[CANCER RESEARCH 59, 3045–3048, July 1, 1999]

Advances in Brief

Association of the NAD(P)H:quinone Oxidoreductase ^{609}C→T Polymorphism with a Decreased Lung Cancer Risk[1]

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Abstract

The NAD(P)H:quinone oxidoreductase gene, *NQO1*, often carries a C→T transition at bp 609, which has been associated with a reduced enzymatic activity and which may result in altered metabolic activation of tobacco smoke procarcinogens. We tested the association of this polymorphism with lung cancer risk in a population-based case-control study of 327 cases and 440 controls of Caucasian, Japanese, or Native Hawaiian ancestry in Hawaii. We found a notable difference in the frequency of the variant allele among Japanese (38%), Caucasians (20%), and Hawaiians (22%). Overall, the variant allele was less frequent in cases than in controls ($P = 0.03$). A significant inverse association was found in Japanese, with adjusted odds ratios of 0.8 (95% confidence interval, 0.4–1.5) and 0.3 (0.1–0.7) for the heterozygous and homozygous variant genotypes, respectively, compared with the homozygous wild-type genotype (P for genetic trend, 0.02). The association did not reach statistical significance in Caucasians and Hawaiians but was in the same direction.

Introduction

Lung cancer, the leading cause of cancer death in the United States, shows marked ethnic/racial variation in incidence (1), which may not be completely due to differences in smoking habits (2). It has been suggested that interindividual variation in the metabolism of tobacco carcinogens may determine susceptibility to lung cancer (3). The frequency of a number of genetic polymorphisms associated with altered capacity to metabolically activate or detoxify tobacco procarcinogens has been found to vary markedly across ethnic/racial groups. Some of these polymorphisms have been associated with lung cancer risk (4–6).

NQO1,[3] formerly referred to as DT diaphorase, is an important enzyme in the metabolism of xenobiotics. It may act as either a detoxification or activation enzyme, depending on the substrate (7, 8). For example, it catalyzes the two-electron reduction of quinoid compounds to the readily excreted hydroquinones, preventing the generation of free radicals and reactive oxygen, thus protecting cells from oxidative damage (9). Alternatively, NQO1 is known to catalyze the activation of some environmental procarcinogens present in tobacco smoke, such as nitroaromatic compounds and heterocyclic amines (7, 10, 11).

A C→T base transition mutation at position 609 of the *NQO1* cDNA has been associated with reduced enzymatic activity (12) and shown to be present in 13–25% of the white population (13). Two previous studies on the association between this polymorphism and lung cancer risk yielded contradictory results, although the studies included different ethnic groups and were not population based (14, 15). Considering its potential role in the modulation of tobacco procarcinogens, we tested the hypothesis that the *NQO1* ^{609}C→T polymorphism is associated with lung cancer risk in a population-based case-control study of 767 Caucasians, Japanese, and Native Hawaiians in Hawaii.

Materials and Methods

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 on the island of Oahu, Hawaii. Other eligibility criteria included age between 26 and 79 years, Oahu residency, no previous history of lung cancer, and ethnicity (≥75% Japanese, ≥75% Caucasian, 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%).

Controls were randomly selected 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 over age 65 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%). The analysis presented here was conducted with the 341 cases (76% of interviewed cases) and 456 population controls (80% of interviewed controls) who donated a blood specimen for the study.

In-person interviews were conducted at the subjects' homes by trained interviewers. On average, cases were interviewed 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 diseases (6). 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, the 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/proteinase K treatment and phenol/chloroform extraction. A PCR-RFLP based assay was used to characterize the *wt* and *vt NQO1* alleles. Using a Perkin-Elmer Corp. 9600 thermocycler, PCR products were generated using 100 ng of genomic DNA as template. The sense primer (5′-TCCTCAGAGTGGCATTCTGC-3′) and antisense primer (5′-TCTCCTCATCCTGTACCTCT-3′) amplify a 230-bp oligonucleotide including the *NQO1* ^{609}C→T polymorphism. This C→T transition creates a new

Received 2/1/99; accepted 5/13/99.

