

# Ethnic Differences in the Lung Cancer Risk Associated with Smoking<sup>1</sup>

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## Abstract

**Mortality trends and ecological data strongly suggest that the lung cancer risk associated with smoking is greater among Hawaiians than among the other ethnic groups in Hawaii. The authors combined data from two consecutive population-based case-control studies to formally test this hypothesis among 740 cases and 1616 controls. A multiple logistic regression analysis adjusting for pack-years of smoking, occupation, education, and age revealed that Hawaiian, Filipino, and Caucasian male smokers were at 121%, 53%, and 46% greater risk for lung cancer than Japanese male smokers. These risk differences were statistically significant, were consistent across sexes and histological types, and were not explained by the type of cigarettes, the level of inhalation, or by cholesterol or  $\beta$ -carotene intake. Additionally, an increased lung cancer risk unrelated to smoking was observed among Chinese women. The possibility that other dietary antioxidants and/or genetic risk factors are responsible for these ethnic differences needs to be investigated.**

## Introduction

Comparisons of cancer risks among ethnic/racial groups have historically been very productive in generating etiological clues. Because incidence patterns for lung cancer usually correlate well with the prevalence of smoking, this approach has rarely been used in lung cancer research. However, the epidemiology of this disease in the multiethnic population of Hawaii presents some unusual features.

Historical data show that in Hawaii, as in other parts of the United States, lung cancer mortality markedly increased after the introduction of manufactured cigarettes early in this century. However, this increase occurred a decade earlier and with a much steeper slope among native Hawaiians than among the other ethnic groups in Hawaii (Caucasians, Japanese, Filipinos, and

Chinese) (1). Because of their lower socioeconomic status, it is unlikely that cigarette consumption was greater among Hawaiians. Thus, the mortality trends are suggestive of a shorter latency period and greater risk associated with smoking for lung cancer among Hawaiians, who now experience one of the highest lung cancer incidence rates in the world (2).

Ecological data are also supportive of a greater lung cancer risk associated with smoking among Hawaiians. For example, among a random sample of 8636 Hawaii residents interviewed by our group in 1975–1976, the lifetime cigarette use of Hawaiians was similar to that of Japanese, despite a 2-fold greater lung cancer incidence among Hawaiians (3).

In order to formally investigate these apparent ethnic differences in the lung cancer risk associated with smoking in Hawaii, we combined the data from two consecutive population-based case-control studies conducted by our group during 1979–1985.

## Materials and Methods

These two studies used the same design and smoking questionnaire (4, 5). Briefly, the cases were identified by the rapid-reporting system of the Hawaii Tumor Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Eligible cases were all patients with histologically confirmed primary lung cancer diagnosed between March 1, 1979, and March 14, 1983 (first study), and between March 15, 1983, and September 30, 1985 (second study), in the main civilian hospital centers on the island of Oahu. Cases were restricted to Oahu residents aged 30 to 84 years of the five main ethnic groups (Caucasian, Japanese, Hawaiian/part-Hawaiian, Filipino, and Chinese). An interview was completed for 65% of all eligible cases (644 men and 254 women). The reasons for nonparticipation were physician refusal (4%), patient refusal (7%), inability to trace the patient or language barrier (9%), and death with the absence of a suitable surrogate for interview (15%).

Two population-based controls were frequency-matched to each case on the basis of sex and 5-year age group. For patients  $\geq 65$  years of age, controls were selected from a 10% random sample of all Oahu residents who were registered with the Health Care Financing Administration. For patients  $< 65$  years of age, we used two methods. Between September 1979 and July 1984, we selected controls by random-digit telephone dialing (6). Because this method was not cost effective, after July 1984 we randomly selected the controls from the participants in an ongoing health survey conducted by the Hawaii State Department of Health among a 2% annual random sample of the state households. Because this

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Table 1 Ethnic distribution of lung cancer cases and controls by sex, Hawaii, 1979-1985

Ethnicity	Male		Female	
	Case	Control	Case	Control
Japanese	179	463	47	203
Caucasian	156	290	91	145
Hawaiian	92	108	47	76
Filipino	56	147	16	46
Chinese	29	88	27	50
Total	512	1096	228	520

survey is mandated by law, the refusal rate is low (<5%). In the present studies, an interview was completed for 65% (1311 men and 530 women) of all eligible controls. Nonparticipation was due to refusal (27%), inability to locate or language barrier (6%), or death with the absence of a surrogate for interview (2%).

