/Val	Val/Val	Ala/Ala	Ala/Val	Val/Val	Ala/Val vs. Ala/Ala	Val/Val vs. Ala/Ala	Ala/Val + Val/Val vs. Ala/Ala
An J (2007)(An et al., 2007) USA	C (771)	1995–2005	Hospital	Oral cavity, pharynx, larynx	455	293	91	454	342	58	0.85 (0.69–1.04)	1.56 (1.09–2.23)	0.96 (0.79–1.16)
XPF 5′-UTR (T2063A)					T/T	T/A	A/A	T/T	T/A	A/A	T/A vs. T/T	A/A vs. T/T	T/A + A/A vs. T/T
Sugimura T (2006) (Sugimura et al., 2006) Japan	A (363)	1988–2004	Hospital	Oral cavity	66	47	9	119	101	21	0.83 (0.53–1.33)	0.77 (0.33–1.78)	0.83 (0.53–1.28)
ERCC1 3′UTR C 8092A					C/C	C/A	A/A	C/C	C/A	A/A	C/A vs. C/C	A/A vs. C/C	C/A + A/A vs. C/C
An J (2007)(An et al., 2007) USA	C (771)	1995–2005	Hospital	Oral cavity, pharynx, larynx	455	326	48	485	315	54	1.10 (0.90–1.34)	0.94 (0.62–1.42)	1.08 (0.89–1.31)
Sturgis EM (2002a)(Sturgis et al., 2002b) USA	NHW (685)	1995–1999	Healthy	Oral cavity, pharynx, larynx	183	116	14	172	127	14	0.85 (0.61–1.19)	0.93 (0.43–2.02)	0.87 (0.63–1.19)
Sugimura T (2006) (Sugimura et al., 2006) Japan	A (363)	1988–2004	Hospital	Oral cavity	75	30	17	130	94	17	0.55 (0.33–0.91)	1.73 (0.83–3.59)	0.73 (0.47–1.14)
Abbasi R (2009)(Abbasi et al., 2009) Germany	C (1026)	1998–2000	Healthy	Larynx	146	87	15	392	218	37	1.07 (0.78–1.46)	1.08 (0.58–2.04)	1.07 (0.80–1.45)
META												1.07 (0.80–1.43)	1.00 (0.87–1.14)
P, Q test											0.063	0.546	0.322
P, Eggers test											0.112	0.420	
XRCC1 Exon 6 Codon 194					C/C	C/T	T/T	C/C	C/T	T/T	C/T vs. C/C	T/T vs. C/C	C/T + T/T vs. C/C
Demokan S (2005) (Demokan et al., 2005) Turkey	A (1936)	---	Healthy	Oral cavity	78	14	3	88	8	2	1.97 (0.78–4.95)	1.69 (0.27–10.39)	1.92 (0.83–4.44)
Hart V (2008)(Harth et al., 2008) Germany	C (612)	1996–1998	Healthy	Oral cavity, pharynx, larynx	217	40	1	259	39	2	1.22 (0.76–1.97)	0.59 (0.05–6.62)	1.19 (0.75–1.91)
Kowalski M (2009) (Kowalski et al., 2009) Poland	C (216)	---	Hospital	Head and neck cancr/NOS	71	21	0	102	22	0	1.37 (0.70–2.98)	---	1.37 (0.70–2.68)

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	40	50	16	77	67	20	1.43 (0.84–2.43)	1.54 (0.71–3.29)	1.46 (0.89–2.40)
Majumder M (2005) (Majumder et al., 2005) India	A (658)	1999–2004	Healthy	Oral cavity	249	58	3	285	57	6	1.16 (0.77–1.74)	0.57 (0.14–2.31)	1.11 (0.75–1.64)
Olshan AF (2002)(Olshan et al., 2002) USA	---	1994–1997	Hospital	Oral cavity, pharynx, larynx	82	16	0	135	26	0	1.01 (0.51–2.00)	---	1.01 (0.51–2.00)
Ramachandran S((2006)Ramachandran et al., 2006) India	A (220)	---	Healthy	Oral cavity	66	37	7	90	19	1	2.65 (1.40–5.02)	9.54 (1.14–79.46)	3.00 (1.62–5.56)