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[1] This research was supported in part by Grant RO1-CA-55874 and Contract NO1-PC-67001 from the National Cancer Institute and by Grant EDT-78 from the American Cancer Society.

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[3] The abbreviations used are: NQO1, NAD(P)H:quinone oxidoreductase; OR, odds ratio; CI, confidence interval; wt, wild type; vt, variant.

*Hin*fI restriction site that is used to distinguish the *vt* from the *wt* allele. The PCR reaction was carried out using a 30-μl reaction with a final concentration of 50 μM deoxynucleotide triphosphates, 2.5 mM $MgCl_2$, 1.0 μM for each primer, and 1 unit of Taq polymerase. After an initial denaturation at 94°C for 4 min, the cycling conditions were as follows: 2 cycles at 94°C for 15 s, 69°C for 15 s, and 72°C for 30 s; 2 cycles at 94°C for 15 s, 67°C for 15 s, and 72°C for 30 s; 31 cycles at 94°C for 30 s, 65°C for 30 s, and 72°C for 1 min; and finally an extension at 72°C for 5 min. The PCR products were then digested with 5 units of *Hin*fI for 3 h at 37°C. The genotype pattern for each PCR product was detected by electrophoresis on a 1.8% agarose gel containing 0.5 μg/ml ethidium bromide (Fig. 1). Each gel included an uncut PCR product as control. Complete digestion of the 230-bp PCR product gave a cut fragment of 195 bp for the *wt* allele and of 151 bp for the *vt* allele.

The statistical analysis used the χ^2 statistic for homogeneity to test for case-control differences in the distribution of the genotypes or other parameters under study. Unconditional logistic regression (16) 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 or never smoked) and separate continuous terms for duration, amount, and $(\text{duration})^2$. The log-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 effect, 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 *vt* alleles (zero, one, and two rare alleles, respectively).

Results

The study population consisted of 327 lung cancer cases and 440 population controls. The mean age was 64.5 years for cases and 65.1 years for controls. Forty % of subjects were Caucasians, 36% were Japanese, and 24% were Hawaiians. No significant differences were noted in the sex and ethnic distributions of the cases and controls who donated a blood sample. Other relevant characteristics of the study population have been reported previously (6).

The frequency distribution of the *wt* and *vt* genotypes for *NQO1* gene among lung cancer cases and controls is presented in Table 1, overall and for each ethnic group. On the basis of the controls, the population frequency of the *vt* allele was 38% in Japanese, 20% in Caucasians, and 22% in Hawaiians. Overall, the genotype distribution was different in cases and controls ($P = 0.07$), and the *vt* allele was less common in cases compared with controls ($P = 0.03$). After stratification on ethnicity, the inverse association between the *vt* allele and lung cancer was statistically significant in Japanese ($P = 0.04$) and of borderline significance in Hawaiians ($P = 0.05$). No association was suggested in Caucasians ($P = 0.78$) in this univariate analysis.

The unadjusted OR for the *wt/vt* and *vt/vt* genotypes, compared with the *wt/wt* genotype, was 0.7 (95% CI: 0.5–1.1) and 0.4 (0.2–0.9), respectively, with a significant trend of decreasing risk with increasing number of *vt* alleles ($P = 0.01$). This trend did not persist after adjustment for covariates, although the point estimate of the OR for the *vt/vt* genotype remained unchanged (0.4; Table 1). A statistically significant inverse association was found in Japanese, with an OR of 0.3 (0.1–0.7) for the *vt/vt* genotype compared with the *wt/wt* genotype, with a *P* for genetic trend of 0.02 (Table 1). A similar decrease in risk for the *vt* allele was also observed in the other two ethnic groups, with ORs of 0.8 (0.4–1.5) and 0.6 (0.2–1.3) for the combined *wt/vt* and *vt/vt* genotypes compared with the *wt/wt* genotype for Caucasians and Hawaiians, respectively (Table 1).

