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HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

Pooled Analysis of Alcohol Dehydrogenase Genotypes and Head and Neck Cancer: A HuGE Review

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Possession of the fast metabolizing alleles for alcohol dehydrogenase (ADH), *ADH1B*2* and *ADH1C*1*, and the null allele for aldehyde dehydrogenase (ALDH), *ALDH2*2*, results in increased acetylaldehyde levels and is hypothesized to increase the risk of head and neck cancer. To examine this association, the authors undertook a Human Genome Epidemiology review on these three genes and a pooled analysis of published studies on *ADH1C*. The majority of Asians had the fast *ADH1B*2* and *ADH1C*1* alleles, while the majority of Caucasians had the slow *ADH1B*1/1* and *ADH1C*1/2* genotypes. The *ALDH2*2* null allele was frequently observed among Asians, though it was rarely observed in other populations. In a pooled analysis of data from seven case-control studies with a total of 1,325 cases and 1,760 controls, an increased risk of head and neck cancer was not observed for the *ADH1C*1/2* genotype (odds ratio = 1.00, 95% confidence interval: 0.81, 1.23) or the *ADH1C*1/1* genotype (odds ratio = 1.14, 95% confidence interval: 0.92, 1.41). Increased relative risks of head and neck cancer were reported for the *ADH1B*1/1* and *ALDH2*1/2* genotypes in several studies. Recommendations for future studies include larger sample sizes and incorporation of relevant ADH and ALDH genes simultaneously, as well as other genes. These considerations suggest the potential for the organization of a consortium of investigators conducting studies in this field.

ADH1B; *ADH1C*; alcohol dehydrogenase; aldehyde dehydrogenase; *ALDH2*; epidemiology; genetics; head and neck neoplasms

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Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ASR, world age-standardized incidence rate per 100,000; CI, confidence interval; CYP, cytochrome P-450; ICD-9, _International Classification of Diseases_, Ninth Revision; OR, odds ratio.

Editor's note: _This article is also available on the website of the Human Genome Epidemiology Network_ (http://www.cdc.gov/genomics/hugenet/default.htm).

Alcohol dehydrogenases (ADHs) are enzymes involved in the metabolism of ethanol to acetaldehyde (1). Subsequent conversion of acetaldehyde to acetate is catalyzed by the mitochondrial enzyme aldehyde dehydrogenase (ALDH) (figure 1). Most of the metabolism of alcohol and aldehyde is carried out in the liver, although extrahepatic metabolism has also been demonstrated in the stomach, gut, and upper aerodigestive tract (2), including some potential metabolism due to oral microflora in the oral cavity (3–5).

GENES

ADH1B and _ADH1C_

Human ADH exhibits different molecular forms resulting in amino acid sequence differences of more than 30 percent and specific tissue distributions. There are five different classes of ADHs and seven different isoenzymes: alpha, beta, and gamma in class I, pi in class II, chi in class III, _ADH7_ in class IV, and _ADH6_ in class V. The class I ADH subunits form homo- or heterodimers (αα, ββ, γγ, αβ, αγ, βγ) (6). The three different class I gene loci, _ADH1A_ (alpha), _ADH1B_ (beta), and _ADH1C_ (gamma), are situated close to each other in the region 4q21–23 (an older nomenclature is _ADH1_, _ADH2_, and _ADH3_ (7)); only _ADH1B_ and _ADH1C_ are polymorphic (8–11).

The polymorphic sites for _ADH1B_ are Arg47His in exon 3 and Arg369Cys in exon 9 (12). The presence of a histidine molecule at amino acid position 47 constitutes the _*2_ allele, and the presence of a cysteine molecule at amino acid position 369 constitutes the _*3_ allele. The polymorphic site for _ADH1C_ is Ile349Val in exon 8, and the presence of a valine molecule at this amino acid position constitutes the _ADH1C*1_ allele (13, 14). The alleles _ADH1C*1_ and _ADH1B*2_ code for "fast" metabolism of ethanol; in vitro, the _ADH1C*1_ allele increases oxidation by approximately 2.5-fold in comparison with _ADH1C*2_, whereas the _ADH1B*1/1_ genotype has only 1 percent and 0.5 percent of the oxidation capability of the _ADH1B*1/2_ and _ADH1B*2/2_ genotypes, respectively (15). Linkage disequilibrium between _ADH1C*1_ and _ADH1B*2_ has been demonstrated in several Caucasian populations (16).

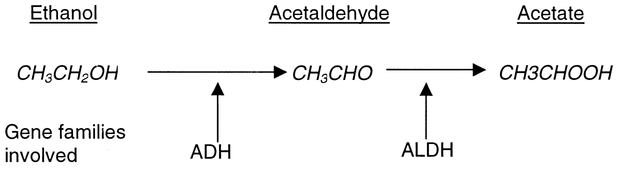

FIGURE 1. The metabolic pathway for alcohol. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase. (Hypothesis: Fast ADH metabolizing genes and slow ALDH metabolizing genes will lead to a peak in acetaldehyde exposure and increased risk of alcohol-related cancers.)

ALDH2

Thus far, 17 ALDH genes have been identified in nine ALDH genotype groups. A major human liver ALDH gene is the mitochondrial _ALDH2_ in class II, located on chromosome 12q24.2. The _ALDH2_ gene contains an inactive _ALDH2*2_ allele (substitution of lysine for glutamine at amino acid position 487), which means that persons who are homozygous are unable to oxidize acetaldehyde and those who are heterozygous do so inefficiently (17, 18). For heterozygous persons, given that the _ALDH2_ isoenzyme is a tetramer and each subunit has a 50 percent chance of being functional, only 1/16th of _ALDH2_ enzymes will be functional (19). This leads homozygous and heterozygous possessors of the _ALDH2*2_ allele to experience a build-up of acetaldehyde that creates a toxic reaction, including flushing, increased heart rate, and nausea.

Prevalence of gene variants

To estimate the prevalence of the _ADH1B_, _ADH1C_, and _ALDH2_ polymorphisms in different populations, we conducted a MEDLINE search (US National Library of Medicine) using the terms "_ADH2_," "_ADH3_," "_ADH1B_," "_ADH1C_," and "_ALDH2_," each in combination with "prevalence" and "case-control." The currently accepted nomenclature for _ADH1B_ and _ADH1C_ is relatively new, and thus the majority of studies we identified used the older nomenclature. We attempted to identify genotype frequencies among control populations from case-control studies, which usually focused on alcoholism, or studies that focused on reporting genotype frequencies. Studies that reported only allele frequencies and not genotype frequencies were not included. For the sake of brevity, we have not included genotype frequencies from all studies in this report, and we excluded studies based on small sample sizes (<100 subjects) when several other reports on that particular ethnic group were available.

The genotype frequencies of the _ADH1B_ polymorphism in different populations are shown in table 1 (20–41). The _ADH1B*1_ "slow" allele was very common among Caucasians, with approximately 95 percent having the homozygous _ADH1B*1/1_ genotype and 5 percent having the heterozygous _ADH1B*1/2_ genotype (38). The _ADH1B*2/2_ genotype was rarely observed in Caucasians. Conversely, the _ADH1B*2_ allele was the most common allele in Asian populations. In African populations, the _ADH1B*1_ allele was the most common, although a third allele, _ADH1B*3_, has also been reported (20, 21).

