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# Incidence of Lung Cancer Among Never-Smoking Asian American, Native Hawaiian, and Pacific Islander Females

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Abstract

Background: Although lung cancer incidence rates according to smoking status, sex, and detailed race/ethnicity have not been available, it is estimated that more than half of Asian American, Native Hawaiian, and Pacific Islander (AANHPI) females with lung cancer have never smoked. **Methods:** We calculated age-adjusted incidence rates for lung cancer according to smoking status and detailed race/ethnicity among females, focusing on AANHPI ethnic groups, and assessed relative incidence across racial/ethnic groups. We used a large-scale dataset that integrates data from electronic health records from 2 large health-care systems—Sutter Health in Northern California and Kaiser Permanente Hawai'i—linked to state cancer registries for incident lung cancer diagnoses between 2000 and 2013. The study population included 1 222 694 females (n = 244 147 AANHPI), 3297 of which were diagnosed with lung cancer (n = 535 AANHPI). **Results:** Incidence of lung cancer among never-smoking AANHPI as an aggregate group was 17.1 per 100 000 (95% confidence interval [CI] = 14.9 to 19.4) but varied widely across ethnic groups. Never-smoking Chinese American females had the highest rate (22.8 per 100 000, 95% CI = 17.3 to 29.1). Except for Japanese American females, incidence among every never-smoking AANHPI female ethnic group was higher than that of never-smoking non-Hispanic White females, from 66% greater among Native Hawaiian females (incidence rate ratio = 1.66, 95% CI = 1.03 to 2.56) to more than 100% greater among Chinese American females (incidence rate ratio = 2.26, 95% CI = 1.67 to 3.02). **Conclusions:** Our study revealed high rates of lung cancer among most never-smoking AANHPI female ethnic groups. Our approach illustrates the use of innovative data integration to dispel the myth that AANHPI females are at overall reduced risk of lung cancer and demonstrates the need to disaggregate this highly diverse population.

Lung cancer among persons who have never smoked is the seventh leading cause of cancer mortality in the United States (1,2). Moreover, an increasing proportion of lung cancers are diagnosed among persons who have never smoked (1,3). Our 2007 study estimated incidence rates of non-small cell lung cancer (NSCLC) by sex and smoking status using data from several large, prospective cohorts and reported substantially higher

rates among females than males who have never smoked (ranging from 15.2 to 20.8 per 100 000 in females and 4.8 to 13.7 in males) (4). Furthermore, we previously reported 24% of non-Hispanic (NH) White females diagnosed with lung cancer have never smoked, and nearly double that proportion (44%) of Asian American, Native Hawaiian, and Pacific Islander (AANHPI) females with lung cancer have never smoked (5). Similarly, in a

study of seven state-based cancer registries with smoking information abstracted from medical records, 57% of AANHPI females with lung cancer had never smoked (6). Smoking-specific lung cancer incidence rates, however, have not been available.

AANHPIs are the fastest growing racial/ethnic population in the United States, increasing by 45% between 2000 and 2019 (7–9). It is a heterogeneous group with people from 30 countries who speak more than 100 languages and represent great diversity in socioeconomic levels, cultural beliefs and behaviors, English proficiency, immigration experience, generational status, and acculturation (10–13). In addition, the proportion of AANHPIs identifying as multiple races or ethnicities is growing, increasing 60% among Asian Americans and 44% among Native Hawaiian and Pacific Islanders (NHPIs) from 2000 to 2010 (7,11). Despite this diversity, AANHPIs have historically been studied as an aggregate, which masks health inequalities across ethnicities. For example, we previously reported that proportions of AANHPI females with lung cancer who never smoked varies from a high of 88% among Chinese American to a low of 16% among Native Hawaiian females (5). In addition, a study of Surveillance, Epidemiology, and End Results (SEER) data for diagnoses from 1990 to 2008 showed that lung cancer incidence rates were lower for most Asian American ethnic groups compared with the NH White group but varied substantially from 12.4 per 100 000 for Asian Indian and Pakistani American females to 31.8 for Vietnamese American females (14). Native Hawaiian females, on the other hand, had rates similar to NH White females (51.6 and 56.9, respectively) in a SEER-13 study (15). These SEER studies, however, could not report rates by smoking status (13,16).

