Minireview

Genetic Polymorphisms and Head and Neck Cancer Outcomes: A Review

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Abstract

Head and neck cancer (HNC) patients have variable prognoses even within the same clinical stage and while receiving similar treatments. The number of studies of genetic polymorphisms as prognostic factors of HNC outcomes is growing. Candidate polymorphisms have been evaluated in DNA repair, cell cycle, xenobiotic metabolism, and growth factor pathways. Polymorphisms of *XRCC1, FGFR*, and *CCND1* have been consistently associated with HNC survival in at least two studies, whereas most of the other polymorphisms have either conflicting data or were from single studies. Heterogeneity and lack of description of patient populations and lack of accounting for multiple comparisons were common problems in a significant proportion of studies. Despite a large number of exploratory studies, large replication studies in well-characterized HNC populations are warranted. (Cancer Epidemiol Biomarkers Prev 2008;17(3):490–9)

Introduction

Head and neck cancers (HNC) are a cause of serious morbidity and mortality in North America. In North America, there are >33,000 new cases of HNC per year and >11,000 deaths (1, 2). The major anatomic sites of primary HNC are the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx (which include the supraglottis, glottis, and subglottis). With smoking and alcohol as major risk factors, HNC will remain an important disease entity for years to come.

Treatment and prognosis for HNC are dependent on several important clinical factors, including stage, anatomic site, and performance status (3). Whereas early HNC are often treated with surgery and/or radiotherapy, management of locally advanced HNC may also involve chemotherapy (particularly in combination with radiation) depending on the patient's overall health status and preference (3). Some anatomic subsites (e.g., larynx and some areas in the oral cavity) appear to have better prognoses, but this may be more related to earlier symptoms leading to diagnosis at an earlier stage. In general, patients with good performance status do better than those with poor performance status, in part, because they can tolerate more aggressive therapies (4-6). Poor performance status is common in HNC patients because of the risk profile of these patients (heavy tobacco and alcohol exposure), which can lead to significant comorbidities that affect treatment and therefore prognosis (4, 5).

Important clinical outcomes in HNC include overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), or progression-free survival (PFS) and the development of second primaries. Second primaries are important because of the high frequency with which they occur. Exposure to alcohol and tobacco produces a carcinogenic field effect, which results in a reported 15% to 20% of patients developing a second primary tumor (SPT) within 5 years after diagnosis (7-14) and a metachronous alcohol- or tobacco-related cancer in up to 5% of patients (15). Several epidemiologic variables, including male gender (16), Asian and African American races (1, 17-19), increasing age (16, 20, 21),

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presence of comorbid conditions (20, 22), alcohol (23, 24) and tobacco consumption (24, 25), are also associated with worse prognosis. Molecular markers, such as human papillomavirus infection (26), tumor markers (26-30), and more recently, genetic polymorphisms, the subject of this review, have been associated with disease outcomes. In addition to survival outcomes in HNC, long-term treatment morbidity is important, and major factors affecting quality of life include facial disfigurement, dysphonia, dysphagia, and xerostomia.

With the completion of the human genome map (31, 32), inherited factors (such as genetic polymorphisms) have become increasingly studied as potential prognostic and predictive factors in a variety of cancers including gastric cancer (33), hematologic malignancies (34), non-small cell lung cancer (35-37), colorectal cancer (38), breast cancer (39), and esophageal cancer (40, 41). Alongside clinical and tumor molecular prognostic factors, genetic polymorphisms may play key roles by increasing the accuracy and validity of outcome prediction models. In the case of HNC, several studies have explored a select few candidate polymorphic variants. Ultimately, replicating these findings in large well-characterized populations will be essential. We reviewed the state of the current literature of polymorphisms and HNC outcomes, with the goal of identifying the most suitable candidate genetic polymorphisms for replication.

Materials and Methods

For the purposes of this review, we defined HNC as squamous cell carcinomas of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx (supraglottis, glottis, and subglottis). We assessed articles that considered the following major outcomes: OS, DFS/PFS, and toxicity (acute or chronic).