The genotype frequencies of the *ADH1C* polymorphism in different populations are shown in table 2 (20, 23, 25–30, 33, 38, 41–54). Neither the *ADH1C*1* allele nor the *ADH1C*2* allele was predominant among Caucasians; approximately 50–70 percent of these persons had the heterozygous *ADH1C*1/2* genotype. In contrast, the *ADH1C*2* allele was relatively uncommon among Asians, and *ADH1C*2/2* homozygosity was rarely reported. The one African study reported a predominance of *ADH1C*1/1* homozygosity, although the absence of Hardy-Weinberg equilibrium suggests a possible misclassification of genotyping data (20).

Table 3 shows the genotype frequencies of *ALDH2* in various populations (24–36, 41, 55–59). Nearly all Caucasians carried the functional *ALDH2*1/1* genotype (24, 41). Similar patterns were seen among populations from Southeast Asia and Oceania, as well as some indigenous populations in Alaska, Mexico, and Chile (24). In contrast, the *ALDH2*2* null allele was frequently observed in East Asian populations, typically with 30 percent *ALDH2*1/2* heterozygosity and 5–10 percent *ALDH2*2/2* homozygosity (24–34, 57–59). A similar pattern was also observed in an indigenous Brazilian population (24). No information on African populations was available.

In summary, the fast metabolizing *ADH1B*2* allele and the null *ALDH2*2* allele seem to be specific to Asian populations, whereas the *ADH1C*2* allele is commonly observed in Caucasian populations. Although data are lacking, it is likely that most of the inherited variation in acetaldehyde levels in Caucasians is determined by *ADH1C*, with minor contributions from *ADH1B* and possibly a cytochrome P-450 (CYP) gene, *CYP2E1* (60). Conversely, it is likely that inherited variation in acetaldehyde levels among Asians is predominantly determined by *ADH1B* and *ALDH*.

Disease

Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx, and larynx (*International Classification of Diseases*, Ninth Revision (ICD-9), codes 140–149 and 161). Cancer of the esophagus (ICD-9 code 150) is sometimes included as a head and neck cancer; however, because of its mixed histology and etiology, with adenocarcinoma predominating over squamous cell carcinoma in some populations, it was excluded from this review. The incidence of head and neck cancers varies widely throughout the world (61). For example, the incidence of oral cavity and pharyngeal cancer in men varies up to 35-fold between high-risk areas such as Sommes, France (world age-standardized incidence rate per 100,000 (ASR) = 43) and low-risk areas such as The Gambia (ASR = 1) (61). For women, oral cavity and pharyngeal cancer incidence rates may vary up to 38-fold between high-risk areas such as South Karachi, Pakistan (ASR = 19) and low-risk areas such as Kangwa County, South Korea (ASR = 0.5) (61). In all populations, rates in men exceed those in women by a factor of 4–10. When subsites within the oral cavity and pharynx are examined, cancer of the oropharynx and hypopharynx account for as many cases as or more cases than cancer of the oral cavity in high-risk European populations, while cancers of the tongue, the floor of the mouth, and other parts of the oral cavity represent the majority of cases in India and the United States (61).

More than 90 percent of cancers of the larynx are squamous cell carcinomas, and the majority originate from the supraglottic and glottic regions of the organ (62). The incidence of laryngeal cancer in men, including all histologic types, is relatively high in southern and central Europe (Zaragoza, Spain: ASR = 18; Lower Silesia, Poland: ASR = 13; Croatia: ASR = 13), southern Brazil (Campinas, Brazil: ASR = 7), Uruguay (Montevideo, Uruguay: ASR = 12), and Argentina (Concordia, Argentina: ASR = 10) and among Blacks in the United States (ASR = 10), while the lowest rates are recorded in Southeast Asia (Beijing, China: ASR = 1.8; Hanoi, Vietnam: ASR = 1.5) and central Africa (Kyadondo County, Uganda: ASR = 1.3) (61). The incidence of laryngeal cancer in women is below 2 per 100,000 in most populations. These rates have not changed markedly during the last two decades.

Lifestyle factors. The main risk factors for head and neck cancer in Western countries are alcohol drinking and tobacco smoking, which in individual studies have been found to account for 75–90 percent of the disease (62, 63). The risk of head and neck cancer increases rapidly with both the frequency and the duration of tobacco and alcohol use, with no evidence of any threshold effect for either. Most studies appear to show increased risks for smokers on the order of 3- to 10-fold relative to never smokers and increased risks for heavy drinkers on the order of 2- to 9-fold relative to light-to-moderate drinkers. The combined impact of tobacco smoking (cigarettes/day) and alcohol consumption (drinks/week) is greater than the sum of the individual effects of these factors and may even exceed a multiplicative effect (64, 65). The high incidence of head and neck cancer in parts of Mediterranean Europe may be due to the higher risk associated with the use of black as opposed to blond tobacco, as well as local alcohol drinking habits (e.g., calvados consumption in Normandy) (65). Areas of high head and neck cancer incidence in non-Western populations are also largely explained by local habits, such as betel quid chewing in South Asia and consumption of very hot mate in South America.

Dietary factors. A diet that is deficient in fruits and vegetables is also a recognized risk factor for head and neck cancer, accounting for possibly 10–15 percent of cases (66). Increased risks have been found with decreasing consumption of fresh fruits and vegetables, as well as vitamins A and C. Conversely, it is possible that frequent dietary consumption of salted meat and fish, as well as pickled vegetables, may represent a risk factor. A topic that has received little attention is the effect of alcohol or tobacco in conjunction with a diet deficient in fruits and vegetables.

Human papillomavirus. Benign lesions of the head and neck, including laryngeal papillomas and oral verrucal papillary lesions, illustrate the potential for human papillomaviruses to infect squamous tissue of the head and neck and raise the possibility that oncogenic human papillomaviruses may be involved in the development of some head and neck cancers (67). The most informative studies regarding head and neck cancer have been based on a network of large serum banks in Norway, Finland, and Sweden comprising

TABLE 1. Genotype frequency of the *ADH1B* polymorphism, by geographic region

Region and study (ref. no.)	Geographic area	Description of subjects	Race/ethnicity	Hardy-Weinberg *p* value	Genotype frequency (percentage)						
					Total no. of subjects	1/1	1/2	2/2	1/3	2/3	3/3
			Africa								
Iron et al., 1992 (20)	Niger	Not specified	Black African	0.26	45	66.7	0.0	0.0	26.7	0.0	6.7
Viljoen et al., 2001 (21)	South Africa	Blood donors	Khoisan-Caucasian	0.04	132	74.1	17.4	1.1	5.1	1.7	0.5
			Americas								
Thomasson et al., 1995 (22)	United States	College students, nonalcoholic	African-American	0.99	326	61.7	0.0	0.0	33.7	0.0	4.6
Wall et al., 2003 (23)	United States	Population-based, nonalcoholics	Native American	0.00	137	83.2	5.8	1.5	8.8	0.7	0.0
Goedde et al., 1992 (24)	United States	Not specified	Alaskan Inuit		27	100.0	0.0	0.0			
	Brazil		Caboclo	0.00	20	90.0	0.0	10.0			
	Chile		Aurocanian		27	100.0	0.0	0.0			
	Mexico		Mestizo	0.67	57	89.5	10.5	0.0			
			Asia								
East Asia											
Shen et al., 1997 (25)	China	Nonalcoholics	Han	0.51	48	12.5	39.6	47.9			
	Korea		Korean	0.41	50	6.0	46.0	48.0			
	Mongolia		Mongolian	0.40	35	17.1	40.0	42.9			
	China		Elunchun	0.11	37	32.4	59.5	8.1			
Goedde et al., 1992 (24)	China	Not specified	Chinese	0.37	86	8.1	47.7	44.2			
Luu et al., 1995 (26)	China	Medical students, nonalcoholic	Chinese	0.53	273	7.7	37.4	55.0			
Chao et al., 1997 (27)	Taiwan	Medical students, nonalcoholic	Taiwanese	0.60	100	6.0	51.0	53.0			
Chen et al., 1996 (28)	Taiwan	Community center	Han	0.16	63	0.0	30.2	69.8			
Thomasson et al., 1991 (29)	Taiwan	Hospital staff, nonalcoholic	Chinese	0.81	47	6.4	40.4	53.2			
Thomasson et al., 1994 (30)	Taiwan		Atayal	0.51	65	1.5	15.4	83.1			
Goedde et al., 1992 (24)	Korea	Not specified	Korean	0.90	177	4.0	31.1	65.0			
Goedde et al., 1992 (24)	Japan	Not specified	Japanese	0.84	32	15.6	50.0	34.4			
Higuchi et al., 1996 (31)	Japan	Hospital staff	Japanese	0.17	451	7.3	34.8	57.9			
Maezawa et al., 1995 (32)	Japan	Not specified	Japanese	0.53	60	3.3	36.7	60.0			
Nakamura et al., 1996 (33)	Japan	Hospital staff, nonalcoholic	Japanese	0.00	97	3.1	55.7	41.2			
Takeshita et al., 2000 (34)	Japan	Hospital	Japanese	0.61	125	6.4	34.4	59.2			

