A review of genetic epidemiology of head and neck cancer related to polymorphisms in metabolic genes, cell cycle control and alcohol metabolism

Introduction

Head and neck cancers (HNC), including oral cavity, oropharynx, hypopharynx and larynx are among the most common types of cancer and represent a major health problem. There are approximately 540,000 new cases and 271,000 deaths annually worldwide for a mortality of approximately 50%. HNC represent approximately 3% of all cancers in the United States, but are much more prevalent in some parts of South America (Brazil, Uruguay and Argentina). Development of HNC is a multifactorial process associated with a variety of risk factors. Tobacco and alcohol consumption are established risk factors for HNC (synergistic in persons who both smoke tobacco and drink alcohol), even though other factors may affect risk. In developing countries, other factors, like betel and tobacco chewing, human papillomavirus infection or drinking hot beverages, also play an important role. In recent years, evidence has accumulated to support the hypothesis that diet may also play an important aetiological role in development of disease, and 10-15% of squamous cell carcinoma of the head and neck (SCCHN) cases in Europe are associated with a low intake of fruit and vegetables. A family history of cancer is another important risk factor for HNC, which implies that genetics contributes to HNC susceptibility.

Materials and methods

Herein, we review the published studies concerning genetic susceptibility to HNC. A variety of genes are associ-
ated with HNC carcinogenesis, including those involved in carcinogen metabolism, alcohol metabolism, folate metabolism, DNA repair, cell-cycle control and oncogenes. We have focused our attention on genes involved in carcinogen metabolism, alcohol metabolism and cell-cycle control.

A PubMed search was performed until to the end of September 2011. The following terms were used: head and neck cancer (with both synonymous and plural forms), as well as the truncated words genetic*, allel*, or polymorphi*.

### Results

The literature search identified the below list of genes:

- **Cytochrome P450 2E1 (CYP2E1)**
- **Cytochrome P450 1A1 (CYP1A1)**
- **Glutathione S-transferase (GSTM1)**
- **Glutathione S-transferase (GSTT1)**
- **Glutathione S-transferase (GSTP1)**
- **N-acetyltransferase 2 (NAT2)**
- **Human microsomal epoxide hydrolase (EPHX1)**
- **Aldehyde dehydrogenase 2 (ALDH2)**
- **Alcohol dehydrogenase isoenzymes (ADH)**
- **X-ray repair cross complementary 1 (XRCC1)**
- **Xeroderma pigmentosum complementary group D (XPD)**
- **Cyclin D1 (CCND1)**
- **P53 tumour suppressor**
- **P73**

Tables I and II report, respectively, a summary of primary studies of genetic polymorphisms in genes involved in carcinogen metabolism, alcohol metabolism and cell-cycle control and the risk of HNC, and a summary of meta-analyses of genetic polymorphisms of the aforementioned gene classes and HNC risk.

Below we discuss the significance of each gene in the etiology of HNC:

- **Cytochrome P450 2E1 (CYP2E1)**, a member of the cytochrome P-450 superfamily, is a naturally ethanol-inducible phase I enzyme. It is mainly involved in the metabolic activation of low molecular weight compounds such as nitrosamines and alcohol metabolism. The variant c2 allele, which contains a novel RsaI/PstI site in the 5'-flanking region of the CYP2E1 gene, appears to be associated with decreased enzyme activity.

- **Cytochrome P450 1A1 (CYP1A1)** is an important phase I enzyme that plays an essential role in the metabolic activation of major classes of pro-carcinogens such as benzopyrene, a prototypic polycyclic aromatic hydrocarbon. An Ile-Val substitution in codon 462 of the CYP1A1 gene, which is in the haem-binding region, results in a 2-fold increase in microsomal enzyme activity and, in Caucasians, is in complete linkage disequilibrium with the CYP1A1 MspI polymorphism, which is also associated with increased catalytic activity. We identified some studies related to the association of CYP1A1 with HNC risk published before July 2007, regarding the relation of the CYP1A1 Ile-Val substitution at codon 462 to HNC. In 4 studies, the risk for HNC in subjects with the Ile/Val and/or Val/Val genotypes was significantly higher than that for subjects with the Ile/Ile genotype, suggesting that the Val allele may be associated with increased risk for HNC. A meta-analysis of studies that examined the association of the CYP1A1 Ile-Val substitution with risk for HNC revealed that the Ile/Val and Val/Val genotypes tend to increase HNC risk with an odds ratio (OR) [95% confidence interval (CI)] compared with Ile/Ile of 1.32 (0.95-1.82). Successive studies suggest that significant differences in the distribution of certain haplotypes of CYPs have been reported, and the prevalence of certain genotype combinations of CYPs and GSTS has indicated the importance of gene-gene interactions in HNSCC risk.