Most interviews were conducted at home. When the subject was too ill or had died, a surrogate interview was sought from the next of kin (usually the spouse) who had lived at least 5 years with the subject. We have shown that smoking and other information from such persons is highly reliable (7). We obtained proxy interviews for 31% of the cases and 6% of the controls.

The questionnaire included a complete lifetime smoking history. Information was collected on the types (nonfiltered cigarettes, filtered cigarettes, cigars or cigarillos, pipes) and usual amount of tobacco products smoked, age when smoking started, the overall duration of tobacco use, the level of inhalation (mouth, throat, chest), and for ex-smokers, age when smoking stopped. In order to simplify the statistical modeling of the smoking effect, we excluded the 61 cases and 193 controls who smoked a pipe or cigars (exclusively or in addition to cigarettes). In addition, 97 cases and 32 controls were excluded because of missing covariates. The ethnic distribution of the cases and controls included in the analysis is presented in Table 1 by sex.

The statistical analysis used multiple unconditional logistic regression analyses (8) adjusting for age and, for males only, education and occupation. The smoking effect was modeled several ways, e.g., including separate categorization for duration and intensity, separate modeling for filtered and nonfiltered cigarettes, and terms for levels of inhalation, age started, or calendar year started.

For both sexes, the best-fitting model was one that included an indicator variable for smoking status (ever, never smoked) and continuous terms for pack-years and (pack-years)<sup>2</sup>. Terms for interaction between race and each of these smoking variables were successively added to this model. The log-likelihood ratio test was used to test the statistical significance of modeled effects.

## Results

Since the control group for this study was randomly selected and, thus, presumably representative of the population, we used the data for the controls to describe the smoking patterns of the five main ethnic groups in Hawaii in relation to their lung cancer incidence (Table 2). Despite more than a 2-fold greater lung cancer incidence, Hawaiian males did not smoke more heavily, inhale more deeply, or smoke for a significantly longer period of time than Japanese males. Among females, lung cancer incidence was similar for Hawaiians and Caucasians, despite a greater lifetime smoking prevalence and intensity in Caucasians.

Next, we conducted a multiple logistic regression analysis with case-control status as dependent variable. As already mentioned in "Materials and Methods," the model which fit the data best was one that included an indicator variable for smoking status (ever/never), and continuous terms for pack-years and (pack-years)<sup>2</sup>. Terms for interaction between race and each of the smoking variables were successively added to this model. Only the smoking status (ever/never) × race interaction terms significantly improved the fit of the model in males ( $P = 0.01$ ). In females, the corresponding interaction test did not quite reach statistical significance ( $P = 0.20$ ), possibly because of the smaller sample size.

In these models, we compared the risk estimates for smoking status (ever/never) among ethnic groups (Table 3). Hawaiian, Filipino, and Caucasian male smokers were at 121%, 53%, and 46% greater risk, respectively, for lung cancer than Japanese male smokers after adjustment for lifetime cigarette consumption. These risk differences were statistically significant. There was no residual effect for race, suggesting that in males the ethnic differences in risk were entirely explained by the interaction with cigarette smoking.

The risk estimates obtained for females were less precise but not inconsistent with those for males (Table 3). However, in this sex, there was a statistically signifi-

Table 2 Smoking patterns and lung cancer incidence by ethnicity and sex, Hawaii, 1979-1985

	Male controls					Female controls				
	Hawaiian (n = 108)	Caucasian (n = 290)	Japanese (n = 463)	Chinese (n = 88)	Filipino (n = 147)	Hawaiian (n = 76)	Caucasian (n = 145)	Japanese (n = 203)	Chinese (n = 50)	Filipino (n = 46)
% current smoker	29.2	25.5	27.2	26.7	26.3	39.0	21.6	12.7	14.0	19.2
% ex-smoker	31.9	43.5	43.3	28.9	32.9	10.4	32.4	13.2	14.0	10.6
% never smoker	38.9	31.0	29.5	44.4	40.8	50.7	46.0	74.2	72.0	70.2
Cigarettes/day <sup>a</sup>	15.6	19.9	16.7	12.7	9.2	7.5	10.0	3.7	3.7	2.1
Duration (years) <sup>a</sup>	35.4	33.9	34.1	33.5	32.9	35.6	36.8	29.5	36.8	40.9
% of smokers inhaling to the chest	69.2	80.3	74.3	71.8	56.0	45.5	62.3	40.5	22.2	0.0
Lung cancer incidence <sup>b</sup>	82.8	66.2	36.0	36.8	26.9	39.7	32.7	10.3	17.5	16.4

<sup>a</sup> Adjusted for age by covariance analysis in each sex.