In this study, we used a linked data resource, including 1 222 694 females (244 147 AANHPI), that integrates electronic health record (EHR) data on race, ethnicity, and smoking status with cancer registry data on incident lung cancer diagnoses (5). We examined lung cancer incidence among females by joint race/ethnicity and smoking status focusing on specific AANHPI single and multi-racial/ethnic groups. We aimed to fill a critical gap in knowledge that has limited our ability to quantify the burden of lung cancer among never-smoking AANHPI females.

Methods

Study Approval

All aspects of the study protocol were approved by the institutional review boards of the State of California Protection for Human Subjects; University of California, San Francisco; Sutter Health; Kaiser Permanente Hawai'i; and the Hawai'i Medical Association.

Study Population

Development of the cohort and dataset has been described (5). The cohort included adults 18 years of age or older with at least one in-person visit to Sutter Health in Northern California or Kaiser Permanente Hawai'i between 2000 and 2013. Individuals were excluded if they did not have sex classified as male or female, had no social history (the portion of the EHR related to patient behavioral, familial, or occupational characteristics) within the study period, had a history of lung cancer at the time of their baseline visit (ie, the first in-person visit during the study period), did not have EHR record of residence in California

(for Sutter Health) or Hawai'i (for Kaiser Permanente Hawai'i) during the study period, had a date of death (per the EHR) before baseline or unknown date of death, or who had no follow-up (ie, baseline date was equivalent to the study end date, date of diagnosis, or date of death). The final pooled cohort comprised 2 211 476 individuals (n = 1 275 838 females; n = 935 638 males). Although our proposed study was intended to investigate the incidence of lung cancer among females who never smoked, the rates among males are also presented in the Supplementary Materials (available online) for some analyses.

EHR Data

Collection and harmonization of EHR data on self-reported race, ethnicity, and smoking status have been described (5). Our race/ethnicity classification algorithm prioritized small AANHPI populations and distinguished between single and multiple races (5). Our AANHPI groupings are any Native Hawaiian, Pacific Islander, Asian Indian only, Chinese only, Filipinx only, Japanese only, Korean only, Vietnamese only, Other single Asian ethnic group only, multiple Asian ethnic groups only (Asian, multiple group), or Asian and non-Asian race (Asian and non-Asian multiple). Individuals not indicating AANHPI were categorized as NH White, Black, Hispanic, multiple (non-AANHPI) races, Other (including American Indian and Alaska Native), and unknown/missing.

We determined smoking status by extracting up to 2 non-missing smoking status values (current, former, passive, never) from EHR social history: 1) the first available value recorded on the day of or after the baseline visit and 2) the last available value recorded before date of lung cancer diagnosis, death, or study end (December 31, 2013) (5). If a patient's extracted smoking status values were discordant, we applied a simple algorithm to classify a single smoking status value of "ever" (at least 1 entry of "current" or "former") or "never" (all nonmissing entries of "never" or "passive"). We excluded 53 144 (4.2%) females and 39 387 (4.2%) males who had unknown smoking status with this approach (5). The final study population thus was comprised of 1 222 694 females and 896 251 males with smoking status.

Lung Cancer Diagnoses and Tumor Characteristics

Sutter Health patients were previously linked to the California Cancer Registry for all invasive cancers diagnosed between 1988 and 2013 (17). The Kaiser Permanente Hawai'i cohort was linked to the Hawai'i Tumor Registry for lung cancers diagnosed between 1973 and 2013 (18). For all lung cancer cases, cancer registry data included date of diagnosis, tumor stage (localized, regional, remote), and tumor histology. Histologic cell types were based on morphology codes as defined by Lewis et al. (19). Incident lung cancer was defined as a diagnosis of invasive lung or bronchus carcinoma (*International Classification of Disease for Oncology*, third edition, site codes C34.0-34.9, excluding morphology codes 8500 and 8580-9999) occurring after the date of the baseline visit and before December 31, 2013. In situ lung cancer (n = 2 females and n = 2 males), noncarcinomas (n = 16 females and n = 16 males), and apparent metastases (n = 1 females and n = 0 males) were not considered as cases. This resulted in 3297 females and 2892 males with incident lung cancer diagnoses for analysis.