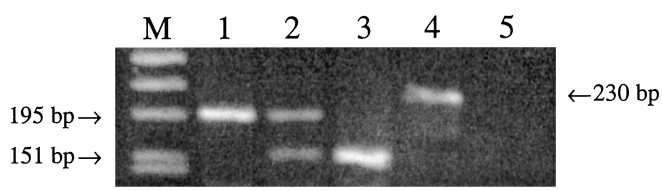

Fig. 1. Genotype pattern for *NQO1* gene polymorphism analyzed by PCR. *Lane M*, *Hin*fI-digested ϕ-X174 DNA molecular weight marker; *Lane 1*, *wt*; *Lane 2*, heterozygous; *Lane 3*, homozygous mutant; *Lane 4*, uncut PCR product; *Lane 5*, negative control. The 151-bp fragment indicates the *vt* allele.

To assess whether the *NQO1 vt* allele may impart different risks for the various lung cancer cell types, we computed the adjusted ORs for lung cancer for each histological type (results not shown). No cell type specificity was detected because similar inverse associations were observed or suggested for adenocarcinoma (*P* for trend, 0.04), squamous cell carcinoma (*P* for trend, 0.07), and small cell carcinoma.

The interaction of *NQO1* genotype (*wt/wt versus wt/vt* or *vt/vt*) and smoking history (≤28 *versus* >28 for pack-years, where 28 represents the median) on the risk of lung cancer was also assessed. The *P*s for interaction for all cell types, squamous cell carcinoma, and adenocarcinoma were 0.58, 0.60, and 0.73, respectively, indicating an absence of interaction with the extent of smoking. Similarly, no interactions were found between *NQO1* and intake of total vegetables or specific food sources of indoles and isothiocyanate (broccoli) or flavonoids (apples, onion, or green tea).

Discussion

Our previous epidemiological studies have demonstrated that ethnic variation in lung cancer incidence in Hawaii is not totally explained by differences in smoking exposure (2). It is possible that genetic susceptibility may play a role in these risk differences. Recently, studies have reported associations between lung cancer and several genetic polymorphisms affecting the activities of enzymes involved in the metabolism of procarcinogens in tobacco smoke (4–6). Although few of these past studies used a population-based design and adequately adjusted risk estimates for smoking, the evidence to date suggests that a number of polymorphic genes may play a role in the etiology of lung cancer (4–6).

Considering the potential role of NQO1 in modulating tobacco smoke-related compounds (7–11), we explored a possible association of the *NQO1* ^{609}C→T mutation with lung cancer. We observed a statistically significant inverse association of this polymorphism with lung cancer in Japanese. The numbers of Caucasians and Native Hawaiians with the *vt* allele were too small to yield conclusive results in these ethnic groups, although the data were also consistent with an inverse association. In addition, we observed a marked ethnic variation in the prevalence of the *NQO1* polymorphism. The *vt NQO1* allele was almost twice as common in Japanese as in Caucasians. This difference in allele frequency and the inverse association between lung cancer and the *NQO1* ^{609}C→T mutation, associated with a lower enzyme activity, are consistent with the lower lung cancer risk observed among Japanese smokers compared with Caucasian smokers (2). Moreover, both the association of the *NQO1* ^{609}C→T mutation with lung cancer and the lower risk of Japanese smokers for this neoplasm, compared with Caucasian smokers, were observed for each main cell type of lung cancer (2).

We are aware of only two previous studies of the *NQO1* ^{609}C→T polymorphism and lung cancer. Wiencke *et al.* (14) conducted a case-control study among a hospital series of 177 lung cancer patients and a convenience sample of 297 controls of African- or Mexican-