<sup>b</sup> Age-adjusted (world standard) lung cancer incidence rate for 1978-1982 (2).

**Table 3** Ethnic comparison of the lung cancer risk associated with cigarette smoking by sex, Hawaii, 1979–1985

Ethnic comparison	Male		Female	
	Odds ratio <sup>a</sup>	(95% CI) <sup>b</sup>	Odds ratio <sup>c</sup>	(95% CI)
Hawaiian vs. Japanese	2.21	(1.49–3.29)	1.67	(0.47–5.96)
Caucasian vs. Japanese	1.46	(1.07–2.01)	2.76	(0.83–9.20)
Filipino vs. Japanese	1.53	(1.00–2.35)	3.73	(0.73–18.98)
Chinese vs. Japanese	1.20	(0.69–2.06)	0.41	(0.11–1.52)

<sup>a</sup> Adjusted for pack-years, (pack-years)<sup>2</sup>, age, education, and occupation.

<sup>b</sup> CI, confidence interval.

<sup>c</sup> Adjusted for pack-years, (pack-years)<sup>2</sup>, age, and residual ethnicity effect.

cant residual effect for race due to a markedly greater lung cancer risk among Chinese women compared to the other groups (first column of Table 4). The results suggest that this increased lung cancer risk among Chinese women is unrelated to smoking.

Because differences in the smoking effect have been reported among cell types of lung cancer, we repeated our analysis for each histological subtype. Unfortunately, the models did not converge for squamous or small cell carcinoma in females, due to small numbers of cases. Table 5 compares the lung cancer risk associated with smoking among ethnic groups for each cell type among males. Except for small cell carcinomas, for which the risk ratios were reduced or reversed, the ethnic differences in risk observed for the other cell types were similar to those found with the entire case series in men. The results for smoking status by ethnicity for adenocarcinoma in females were very similar (data not shown) to those obtained with all cases in this sex. The residual effect of ethnicity on the risk of female adenocarcinoma was also similar to that observed in the model including all female cases (Table 4).

Finally, we introduced in our models the dietary variables  $\beta$ -carotene and cholesterol intake, which were associated with lung cancer risk in these data (4, 5, 9, 10). The odds ratios for the ethnic differences in the lung cancer risk associated with cigarette smoking were not materially affected by this further adjustment.

We also investigated possible sex differences in the lung cancer risk associated with smoking in a logistic model with common variables for male and female subjects. None of the tests for interaction between an indicator variable for sex and the various smoking variables were statistically significant ( $P$ 's  $\geq 0.5$ ). A similar analysis for cases with adenocarcinoma yielded comparable results.

## Discussion

In this case-control study, we were able to confirm the ethnic differences in the lung cancer risk associated with smoking that were suggested by the descriptive epidemiology of this disease in Hawaii. These risk differences were highly significant, were consistent across sexes and histological types, and were not explained by the type of cigarettes, the level of inhalation, or  $\beta$ -carotene or cholesterol intake.

Native Hawaiians appear to be particularly susceptible to the carcinogenic effect of smoking. This is con-

**Table 4** Residual ethnicity effect on lung cancer risk among females

Ethnic comparison	All cell types (n = 228) <sup>a</sup>		Adenocarcinoma (n = 111)	
	Odds ratio <sup>b</sup>	(95% CI) <sup>c</sup>	Odds ratio	(95% CI)
Hawaiian vs. Japanese	0.86	(0.31–2.41)	1.10	(0.38–3.14)
Caucasian vs. Japanese	0.46	(0.17–1.27)	0.59	(0.21–1.64)
Filipino vs. Japanese	0.61	(0.17–2.14)	0.51	(0.11–2.31)
Chinese vs. Japanese	3.38	(1.67–6.83)	3.19	(1.46–6.99)

<sup>a</sup> No. of cases.

<sup>b</sup> Adjusted for age, smoking status, pack-years, (pack-years)<sup>2</sup>, and race  $\times$  smoking interaction.

<sup>c</sup> CI, confidence interval.

sistent with the lung cancer incidence rates observed in Hawaiians and other Polynesians (e.g., New Zealand Maoris), which are among the highest in the world (2). Hawaiians, and Polynesians in general, have very high rates for several other cancers, including breast and stomach (2). It is unknown whether the same underlying factors could be responsible for their increased cancer risk at all of these sites.