Search Strategy. Literature searches of MEDLINE (1950-July 2007), PubMed (1950-July 2007), EMBASE (1980-July 2007), CINAHL (1982-July 2007), and All EBM Reviews (to July 2007) were done using keywords and MeSH terms. Included MeSH terms were ''polymorphism, single nucleotide,'' ''head and neck neoplasms,'' ''neoplasms,'' ''outcome assessment (healthcare),'' ''outcome and process assessment (healthcare),'' ''survival,'' ''radiotherapy,'' ''chemotherapy,'' ''drug therapy,'' and ''humans.'' Keywords included ''polymorphism*,'' ''single nucleotide polymorphism*,'' ''SNP*,'' ''head and neck cancer,'' ''neoplasm*,'' ''cancer*,'' ''carcinoma*,'' ''outcome*,'' ''survival,'' ''toxicity,'' ''response*,'' ''radiotherapy,'' and ''chemotherapy.'' Searches were limited to human studies and the English language. Citation lists of retrieved articles were checked to ensure sensitivity of the search strategy. We excluded studies that presented aggregate data for several cancers but not of HNC alone.

Study Selection. The list of retrieved articles was examined. Duplicates and obviously unrelated articles were eliminated from the list by a single reviewer (J.H.). Abstracts of remaining articles were examined by two reviewers (J.H. and D.C.) to determine if the full-text article should be obtained. In the event the reviewers disagreed or there was insufficient evidence in the abstract to determine the relevance of the article, the full text was obtained.

Articles published in English-language, peer-reviewed journals that assessed the relationship between germ-line polymorphic variants and major outcomes of interest were included. We excluded single case reports and opinion pieces, such as editorials and letters to the editor.

Results

Summary. The literature search found 398 articles. After removal of duplicate entries and obviously unrelated studies, 105 abstracts and 48 full-text articles were reviewed. Eventually, only 22 studies were identified that evaluated polymorphisms and HNC outcomes/prognosis; the remaining abstracts and full-text articles did not pertain to HNC, polymorphisms, and/or outcomes. All of these studies were case series or cohort observational studies or subsets of cohort, case-control, or randomized controlled studies. Study populations were predominantly Caucasian or Asian (reported or inferred based on the academic affiliation of authors or hospital location). Study size varied widely (median n = 110; range, 27-312). For study size determination, we only included the subset of individuals who had genotyping done, not the entire study population. More than half of the studies evaluated a mixed population of HNC sites, whereas 10 focused on specific subanatomic sites, particularly oral cavity lesions (Table 1). Twenty studies conducted multivariate analyses. Although the specific prognostic variables included in multivariate analyses varied, 13 (65%) studies included analyses that adjusted for three or more variables (range, 1-7 variables).

Most of the articles used OS or DFS as the primary outcome (Table 1). One study chose a primary toxicity outcome of gastrostomy tube dependence at 180 days (42), and another study chose a primary outcome consisting of nonresponsiveness to cisplatin-based chemotherapy (43). Two studies also evaluated DSS in addition to OS/DFS (44, 45).

Almost half of the polymorphisms studied were part of DNA repair pathways. There were three polymorphisms that had at least two studies with consistent positive associations: *CCND1 A870G, FGFR4 Gly^{388}Arg*, and *XRCC1 Arg^{399}Gln*. Conflicting data were present for *GSTM1, GSTT1*, and *XPD Lys^{751}Gln*. An additional dozen associations were found in single unreplicated studies (Table 2). Practically all studies identified themselves as exploratory or in need of validation or replication.

DNA Repair Polymorphisms. DNA repair pathways and their polymorphisms are among the best studied in cancer risk and prognosis (36, 37, 46-69). Carcinogenesis involves accumulation of DNA mutations, eventually leading to loss of host control and neoplastic transformation. For a disease such as HNC where SPT are frequent because of a field effect, this endpoint may be affected by any increased predisposition to host DNA damage. However, an increased predisposition to DNA damage may also prove beneficial in treatment, as both platinum agents and radiation rely on DNA damage as part of their mechanisms of tumor cell killing. Additionally, treatment toxicities, an important clinical endpoint, may be modulated by DNA repair capacity, because the

