Relationships of TP53 Codon 72 and HRAS1 Polymorphisms with Lung Cancer Risk in an Ethnically Diverse Population

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Abstract

Tobacco smoking is a strong cause of lung cancer. However, because only a small proportion of smokers develop the disease, other factors, including genetic susceptibility, may be important in determining lung cancer risk. Polymorphisms in the TP53 tumor suppressor gene and HRAS1 proto-oncogene have been associated in some studies with this cancer; we sought to replicate these associations in an ethnically diverse population in Hawaii. We conducted a population-based case-control study among 334 incident lung cancer cases and 446 controls of Caucasian, Japanese, or Native Hawaiian origin. In-person interviews collected detailed information on lifestyle risk factors. DNA was extracted from peripheral blood leukocytes, and genotyping was performed using a PCR-based assay for the TP53 codon 72 polymorphism and Southern blot analysis and PCR for allelic polymorphisms in the HRAS1 minisatellite. Logistic regression analyses were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for smoking and other risk factors. The presence of two rare HRAS1 alleles was associated with a 2.2-fold (95% CI, 1.0–5.0) increased lung cancer risk for all ethnic groups combined. The association was present in Native Hawaiians (OR, 5.2; 95% CI, 1.1–24.4) and was suggested for Japanese (OR, 2.8; 95% CI, 0.6–12.5); no association was observed in Caucasians (OR, 0.8; 95% CI, 0.2–3.6). This association was also observed for each lung cancer cell type. The presence of only one rare allele did not increase risk for any ethnic group or cell type. No significant association was found between the TP53 codon 72 polymorphism and lung cancer [OR, 1.4 (95% CI, 0.8–2.4) for the Pro/Pro genotype compared with the Arg/Arg genotype]. This study suggests that the presence of two rare HRAS1 alleles confers an increased lung cancer risk in Native Hawaiians and Japanese but possibly not in Caucasians. The amino acid replacement of arginine by proline at codon 72 of TP53 appears not to be important in determining lung cancer risk in this population.

Introduction

Tobacco smoking has been established as a strong cause of lung cancer. However, because only a small proportion of smokers ever develop the disease, it has been suggested that genetic susceptibility may significantly contribute to risk. Indeed, several polymorphic genes that control the metabolic activation or detoxification of tobacco carcinogens have been found to be associated with lung cancer risk (1). Polymorphisms in genes directly involved in tumorigenesis, such as TP53 and H-ras (HRAS), have also been proposed to contribute to individual susceptibility to lung cancer.

The tumor suppressor gene TP53 is a key and potent mediator of cellular responses against genotoxic insults (reviewed in Ref. 2). This gene encodes for a transcription factor that regulates the expression of different cell cycle-related genes (3). The TP53 gene has been shown to be a frequent target for somatic alterations in lung cancer, especially squamous cell carcinoma (4). A large number of tumors, including those in the lung, show TP53 mutations or deletions that result in the loss of tumor suppressor function, disrupting growth-regulatory mechanisms in the cell (5).

The TP53 gene exhibits a polymorphism at codon 72 involving a single base change that causes an amino acid replacement of arginine (CGC) by proline (CCC) in the trans-activation domain of p53 (6). Whether this variant of the wild-type p53 protein is functionally different is unknown. It has been reported that the Arg 72-p53 isoform shows increased susceptibility to E6/ubiquitin-mediated degradation (7). However, the genotype Pro/Pro has been associated with an increased risk of lung cancer in Japanese (8) and Taiwanese (9), as well as in young African-Americans (10). In contrast, no significant association was observed in other studies conducted in African and European Americans (11) and in Swedes (12). The inconsistency in past data emphasizes the importance of conducting additional, larger studies targeting different populations.

The human HRAS gene is associated with a RFLP resulting from a VNTR (variable number of tandem repeat) of a 28-bp consensus sequence in the 3’ flanking region (HRAS1, Ref. 13). Four common alleles have been described that are thought to have served as progenitors...
for the remaining “rare” alleles through a mutational process. This VNTR has been shown to have transcriptional enhancer activity that may alter H-ras expression and play a role in tumorigenesis (14). H-ras is a GTP binding protein and is an important component of one of the major signal transduction pathways in the cell (15). Krontiris et al. (16) found a significantly higher frequency of HRAS1 rare alleles in patients with cancer at different sites compared with controls. A number of studies have reproduced this association for lung cancer (17–20), although others have not (21).