Sturgis EM (1999)(Sturgis et al., 1999) USA	NHW (565) MA (39) AA (23)	1995–1998	Hospital	Oral cavity, oro/hypopharynx, larynx	180	22	1	363	61	0	0.72 (0.43–1.22)	6.04 (0.24–149.04)	0.76 (0.46–1.27)
Tae K (2004)(Tae et al., 2004) Korea	A (315)	1997–2001	Hospital	Oral cavity, oro/hypopharynx, larynx	59	52	9	101	39	5	2.28 (1.35–3.85)	3.08 (0.98–9.62)	2.37 (1.43–3.93)
Yen CY (2008)(Yen et al., 2008) Taiwan	A (2010)	---	Hospital	Oral squamous cell carcinoma/NOS	48	40	15	54	35	9	1.28 (0.70–2.33)	1.87 (0.75–4.67)	1.41 (0.81–2.45)
Varzim G (2003)(Varzim et al., 2003) Portugal	C (266)	1998–1999	Healthy	Larynx	80	8	0	160	18	0	0.88 (0.37–2.13)	---	0.89 (0.37–2.13)
Matullo G (2006)(Matullo et al., 2006) France, Italy, Spain, United Kingdom, The Nederlands, Greece, Germany, Denmark	C (1176)	1993–1998	Healthy	Oral cavity, pharynx, larynx	78	4	0	951	141	2	0.34 (1.24–0.96)	2.42 (0.11–50.93)	0.34 (0.12–0.95)
Rydzanicz M (2005) (Rydzanicz et al., 2005) Poland	C (325)	---	Healthy	Oral cavity and larynx	165	16	1	129	14	0	0.89 (0.42–1.90)	2.35 (0.09–58.10)	0.95 (0.45–2.00)
Csejtei A (2009)(Csejtei et al., 2009) Hungary	C (211)	2000–2003	Healthy	Head and neck cancer/NOS	96	11	1	85	15	2	0.65 (0.28–1.49)	0.44 (0.04–4.97)	0.63 (0.28–1.38)
Gajecka M (2005)(Gajecka et al., 2005b) Poland	C (615)	---	Healthy	Larynx	262	27	1	291	33	1	0.91 (0.53–1.55)	1.11 (0.07–17.85)	0.91 (0.54–1.55)
META												1.69 (1.10–2.58)	
P, Q test											0.018	0.646	0.005
P, Eggers test											0.621	0.902	0.535

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
XRCC1 Exon 10 Codon 399					G/G	G/A	A/A	G/G	G/A	A/A	G/A vs. G/G	A/A vs. G/G	G/A + A/A vs. G/G
Demokan S (2005) (Demokan et al., 2005) Turkey	A (1936)	---	Healthy	Oral cavity	42	41	12	39	46	13	0.82 (0.45–1.51)	0.85 (0.34–2.10)	0.83 (0.47–1.48)
Hart V (2008)(Harth et al., 2008) Germany	C (612)	1996–1998	Healthy	Oral cavity, pharynx, larynx	114	166	30	143	121	36	1.72 (1.22–2.41)	1.04 (0.60–1.79)	1.57 (1.13–2.16)
Huang WY (2005)(Huang et al., 2005)	W (2,250) B (258) O (186)	1997–2006	Healthy	Oral cavity, pharynx, larynx	266	219	40	338	338	81	0.82 (0.65–1.04)	0.62 (0.41–0.94)	0.79 (0.63–0.98)
Kowalski M (2009) (Kowalski et al., 2009) Poland	C (216)	---	Hospital	Head and neck cancer/NOS	37	44	11	49	53	22	1.09 (0.61–1.97)	0.66 (0.28–1.53)	0.97 (0.56–1.68)
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	55	45	6	67	74	23	0.74 (0.44–1.23)	0.31 (0.12–0.83)	0.64 (0.39–1.05)
Majumder M (2005) (Majumder et al., 2005) India	A (658)	1999–2004	Healthy	Oral cavity	135	143	32	158	163	27	1.02 (0.84–1.28)	1.38 (0.79–2.43)	1.08 (0.79–1.47)