Table 1. Summary of 22 publications reviewed

First author (reference)	Country	*n* analyzed	Primary outcomes	Multivariate analysis (yes/no)	Polymorphisms evaluated
(A) Not otherwise specified, non-nasopharyngeal, or all HNC (12 studies in descending order of sample size)					
Holley (79)	Germany	294	DFS	Yes	*CCND1 A870G* *CCND1 G1722C*
Matthias (78)	Germany	224	DFS	Yes	*CCND1 A870G*
Matthias (24)	Germany	312	DFS	Yes	*CCND1 A870G* *TNFα TNFBID5 haplotype (list of genes with nonspecified polymorphisms: GSTM1, GSTM3, GSTT1, GSTP1, CYP2D6, CYP1A1, CYP2E1, various MHC)*
Minard (97)	United States	303	SPT	Yes	*GSTM1 deletion* *GSTT1 deletion*
Geisler (44)	United States	185	OS DSS Time to recurrence	Yes	*GSTT1 deletion* *GSTM1deletion* *GSTP1 $Ile^{105}Val$* *XRCC1 $Arg^{399}Gln$* *XRCC1 $Arg^{194}Trp$*
Blons (43)	France	148	Response to cisplatin chemotherapy	Yes	*MMP1 -1607insG* *MMP3 -1612insA* *MMP7 -A181G* *MMP7 -C153T*
Etienne-Grimaldi (90)	France	112	DSS	No	*EGFR intron 1 CA repeat*
Carles (70)	Spain	108	Time to progression OS	Yes	*XPA 5UTR (rs1800975)* *XPC $Lys^{940}Gln$* *XPD $Lys^{751}Gln$* *ERCC1 $Lys^{259}Thr$* *ERCC5 $His^{1104}Asp$* *ERCC5 C581T* *XRCC5 3UTR (rs1051677)* *XRCC5 3UTR (rs1051685)* *XRCC1 $Arg^{399}Gln$*
Quintela-Fandino (65)	Spain	103	OS Chemoresponse	Yes	*ERCC1 C8092A* *XPD $Asp^{312}Asn$* *XRCC1 $Arg^{399}Gln$* *XPD $Lys^{751}Gln$*
da Costa Andrade (89)	Brazil	75	OS	Yes	*FGFR4 $Gly^{388}Arg$*
Sullivan (81)	Italy	70	PFS OS Treatment response	No	*p53 $Arg^{72}Pro$*
Wang (103)	United States	27	OS	Yes	*DNMT3B6 C-149T*
(B) Oral cavity and/or oropharynx cancers (7 studies in descending order of sample size)					
Gal (45)	United States	279	SPT OS DSS	Yes	*XRCC1 $Arg^{399}Gln$* *XRCC3 $Thr^{241}Met$* *XPD $Lys^{751}Gln$* *MGMT $Leu^{84}Phe$* *MGMT $Val^{143}Ile$*
Tsai (111)	Taiwan	130	Recurrence rate	No	*Urokinase 3′-UTR C4065T*
Kornguth (42)	United States	122	Toxicity (g-tube dependency)	Yes	*ERCC4 G1244A* *ERCC4 T2505C*
Wong (101)	Taiwan	118	OS	No	*CTLA-4 A49G*
Streit (88)	Germany	104	OS	No	*FGFR4 $Gly^{388}Arg$*
Worrall (92)	United Kingdom	100	Time to recurrence	Yes	*GSTM1 deletion* *GSTM3 exon 6/7 *A/*B* *GSTT1 deletion* *CYP1A1 3′ exon 7* *CYP1A1 exon 7 Ile→Val* *CYP2D6 4/3/5*
Sanguansin (102)	Thailand	32	UNK	No	*hMSH2 at IVS C211+9G*
(C) Nasopharyngeal or laryngeal cancers (3 studies in descending order of sample size)					
Kondo (100)	Japan, Taiwan	83	OS	Yes	*MMP1 1G 1607 2G*
Monteiro (112)	Portugal	71	OS	Unknown	*hOGG1 $Ser^{326}Cys$*
Monteiro (80)	Portugal	66		Unknown	*CCND1 A870G*

NOTE: DFS represents DFS but also recurrence-free survival and PFS where appropriate.

same DNA damage that occurs within the tumor may also take place in normal tissues as a side effect of therapy. It is therefore of great importance to consider overall how the polymorphism may affect multiple endpoints such as survival, toxicity, and SPT outcomes.