In this study, we investigated the associations of the TP53 codon 72 and HRAS1 polymorphisms with lung cancer risk in various ethnic groups in Hawaii. We conducted a large population-based case-control study among Caucasians, Japanese, and Native Hawaiians on the island of Oahu.

Materials and Methods

The human subjects protocol for this study was approved by the Committee on Human Studies of the University of Hawaii and by the Institutional Review Board of each participating hospital. We also obtained written informed consent from all subjects.

Lung cancer patients were identified by the rapid-reporting system of the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Eligible cases were all patients with histologically confirmed primary lung cancer who were diagnosed between January 1, 1992 and March 31, 1997, in all main medical centers of Oahu, Hawaii. Other eligibility criteria included age between 26 and 79 years, Oahu residency, no previous history of lung cancer, and appropriate ethnicity (75% + Japanese, 75% + Caucasian, or any Hawaiian/part Hawaiian heritage). An interview was completed for 64% of the eligible cases. The main reasons for nonparticipation were patient refusal (17%), physician refusal (2%), and death with absence of a suitable surrogate for interview (17%). The demographics and clinical characteristics of interviewed cases were similar to those of non-interviewed cases, except that the former were more likely to be Hawaiian (25% versus 19%), were less likely to have a distant metastasis (37% versus 50%), and were younger by an average of 1 year.

Controls were selected randomly from a list of Oahu residents interviewed by the State of Hawaii Department of Health as part of a health survey of a 2% random sample of state households. This source was supplemented with controls from Health Care Financing Administration participants on Oahu. One control was matched to each case on sex, ethnicity, and age (+2 years). The overall participation rate for the controls was 62%. Reasons for nonparticipation included refusal (25%), inability to locate (10%), serious illness (1%), and death (2%). Compared with non-interviewed controls, interviewed controls were similar in their sex and race distribution but were younger by an average of 1 year. Seventy-six % of interviewed cases (341 cases) and 80% of interviewed controls (456 controls) donated a blood sample. There were no differences in the age, sex, and race distributions of controls who gave a blood sample compared with those who did not. However, cases who gave blood were younger by an average of 1 year and were less likely to have a distant metastasis than those who refused the blood donation. The analysis presented here was conducted with the 334 cases and 446 population controls whose DNA was still available.

In-person interviews were conducted at the subjects’ homes by trained interviewers. On average, cases were inter-

viewed within 4 months of diagnosis. The questionnaire included detailed demographic information, including ethnic origin of each grandparent, a lifetime history of tobacco and alcohol use, a quantitative food frequency questionnaire, various relevant medical conditions and occupational exposures, and a family history of lung disease. Information was collected on the types (nonfiltered cigarettes, filtered cigarettes, cigars, and pipes) of tobacco product ever smoked daily for at least 6 months and, for each tobacco product, usual amount per day, age when started, the overall duration of use, and for ex-smokers, age when smoking stopped. We also inquired about any periods of smoking cessation for each tobacco product during the subject’s life.

Laboratory personnel were blinded to the case-control status of the subjects. DNA was purified from peripheral blood lymphocytes by standard SDS/protease K treatment and phenol/chloroform extraction (22). Genotyping of the TP53 codon 72 alleles was carried out by PCR amplification using primers 5′-ATCTACAGTCCCCTTGCCG-3′ and 5′-GCAACTGAC-CGTTGCAAGTCA-3′, using a modified protocol by Kawajiri et al. (8). Amplification was performed in a thermal cycler with initial denaturation at 94°C for 4 min, followed by 25 cycles of denaturation at 94°C for 1 min, annealing at 60°C for 1 min, extension at 72°C for 1 min, and final annealing and extension steps at 60°C for 1 min and 72°C for 5 min. PCR products were subjected to electrophoresis on a 2% agarose gel after digestion with BstUI. Genotype Arg/Arg (AA) was determined by 169- and 127-bp fragments, Pro/Pro (PP) was detected by a 296-bp fragment, whereas heterozygotes (AP) were determined by the presence of all three bands (Fig. 1).