Table continues

approximately 900,000 subjects (68–70). In an analysis of 292 persons with oral, pharyngeal, or laryngeal cancer and 1,568 matched controls, an increased risk (odds ratio (OR) = 2.2, 95 percent confidence interval (CI): 1.4, 3.4) was observed for human papillomavirus 16 seropositivity after adjustment for cotinine levels. The largest series of head and neck cancer cases investigated for human papillomavirus DNA was a series of 253 US cases (71). Detection of human papillomavirus was most common in the oropharynx (57 percent of oropharyngeal cases) and was moderately frequent in the larynx (19 percent), oral cavity (12 percent), and hypopharynx (10 percent).

Genetic susceptibility. Given that the majority of heavy drinkers and smokers do not develop head and neck cancer, a genetic component for these cancers seems plausible. Figure 2 illustrates a broad mechanism by which families of genes may be involved in head and neck cancer. These could include genes that may influence behavior, which might lead to increased alcohol or tobacco consumption, as well as phase I and phase II metabolizing genes (such as *ADH*, *ALDH*, *CYP*, and *N*-acetyltransferase genes) that are likely to be important in determining internal carcinogenic dose (72). The subsequent development of DNA mutations, repair of these errors, or cell apoptosis might also be regulated by

TABLE 1. Continued

Region and study (ref. no.)	Geographic area	Description of subjects	Race/ethnicity	Hardy-Weinberg *p* value	Genotype frequency (percentage)						
					Total no. of subjects	1/1	1/2	2/2	1/3	2/3	3/3
Southeast Asia											
Goedde et al., 1992 (24)	Philippines	Not specified	Filipino	0.24	57	19.3	40.4	40.4			
	Malaysia		Malaysian	0.92	65	16.9	47.7	35.4			
	Thailand		Thai	0.48	111	45.9	41.4	12.6			
Osaka et al., 2003 (35)	Thailand	Population-based	Thai	0.72	153	29.4	51.0	19.6			
Boonyaphiphat et al., 2002 (36)	Thailand	Hospital, nonalcoholic	Thai	0.03	261	36.0	53.3	10.7			
Iron et al., 1992 (20)	Vietnam	Not specified	Vietnamese	0.90	42	59.5	35.7	4.8			
Goedde et al., 1992 (24)	India	Not specified	Indian	0.00	167	85.0	10.2	4.8			
Europe											
Rodrigo et al., 1999 (37)	Spain	Not specified	Caucasian	0.31	200	86.5	13.5	0.0			
Borras et al., 2000 (38)	Spain	Hospital staff and blood donors, nonalcoholic	Caucasian	0.73	37	89.2	10.8	0.0			
	France		Caucasian		40	100.0	0.0	0.0			
	Germany		Caucasian	0.94	41	97.6	2.4	0.0			
	Poland		Caucasian	0.90	66	97.0	2.9	0.0			
	Sweden		Caucasian	0.81	40	93.0	7.0	0.0			
Goedde et al., 1992 (24)	Sweden	Not specified	Caucasian	0.96	90	98.9	1.1	0.0			
	Germany		Caucasian	0.52	233	91.8	8.2	0.0			
	Finland		Caucasian	0.91	85	97.6	2.4	0.0			
	Hungary		Caucasian	0.55	115	89.6	10.4	0.0			
Ogurtsov et al., 2001 (39)	Russia	Not specified	Russian	0.16	50	30	58	12			
Middle East											
Goedde et al., 1992 (24)	Turkey	Not specified		0.67	44	77.3	20.5	2.3			
Oceania											
Amadeo et al., 2000 (40)	Tahiti	Nonalcoholics	Polynesian	0.96	21	38.1	47.6	14.3			
Chambers et al., 2002 (41)	New Zealand	Blood donors	Polynesian	0.62	56	30.4	46.4	23.2			
			Asian	0.01	19	15.8	15.8	68.4			
Amadeo et al., 2000 (40)	Tahiti	Nonalcoholics	Polynesian-Chinese	0.87	11	9.1	45.5	45.5			
			Polynesian-Caucasian	0.25	23	26.1	60.9	13.0			
Chambers et al., 2002 (41)	New Zealand	Blood donors	Caucasian	0.90	17	94.1	5.9	0.0			
Goedde et al., 1992 (24)	Papua New Guinea	Not specified	Papua New Guinean	0.03	204	87.7	10.8	1.5			
	Australia		Aborigine	0.67	22	45.5	40.9	13.6			

DNA repair genes or tumor suppressor genes (73). The efficiency of these genes may vary strongly between individuals, providing a further basis for differences in risk. Most genetic studies of head and neck cancer have focused on genes responsible for metabolizing potential carcinogens, specifically phase I genes such as *CYP2E1* and *CYP1A1* and phase II genes such as those of the glutathione *S*-transferase and *N*-acetyltransferase families. Inconclusive evidence for associations of head and neck cancer with the null genotypes of the glutathione *S*-transferase *M1* and *T1* genes was reported in a prior Human Genome Epidemiology review (74). An overview of *CYP* and *N*-acetyltransferase polymorphisms in the risk of head and neck cancer also suggested no consistent associations (72).