The pooled data indicated that CYP1A1 MspI polymorphism might be a risk factor for laryngeal cancer, particularly in Caucasians. For Asians, it might slightly increase the susceptibility to laryngeal cancer. However, the data failed to demonstrate a marked association between the CYP1A1 exon 7 polymorphism and laryngeal cancer risk. The CYP1A1 exon 7 polymorphism...
was associated with oral and pharyngeal cancer only for ever smokers, when studied independently in the pooled analysis, although the CYP1A1MspI variant homozygote allele (m2/m2) was significantly associated with this cancer in both the meta-analysis and pooled analysis. When analyzing the complete genotype of GSTM1 deletion and CYP1A1 MspI polymorphism, the risk of oral and pharyngeal cancers seems to be higher for never smokers than for ever smokers. It should be highlighted that the results of the pooled analysis varied according to the type of controls considered, indicating that a selection bias might be present in some studies, and therefore the results should be considered with caution. There is no indication for population testing of these genes as risk factors for oral and pharyngeal cancer. Overall, Zhou et al. 2009 reported that variant genotypes of CYP1A1 might not be risk factors for oral cancer.

- The glutathione S-transferases are a family of phase II xenobiotic metabolizing enzymes catalyzing the conjugation reactions of reactive intermediates of electrophilic compounds with cytosolic glutathione. Based on sequence similarities, human cytosolic glutathione S-transferases are mainly coded for at 5 loci: GSTA (a), GSTT1 (h), GSTM1 (l), GSTP1 (p), and GSTM3 (c). Polymorphisms in these genes, possibly by altering their expression and functional activities, may affect carcinogen activation/detoxification and DNA repair. Three alleles have been identified at the glutathione S-transferase M1 (GSTM1) locus: GSTM1*0, GSTM1*A, and GSTM1*B. Two major alleles have been identified at the glutathione S-transferase T1 (GSTT1) locus: GSTT1*A1 and GSTT1*A0. Previous studies showed that a homozygous deletion (0/0), or null genotype, at either the GSTM1 locus or the GSTT1 locus resulted in enzyme function loss, and thus it was hypothesized to be related to the susceptibility to HNC.

- For HNCs since July 2007, 36 ORs from 58 studies of the null GSTM1 genotype vs the positive genotype were > 1, suggesting that the null GSTM1 genotype may be associated with increased risk for HNC. Sixteen 17 35-49 of the 21 studies 14 47 56-74 showed a significantly higher risk for HNC in subjects with the null GSTM1 genotype than in subjects with the positive genotype. Two meta-analyses 50 51 of studies that examined the association of GSTM1 with risk for HNC revealed that the null genotype significantly increases the risk with ORs (95%CI) of 1.23 (1.06-1.42) and 1.50 (1.21-1.87) compared with the positive genotype. Successive studies suggest that GSTM1 has been reported to detoxify the bioreactive diol-exoxides of PAHs, which is important in environmental and occupational carcinogenesis. The data supported that GSTM1 deficiency was associated with laryngeal cancer risk.