X-ray repair cross-complementing group 1 (*XRCC1*) is a key DNA repair gene in the base excision repair pathway and is involved with radiation-related DNA repair. Three studies (44, 45, 65) found that the variant *Gln* allele of *XRCC1* was associated with either improved OS or prolonged time to recurrence. These studies involved relatively large samples (n = 103-279). In contrast, a smaller study of 98 individuals genotyped for *XRCC1* $Arg^{399}Gln$ found no association with outcome (70). *XRCC1* $Arg^{399}Gln$ therefore represents an excellent candidate polymorphism suitable for replication in large prospective cohort studies.

Two studies (65, 70) analyzed multiple DNA repair pathway polymorphisms using an approach of adding ''at-risk'' alleles across several polymorphic variants and then comparing groups with differing numbers of ''at-risk'' alleles with OS. These exploratory joint analyses have been used in other cancers for both risk and outcomes (71-75). These multiple polymorphism studies highlight pitfalls: modest sample sizes (n = 100) with multiple comparisons (exceeding 10 for either study). Further, in Carles et al.'s study, the rationale for selection of polymorphisms was unclear and the possibility of bias was introduced by selective incorporation of polymorphisms in the models (70). Thus, replication in other larger data sets is warranted.

Data for other DNA repair polymorphisms were less consistent (45, 65), were from unreplicated studies (45, 65, 74), or were not associated with outcome at all.

Cell Cycle. Cyclin D1 (the protein encoded by the *CCND1* gene) plays a critical role in cell cycle regulation, and its overexpression has been associated with cell proliferation (27, 76). The *CCND1 A870G* polymorphism has been associated with response to neoadjuvant radiotherapy in rectal cancer and has reasonable functional data (77). In HNC outcomes, there are two independent groups of studies of *CCND1* polymorphisms. Three publications, with significant overlap (24, 78, 79), reported that the *G/G* genotype was associated with reduced DFS [hazard ratio (HR), 2.3-3.72]. An independent study drew a similar conclusion in 66 laryngeal cancer patients of all stages (80). Thus, *CCND1 A870G* represents a reasonable polymorphism to validate prospectively in larger scale studies. A second polymorphism, *CCND1 G1722C*, in strong linkage disequilibrium with *CCND1 A870G* was also associated with HNC outcome (79).

Sullivan et al. evaluated the role of the *p53* $Arg^{72}Pro$ polymorphism through *in vitro* and *in vivo* tests (81). It was postulated that the wild-type *p53 Arg/Arg* genotype, if retained as wild-type in the tumor itself, would lead to superior apoptosis-inducing activity after being challenged by platinum chemotherapy. This, in turn, translates into a greater clinical response (that is, more tumor cells enter apoptosis) in the wild-type patients. To validate their cell line results, 70 cisplatin-based chemoradiotherapy-treated patients showed that the combination of having the wild-type *Arg/Arg* genotype in both blood and tumor had the longest median OS. This intriguing result awaits replication.

Growth Factor Pathways. *Fibroblast growth factor receptor 4* (*FGFR4*) is a tyrosine kinase receptor with a central role in cell growth (82). The *FGFR4* $Gly^{388}Arg$ polymorphism has been associated in some studies with worse prognosis in cancers of the breast, lung, and prostate cancers as well as high-grade soft tissue sarcoma (83-85) but not in other cancer studies (86, 87). In HNC, two studies of the *FGFR* $Gly^{388}Arg$ polymorphism each found that the *Arg* allele was associated with worse OS. Streit et al. found that individuals with high protein expression of *FGFR4* who also carried the *FGFR4 Arg* allele had poorer prognosis than individuals carrying *Gly/Gly*, but this finding was based on the 17 high expressors of *FGFR4* (88). da Costa Andrade et al. found an overall worsening of prognosis in individuals carrying the *FGFR Arg* allele (adjusted HR, 2.18; P = 0.004; n = 75; ref. 89). These two studies have consistent results but involve relatively small and poorly described patient populations, arguing for validation prospectively.