Even though alcohol is a major risk factor for head and neck cancer, the mechanism by which it causes the disease is unclear, especially since pure ethanol does not act as a carcinogen in experimental models (75). One possibility is that the carcinogenic effect of alcoholic beverages is due to acetaldehyde, the initial metabolite of ethanol. Acetaldehyde is a recognized mutagen and animal carcinogen, although specific evidence that it is a cause of head and neck cancer in humans has not been established. However, given that fast alcohol metabolizers will have the greatest peak exposure to

TABLE 2. Genotype frequency of the *ADH1C* polymorphism, by geographic region

Region and study (ref. no.)	Geographic area	Description of subjects	Race/ethnicity	Hardy-Weinberg *p* value	Genotype frequency (percentage)			
					Total no. of subjects	1/1	1/2	2/2
			Africa					
Iron et al., 1992 (20)	Niger	Not specified	Black African	0.00	45	75.6	0.0	24.4
			Americas					
Harty et al., 1997 (42)	Puerto Rico	Population-based	Caucasian, Black, Mestizo, other	0.80	146	38.4	50.0	12.5
Olshan et al., 2001 (43)	United States	Hospital	African-American, Caucasian	0.89	194	38.7	47.4	13.9
Schwartz et al., 2001 (44)	United States	Population-based	Caucasian, African-American, other	0.01	541	36.4	43.2	20.3
Freudenheim et al., 1999 (45)	United States	Population-based	Caucasian	0.85	356	34.6	48.9	16.6
Sturgis et al., 2001 (46)	United States	Hospital	Non-Hispanic Caucasian	0.11	575	31.3	52.5	16.5
Chen et al., 2001 (47)	United States	Population-based	94% Caucasian	0.34	1,113	38.3	46.1	15.6
Hines et al., 2000 (48)	United States	Population-based, nurses	85% Caucasian	0.85	621	34.0	48.3	17.7
Hines et al., 2001 (49)	United States	Population-based, physicians	93% Caucasian	0.47	770	36.2	46.9	16.9
Segal, 1999 (50)	United States	Population-based	Yupik Inuit	0.00	69	29.0	31.9	39.1
Wall et al., 2003 (23)	United States	Population-based, nonalcoholics	Native American	0.04	137	69	49	19
			Asia					
Shen et al., 1997 (25)	China	Nonalcoholics	Han	0.21	48	85.4	12.5	2.1
	Korea		Korean	0.00	50	86.5	9.6	0.0
	Mongolia		Mongolian	0.51	35	80.0	20.0	0.0
	China		Elunchun	0.34	37	73.0	27.0	0.0
Luu et al., 1995 (26)	China	Medical students, nonalcoholic	Chinese	0.06	273	79.9	20.1	0.0
Chao et al., 1997 (27)	Taiwan	Medical students, nonalcoholic	Taiwanese	0.34	100	88.0	11.0	1.0
Chen et al., 1996 (28)	Taiwan	Community center	Han	0.69	62	90.3	9.7	0.0
Thomasson et al., 1994 (30)	Taiwan	Not specified	Atayal	0.95	63	98.4	1.6	0.0
Thomasson et al., 1991 (29)	Taiwan	Hospital staff, nonalcoholic	Chinese	0.70	47	89.4	10.6	0.0
Nakamura et al., 1996 (33)	Japan	Hospital staff, nonalcoholic	Japanese	0.67	97	91.7	8.2	0.0
Iron et al., 1992 (20)	Vietnam	Not specified	Vietnamese	0.00	46	84.8	2.2	13.0
			Europe					
Borras et al., 2000 (38)	Spain	Hospital staff and blood donors, nonalcoholic	Caucasian	0.03	37	18.9	67.6	13.5
	France		Caucasian	1.00	40	37.5	47.5	15.0
	Germany		Caucasian	0.86	41	22.0	51.2	26.8
	Poland		Caucasian	0.75	66	28.8	51.5	19.7
	Sweden		Caucasian	0.80	40	40.0	45.0	15.0
Bouchardy et al., 2000 (51)	France	Hospital	Caucasian	0.04	167	36.5	41.3	22.2
Coutelle et al., 1997 (52)	France	Alcoholics	Caucasian	0.01	38	18.4	71.5	10.5
Zavras et al., 2002 (53)	Greece	Hospital	Caucasian	0.45	99	49.5	39.4	11.1
Grove et al., 1998 (54)	United Kingdom	Hospital staff	Caucasian	0.44	121	34.7	51.2	14.0
			Oceania					
Chambers et al., 2002 (41)	New Zealand	Blood donors	Caucasian	1.00	35	34	49	17
			Asian	0.72	20	85	15	0
			Polynesian	0.23	53	58	40	2

TABLE 3. Genotype frequency of the *ALDH2* polymorphism, by geographic region

Region and study (ref. no.)	Geographic area	Description of subjects	Race/ethnicity	Hardy-Weinberg *p* value	Genotype frequency (percentage)			
					Total no. of subjects	1/1	1/2	2/2
Americas								
Goedde et al., 1992 (24)	Brazil	Not specified	Caboclo	0.31	23	65.2	34.8	0.0
	Chile		Aurocanian		7	100.0	0.0	0.0
	Mexico		Mestizo		61	100.0	0.0	0.0
	United States		Alaskan Inuit		27	100.0	0.0	0.0
Gill et al., 1997 (55)	United States	Hospital	Native American		105	100.0	0.0	0.0
McCarthy et al., 2000 (56)	United States	College students	Asian American	0.03	171	53.8	43.3	2.9
Asia								
East Asia								
Shen et al., 1997 (25)	China	Nonalcoholics	Han	0.67	48	58	38	4
	Korea		Korean	0.03	50	34	60	6
	Mongolia		Mongolian	0.58	35	83	17	0
	China		Elunchun	0.09	37	86	11	3
Goedde et al., 1992 (24)	China	Not specified	Chinese	0.38	132	69.7	28.8	1.5
Luu et al., 1995 (26)	China	Medical students, nonalcoholic	Chinese	0.03	273	52.7	43.2	4.0
Chao et al., 1997 (27)	Taiwan	Medical students, nonalcoholic	Taiwanese	0.89	100	50.0	41.0	9.0
Thomasson et al., 1991 (29)	Taiwan	Hospital staff, nonalcoholics	Chinese	0.31	47	52	36	12
Chen et al., 1996 (28)	Taiwan	Community center	Han	0.69	63	57.1	38.1	4.8
Thomasson et al., 1994 (30)	Taiwan	Not specified	Atayal	0.05	65	90.9	7.6	1.5
Goedde et al., 1992 (24)	Korea	Not specified	Korean	0.60	218	71.6	2.7	1.8
Lee et al., 1997 (57)	Korea	Blood donors	Korean	0.57	481	70.9	26.2	2.9
Goedde et al., 1992 (24)	Japan	Not specified	Japanese	0.14	53	54.7	43.4	1.9
Higuchi et al., 1996 (31)	Japan	Hospital staff	Japanese	0.42	451	58.5	35.0	6.4
Maezawa et al., 1995 (32)	Japan	Not specified	Japanese	0.25	60	56.7	33.3	10.0
Nakamura et al., 1996 (33)	Japan	Hospital staff, nonalcoholics	Japanese	0.04	97	59.8	29.9	10.3
Takeshita et al., 2000 (34)	Japan	Hospital	Japanese	0.69	125	52.0	39.2	8.8
Fujii et al., 1998 (58)	Japan	Not specified	Japanese	0.77	297	59.9	35.4	4.7
Kamino et al., 2000 (59)	Japan	Hospital	Japanese	0.04	447	62.6	60.9	6.5
Southeast Asia								
Goedde et al., 1992 (24)	Philippines	Not specified	Filipino	0.24	86	98.8	1.2	0.0
	Malaysia		Malaysian	0.76	73	93.2	6.8	0.0
	Thailand		Thai	0.58	111	90.1	9.9	0.0
Boonyaphiphat et al., 2002 (36)	Thailand	Hospital, nonalcoholics	Thai	0.02	261	82.4	15.3	2.3
Osaka et al., 2003 (35)	Thailand	Population-based	Thai	0.61	153	92.2	7.8	0.0
Goedde et al., 1992 (24)	India	Not specified	Indian	0.00	179	96.6	2.8	0.5
Europe								
Goedde et al., 1992 (24)	Germany	Not specified	Caucasian		193	100.0	0.0	0.0
	Sweden		Caucasian		99	100.0	0.0	0.0
	Finland		Caucasian		100	100.0	0.0	0.0
	Hungary		Caucasian	0.89	117	97.4	2.6	0.0
Middle East								
Goedde et al., 1992 (24)	Turkey	Not specified	Caucasian		57	100.0	0.0	0.0
Oceania								
Chambers et al., 2002 (41)	New Zealand	Blood donors	Caucasian		14	100	0	0
			Asian	0.57	14	64	29	7
			Polynesian		55	100	0	0
Goedde et al., 1992 (24)	Papua New Guinea	Not specified	Papua New Guinean	0.95	242	99.2	0.8	0.0
	Australia		Aborigine		37	100.0	0.0	0.0