- We identified 23 ORs from 42 studies published before July 2007 of the null GSTT1 genotype vs the positive genotype that were > 1, and 7 studies 39-44 48 52-55 showing a significantly higher risk for HNC in subjects with the null genotype than with the positive genotype, suggesting that the null GSTT1 genotype may be associated with increased risk for HNC. A meta-analysis 30 of studies that examined the association of GSTT1 with risk of HNC revealed that the null genotype tends to increase HNC risk with ORs (95%CI) of 1.17 (0.98-1.40) compared with positive genotype. For GSTP1, four 56-59 of the 21 studies 14-47 56-74 showed a significantly higher risk for HNC in individuals with the Ile/Val and/or Val/Val genotypes than in those with the Ile/Ile genotype. No studies showed a significantly lower risk with the Ile/Val and/or Val/Val genotypes.
than the Ile/Ile genotype. The 105 Val allele might be associated with an increased risk for HNC. One meta-analysis revealed that the Ile/Val and Val/Val genotypes tend to increase HNC risk with ORs (95% CI) of 1.10 (0.92–1.31) compared with the positive genotype 3.50. There have been no studies after July 2007 investigating the correlation between HNC and GSTP1.

- **Human arylamine N-acetyltransferases** play a key role in the metabolism of drugs and environmental chemicals and in the metabolic activation and detoxification of procarcinogens. Phenotyping analyses have revealed an association between NAT enzyme activities and the risk of developing several forms of cancer 12.75. The NAT2 isoenzyme functions to both activate and deactivate arylamine and hydrazine drugs and carcinogens. Polymorphisms in this gene are responsible for the N-acetylation polymorphism in which human populations segregate into rapid, intermediate and slow acetylator phenotypes. Polymorphisms in NAT2 are also associated with higher incidences of cancer and drug toxicity. A second arylamine N-acetyltransferase gene (NAT1) is located near NAT2 (RefSeq, Jul 2008). For HNC, all 7 ORs 14,23,64,76 for the slow NAT2 genotype vs the rapid genotype were > 1, suggesting that the slow NAT2 genotype may be associated with an increased risk for HNC 3.7. Ying XJ 80, in his meta-analysis published in 2011, claimed that there was overall lack of association between NAT2 polymorphism and laryngeal cancer risk; however, NAT2 slow acetylation may contribute to a risk factor for laryngeal cancer in Asians, but not in Caucasians. In 2008, Buch 81 published results that demonstrated how fast NAT2 acetylation was a risk factor for oral cancer. Demokan in 2010 82 published that NAT1 and NAT2 gene combinations may influence the risk of developing head and neck cancer.

- **Human microsomal epoxide hydrolase (EPHX1)** plays an important role during xenobiotic detoxification of exogenous chemicals such as polycyclic aromatic hydrocarbons (PAHs), which are produced during the use of coal tar, cokke, bitumen or during cigarette smoking 32,83. Two amino acid-altering polymorphisms, Tyr113His and His139Arg, have been identified in EPHX1 and both are associated with alterations in mEH activity. The EPHX1 His113 variant shows a 40% decrease in EH activity, whereas the EPHX1 Arg139 variant shows 25% increased enzyme activity 2. A comprehensive systematic review of available studies published up to 2011, consisting of 91 studies, 84 (31,144 cases and 42,439 controls) for Tyr113His and 77 (28,496 cases and 38,506 controls) for His139Arg 83. Results of analysis of these two polymorphisms in different cancer types revealed that the low activity allele (H) of Y113H was highly associated with decreased risk of lung cancer (OR = 0.88, 95% CI = 0.80–0.96; p = 0.005) and HNC (OR = 0.86, 95% CI = 0.77–0.97; p = 0.014); the high activity allele (R) of H139R was significantly associated with increased risk of lung cancer (OR = 1.18, 95% CI = 1.04–1.33; p = 0.010), but not of HNC (OR = 1.05, 95% CI = 0.93–1.17, p = 0.447). However, the homozygous variant (RR) of H139R showed increased risk of HNC (OR = 1.34, 95% CI = 0.98–1.82, p = 0.065).

- **Aldehyde dehydrogenase 2 (ALDH2)** is a key gene in alcohol metabolism, and determines blood acetaldehyde concentrations after drinking 10. A single point alteration in ALDH2 results in the ALDH2*2 allele. The protein encoded by ALDH2*2 has a Glu to Lys substitution at residue 487, resulting in an inactive subunit and the inability to metabolize acetaldehyde. The ALDH2*2 allele is rare in Western populations, but prevalent in East Asian populations. ALDH2*2/*2 homozygotes have serum acetaldehyde levels that are 13 times higher and heterozygotes have levels 4 times higher than those in *1/*1 homozygotes. Six studies 11,40, 84,87 reported a relation between ALDH2 polymorphisms and risk for HNC, and all were conducted in Japanese populations. Four studies 35,79,80,82 showed a significantly increased risk for HNC in *1/*2 heterozygotes compared with *1/*1 homozygotes 2. Mc Kay et al. found that five genetic variants at three loci, 4q21, 4q23 and 12q24, were significantly associated with HNC risk 10.