Li C (2007)(Li et al., 2007)	NHW (1684)	1995–2003	Hospital	Oral cavity, oro/hypopharynx, larynx	335	374	121	360	385	109	1.04 (0.84–1.28)	1.19 (0.88–1.60)	1.08 (0.89–1.31)
Ramachandran S((2006)Ramachandran et al., 2006) India	A (220)	---	Healthy	Oral cavity	46	48	16	73	33	4	2.30 (1.29–4.10)	6.34 (1.99–20.17)	2.75 (1.59–4.75)
Sturgis EM (1999)(Sturgis et al., 1999) USA	NHW (565) MA (39) AA (23)	1995–1998	Hospital	Oral cavity, oro/hypopharynx, larynx	94	77	32	181	197	46	0.75 (0.52–1.08)	1.33 (0.80–2.24)	0.86 (0.62–1.21)
Tae K (2004)(Tae et al., 2004) Korea	A (315)	1997–2001	Hospital	Oral cavity, oro/hypopharynx, larynx	69	51	9	86	64	7	0.99 (0.611–1.61)	1.60 (0.56–4.52)	1.05 (0.66–1.68)
Varzim G (2003)(Varzim et al., 2003) Portugal	C (266	1998–1999	Healthy	Larynx	37	40	11	80	80	18	1.08 (0.62–1.86)	1.32 (0.56–4.07)	1.13 (0.67–1.89)
Matullo G (2006)(Matullo et al., 2006) France, Italy, Spain, United Kingdom, The Nederlands, Greece, Germany, Denmark	C (1176)	1993–1998	Healthy	Oral cavity, pharynx, larynx	34	38	10	484	482	128	1.02 (0.92–1.12)	1.11 (0.53–2.31)	1.12 (0.71–1.77)
Rydzanicz M (2005) (Rydzanicz et al., 2005)	C (325)	---	Healthy	Oral cavity and larynx	63	98	21	59	63	21	1.46 (0.91–2.34)	0.13 (0.05–0.33)	1.33 (0.84–2.08)

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
Poland													
Csejtei A (2009)(Csejtei et al., 2009) Hungary	C (211)	2000–2003	Healthy	Head and neck cancer/NOS	50	47	11	53	41	8	1.22 (0.69–2.15)	1.46 (0.54–3.92)	1.25 (0.73–2.16)
Gajecka M (2005)(Gajecka et al., 2005b) Poland	C (615)	---	Healthy	Larynx	106	153	34	124	145	50	1.23 (0.87–1.74)	0.80 (0.48–1.32)	1.12 (0.81–1.56)
META													
P, Q test											0.014	0.000	0.004
P, Eggers test											0.360	0.868	0.355
XRCC1 Exon 9 Codon 280					G/G	G/A	A/A	G/G	G/A	A/A	G/A vs. G/G	A/A vs. G/G	G/A + A/A vs. G/G
Hart V (2008)(Harth et al., 2008) Germany	C (612)	1996–1998	Healthy	Oral cavity, pharynx, larynx	283	28	1	270	30	0	0.89 (0.51–1.53)	2.86 (0.11–70.57)	0.92 (0.54–1.58)
Majumder M (2005) (Majumder et al., 2005) India	A (658)	1999–2004	Healthy	Oral cavity	228	79	3	264	81	3	1.12 (0.79–1.61)	1.15 (0.23–5.79)	1.13 (0.79–1.61)
Ramachandran S((2006)Ramachandran et al., 2006) India	A (220)	---	Healthy	Oral cavity	77	31	2	83	26	1	1.28 (0.70–2.35)	2.15 (0.19–24.25)	1.32 (0.73–2.39)
Tae K (2004)(Tae et al., 2004) Korea	A (315)	1997–2001	Hospital	Oral cavity, oro/hypopharynx, larynx	113	21	1	139	29	0	0.89 (0.48–1.64)	3.68 (0.14–91.38)	0.93 (0.51–1.71)