Our main method to investigate the MspII/HpaII polymorphism at the HRAS1 VNTR locus was Southern blot analysis. However, samples for which no conclusive results were obtained by Southern blot and for which DNA was still available (n = 39) were assayed by a PCR-based assay (see below). Overall, with these two methods, we obtained results for 312 cases (93.4%) and 431 controls (96.6%). For Southern blot analysis, high molecular weight DNA (3 μg) isolated from peripheral blood lymphocytes was subjected to digestion with MspII/HpaII at 37°C overnight. Restriction fragments were separated by electrophoresis at 4°C on a 1.5% agarose gel run at ~70 V the first day and raising the voltage to 120 V the second day, if required. Standards for the four common alleles (A1, A2, A3, and A4), as well as for some rare alleles, were used on each gel to facilitate allelotyping. After electrophoresis, gels were treated one time for 15 min with depurinating solution (0.25 M HCl), two times for 22 min with denaturing solution (1.5 M NaCl, 0.5 M NaOH), and two times for 30 min with neutralizing solution (1.5 M NaCl, 0.5 M Tris-Cl, pH 7.0). DNA was transferred to nylon membranes in 10× SSC overnight and was

![Fig. 1. Detection of TP53 codon 72 polymorphism by BstUI digest. Lane M, HindIII-digested phiX174 DNA molecular weight marker; Lane 1, Arg homozgyote with 169- and 127-bp fragments; Lane 3, Pro homozygote with 296-bp fragment; Lane 2, Arg/Pro heterozygote with all three bands at 296, 169, and 127 bp, Lane 4, uncut PCR product; Lane 5, negative control.](image-url)
permanently bound to the membrane via baking or UV cross-linking. Membranes were prehybridized (2–3 h) and hybridized overnight in 6× SSC, 5× Denhardt’s, 1% SDS, 100 mg/ml salmon sperm DNA, 1% dextran sulfate, and 50% formamide at 42°C. The probe used for hybridization was the full-length, 6.6-kb human HRAS1 fragment of pUC EJ 6.6 from R. Weinberg (American Type Culture Collection, Rockville, MD) and was 32P-labeled using the Prime-a-Gene labeling system (Promega Corp., Madison, WI) following manufacturer’s protocol. Blots were washed in 2× SSC/1% SDS one time for 15 min at 52°C and two times for 15 min at 60°C and autoradiographed (Fig. 2).

The PCR assay used to genotype a subset of the samples for the HRAS1 VNTR polymorphism was a protocol modified from Decorte et al. (23) and Krontiris et al. (24) with the primers HRASE (forward) 5’-GTCTGTGGACCTTGGAAG-TAGG-3’ and HRASD (reverse) 5’-GTCCTGCTCTGG-GATTGGG-3’. DNA amplification included 50–100 ng of DNA, 200 μM deoxynucleotide triphosphates (each), 1.5 mM MgCl2, 500 μM each primer, and 2.5 units of Taq polymerase (Perkin-Elmer Corp.). Conditions were 5 min at 95°C, 30 cycles of 94°C for 30 s, 74°C for 5 min, and a final extension of 10 min at 74°C. Products were separated on a 2% Seakem agarose gel, transferred to a nylon membrane, hybridized with a digoxigenin-labeled probe (plasmid HRAS1 BamHI fragment of pUC EJ 6.6), and visualized with the CSPD nonradioactive detection system (Boehringer-Mannheim). The common alleles A1, A2, A3, and A4 gave fragment sizes of 2152, 2544, 3216, and 3748 bp, respectively.

The statistical analysis used the χ2 test for association to test for case-control differences in the distribution of the genotypes or other parameters under study. Unconditional logistic regression (25) was used to compute ORs and 95% CIs, with adjustment for several covariates found associated with risk (sex and race, using indicator variables; age, smoking duration and amount, and saturated fat and total vegetable intakes, as continuous variables). Several ways of modeling the smoking effect were explored, and the best fitting model was one that included an indicator variable for smoking status (ever, never smoked) and separate continuous terms for duration, amount, and (duration)2. The likelihood ratio test was used to test the statistical significance of modeled effects. We also used this test to determine the significance of multiplicative interactions among certain variables with respect to lung cancer risk. The test compared a main effects, no interaction model with a fully parameterized model containing all possible interaction terms for the variables of interest. Gene dosage effects were modeled by assigning the value 1, 2, or 3 to the genotype variable according to the subject’s number of variant alleles (zero, one, and two variant alleles, respectively).