- **ADH isoenzymes**, which are primarily involved in ethanol oxidation, consist of subunits encoded by ADH2 and ADH3. In contrast to ADH2, ADH3 is highly polymorphic in Caucasians. Of the 2 allelic variants, the ADH3*1 allele is associated with higher enzyme activity than the ADH3*2 allele and occurs in Caucasians at frequencies of 55–63%. In 5,19,37,88–93 of 8 studies 19,37,88–93, ADH3*2/*1 heterozygotes showed decreased risk for HNC compared with *2/*2 homozygotes. However, in 9 studies 19,37,88–93, ADH3*1/*1 homozygotes showed increased risk for HNC 2. In accordance with Mc Kay and co-workers, three independent variants, ADH1B (rs1229984), ADH7 (rs1573496) and ADH1C (rs698), have also been associated with HNC risk in European populations. The effects of these three variants were generally present for each HNC subsites, but more pronounced in oesophageal cancers and males. Strong heterogeneity was found with rs1229984 when stratifying by alcohol consumption.

- **Polymorphisms in X-ray repair cross complementing protein 1 (XRCC1)**, including Arg194Trp, Arg280His and Arg399Gln, have been described. Although the biochemical and biologic characteristics of the variants have not been determined, it has been reported that individuals with the XRCC1 399Gln variant show increased sister chromatid exchange after treatment with a tobacco-specific carcinogen 5. However, as already described by Gonzalez et al. 94 in 2002, the functional roles for these polymorphisms are unknown, even if
they are associated with high risk in non-smokers and in non-alcohol drinkers. The results for the relationship between XRCC1 polymorphisms and HNC are inconsistent as highlighted in two meta-analyses published in 2005.

- Xeroderma pigmentosum complementary group D (XPD) has 2 functions: nucleotide excision repair and basal transcription as part of the transcription factor complex, TFIH. Polymorphisms, such as 22,541AC and 35,931CA, have been identified. Individuals homozygous for the variant genotype of XPD have suboptimal DNA repair capacity. Hiyama et al. in 2008 analyzed 4 studies of the genotype at nucleotide 22,541 and 5 studies of the genotype at nucleotide 35,931 of XPD. According to these investigations, individuals homozygous for the variant genotype of XPD have suboptimal DNA repair capacity.

- The CCND1 gene encodes a key cell cycle regulatory protein, cyclin D1, which regulates transition from $G_1$ to the $S$ phase during cell division. High activity of cyclin D1 leads to premature cell passage through the $G_1$-$S$ transition, resulting in propagation of unrepaired DNA damage and accumulation of genetic errors, therefore leading to selective advantage for abnormal cell proliferation. Numerous studies found that CD1 G/A870 single nucleotide polymorphism is associated with two different splice variant transcripts: CD1a and CD1b. CD1a encodes for the full-length native form of the CD1 protein, and CD1b encodes for a truncated alternate CD1 protein. This strongly suggests that individuals with numerous copies of the CCND1-870A are more likely to bypass the $G_1$-$S$ checkpoint, thus contributing to cancer development. Hiyama et al. evaluated six ORs from 9 studies of the GA genotype vs. the GG genotype which at nucleotide position 870 were $< 1$, and 7 ORs of the AA genotype vs GG which were $< 1$. These results are statistically relevant and suggest that the A allele may be associated with decreased risk for HNC. On the basis of the studies published in 2011, cell cycle regulation may play a role in oral carcinogenesis and the CCND1 rs9344 polymorphism may be a useful biomarker for oral oncology. The data reported in the literature indicates that CD1 genotype and protein expression as important risk markers for laryngeal cancer and suggest future trials targeting upstream regulators of CD1 transcription.