META											1.06 (0.83–1.35)	1.74 (0.55–5.52)	1.08 (0.85–1.37)
P, Q test											0.749	0.901	0.790
P, Eggers test											0.648	0.003	0.737
XRCC3 Thr241Met					Thr/Thr	Thr/Met	Met/Met	Thr/Thr	Thr/Met	Met/Met	Thr/Met vs. Thr/Thr	Met/Met vs. Thr/Thr	Thr/Met + Met/Met vs. Thr/Thr
Kietthubthew S (2006) (Kietthubthew et al., 2006) Thai	A (304)	1998–1999	Hospital	Oral cavity	83	22	1	140	23	1	1.61 (0.84–3.07)	1.68 (0.10–27.32)	1.62 (0.86–3.04)
Majumder M (2005) (Manuguerra et al., 2006) India	A (658)	1999–2004	Healthy	Oral cavity	201	97	12	220	120	8	0.88 (0.63–1.22)	1.09 (0.48–2.49)	0.90 (0.66–1.24)
Huang WY (2005)(Huang et al., 2005)	W (2,250) B (258) O (186)	1997–2006	Healthy	Oral cavity, pharynx, larynx	232	223	61	329	334	97	0.94 (0.74–1.20)	1.41 (0.95–2.10)	1.02 (0.81–1.28)

Author (year) Country	Ethnic Groups (n)	Recruitment Period	Control Source	Tumor Sites	Cases (n)			Controls (n)			Crude OR (95% CI)		
Yen CY (2008)(Yen et al., 2008) Taiwan	A (2010	---	Hospital	Oral squamous cell carcinoma/NOS	96	7	0	89	9	0	0.72 (0.25–2.01)	---	0.72 (0.26–2.02)
Werbrouck J (2008) (Werbrouck et al., 2008) Belgium	C (309)	2004–2006	Healthy	Oral cavity, pharynx, larynx	69	59	29	44	75	33	0.50 (0.30–0.83)	0.63 (0.33–1.20)	0.54 (0.34–0.87)
Benhamou S (2004) (Benhamou et al., 2004) France	C (422)	1988–1992	Healthy	Oral cavity, pharynx, larynx	42	54	23	47	89	30	0.67 (0.39–1.16)	1.11 (0.54–2.28)	0.77 (0.46–1.28)
Matullo G (2006)(Matullo et al., 2006) France, Italy, Spain, United Kingdom, The Nederlands, Greece, Germany, Denmark	C (1176)	1993–1998	Healthy	Oral cavity, pharynx, larynx	29	39	14	383	544	167	0.95 (0.58–1.56)	1.11 (0.57–2.15)	0.98 (0.62–1.57)
Rydzanicz M (2005) (Rydzanicz et al., 2005) Poland	C (325)	---	Healthy	Oral cavity, larynx	22	71	89	14	71	58	0.64 (0.30–1.34)	0.98 (0.46–2.06)	0.79 (0.39–1.60)
Gajecka M (2005)(Gajecka et al., 2005b) Poland	C (615)	---	Healthy	Larynx	135	125	33	144	131	47	1.02 (1.72–1.43	0.75 (0.45–1.24)	0.95 (0.69–1.30)
Shen H (2002)(Shen et al., 2002) USA	NHW (721)	1995–2001	Healthy	Oral cavity, pharynx, larynx	150	159	58	141	170	43	0.88 (0.64–1.21)	1.27 (0.80–2.00)	0.96 (0.71–1.29)
META											0.89 (0.78–1.01)	1.07 (0.88–1.31)	0.93 (0.82–1.05)
P, Q test											0.277	0.521	0.370
P, Eggers test											0.457	0.641	0.486

Abbreviations: C= Caucasians, A= Asians, NHW= Non-Hispanic whites, MA= Mexican-Americans, AA= African-Americans, HA= Hispanic-Americans, NCh= Native Chinese, B= Black, O= Others, NOS= not otherwise specified,