TABLE 4. Findings from published studies on the association of the *ADH1B*, *ADH1C*, and *ALDH2* genotypes with head and neck cancer

Region and study (ref. no.)	Ethnicity	Country	No. and type of cancer cases						No. and type of controls		Prevalence of genotype				
			Oral	Pharyngeal	Oral/ pharyngeal not specified	Laryngeal	Total	Incident/ prevalent	No.	Hospital/ population	Genotype	Cases No.	Cases %	Controls No.	Controls %
						ADH1C genotype									
Coutelle et al., 1997 (52)	Caucasian	France	14	7	0	18	39	Prevalent	38	Alcoholics	2/2	6	15.4	4	10.5
											2/1	14	35.9	27	71.5
											1/1	19	48.7	7	18.4
Harty et al., 1997 (42)	Mixed	Puerto Rico	115	24	7	0	146	Incident	146	Population	2/2	18	12.3	20	13.7
											2/1	59	40.4	70	47.9
											1/1	69	47.3	56	38.4
Bouchardy et al., 2000 (51)	Caucasian	France	69	52	3	120	244	Incident	167	Hospital	2/2	57	23.4	37	22.2
											2/1	100	41.0	69	41.3
											1/1	87	35.7	61	36.5
Zavras et al., 1999 (45)	Caucasian	Greece	93	0	0	0	93	Incident	99	Hospital	2/2	10	12.3	11	11.1
											2/1	33	35.5	39	39.4
											1/1	50	53.8	49	49.5
Schwartz et al., 2001 (44)	Mixed	United States	257	76	0	0	333	Incident	541	Population	2/2	59	17.7	110	20.3
											2/1	159	47.8	234	43.2
											1/1	115	34.5	197	36.4
Sturgis et al., 2001 (46)	Caucasian	United States	121	102	0	75	298	Incident	575	Hospital	2/2	55	18.5	95	16.5
											2/1	149	50.0	300	52.5
											1/1	94	31.5	180	31.3
Olshan et al., 2001 (43)	Mixed	United States	89	31	4	48	172	Incident	194	Hospital	2/2	18	10.5	27	13.9
											2/1	69	40.1	92	47.4
											1/1	85	49.4	75	38.7
Total			758	292	14	261	1,325		1,760		2/2	223	16.8	304	17.3
											2/1	583	44.0	831	47.2
											1/1	520	39.2	626	35.5
						ADH1B genotype									
Yokoyama et al., 2001 (78)	Japanese	Japan	0	0	16	18	34	Incident	526	Alcoholics	2/2	11	32.4	381	72.4
											2/1				
											1/1	23	67.6	145	27.6

ALDH2 genotype															
Katoh et al., 1999 (76)	Japanese	Japan	92	0	0	0	92	Incident	147	Hospital	2/2	2	2.2	8	5.4
											2/1	42	45.7	61	41.5
											1/1	48	52.1	78	53.1
Nomura et al., 2000 (77)	Japanese	Japan	110	4	0	0	114	Incident	33	Hospital	2/2	0	0.0	0	0.0
											2/1	36	33.0	5	15.1
											1/1	73	67.0	28	84.9
Yokoyama et al., 2001 (78)	Japanese	Japan	0	0	16	18	34	Incident	526	Alcoholics	2/2	0	0.0	0	0.0
											2/1	23	67.6	50	9.5
											1/1	11	32.4	476	90.5

acetaldehyde, it has been hypothesized that possession of *ADH1B* and *ADH1C* genotypes encoding for fast alcohol metabolism will confer an increased risk of head and neck cancer. Similarly, the null *ALDH2*2* allele may contribute to an increased level of acetaldehyde and act as a risk factor for head and neck cancer. Therefore, a prime hypothesis is that possession of the *ADH1C*1*, *ADH1B*2*, and *ALDH*2* alleles, either singularly or in combination, will confer an increased risk of head and neck cancer among persons who consume alcohol. Although ethanol and water are the main components of alcoholic beverages, known carcinogens such as nitrosamines can also be present as contaminants (75). Polymorphisms in the genes that metabolize carcinogenic contaminants may also play a role in carcinogenesis.

Associations and interactions

To examine the association between *ADH1B*, *ADH1C*, and *ALDH2* polymorphisms and head and neck cancer, we undertook a pooled analysis of all relevant studies. We conducted a MEDLINE search to identify all studies published before December 2002, without restriction on language, using the keywords "*ADH2*," "*ADH3*," "*ADH1B*," "*ADH1C*," and "*ALDH2*." We subsequently reviewed the reference lists of all published studies to confirm that all relevant studies had been identified. As we noted above, the studies were restricted to oral cavity, pharyngeal, and laryngeal cancers. The results of this search brought the total number of published case-control studies on head and neck cancer to 10: seven studies on *ADH1C* (42–44, 46, 51–53), two studies on *ALDH2* (76, 77), and one study on both *ADH1B* and *ALDH2* (78).

Given the benefits of pooling original data from a series of studies over meta-analysis of published results (79), we contacted the investigators from the seven groups that had conducted studies on *ADH1C* and asked them to provide their original data on tobacco and alcohol exposure and genotype. All seven groups of investigators agreed to this request and provided data on the following variables: 1) head and neck cancer subsite according to ICD-9 code or *International Classification of Diseases for Oncology* three-digit code; 2) age at diagnosis (or on the corresponding date for controls); 3) sex; 4) *ADH1C* genotype; 5) tobacco smoking status (never/ex-/current); and 6) alcohol consumption status (never/ex-/current). Institutional review board approval had been obtained for each of the individual studies, and personal identifiers were not included in the pooled data. The definition of current smoking and current drinking was generally taken as smoking or drinking 1 year prior to interview. For the data of Olshan et al. (43), smoking status (ex- vs. current) had to be determined from smoking duration, under the assumption that subjects had started smoking at age 20 years. A similar assumption was made for determination of current alcohol consumption in the data of Zavras et al. (53). These assumptions are likely to have led to underestimation of the numbers of current smokers and current drinkers in those two studies, respectively, since smokers in the study by Olshan et al. (43) and drinkers in the study by Zavras et al. (53) who commenced their use before the age of 20 years would have been classified as ex-smokers and ex-drinkers.

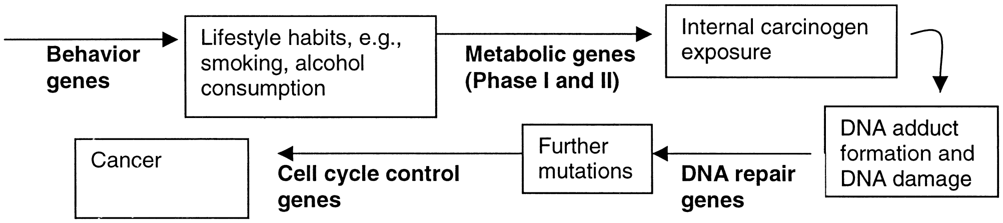
Behavior genes
Lifestyle habits, e.g., smoking, alcohol consumption
Metabolic genes (Phase I and II)
Internal carcinogen exposure
DNA adduct formation and DNA damage
DNA repair genes
Further mutations
Cell cycle control genes
Cancer

FIGURE 2. The potential role of genetic susceptibility in the pathway to head and neck cancer.