In another growth factor pathway, a single study of the *epidermal growth factor receptor* (*EGFR*) *intron 1* CA dinucleotide polymorphism found no association with outcome based on a French population of 112 consecutive HNC patients with poorly described characteristics (90).

Xenobiotic Metabolism. *Cytochrome P450* (*CYP*) enzymes are involved in phase I metabolism of drugs and other xenobiotics. They play an important role in the activation/inactivation of carcinogens, and the activation/inactivation of chemotherapy drugs, and as such are important determinants of cancer risk and outcome respectively (91). One study showed *CYP2D6* to be significantly associated with time to development of first cervical lymph node metastases (HR, 3.6; P = 0.04), but the number of studied patients was small (n = 20) and follow-up time was short (2 years; ref. 92). The other *CYP* polymorphisms were not significant.

Glutathione S-transferases (*GST*) are a group of enzymes involved in phase II detoxification of carcinogens; GST overexpression has been implicated in acquired resistance to chemotherapy drugs (93). GST polymorphisms may be prognostic in cancers of the prostate (94) and lung (95) cancer and non-Hodgkin's lymphoma (96). Four studies found conflicting results between the GST polymorphisms and HNC outcomes (24, 44, 92, 97).

Matrix Metalloproteinases, Inflammatory, and Other Pathways. The *matrix metalloproteinases* (*MMP*) have been postulated to interact with the *Fas/Fas ligand* pathways (98) and modulate patient response to cisplatin and 5-fluorouracil (99). Blons et al. reported that the *MMP3 6A/6A* genotype had significantly higher response to chemotherapy in a study involving a well-characterized sample of 148 patients of all stages undergoing neoadjuvant cisplatin/5-fluorouracil chemotherapy followed by either surgery or radiation (43). In contrast, the *MMP1 -1607insG*, *MMP7 -A181G*, and *MMP7 -C153T* polymorphisms were not associated with outcomes based on small studies (43, 100). Single unreplicated studies also suggest potential roles for polymorphisms of the immunologic pathway (101, 102) and of DNA methylation (103) in HNC prognosis.