## Results

The characteristics of the lung cancer cases and population controls have been published previously (26). Forty % of subjects were Caucasian, 36% Japanese, and 24% Hawaiian. Sixty-three % were males and 37% were females. Because not all interviewed subjects donated a blood sample and therefore matching was broken, we compared the sex and ethnic distributions of the cases and controls in the analysis and found no significant differences. Table 1 shows the distributions of the alleles at the loci studied among ethnic groups, based on the controls. Clear ethnic differences were observed in the frequencies of these alleles. The frequency of the variant p53 Pro allele was 32.6% for Japanese, 27.7% for Caucasians, and 48.1% for Hawaiians. The overall frequency for rare HRAS1 alleles was 20.1% for Japanese, 16.9% for Caucasians, and 27.0% for Hawaiians. Among Japanese, the HRAS1 A2 common allele was found in none of the controls and in one of the cases, indicating the rarity of this allele in this ethnic group.

Table 2 presents the lung cancer ORs and 95% CIs for p53 and HRAS1 genotypes for all subjects combined and each ethnic group, after adjustment for covariates. No statistically significant association was found between the p53 codon 72 variant allele and lung cancer risk. Compared with the homozygous wild-type genotype (Arg/Arg), the OR for the homozygous variant genotype (Pro/Pro) was 1.4 (95% CI, 0.8–2.4). In contrast, compared with carrying two common alleles, the presence of two rare HRAS1 alleles was associated with a 2.2-fold (95% CI, 1.0–5.0) increased lung cancer risk overall. This association was suggested in both sexes [males: OR, 2.8 (95% CI, 1.0–7.9); females: OR, 1.6 (95% CI, 0.4–6.9)]. The corresponding ORs for Japanese and Native Hawaiians (both sexes combined) was 2.8 (95% CI, 0.6–12.5) and 5.2 (95% CI, 1.1–24.4), respectively. No association was observed in Caucasians [OR, 0.8 (95% CI, 0.2–3.6)]. No increased risk of lung cancer was found for subjects who carried one rare and one common alleles; one rare and one variant allele; and two variant alleles, respectively.
Table 2 ORs (95% CIs) for lung cancer by TP53 and HRAS1 genotypes

<table>
<thead>
<tr>
<th>Allele</th>
<th>All</th>
<th>OR (95% CI)</th>
<th>Japanese</th>
<th>OR (95% CI)</th>
<th>Caucasian</th>
<th>OR (95% CI)</th>
<th>Hawaiian</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (^b)</td>
<td></td>
<td>n (P)</td>
<td></td>
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<td>n (P)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>144/197</td>
<td>1.0</td>
<td>41/82</td>
<td>1.0</td>
<td>84/87</td>
<td>0.8</td>
<td>19/28</td>
<td>1.0</td>
</tr>
<tr>
<td>Arg/Pro</td>
<td>138/192</td>
<td>0.9 (0.6–1.4)</td>
<td>51/65</td>
<td>1.2 (0.6–2.1)</td>
<td>46/76</td>
<td>0.8 (0.4–1.4)</td>
<td>41/51</td>
<td>1.3 (0.5–3.4)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>52/57</td>
<td>1.4 (0.8–2.4)</td>
<td>19/23</td>
<td>1.5 (0.7–3.4)</td>
<td>8/10</td>
<td>1.4 (0.4–4.8)</td>
<td>25/24</td>
<td>1.3 (0.6–3.8)</td>
</tr>
<tr>
<td></td>
<td>Pro/Pro (P = 0.44)</td>
<td>1.0 (0.7–1.5)</td>
<td>Pro/Pro (P = 0.32)</td>
<td>1.3 (0.7–2.2)</td>
<td>Pro/Pro (P = 0.76)</td>
<td>0.8 (0.5–1.5)</td>
<td>Pro/Pro (P = 0.64)</td>
<td>1.3 (0.5–3.2)</td>
</tr>
<tr>
<td>HRAS1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 rare</td>
<td>209/276</td>
<td>1.0</td>
<td>63/103</td>
<td>1.0</td>
<td>97/119</td>
<td>1.0</td>
<td>49/54</td>
<td>1.0</td>
</tr>
<tr>
<td>1 rare</td>
<td>86/134</td>
<td>0.9 (0.6–1.4)</td>
<td>38/53</td>
<td>1.2 (0.6–2.2)</td>
<td>29/43</td>
<td>0.8 (0.4–1.6)</td>
<td>19/38</td>
<td>0.8 (0.3–2.1)</td>
</tr>
<tr>
<td>2 rare</td>
<td>17/21</td>
<td>2.2 (1.0–5.0)</td>
<td>5/6</td>
<td>2.8 (0.6–12.5)</td>
<td>4/7</td>
<td>0.8 (0.2–3.6)</td>
<td>8/8</td>
<td>5.2 (1.1–24.4)</td>
</tr>
<tr>
<td></td>
<td>HRAS1 (P = 0.36)</td>
<td>2.3 (1.0–5.1)</td>
<td>HRAS1 (P = 0.26)</td>
<td>2.7 (0.6–11.6)</td>
<td>HRAS1 (P = 0.56)</td>
<td>0.8 (0.2–3.8)</td>
<td>HRAS1 (P = 0.17)</td>
<td>5.6 (1.2–25.3)</td>
</tr>
</tbody>
</table>