Information on amount of alcohol consumption among current drinkers was available for all studies except one (52). Subsequently, the number of drinks consumed per week among current drinkers was stratified into three groups: 1–19, 20–59, and ≥60. All subjects in the one study that was restricted to alcoholics (46), which did not provide actual numbers of drinks, were assumed to have consumed 60 or more drinks per week. The cutoff points for the number of drinks per week among current drinkers were chosen thus, because "60 or more" refers to the alcoholics in one study (46), "0.1–19.9" equates approximately to recommended levels for men, and "20–59.9" is the intermediate level between the two. The inclusion criteria for cancer subsites consisted of ICD-9 codes 141 and 143–145 for oral cancer, ICD-9 codes 146, 148, and 149 for pharyngeal cancer, and ICD-9 code 161 for laryngeal cancer. ICD-9 code 140 (lip cancer) was included in one study (43) that had two cases. ICD-9 code 142 (salivary gland) and ICD-9 code 147 (nasopharynx) were excluded.

Hardy-Weinberg equilibrium for the three *ADH1C* genotypes was assessed separately for both cases and controls in each study. A priori, it would be expected that the *ADH1C* genotype frequencies among controls would be in Hardy-Weinberg equilibrium, though not necessarily among cases (80). Heterogeneity in genotype frequencies between the seven studies was analyzed among the controls using the Kruskal-Wallis test. Subsequently, odds ratios and 95 percent confidence intervals were calculated for possession of one or two fast *ADH1C*1* alleles compared with the slow *ADH1C*2/2* genotype, both overall and for head and neck cancer subsites, as well as after stratifying for alcohol consumption status. Odds ratios were estimated using unconditional logistic regression, adjusting where necessary for age, sex, and study. Additional adjustment for tobacco use did not materially affect the results. The test for trend in possessing 0, 1, or 2 *ADH1C*1* alleles was also calculated. We assessed departures from multiplicative interaction by including interaction terms in the appropriate logistic regression models and comparing the models by means of a likelihood ratio test (81).

Given that only one study was identified for head and neck cancer and *ADH1B* and three studies were identified for *ALDH2* (one of which was conducted among alcoholics), pooling of the original data from these studies was deemed unnecessary, and the published results are presented separately.

RESULTS

Pooled analysis of *ADH1C* studies

Selected characteristics of the seven studies on *ADH1C* are presented in table 4. The total pooled data set included 1,325 cases and 1,760 controls. The 1,325 cases included 758 cancers of the oral cavity (57 percent), 292 pharyngeal cancers (22 percent), and 261 laryngeal cancers (20 percent).

An overall departure from Hardy-Weinberg equilibrium was observed for the *ADH1C* genotype among the cases (p = 0.03), though not among the controls (p = 0.9). When it was analyzed by study, this excess was significant for only one study (51) (p = 0.034), though the differences between observed and expected frequencies for both homozygous genotypes were less than 5 percent. Although no overall departure from Hardy-Weinberg equilibrium was observed among the controls, statistically significant differences in study-specific frequencies were observed. For Schwartz et al. (44), the differences between observed and expected homozygous genotypes were less than 5 percent, whereas for Coutelle et al. (52), a substantial excess of the heterozygous *ADH1C*1/2* genotype was observed (71 percent observed vs. 49.7 percent expected) (p = 0.033). The variation in control genotype frequencies among the seven studies was of borderline significance (p = 0.05).

Table 5 presents the associations between head and neck cancer and *ADH1C* genotype, overall and by drinking category. No significantly increased risk of head and neck cancer was observed for possession of the *ADH1C*1/2* heterozygous genotype (OR = 1.00, 95 percent CI: 0.81, 1.23) or the *ADH1C*1/1* homozygous genotype (OR = 1.14, 95 percent CI: 0.92, 1.41). Similarly, when the analysis was conducted by subsite, there was no evidence of any increased risk for possession of either one or two fast metabolizing alleles, or any evidence of a dose response with increasing number of fast alleles for cancers of the pharynx or larynx. The risk of oral cancer may be increased by the *ADH1C*1/1* genotype (OR = 1.27, 95 percent CI: 0.97, 1.66). Similarly, when data were stratified by drinking status, there was no significant evidence for differing effects of *ADH1C* genotype between current, former, and never drinkers (p for interaction > 0.20).

The individual results of the six studies with information on amount of alcohol consumed are presented in table 6. One study (42) observed a large increase in risk for the *ADH1C*1/1* genotype among heavy drinkers (≥60 drinks/week), based on 39 cases and six controls. Two other studies

TABLE 5. Results of pooled analysis of data from seven case-control studies on the association of the *ADH1C* genotype and alcohol consumption with head and neck cancer

Type of head/neck cancer and *ADH1C* genotype	Overall results*			Alcohol drinking status: Never drinkers			Ex-drinkers			Current drinkers			*p* for interaction
	No. of cases/ controls	OR†	95% CI†	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	
All types													
2/2	223/304	1.00		20/70	1.00		50/57	3.11	1.64, 5.90	153/177	2.85	1.62, 5.00	0.223
1/2	583/831	1.00	0.81, 1.23	85/207	1.36	0.78, 2.40	127/175	2.59	1.48, 4.54	371/449	2.82	1.65, 4.82	
1/1	519/625	1.14	0.92, 1.41	73/174	1.36	0.77, 2.42	147/120	4.08	2.32, 7.19	299/330	2.94	1.71, 5.05	
Dose response		*p* = 0.154											
Oral													
2/2	110/304	1.00		12/70	1.00		30/57	3.07	1.39, 6.76	68/177	2.54	1.25, 5.18	0.160
1/2	339/831	1.13	0.87, 1.47	50/207	1.31	0.64, 2.66	69/175	2.40	1.19, 4.86	220/449	3.18	1.62, 6.21	
1/1	309/625	1.27	0.97, 1.66	50/174	1.45	0.71, 2.95	92/120	4.15	2.06, 8.39	167/330	3.04	1.54, 5.97	
Dose response		*p* = 0.067											
Pharyngeal													
2/2	64/293	1.00		4/62	1.00		12/55	3.25	0.98, 10.8	48/176	4.01	1.36, 11.8	0.515
1/2	118/792	0.68	0.48, 0.95	16/187	1.27	0.41, 3.95	33/162	2.88	0.97, 8.58	69/443	2.26	0.78, 6.52	
1/1	110/576	0.89	0.63, 1.26	11/150	1.15	0.35, 3.76	30/103	4.12	1.37, 12.4	69/323	3.12	1.08, 9.05	
Dose response		*p* = 0.881											
Laryngeal													
2/2	46/163	1.00		4/53	1.00		8/29	2.80	0.74, 10.5	34/81	2.26	0.72, 7.06	0.679
1/2	120/488	0.99	0.65, 1.50	19/148	1.45	0.46, 4.56	21/106	2.09	0.66, 6.63	80/234	2.24	0.76, 6.64	
1/1	95/323	1.17	0.76, 1.80	12/117	1.12	0.33, 3.74	22/65	3.51	1.10, 11.2	61/141	2.62	0.87, 7.85	
Dose response		*p* = 0.387											

* Results were adjusted for age, sex, study center, and alcohol drinking status.