Although the study population is enriched for AANHPI groups in the United States, it is generally representative of the

target populations of California and Hawai'i in regard to race/ethnicity and smoking prevalence among the cohort and in regard to race/ethnicity among lung cancer cases; a detailed account of the representativeness of the cohort has been published (18).

Statistical Analyses

All statistical analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC). We used frequencies and percentages to describe the age and race/ethnicty of the cohort population and individuals diagnosed with lung cancer according to sex and smoking status. We also describe the distribution of age and race/ethnicity among females diagnosed with lung cancer according to histology and stage at diagnosis. We followed SEER guidance on suppression of table cells with less than 5 cases.

Follow-up time for lung cancer incidence was defined as days from the baseline visit to the earliest of lung cancer diagnosis, death, or December 31, 2013. Median follow-up was 4.8 (interquartile range [IRR] = 2.6 to 9.2) years.

Age-adjusted incidence rates (AAIR) represent the number of cases per 100 000 person-years at risk. Among groups defined by sex and race/ethnicity, AAIRs were calculated for overall lung cancer and for lung cancer stratified by smoking status. We also calculated AAIRs for the NSCLC and adenocarcinoma subtypes; AAIRs for other subtypes could not be calculated because of low frequencies of cases among persons who never smoked. To calculate AAIRs, we first calculated age-specific incidence rates for 15 age groups of the cohort by dividing the number of cases by the corresponding person-years of at-risk follow-up time in each age group. These age-specific rates were then standardized to the United States 2000 population, summed over age groups, and multiplied by 100 000 to obtain the AAIR. Ninety-five percent confidence intervals (CIs) were calculated using the Fay and Feuer method (20) with the modification by Tiwari et al. (21) for the upper confidence level. Incidence rate ratios with 95% confidence intervals were calculated within each stratum of smoking status by dividing the AAIR for each racial/ethnic group by the AAIR for the NH White group (22). P values were all 2-sided, and P values less than .05 were considered statistically significant. We followed the Centers for Disease Control guidance on suppression of incidence rates based on a case count of less than 16 (23). Thus, because of low frequencies of cases among Asian Indian, Vietnamese, and Korean American females in all smoking categories, these ethnic groups were aggregated with "Other Asian" for analyses of incidence rates and incidence rate ratios.

To account for differential misclassification of smoking by case status, we conducted a sensitivity analysis whereby AAIRs were recalculated with smoking status defined using 2 smoking status values that were at least 3 months prior to the date of diagnosis among cases. To account for potential loss to follow-up by state cancer registries because of an out-of-state move, we conducted a sensitivity analysis whereby individuals whose last known address in the EHR was out of state were censored at the date of the first out-of-state address. To assess the impact of unknown or missing race/ethnicity in EHRs, we calculated standardized incidence rate ratios as a relative measure across racial/ethnic groups; expected rates for each racial/ethnic group were calculated with the rate among all females including or, in a separate analysis, not including females with unknown or missing race/ethnicity. Confidence intervals were calculated using Byar approximation (24).

Results

The distributions of age at baseline, baseline year, and race/ethnicity according to smoking status among all females in the cohort and females diagnosed with lung cancer are presented in Table 1. There were 535 incident lung cancer diagnoses among 244 147 AANHPI females; 43.9% of AANHPI females with lung cancer never smoked. Analogous distributions among males are available in Supplementary Table 1 (available online). Table 2 presents the distribution of females with lung cancer by age at diagnosis, year of baseline visit, and race/ethnicity according to smoking status as well as lung cancer histology and stage. Across all racial/ethnic groups, adenocarcinoma accounted for 64.5% of lung cancers among females who never smoked compared with 46.5% among those who ever smoked. Among AANHPI females with lung cancer who never smoked, 77.0% were diagnosed with the adenocarcinoma histologic subtype.