Table 1 *Distribution of subjects by NQO1 genotype and ORs for lung cancer*

Ethnicity	*NQO1* genotype				
	wt/wt	*wt/vt*	*vt/vt*	P^a	*P* for trend[b]
All					
Case (%)	196 (59.9)	115 (35.2)	16 (4.9)		
Control (%)	229 (52.0)	179 (40.7)	32 (7.3)	0.07	
OR[c] (95% CI)	1.0	1.2 (0.5–2.7)	0.4 (0.1–2.1)		0.67
Japanese					
Case (%)	54 (49.5)	48 (44.0)	7 (6.4)		
Control (%)	64 (38.3)	78 (46.7)	25 (15.0)	0.04	
OR (95% CI)	1.0	0.8 (0.4–1.5)	0.3 (0.1–0.7)		0.02
Caucasian					
Case (%)	81 (60.0)	49 (36.3)	5 (3.7)		
Control (%)	105 (61.4)	62 (36.3)	4 (2.3)	0.78	
OR (95% CI)	1.0	0.8 (0.4–1.5)			
Hawaiian					
Case (%)	61 (73.5)	18 (21.7)	4 (4.8)		
Control (%)	60 (58.8)	39 (38.2)	3 (2.9)	0.05	
OR (95% CI)	1.0	0.6 (0.2–1.3)			

[a] *P* for χ^2 test.
[b] *P* for the genotype variable assigned the values 1, 2, or 3 according to the subject's number of *vt* allele (0, 1, and 2, respectively).
[c] OR (and 95% CI) adjusted for age, sex, ethnicity, smoking status, years of smoking, (years of smoking)^2, number of cigarettes/day, and saturated fat and total vegetable intakes.

American ethnicity. Consistent with our results, they reported a direct association of lung cancer with the *wt* homozygous genotype (OR, 1.90; 95% CI, 1.04–3.46) in Mexican-Americans, compared with the other two combined genotypes. The association was weaker in African-Americans (OR, 1.36; 95% CI, 0.75–2.31). The *vt* allele was more common in Mexican-Americans (42%) than in African-Americans (22%), correlating with the risk of lung cancer among these ethnic groups (14).

Roswold *et al.* (15) compared the frequency of the *NQO1* ^{609}C→T mutation among a group of 150 predominantly white lung cancer patients, 82 unrelated individuals who were part of a reference series from the Centre d'Etude du Polymorphisme Humain, and 77 employees and volunteers from their institution. Contrary to our findings, the frequency of the *NQO1 vt* allele was found to be higher in lung cancer cases compared with the Centre d'Etude du Polymorphisme Humain controls ($P = 0.02$) but not compared with the local controls ($P = 0.70$; Ref. 15). The data analysis did not include adjustment for lifetime history of smoking, which is known to induce NQO1. Other known NQO1 inducers include flavonoids, indoles, and isothiocyanate (17, 18). Thus, beside smoking, specific dietary exposures may confound the association of *NQO1* with lung cancer. We were able to consider these factors as potential confounders and modifying variables in the present study.

The lower lung cancer risk observed in individuals with the *vt* allele (who are expected to have a decreased NQO1 activity) in this study is consistent with a role for NQO1 in the metabolic activation of putative lung carcinogens. In this regard, it should be noted that NQO1 has been shown to activate a class of nitrosamines including 1,6-, 1,3-, and 1,8-dinitropyrenes (19, 20). Laboratory studies have shown that these dinitropyrenes are potent lung carcinogens in rats (21, 22). Cigarette smoke condensate, treated with nitric oxide or Chinese cabbage pickles *in vitro* to induce nitrosation, has been shown to lead to the formation of 1-nitropyrene and 1,3-dinitropyrene (23). Further study of the role of NQO1 in the metabolic activation of nitropyrene in lung carcinogenesis may help in better understanding the relationship of the *NQO1* ^{609}C→T polymorphism and this disease in humans.

Acknowledgments

We thank the Hawaii Tumor Registry, Castle Medical Center, Kaiser-Permanente Medical Center, Kuakini Medical Center, Queen's Medical Center, Straub Clinic and Hospital, St. Francis Medical Center, Tripler Medical Center, and Wahiawa General Hospital for their collaboration. We also thank Ronette Hunt, Barbara Burden, Geraldine Kaneshiro, and Yun Oh Jung for technical assistance.

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Cancer Res 1999;59:3045-3048.