Table 2. Polymorphisms with at least one positive prognostic results

Genetic polymorphism	First author (reference)	Variant	Outcome measure	Estimate	Comments
Polymorphisms with a positive association across two or more studies					
CCND1 A870G	Matthias (78)	*G/G vs A/A*	DFS	AHR, 3.72 (1.37-10.09); $P = 0.010$	Matthias et al. (24) found association at 5 y with DFS of AHR, 2.3 (0.9-8.3)
	Holley et al. (79) have similar data and are based on same data set.	*A/G vs A/A*	DFS	AHR, 1.38 (0.50-3.82); $P = 0.531$	
	Monteiro (80)	*G/- vs A/A*	OS	Variant had worse OS; $P = 0.0095$	Monteiro et al. (80) did not find a relationship with DFS.
FGFR4 Gly^{388}Arg	da Costa Andrade (89)	*Arg/- vs Gly/Gly*	OS	AHR,* 2.18 (1.05-4.55); $P = 0.04$	
	Streit (88)	*Arg/- vs Gly/Gly*	OS	Variant had worse OS; log-rank $P = 0.032$ in subgroup of patients with high *FGFR4* expression	
XRCC1 Arg^{399}Gln	Gal (45)	*Gln/- vs Arg/Arg*	OS	AHR, 0.68 (0.47-0.97); $P = 0.03$	
		Gln/Gln vs Arg/Arg	OS	AHR, 0.77 (0.40-1.50); $P = 0.44$	
		Arg/Gln vs Arg/Arg	OS	AHR, 0.66 (0.45-0.96); $P = 0.03$	
	Geisler (44)	*Gln/- vs Arg/Arg*	OS	AHR, 1.06 (0.64-1.76); $P = 0.82$	Geisler et al. (44) found no association with OS or DSS.
			Time to recurrence	AHR, 0.38 (0.18-0.81); $P = 0.01$	Quintela-Fandino et al. (65) found an association with response to cisplatin chemotherapy; $P = 0.017$.
	Quintela-Fandino (65)	*Gln/- vs Arg/Arg*	OS	Variants had improved OS (median OS not reached for either category); $P = 0.0044$	
Polymorphisms with conflicting results for association					
XPD Lys^{751}Gln	Quintela-Fandino (65)	*Gln/- vs Lys/Lys*	OS	Median OS NR vs 20 mo; $P = 0.0012$	
	Gal (45)	*Gln/- vs Lys/Lys*	OS	AHR, 1.06 (0.74-1.51); $P = 0.74$	Gal et al. (45) found no association with DSS.
		Gln/Gln vs Lys/Lys	OS	AHR, 1.05 (0.72-1.53); $P = 0.80$	
		Gln/Lys vs Lys/Lys	OS	AHR, 1.12 (0.62-1.98); $P = 0.73$	
GSTM1 deletion	Minard (97)	*Null vs Present*	SPT	AHR, 1.99 (1.11-3.56);	
	Geisler (44)	*Present vs Null*	DFS	AHR, 0.97 (0.55-1.73); $P = 0.92$	Geisler et al. (44) found no associations with OS or DSS.
	Matthias (24)	*Present vs Null*	DFS	Specific data not provided but NS	
GSTT1 deletion	Geisler (44)	*Present vs Null*	OS	AHR, 2.37 (1.13-4.97); $P = 0.02$	Geisler et al., Minard et al., Worrall et al., and Matthias et al. separately found no relationships with DFS/SPT (24, 44, 92, 97).
		Present vs Null	DSS	AHR, 3.35 (1.33-8.41); $P = 0.01$	
Polymorphism pathway analyses					
ERCC1 C8092A *XPD Asp^{312}Asn* *XPD Lys^{751}Gln* *XRCC1 Arg^{399}Gln*	Quintela-Fandino (65)	No. of DNA polymorphic variants (combined analysis)	OS	AHR, 175 comparing 7 variant alleles to 0 variant alleles across four polymorphisms; $P < 0.001$	An increasing number of polymorphic variants was associated with worse OS.

(*Continued on the following page*)

Table 2. Polymorphisms with at least one positive prognostic results (Cont'd)

Genetic polymorphism	First author (reference)	Variant	Outcome measure	Estimate	Comments
Polymorphism pathway analyses					
ERCC1 Lys^{259}Thr *ERCC5 His^{1104}Asp* *ERCC5 C581T* *XPA 5′UTR*	Carles (70)	No. of DNA polymorphic variants (combined analysis)	OS Time to progression	99.6 mo (4 favorable genotypes) vs 9.7 mo (4 unfavorable genotypes); $P = 0.0002$ 99 vs 7.2 mo; $P = 0.0003$	An increasing number of polymorphic variants was associated with worse OS and worse time to progression.
Polymorphisms with an association in a single study					
XRCC3 Thr^{241}Met	Gal (45)	*Met/- vs Thr/Thr*	Any SPT	AHR, 1.62 (0.98-2.67); $P = 0.059$	*Met/Met* also significant for any upper aerodigestive tract cancer and for HNC separately. No association with OS
		Met/Met vs Thr/Thr		AHR, 2.65 (1.29-5.45); $P = 0.008$	
		Thr/Met vs Thr/Thr		AHR, 1.38 (0.81-2.37); $P = 0.24$	
ERCC1 A98C	Carles (70)	*C/C vs A/A*	PFS	ARR, 6.922; $P = 0.009$	
XPD Asp^{312}Asn	Quintela-Fandino (65)	*Asn/- vs Asp/Asp*	OS	Median OS NR vs 30 mo; $P = 0.001$	
ERCC4 T2505C	Kornguth (42)	*C/- vs T/T*	Need for 180-d g-tube	ARR, 0.20 (0.06-0.7)	
DNMT3B6 -C149T	Wang (103)	*C/C and T/T vs CT*	OS	AHR, 4.829; $P = 0.004$	
CCND1 G1722C	Holley (79)	*C/C vs G/G*	DFS	AHR, 7.3 (1.1-27.2); $P = 0.003$	
		G/C vs G/G	DFS	AHR, 1.6 (0.6-4.8); $P = 0.36$	
p53 Arg^{72}Pro	Sullivan (81)	*Pro/Pro vs Arg OS/PFS*	*Pro/Pro* does worse; log-rank $P < 0.0001$		
*CYP2D6 *4/*3/*5*	Worrall (92)	*Var/Var vs Wt/-*	PFS/DFS	AHR, 3.6 (1.1-12.5); $P = 0.040$	Matthias et al. (24) studied an unspecified polymorphism of *CYP2D6* and found no relationship with DFS.
CTLA-4 A49G	Wong (101)	*A/A vs A/G vs G/G*	OS	Variant survival worse; log-rank $P = 0.003$	
hMSH2 at IVS C211+9G	Sanguansin (102)	*G/- vs C/C*	DFS	Unadjusted OR, 10.67; $P = 0.030$	
MMP3 -1607insG	Blons (43)	*6A/6A vs 5A/5A*	Nonresponse to cisplatin	AOR, 0.15 (0.04-0.6); $P = 0.008$	
		5A/6A vs 5A/5A		AOR, 0.6 (0.3-1.28); $P = 0.18$	
TNF B1D5 haplotype of TNFα	Matthias (24)	*Haplotype present vs absent*	DFS at 5 y	AHR, 3.9 (1.38-14.44); $P = 0.022$	Not statistically significant DFS at 2 y