- Dysfunction in the $p53$ tumour suppressor gene (located at 17p13) is implicated in many cancers, including HNC, and has received the most attention. The production of $p53$ is increased in response to cellular insults or DNA damage, and $p53$ then induces cell cycle arrest at the $G_1/S$ junction. If the damage is irreparable, $p53$ can initiate cell death by apoptosis. The steady-state concentration of $p53$ in normal cells is low, and the half-life of normal (wild type) $p53$ is short. In contrast, if the $p53$ gene is mutated, the genetic product is often present at high concentrations. Even if the concentration is important, mutations in the $TP53$ gene frequently occur. Mutations in $p53$ are present in 50-60% of head and neck cancers. Hiyama published in 2008 that a G-to-C polymorphism in codon 72 of exon 4 results in an Arg-to-Pro substitution. Although both variants are morphologically wild-type, the Pro/Pro genotype is less effective in suppressing cellular transformation. Individuals with the Pro/Pro genotype showed a higher risk for HNC than individuals with the Arg/Arg genotype in 15 studies of 19 studies. In 2010, Zhou provided a more precise estimation of the relationship between $P53$ and head and neck cancers. There was no evidence to suggest that $TP53$ codon 72 polymorphisms may be a risk factor for oral carcinoma. However, $TP53$ codon 72 polymorphisms may be a risk factor for NPC. The homozygote Pro/Pro genotype could significantly increase susceptibility to NPC, whereas the Arg allele markedly decreases NPC risk. Bradford and Poeta published that mutations in tumour protein 53 (TP53) may be correlated with aggressive HNSCC disease and relative radioresistance. In the December 2007 issue of the New England Journal of Medicine, a team of NIDCR grantees and colleagues evaluated the prognostic value of $TP53$ mutations in 420 head-and-neck cancer patients treated with surgery only and whose survival was tracked for several years thereafter. Detecting $TP53$ alterations in the tumours of 53% of participants, it was found that these mutations were associated with decreased overall survival.

- $P73$ encodes a member of the $p53$ family of transcription factors involved in cellular responses to stress and development. It maps to a region on chromosome 1p36 that is frequently deleted in neuroblastoma and other tumours, and thought to contain multiple tumour suppressor genes. The demonstration that this gene is monoallelically expressed (likely from the maternal allele) supports the notion that it is a candidate gene for neuroblastoma. Many transcript variants resulting from alternative splicing and/or use of alternate promoters have been found for this gene, but the biological validity and the full-length nature of some variants have not been determined (RefSeq, Feb 2011). Hypermethylation of $TP73$ is reported in nasopharyngeal carcinomas with a frequency of 20% in 2006. Ferru in 2006, by comparison to normal thyroid tissue surrounding tumours, observed significant down regulation of $TP73$ transcripts in adenomas and in differentiated carcinomas. Chen published in 2004 that $p73$ expression may be associated with the differentiation of oral stratified squamous epithelium, an early event in human oral carcinogenesis, and associated with the nodal status of patients with oral carcinoma and a possible indicator for malignant change of oral epithelial dysplasia.
Discussion and conclusions

Molecular epidemiologic studies have provided evidence that individual susceptibility to cancer is mediated by both genetic and environmental factors. Interest in the role of genetic polymorphisms in HNC has increased recently, possibly due to advances in DNA analysis technologies or our knowledge of the human genome.

The most intensively-studied genes are those encoding enzymes that metabolize carcinogens and include GSTM1, GSTT1 and GSTP1. This is likely because these variants are well characterized, and increased cancer risk associated with these variations is plausible. A considerable amount of work has been done on these genes in relation to risk for HNC. One of the major problems of these studies is that many have a small sample size (< 100 cases or < 100 controls). Overall, by summarizing the results of the published meta-analyses of the association between genetic polymorphisms and HNC risk, a statistically significant risk was reported for 3 polymorphisms, namely:

- Glutathione S-transferase (GSTM1), 2 meta-analyses;
- Glutathione S-transferase (GSTT1), 1 meta-analysis;
- Human microsomal epoxide hydrolase (EPHX1), 2 meta-analyses.