† OR, odds ratio; CI, confidence interval.

(51, 52) that included a greater number of cases and controls who were heavy drinkers did not observe this association. Heterogeneity was observed between individual studies in the upper two categories of current drinkers, but interpretation of findings from the individual studies is limited by the small number of subjects in these categories. Pooled analysis of these six studies showed some evidence of interaction between *ADH1C* genotype and amount of alcohol consumed ($p = 0.039$); this appeared to be primarily due to an increased risk among heavy drinkers (≥60 drinks per week) associated with the *ADH1C*1/1* genotype in the studies by Harty et al. (42) and Olshan et al. (43).

ADH1B study

One case-control study on head and neck cancer and the *ADH1B* genotype was identified (78) (table 7). The study included 34 alcoholic male patients with squamous cell carcinomas of the head and neck as cases and 526 male alcoholics without cancer as controls. An overall odds ratio of 6.68 (95 percent CI: 2.81, 15.90) was observed for head and neck cancer and *ADH1B*1/1* in comparison with **1/2* or **2/2* after adjustment for age, daily alcohol consumption, amount of cigarette smoking, and the *ALDH2* genotype. These findings, which were significant, were the inverse of what was expected on the basis of the known function of *ADH1B*. Odds ratios from this study for sites within the head and neck were 5.48 (95 percent CI: 1.77, 17.0) for oropharyngeal cancer and 6.57 (95 percent CI: 1.62, 21.3) for laryngeal cancer (table 7).

ALDH2 studies

Three Japanese studies have investigated the relation between the *ALDH2* genotype and oral, pharyngeal, and laryngeal cancers (76–78) (table 7). The study of alcoholics by Yokoyama et al. (78) identified a strong but imprecise relative risk associated with the heterozygous genotype as compared with the fully functional *ALDH2*1/1* genotype for oropharyngeal cancer (OR = 20.83, 95 percent CI: 6.62, 65.5). A case-control study of 114 oral and pharyngeal cancer cases and 33 hospital controls reported an odds ratio of 2.9 (95 percent CI: 1.1, 7.8) for *ALDH2* heterozygosity relative to the fully functional *ALDH*1/1* homozygosity (77). A third case-control study of 92 oral cancer cases and 147 hospital controls identified no association for either the nonfunctional genotype or the heterozygous genotype (76). These results suggest a possibly increased risk of head and neck cancer associated with possessing one inactive *ALDH2*2* allele but not two inactive alleles.

TABLE 6. Association of the *ADH1C* genotype and alcohol consumption with head and neck cancer among current drinkers*

Study (ref. no.) and *ADH1C* genotype	Current drinkers†			Alcohol consumption (no. of drinks per week)											
				0 (never drinkers)			0.1–19.9			20–59.9			≥60		
	No. of cases/ controls	OR‡	95% CI‡	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Coutelle et al., 1997 (52)															
2/2	6/4	1.00											6/4	1.00	
1/2	14/27	0.67	0.11, 4.08										14/27	0.67	0.11, 4.08
1/1	19/7	2.69	0.39, 18.6										19/7	2.69	0.39, 18.6
Harty et al., 1997 (42)															
2/2	9/7	1.00		1/5	1.00		1/4	1.25	0.05, 29.6	6/2	20.0	1.16, 345	2/1	13.8	0.48, 394
1/2	29/34	0.66	0.18, 2.42	10/21	2.60	0.26, 25.9	6/20	1.95	0.17, 22.6	8/10	5.57	0.45, 69.0	15/4	25.9	1.95, 344
1/1	36/26	1.08	0.29, 4.03	6/15	2.13	0.20, 22.5	4/19	1.42	0.11, 17.9	10/6	11.4	0.91, 143	22/1	144	6.53, 3193
Bouchardy et al., 2000 (51)															
2/2	50/32	1.00		2/2	1.00		3/4	0.76	0.06, 9.02	21/18	1.14	0.15, 8.98	26/10	2.54	0.31, 20.6
1/2	77/56	0.94	0.52, 1.69	11/6	1.76	0.19, 15.9	6/9	0.61	0.07, 5.67	38/33	1.09	0.14, 8.19	33/14	2.31	0.30, 18.1
1/1	69/41	1.08	0.59, 2.00	7/15	0.45	0.05, 3.94	3/8	0.34	0.03, 3.67	29/23	1.19	0.15, 9.14	37/10	3.66	0.46, 29.4
Zavras et al., 2002 (53)															
2/2	1/1	1.00		3/8	1.00		1/1	2.38	0.11, 53.1						
1/2	12/6	2.35	0.08, 69.6	11/20	1.42	0.30, 6.57	4/3	5.38	0.65, 44.6	3/3	3.47	0.39, 30.8	5/0		
1/1	10/7	2.02	0.07, 59.0	17/24	1.92	0.44, 8.50	4/4	2.84	0.40, 19.9	3/3	3.84	0.43, 34.4	3/0		
Olshan et al., 2001 (43)															
2/2	10/8	1.00		3/12	1.00		4/7	2.71	0.44, 16.9	2/1	11.0	0.58, 208	4/0		
1/2	36/27	0.73	0.19, 2.74	13/45	0.94	0.22, 4.03	17/22	2.45	0.56, 10.6	10/5	7.82	1.35, 45.4	9/0		
1/1	43/27	0.77	0.21, 2.86	15/34	1.68	0.39, 7.26	15/21	2.38	0.54, 10.5	17/5	12.0	2.23, 64.6	11/1	42.5	3.61, 499
Schwartz et al., 2001 (44)															
2/2	44/86	1.00		1/4	1.00		28/80	1.64	0.17, 15.5	10/6	9.09	0.79, 104	6/0		
1/2	120/173	1.32	0.84, 2.10	6/18	1.59	0.15, 17.3	76/153	2.41	0.26, 22.2	33/17	10.1	1.02, 99.6	11/3	19.2	1.49, 248
1/1	76/154	1.08	0.66, 1.75	9/18	2.29	0.22, 23.9	52/146	1.75	0.19, 16.2	18/6	15.8	1.43, 175	6/2	16.4	1.06, 253
Overall§															
2/2	120/138	1.00		10/31	1.00		37/96	1.43	0.62, 3.32	39/27	6.29	2.53, 15.6	44/15	16.4	6.09, 44.0
1/2	288/323	1.04	0.75, 1.43	51/110	1.46	0.66, 3.24	109/207	1.94	0.89, 4.26	92/68	5.40	2.39, 12.2	87/48	12.5	5.24, 30.0
1/1	253/262	1.10	0.79, 1.54	54/106	1.65	0.75, 3.66	78/198	1.43	0.65, 3.16	77/43	6.97	3.01, 16.1	98/21	29.8	11.8, 75.4

* Includes current drinkers for whom the actual number of drinks consumed per week was known; does not include data from the study by Sturgis et al. (46).
† Results were adjusted for age, sex, and alcohol consumption.
‡ OR, odds ratio; CI, confidence interval.
§ Results were adjusted for age, sex, and study center.

DISCUSSION

Large differences in genotype distribution were observed between different ethnic groups for all three ADH and ALDH genes, with the fast metabolizing *ADH1B*2* and *ADH1C*1* alleles and the nonfunctional *ALDH2*2* allele being seen more commonly in Asian populations. Furthermore, while the few existing studies suggest an increased risk of head and neck cancer for the *ALDH2*1/2* and *ADH1B*1/1* genotypes, the combined analysis of all seven published case-control studies on *ADH1C* fast alleles does not provide consistent evidence for a major role of this genetic variant in head and neck cancer overall. However, among current drinkers, there was evidence of an interaction between the *ADH1C*1/1* genotype and high levels of alcohol consumption.