Figure 1 shows AAIRs for lung cancer among never- and ever-smoking females by race/ethnicity. The rate we observed among all never-smoking females in our cohort was 13.1 per 100 000 (95% CI = 12.2 to 14.0). Incidence of lung cancer among never-smoking AANHPI females as an aggregate group was 17.1 per 100 000 (95% CI = 14.9 to 19.4). However, AAIRs varied widely across AANHPI groups, from 6.4 (95% CI = 3.6 to 10.0) among Japanese American to 22.8 (95% CI = 17.3 to 29.1) among Chinese American females who never smoked. The rate among Native Hawaiian and Pacific Islander females who never smoked was 15.2 (95% CI = 10.2 to 21.2). A similar pattern was observed for the adenocarcinoma subtype. The AAIR among ever-smoking AANHPI females in the aggregate was 66.5 (95% CI = 59.1 to 74.4). Across AANHPI ethnic groups, AAIRs ranged from 41.3 (95% CI = 29.1 to 55.7) among Japanese American females to 102.4 (95% CI = 83.5 to 123.3) among Native Hawaiian females who ever smoked. AAIRs for lung cancer among never- and ever-smoking males by race/ethnicity are in Supplementary Figure 1 (available online). Our results show that the group of females with unknown or missing race/ethnicity, especially those who ever smoked, have a particularly high risk of lung cancer (Figure 1). An examination of registry data on race/ethnicity among females with lung cancer and unknown or missing EHR race/ethnicity indicated that 82.9% had NH White race/ethnicity (61.8% of those with known EHR race/ethnicity were NH White).

Figure 2 shows smoking-specific race/ethnicity IRRs among females. Among females who never smoked, AAIRs of all histologies combined and adenocarcinoma among every AANHPI group, except Japanese American females, were higher than that of NH White females, from 66% greater among Native Hawaiian (IRR = 1.66, 95% CI = 1.03 to 2.56) to more than 120% greater among Chinese American females (IRR = 2.26, 95% CI = 1.67 to 3.02). Among females who ever smoked, Native Hawaiian females (in addition to Black females and females with multiple non-AANHPI races) had higher incidence of lung cancer compared with NH White females.

Incidence of overall lung cancer among females and males not stratified by smoking are in Supplementary Table 2 (available online), and incidence of the NSCLC subtype stratified by smoking status are in Supplementary Table 3 (available online). In general, AAIRs for overall lung cancer reported here are comparable to those previously reported for AANHPI (14,15,25–27).

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Table 1. Cohort and sociodemographic characteristics among all females and females diagnosed with lung cancer according to smoking status in the Sutter Health and Kaiser Hawai'i cohort, 2000-2013