As demonstrated by 2 meta-analyses, GSTM1 deficiency was associated with laryngeal cancer risk. Strikingly, the results showed lack of associations between GSTM1 null genotypes and laryngeal cancer risk in Caucasians or Asians. The combination of the GSTM1 null plus the CYP1A1 (m1m2) variant genotypes increased the risk of oral and pharyngeal cancer. Previous meta-analysis and pooled analysis have reported an association between the GSTM1 null genotype and head and neck tumours, but did not analyze ethnic specific or subsite specific differences. Varela-Lema et al. evaluated ethnic specific and subsite specific differences in a pooled analysis, and confirmed that there was no association of the GSTM1 null genotype with oral and pharyngeal cancers in Caucasians. Although not statistically significant, African American and African populations seemed to be almost twice as likely to have the GSTM1 null genotype. This lack of statistical significance might also be attributed to the small number of African American and African subjects included in this pooled analysis. There was also an association between GSTM1 null genotypes and smoking status.

Deletion of GSTM1 might contribute to the tumorigenesis and progression of nasopharyngeal cancer. GSTT1 deletion might also have an association with increased nasopharyngeal cancer risk, as demonstrated by a meta-analysis. A successive study has demonstrated that the data failed to show a significant association of GSTT1 null genotype with increased susceptibility to nasopharyngeal cancer. This discrepancy might be due to several reasons. For GSTT1, a gene that is highly conserved during evolution, major ethnic differences exist in frequency distribution. In East Asia, highest percentages of individuals with the GSTT1 null genotype have been reported. Interestingly, the incidence of nasopharyngeal cancer is high in East Asia, but is low in other regions worldwide. It thus appears that GSTT1 deletion may have an association with increased nasopharyngeal cancer risk. Nevertheless, it indicates that although many people in East Asia carry GSTT1 null genotype, but only a relatively small number of people develop nasopharyngeal cancer, implying that GSTT1 deletion might not be a key event increasing susceptibility to nasopharyngeal cancer. Additionally, as only 4 small studies have been published on GSTT1, it is likely that the discrepancy may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may yield a fluctuated risk estimate. Zhang et al. did not find a significant association between the null genotype of GSTT1 and oral cancer risk in Asians or Caucasians. Heterogeneity exists between studies, and a significant multiplicative interaction between the null genotype of GSTT1 and smoking status has not been found, although small sample sizes may be a reason for the lack of statistical significance.

Two meta-analyses for the EPHX1 gene demonstrated dissimilar results. The Y113H allele may have a potential protective effect on tobacco-related carcinogenesis of lung and HNC, whereas the homozygous variant of H139R allele, instead, may have a harmful effect.

Moreover, cigarette-smoking status may influence the association of EPHX1 enzyme activity and the related cancer risk.

Many primary studies had focalized their attention on alcohol metabolic genes. In particular, Mc Kay et al. found that five genetic variants at three loci, 4q21, 4q23 and 12q24, were significantly associated with HNC risk. The 12q24 variant is positioned in an extended region of LD that contains multiple genes. Candidate genes include the aldehyde dehydrogenase 2 (ALDH2). In accordance with Mc Kay and co-workers, three independent variants of the ADH gene have been associated with HNC risk in European populations. The effects of these three variants were generally present for each HNC subsites, but more pronounced in esophageal cancers and males. Strong heterogeneity was found with rs1229984 when stratifying by alcohol consumption. Notably, an association was observed in “ever drinkers-never smokers”, but not in “never drinkers-ever smokers”, suggesting that the effect with the rs1229984 variant is mediated through alcohol rather than tobacco smoking. In contrast, the lack of heterogeneity for rs1573496 when stratifying by alcohol use may imply differences in the mechanism of carcinogenesis among these ADH variants. Several studies have suggested rs1229984 may influence alcohol consumption behaviour.

The integration of genome-based knowledge into healthcare has the potential to improve primary and secondary...
Among the greatest promises of genomic medicine is that the unravelling of the genetic origins of common diseases will eventually lead to individualized medicine, in which prevention and treatment strategies are personalized on the basis of the results of predictive genetic tests. Findings from meta-analyses of genetic association studies have the potential to provide a comprehensive view of the impact of genetic risk factors in disease aetiology, especially when exploring gene-environment interactions.

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Received: December 1, 2011 - Accepted: December 20, 2011

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