In contrast, this study also suggests that the lung cancer risk associated with smoking may be lower in Japanese than in other ethnic groups, including whites. The data published from Japan appear consistent with our observation. The lung cancer risk associated with the extent of smoking reported in epidemiological studies conducted in Japan have been several times lower than in studies conducted in the United States or Europe (11). Indeed, Japan was a notable outlier in Doll and Peto's international correlation between lung cancer mortality in the mid-1970s and manufactured cigarette consumption 20 years previously (12). Lung cancer mortality in Japan was about half that expected from the amount of cigarette consumption. However, it has recently been proposed that the apparently reduced lung cancer risk in Japan was artifactual and was indeed explained by the severe shortage of cigarettes experienced in that country during and shortly after World War II (13). A similar argument cannot be made for Hawaii Japanese since there is no basis for concluding that any war-related shortage in Hawaii would have applied selectively to Japanese.

In this study, we were also able to confirm the increased lung cancer risk already reported for the predominantly nonsmoking Chinese female populations of Asia and the United States, including Hawaii (14–18). In agreement with most previous studies, our data suggest that this increased risk is unrelated to smoking or  $\beta$ -carotene intake. Other factors which have been proposed and for which we did not have information include prior lung disease, cooking oil fumes, and sex hormones (19, 20).

Several possible reasons for these ethnic variations in the lung cancer risk associated with smoking need to be investigated. Although our data suggest that  $\beta$ -carotene and cholesterol intakes do not explain these differences, other aspects of diet may be responsible. In agreement with several laboratory studies (21–23), we have recently published data suggesting that other carotenoids (e.g., lycopene and lutein), as well as other vegetable constituents (e.g., phenols, indoles, isothiocyanates, etc.),

Table 5 Ethnic comparison of the male lung cancer risk associated with cigarette smoking by cell type

Ethnic comparison	Squamous cell (n = 171) <sup>a</sup>		Small cell (n = 78)		Adenocarcinoma (n = 178)	
	Odds ratio <sup>b</sup>	(95% CI) <sup>c</sup>	Odds ratio	(95% CI)	Odds ratio	(95% CI)
Hawaiian vs. Japanese	2.19	(1.24-3.87)	1.70	(0.82-3.51)	2.11	(1.19-3.71)
Caucasian vs. Japanese	1.50	(0.94-2.38)	0.90	(0.47-1.74)	1.66	(1.05-2.60)
Filipino vs. Japanese	1.66	(0.98-3.53)	0.96	(0.38-2.45)	1.82	(1.00-3.30)
Chinese vs. Japanese	1.57	(0.74-3.33)	0.49	(0.11-2.18)	1.68	(0.80-3.54)

<sup>a</sup> No. of cases.

<sup>b</sup> Adjusted for age, education, occupation, pack-years, and (pack-years)<sup>2</sup>.

<sup>c</sup> CI, confidence interval.

may be protective against lung cancer in humans (5). Thus, intake of these dietary components may play a role in explaining these ethnic differences.

Certain genetic risk factors which have been described for lung cancer also need to be considered. The genetically determined ability to metabolize the anti-hypertensive drug debrisoquine has recently been associated with lung cancer (24). Compared to "poor" and "intermediate" metabolizers, "extensive" metabolizers have been consistently found to have a 5- to 6-fold increased risk for lung cancer, independently of the extent of smoking (24). The ability to metabolize this drug has been proposed as a marker for the ability to activate procarcinogens in tobacco smoke. Racial differences in the metabolism of several other drugs have been well described (25). Thus, it is possible that genetic differences in the ability to activate or detoxify carcinogens exist among ethnic groups and are at least partially responsible for these ethnic differences in lung cancer risk.

The possible limitations of our results need to be discussed. Although we collected detailed information on smoking and gave great care to the way we modeled the smoking effect in our logistic regression analysis, we cannot exclude the possibility that differential recall in some ethnic groups is responsible for our results. However, this seems unlikely, given the consistency between our findings and the ecological data on lung cancer in Hawaii. Some bias may also have resulted from our use of surrogate interviews. To investigate this possibility, we repeated our analyses, excluding surrogate respondents. As expected from past results (5, 7), we found very good agreement between the results of the two analyses.

In conclusion, this case-control study concurs with the descriptive epidemiology of lung cancer in Hawaii in strongly suggesting that substantial ethnic differences in the lung cancer risk associated with smoking exist in our population. These differences provide unique opportunities to study the interactions of genetic and environmental factors in lung cancer development.

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