*Likely to be adjusted HR (AHR), as original report used Cox proportional hazards, although they reported as adjusted relative risks. ARR, adjusted relative rate; AOR, adjusted odds ratio.

Discussion

In our overall assessment of the literature, several common concerns emerged about the published studies as a whole, representing the challenges of a maturing field. Firstly, there was often inadequate reporting of key aspects of the underlying population. Most studies had at least one to several of the following key categories incompletely reported: country of study and source of population (e.g., community, hospital-based, convenient sample); inclusion/exclusion criteria for participants; study design (e.g., retrospective cohort); population characteristics for general demographic variables and clinically important prognostic factors (e.g., stage, ethnicity, performance status, treatment); explanations of why only subsets were analyzed; demographic comparisons of patients included against those excluded from analysis; and detailed descriptions of both genotyping quality control measures and statistical methods. Secondly, there was a lack of discussion of the implications of multiple comparisons. Most studies evaluated more than one polymorphic variant, but none took multiple comparisons into account in the analysis. With many of the unadjusted P-values only slightly below $P = 0.05$, the potential for false positive results is high. Thirdly, there is possible publication bias. Seventeen studies (77%) had at least one statistically significant primary result ($P < 0.05$ or confidence interval not crossing 1), and almost all

had at least one secondary positive association. Given that the usual *a priori* chances of a positive result in a genetic polymorphisms association study are significantly lower, publication bias may be a factor.

Toxicity is always difficult to measure objectively. Only one study evaluated toxicity as an endpoint (42). New methodologies and more accurate measurements of dose delivery may promote future toxicity studies. It was also promising to see some studies evaluate specific subsets of uniformly-treated patients, such as Stage I and II patients treated with radiation (70, 97), or HNC patients treated with surgery (24, 78, 79, 88, 89, 103), in addition to performing multivariate analyses to adjust for additional prognostic factors. This reflects a shift towards better understanding of the impact of clinical prognostic factors on outcome as well as how prognostic factors in general are utilized in clinical practice.

The majority of the published studies evaluated general prognostic polymorphic markers, rather than predictive markers. A biomarker is prognostic if it predicts outcome independent of therapy. If the biomarker differentially predicts outcome in patients receiving a specific therapy compared to patients not receiving that specific therapy, then it is a predictive marker. Thus, predictors of toxicity are generally considered to be predictive, while predictors of outcome can be either prognostic or predictive. Quintela-Fandino et al. (65) focused on cisplatin-treated patients, tying the evaluation of DNA repair polymorphisms to the mechanism of cisplatin function, thus meeting half of the definition of a predictive marker. However, because no control group was present to show that DNA repair polymorphisms predict outcome differently (or not at all) in non-cisplatin-treated patients, one cannot be certain that the DNA repair polymorphisms in question were truly predictive of therapy outcome or simply prognostic.