\(a\) Adjusted by logistic regression for age, sex, ethnicity, smoking status, years of schooling, (years of schooling)\(^2\), number of cigarettes/day, and saturated fat and total vegetable intakes.

\(b\) Number of cases/number of controls.

\(c\) \(P\) for genetic trend.

Table 3 ORs (95% CIs) for lung cancer cell types by TP53 and HRAS1 genotypes

<table>
<thead>
<tr>
<th>Allele</th>
<th>Squamous cell carcinoma</th>
<th>OR (95% CI)</th>
<th>Adenocarcinoma</th>
<th>OR (95% CI)</th>
<th>Small cell carcinoma</th>
<th>OR (95% CI)</th>
<th>Other</th>
<th>OR (95% CI)</th>
</tr>
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<td></td>
<td>n (b)</td>
<td></td>
<td>n (P)</td>
<td></td>
<td>n (P)</td>
<td></td>
<td>n (P)</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>27/197</td>
<td>1.0</td>
<td>67/197</td>
<td>1.0</td>
<td>26/197</td>
<td>1.0</td>
<td>24/197</td>
<td>1.0</td>
</tr>
<tr>
<td>Arg/Pro</td>
<td>35/192</td>
<td>1.0 (0.5–1.8)</td>
<td>69/192</td>
<td>1.0 (0.6–1.6)</td>
<td>16/192</td>
<td>0.4 (0.2–1.0)</td>
<td>18/192</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Pro/Pro</td>
<td>12/57</td>
<td>1.0 (0.4–2.6)</td>
<td>22/57</td>
<td>1.2 (0.6–2.4)</td>
<td>9/57</td>
<td>1.4 (0.5–4.0)</td>
<td>9/57</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td></td>
<td>TP53 (P = 0.95)</td>
<td>52/197</td>
<td>TP53 (P = 0.61)</td>
<td>112/197</td>
<td>TP53 (P = 0.65)</td>
<td>27/197</td>
<td>TP53 (P = 0.46)</td>
<td>24/197</td>
</tr>
<tr>
<td>HRAS1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 rare</td>
<td>46/276</td>
<td>1.0</td>
<td>112/276</td>
<td>1.0</td>
<td>27/276</td>
<td>1.0</td>
<td>24/276</td>
<td>1.0</td>
</tr>
<tr>
<td>1 rare</td>
<td>19/134</td>
<td>0.7 (0.3–1.3)</td>
<td>36/134</td>
<td>0.8 (0.5–1.2)</td>
<td>16/134</td>
<td>1.6 (0.7–3.6)</td>
<td>15/134</td>
<td>0.9 (0.6–1.3)</td>
</tr>
<tr>
<td>2 rare</td>
<td>5/21</td>
<td>2.5 (0.6–9.8)</td>
<td>6/21</td>
<td>2.0 (0.7–5.8)</td>
<td>3/21</td>
<td>3.7 (0.7–21.3)</td>
<td>3/21</td>
<td>2.1 (0.9–4.8)</td>
</tr>
<tr>
<td></td>
<td>HRAS1 (P = 0.98)</td>
<td>24/134</td>
<td>HRAS1 (P = 0.93)</td>
<td>62/134</td>
<td>HRAS1 (P = 0.99)</td>
<td>27/134</td>
<td>HRAS1 (P = 0.59)</td>
<td>24/134</td>
</tr>
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</table>

\(a\) Adjusted by logistic regression for age, sex, ethnicity, smoking status, years of schooling, (years of schooling)\(^2\), number of cigarettes/day, and saturated fat and total vegetable intakes.

\(b\) Number of cases/number of controls.

\(c\) \(P\) for genetic trend.

common HRAS1 allele, overall [OR, 0.9 (95% CI, 0.6–1.4)] and in each ethnic group.