Of the two initial studies (42, 52), which supported a role for *ADH1C* in head and neck cancer, the study by Coutelle et al. (52) differed from the other six studies because it was restricted to a small group of alcoholic men. This selection of alcoholics may explain the lack of Hardy-Weinberg equilibrium in the control population, where a surplus of *ADH1C*2/1* heterozygotes was observed at the expense of *ADH1C*1/1* homozygotes; it is possible that *ADH1C*1/1* homozygotes are less likely to become alcoholic because of the side effects associated with rapid ethanol metabolism (82). In the original analysis of Coutelle et al. (52), *ADH1C*1/1* homozygotes were compared with **1/2* heterozygotes and *2/2* homozygotes combined, although the increased risk for *ADH1C*1/1* is less apparent when **2/2* homozygotes are taken as the reference category. Pooled

TABLE 7. Association of the _ADH1B_ and _ALDH2_ genotypes with head and neck cancer

Study (ref. no.)	Genotype	Oral/pharyngeal cancer			Laryngeal cancer		
		No. of cases/ controls	OR*	95% CI*	No. of cases/ controls	OR	95% CI
Yokoyama et al., 2001 (78)†	_ADH1B_						
	1/1 vs. 1/2 or 2/2‡	16/526	5.48	1.77, 17.0	18/526	6.57	1.62, 21.3
	ALDH2						
Katoh et al., 1999 (76)	2/2 vs. 1/1‡	92/147	0.35	0.57, 2.17			
	1/2 vs. 1/1‡		1.18	0.65, 2.13			
Nomura et al., 2000 (77)	1/2 vs. 1/1	114/33	2.9	1.1, 7.8			
Yokoyama et al., 2001 (78)†	1/2 vs. 1/1‡	16/526	20.83	6.62, 65.49	18/526	28.92	8.66, 96.6

* OR, odds ratio; CI, confidence interval.

† Alcoholic subjects.

‡ Adjusted for alcohol consumption.

analyses of the association between _ADH1C*1/1_ and head and neck cancer were also conducted after exclusion of the Coutelle et al. data, but the results did not change materially.

In the study by Harty et al. (42), while no overall association was seen for _ADH1C_, a 10-fold greater risk of oropharyngeal cancer was observed among heavy drinkers for _ADH1C*1/1_ homozygotes as compared with _*2/2_ homozygotes ($p = 0.04$); this is similar to the results shown in table 6, which used a slightly different cutoff point to define the heaviest drinkers. However, this comparison was based on very small numbers of subjects, leading to unstable estimates. In addition, the comparison of cases in the intermediate alcohol consumption group (15–56 drinks per week in the original analysis) showed an opposite association, with a twofold higher risk for the _ADH1C*2/2_ genotype as opposed to _*1/1_. In the absence of any association with _ADH1C*1/1_ among intermediate alcohol drinkers, and with the benefit of hindsight from five additional studies, it is possible that these patterns in the study by Harty et al. represented a chance finding.

Of the subsequent five studies (43, 44, 46, 51, 53), only one had a large number of heavy-drinker cases and controls (51), allowing possible replication of these findings in heavy drinkers, but no significant association was observed. Also of interest is the fact that two of these five studies suggested a greater increase in risk with increasing alcohol consumption with the _ADH1C*2_ allele, though the reasons for this are unclear (44, 53).

While it is unlikely that the _ADH1C*1_ allele has a major effect on risk of head and neck cancer, a more moderate association cannot be ruled out by our analysis (e.g., a 40 percent increase in overall risk or a 100 percent increase among heavy drinkers). A 40 percent increase in risk for a genotype that is present in one third of the population would still result in a population attributable risk of approximately 12 percent for all head and neck cancers and a population attributable risk of 25 percent among heavy drinkers.

Potential limitations of the pooled analysis include publication bias and population admixture. The seven case-control studies were identified from published studies; thus, publication bias could potentially have led to bias away from the null through the inclusion of more studies with positive findings. However, the overall null results from our pooled analysis suggested that positive studies were not overrepresented. In extreme situations, population admixture can lead to confounding. Three of the case-control studies included persons of different races (42–44). However, when we tested for Hardy-Weinberg equilibrium among our controls, departure from Hardy-Weinberg equilibrium was not detected, which suggests that population admixture may not have been a major drawback. Furthermore, since the studies in the pooled analysis were mostly studies of Caucasians and the genotype distribution for the _ADH1C_ polymorphism differs by race, the risk estimates may only be generalizable to the Caucasian population.

Regarding _ADH1B_, the increased risk of head and neck cancer for _ADH1B*1/1_ (the slow genotype) in the one study that tested for this association was contrary to the hypothesis that fast metabolism of alcohol would lead to increased peak acetaldehyde exposure and therefore greater risk. With the use of alcoholic controls, there is a possibility that this odds ratio was underestimated. However, this association may simply reflect residual confounding by alcohol consumption. Similar to the case among _ALDH2*2/2_ carriers, alcohol consumption among persons who possess the _ADH1B*2/2_ genotype is likely to be substantially lower than that in the rest of the population because of the occurrence of a toxic reaction. Indeed, the one study on _ADH1B_ conducted in the Japanese population did not adjust for alcohol consumption, though all participants were alcohol drinkers (78). Similarly, for _ALDH2_, an increased risk was not observed for the nonfunctional _ALDH2*2/2_ genotype. This may represent an absence of alcohol consumption or very low consumption among such persons. These findings point to the necessity for careful control of alcohol consumption or stratification by alcohol consumption in the analyses in genetic studies on _ADH1B_ and _ALDH2_. However, an increased risk was observed for the semifunctional _ALDH2*1/2_ genotype in two of the three studies that investigated this (77, 78). Such a finding is consistent with an increased risk due to inefficient acetaldehyde metabolism and increased local exposure to acetaldehyde. Since the reviews on *ADH1B* and *ALDH2* included only Japanese studies, these results may be more generalizable to the ethnic Asian population.

Concerning future studies on the role of ADH and ALDH genes in head and neck cancer, several improvements over previous studies can be recommended. Larger studies that accurately measure the association with individual genes in particular subgroups (e.g., defined by alcohol consumption or ethnicity) and that incorporate joint analysis of relevant ADH and ALDH genes simultaneously, as well as other genes that may be involved in alcohol metabolism (such as *CYP2E1*), are necessary. Mechanistic studies would be of much use for clarifying the role of individual ADH and ALDH genes in acetaldehyde exposure, including an assessment of combinations of these genes. Also of interest would be an assessment of the relation of acetaldehyde levels with different patterns of alcohol consumption, including binge drinking and moderate chronic consumption. The role of ADH and ALDH genes should also be assessed with respect to intermediate markers, including acetaldehyde adducts in head and neck tissue. Finally, given the relative rarity of head and neck cancers at any particular study center, these considerations suggest the potential for the organization of a consortium of investigators conducting studies in this field.

Laboratory tests

Methods of genotyping for the *ADH1B* and *ADH1C* polymorphisms (83, 84) and the *ALDH2* polymorphism (85) by means of the polymerase chain reaction and restriction fragment length polymorphism techniques have been described previously.

Population testing

No studies on the effectiveness or efficacy of genetic testing for *ADH1B*, *ADH1C*, or *ALDH2* are available.

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APPENDIX

Internet Sites

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