This raises another issue. To truly evaluate whether a polymorphism is predictive or prognostic, the analysis should use samples obtained from either a randomized controlled clinical trial comparing two or more different treatments or an observational study of patients treated heterogeneously for nonclinical reasons (e.g., limited access to drugs), because a comparison of patients treated and not treated with the therapy in question is needed to prove that a marker is predictive. Distinguishing between predictive and prognostic factors is important, because one could potentially use a predictive marker to help individualize patient treatment plans, whereas a general prognostic marker can only stratify a patient into different prognostic groups and may be one step further removed from having utility in therapy selection.

None of the studies used a haplotype tagging approach in polymorphism selection. In circumstances when a gene is known or highly suspected to be important for prognosis but there are little data on the function of its associated polymorphisms, a tagging approach may be useful. Resequencing data are analyzed to determine which polymorphisms are inherited together, in a block, or ''haplotype.'' These blocks divide the gene into smaller segments that is inherited as a unit generally. A specific polymorphism that reflects the genetic variation in a specific segment is known as a tagging polymorphism. Thus, the vast majority of genetic variation in a gene can be measured by evaluating a select number of tagging polymorphisms, typically identified through *in silico* prediction programs. This method is more comprehensive than the usual candidate polymorphism selection process. The attraction to using this approach is that one does not need to worry about polymorphism functionality during polymorphism selection. A functional polymorphism might be missed in a tagging approach, but this functional polymorphism should be linked to a tagging polymorphism. New and future studies should consider this alternative approach as complementary to the standard candidate selection procedures that choose based on known, predicted, or putatively functional polymorphisms.

Genome-wide and multistage test validation or multiple replication approaches, pathway and bioinformatic analytical approaches to high-dimensionality data, the development of large comprehensive institutional biobanks, careful prospective documentation of all clinical outcomes, and the incorporation of correlative tissue banking into randomized controlled studies could soon change the way we evaluate polymorphic variants in cancer outcomes. For example, in cancer risk analyses, one approach to the problems of multiple comparisons and false-positive results has been to use a multistage training validation approach. The first stage is to identify candidate polymorphic variants that are associated with outcomes of interest, casting a wide net over potential polymorphic prognostic factors.

In subsequent stages, additional independent set(s) of patients with similar demographic and risk characteristics to the original are used to confirm results from the original study for a predetermined small proportion of the original large exploratory set of candidate polymorphisms. The multistage approach still requires an adequate sample size in each step and robust analytical approaches (104, 105). Application of these approaches (currently used in risk analyses) to the cancer outcomes setting has enormous potential. A final benefit of comprehensive tissue banking initiatives will be the ability to examine gene and protein expression alongside polymorphic variants, thereby enabling correlation of tumor and host biology. Some studies have already started to do this, albeit with limitations due to lack of availability of large numbers of biological specimens (79, 81, 88).

Conclusion

We reviewed the field of polymorphic variants and outcomes in HNC. Published studies have all used a standard candidate genetic polymorphism approach. Almost all studies evaluated survival outcomes, with only one examining a toxicity outcome. We found that three genetic polymorphisms had consistent associations with survival outcomes across at least two studies: *CCND1 A870G, XRCC1 Arg*^{399}*Gln*, and *FGFR4 Gly*^{388}*Arg*, and these three polymorphisms should be at the top of the list for replication in large studies. All three are well-known polymorphisms with prognostic implications in other cancers (36-38, 63, 77, 83-85, 106-110). DNA repair pathways continue to be the most studied pathways for HNC outcomes. The vast majority of studies were exploratory in nature resulting in the need to

validate or replicate results in larger, well-characterized populations of patients. Novel haplotype tagging and multistage dense genotyping approaches should be considered.

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