The ORs for p53 and HRAS1 genotypes are presented by lung cancer cell type (squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and others) in Table 3. No significant association was observed between the p53 codon 72 polymorphism and any cell type. The presence of two rare HRAS1 alleles was associated with a 2–4-fold increase in risk for each lung cancer cell type (Table 3). The presence of one rare HRAS1 allele did not confer any significant risk increase for any cell type. Finally, the interactions of p53 and HRAS1 genotypes with pack-years of cigarette smoking were investigated. No interaction was detected.

Discussion

In this population-based case-control study, inheritance of two rare HRAS1 alleles was found to be associated with a 2-fold increased risk of lung cancer, whereas the presence of one rare HRAS1 allele did not appear to increase risk for this disease. This association was observed in two of the three ethnic groups studied, was consistent across sexes, and was present for each lung cancer cell type. No statistically significant association was found between lung cancer and the TP53 codon 72 polymorphism, overall, or for any sex, ethnic group, or cell type.

The frequencies for the TP53 codon 72 proline variant allele found in this study (33% for Japanese and 28% for Caucasians) are comparable with those in past studies (35–40% for Japanese and 21–29% for Caucasians; Ref. 27). Similarly, the overall frequencies of rare HRAS1 alleles in our study (20% for Japanese and 17% for Caucasians) were consistent with those reported previously for Japanese (22%) and Caucasians (4–22%; Refs. 20, 28–31).

Past reports on the association of the TP53 codon 72 variant allele and lung cancer have been inconsistent. Studies conducted in Asians and Mexican Americans suggested a 2-fold increased lung cancer risk for the Pro/Pro genotype (8, 9, 10). However, the risk increase was smaller (1.4–1.6-fold) and non-statistically significant in studies conducted in African-Americans (10) and Caucasians (11, 12, 32). Our data are in agreement with the latter group of studies in suggesting that the TP53 codon 72 polymorphism is likely to play only a minor role in determining genetic susceptibility to lung cancer.

Birgander et al. (12) have recently considered inheritance of pairwise haplotypes of three polymorphic TP53 loci in relationship to lung cancer risk. They found that, although the codon 72 proline variant was not a risk factor for lung cancer, the proline/intron three A1 haplotype was significantly more common in lung cancer patients than in controls. Thus, more
studies exploring the relationship between TP53 haplotypes and lung cancer appear warranted.

Although studies of the HRAS1 VNTR and lung cancer risk have still been few, their results are relatively consistent in suggesting an association (18, 19, 21, 24, 33). Three recent meta-analyses have estimated the lung cancer ORs for the presence of rare alleles at 1.55 (95% CI, 1.01–2.39; Ref. 25), 1.9 (95% CI, 1.3–2.8; Ref. 28), and 1.69 (95% CI, 1.29–2.12; Ref. 20). The present study, with an overall 2.2-fold increase in risk, is thus consistent with past data. However, it is unclear why, in contrast to most past studies (18, 19, 20, 24, 34), we failed to find an association between the rare HRAS1 alleles and lung cancer among Caucasians. This may merely be attributable to chance.

In this study, a particularly high lung cancer risk estimate (OR, 5.6) for the rare HRAS1 alleles was found among Native Hawaiians. This is of interest because this Polynesian population has a high allele frequency for this polymorphism (Table 1), compared with other ethnic groups. However, because our results are based on small numbers of Hawaiians (76 cases and 100 controls), they need to be reproduced, preferably with a prospective design.

Krontiris et al. (24) have proposed, based on recent findings on the functional properties of the HRAS1 minisatellite (36), that mutations in HRAS1 disrupt the controlled expression of nearby genes, including HRAS, by interacting directly with transcriptional regulatory mechanisms. Because HRAS encodes a protein that is involved in mitogenic signal transduction and differentiation, the association between the HRAS1 minisatellite and cancer risk is biologically plausible. It has also been suggested that the rare HRAS1 alleles may be in linkage disequilibrium with another gene important in tumorigenesis on chromosome 11 (14). Alternatively, the rare alleles may be a marker of genomic instability because an increased occurrence of mitosis 11 (14). Alternatively, the rare alleles may be in linkage disequilibrium with another gene important in tumorigenesis on chromosome 11 (14). Alternatively, the rare alleles may be a marker of genomic instability because an increased occurrence of chromosome 11 (14). Alternatively, the rare alleles may be a marker of genomic instability because an increased occurrence of chromosome 11 (14).

Acknowledgments

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References

Relationships of TP53 Codon 72 and HRAS1 Polymorphisms with Lung Cancer Risk in an Ethnically Diverse Population


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