Characteristic	Female cohort			Female incident lung cancer cases		
		Smoking status			Smoking Status	
	Total No. (%)[a]	Never No. (%)	Ever No. (%)	Total No. (%)[a]	Never No. (%)	Ever No. (%)
Total	1 222 694 (100.0)	889 870 (72.8)	332 824 (27.2)	3297 (100.0)	884 (26.8)	2413 (73.2)
Age at baseline/ diagnosis, y[b]						
18-29	345 599 (28.3)	272 851 (79.0)	72 748 (21.0)	5 (0.2)	—	—
30-39	253 666 (20.7)	198 435 (78.2)	55 231 (21.8)	37 (1.1)	23 (62.2)	14 (37.8)
40-49	214 981 (17.6)	154 146 (71.7)	60 835 (28.3)	119 (3.6)	55 (46.2)	64 (53.8)
50-59	177 066 (14.5)	116 551 (65.8)	60 515 (34.2)	407 (12.3)	107 (26.3)	300 (73.7)
60-69	116 361 (9.5)	71 997 (61.9)	44 364 (38.1)	903 (27.4)	217 (24.0)	686 (76.0)
70-79	70 032 (5.7)	44 193 (63.1)	25 839 (36.9)	1051 (31.9)	232 (22.1)	819 (77.9)
≥80	44 989 (3.7)	31 697 (70.5)	13 292 (29.5)	775 (23.5)	246 (31.7)	529 (68.3)
Baseline year						
2000-2004	326 811 (26.7)	227 712 (69.7)	99 099 (30.3)	1724 (52.3)	460 (26.7)	1264 (73.3)
2005-2009	404 724 (33.1)	294 143 (72.7)	110 581 (27.3)	976 (29.6)	257 (26.3)	719 (73.7)
2010-2013	491 159 (40.2)	368 015 (74.9)	123 144 (25.1)	597 (18.1)	167 (28.0)	430 (72.0)
Race/Ethnicity						
Any AANHPI	244 147 (20.0)	198 208 (81.2)	45 939 (18.8)	535 (16.2)	235 (43.9)	300 (56.1)
Any NHPI	42 627 (3.5)	25 139 (59.0)	17 488 (41.0)	178 (5.4)	31 (17.4)	147 (82.6)
Native Hawaiian[c]	26 467 (2.2)	14 658 (55.4)	11 809 (44.6)	144 (4.4)	23 (16.0)	121 (84.0)
Pacific Islander[d]	16 160 (1.3)	10 481 (64.9)	5679 (35.1)	34 (1.0)	8 (23.5)	26 (76.5)
Asian (single or multiple)	201 520 (16.5)	173 069 (85.9)	28 451 (14.1)	357 (10.8)	204 (57.1)	153 (42.9)
Asian (single group)	167 135 (13.7)	146 518 (87.7)	20 617 (12.3)	261 (7.9)	158 (60.5)	103 (39.5)
Asian Indian	36 382 (3.0)	35 458 (97.5)	924 (2.5)	6 (0.2)	6 (100.0)	0 (0.0)
Chinese	37 982 (3.1)	35 622 (93.8)	2360 (6.2)	67 (2.0)	59 (88.1)	8 (11.9)
Japanese	19 441 (1.6)	14 453 (74.3)	4988 (25.7)	57 (1.7)	18 (31.6)	39 (68.4)
Filipinx	35 852 (2.9)	28 841 (80.4)	7011 (19.6)	76 (2.3)	42 (55.3)	34 (44.7)
Korean	6429 (0.5)	4887 (76.0)	1542 (24.0)	19 (0.6)	6 (31.6)	13 (68.4)
Vietnamese	4329 (0.4)	4012 (92.7)	317 (7.3)	5 (0.2)	5 (100.0)	0 (0.0)
Other Asian	26 720 (2.2)	23 245 (87.0)	3475 (13.0)	31 (0.9)	22 (71.0)	9 (29.0)
Asian (multiple group)	34 385 (2.8)	26 551 (77.2)	7834 (22.8)	96 (2.9)	46 (47.9)	50 (52.1)
Asian only	10 082 (0.8)	8461 (83.9)	1621 (16.1)	16 (0.5)	12 (75.0)	—
Asian and non-Asian	24 303 (2.0)	18 090 (74.4)	6213 (25.6)	80 (2.4)	34 (42.5)	46 (57.5)
Non-Hispanic White	518 152 (42.4)	348 492 (67.3)	169 660 (32.7)	1297 (39.3)	306 (23.6)	991 (76.4)
Black	35 488 (2.9)	23 995 (67.6)	11 493 (32.4)	82 (2.5)	13 (15.9)	69 (84.1)
Hispanic	100 070 (8.2)	79 235 (79.2)	20 835 (20.8)	72 (2.2)	31 (43.1)	41 (56.9)
Non-AANHPI multiple	38 228 (3.1)	26 055 (68.2)	12 173 (31.8)	94 (2.9)	14 (14.9)	80 (85.1)
Other (including AIAN)	25 195 (2.1)	19 220 (76.3)	5975 (23.7)	18 (0.5)	—	14 (77.8)
Unknown	261 414 (21.4)	194 665 (74.5)	66 749 (25.5)	1199 (36.4)	281 (23.4)	918 (76.6)

[a]Column percentages are provided in Total columns. All other columns with proportions present row percentages. AANHPI = Asian American, Native Hawaiian, and Pacific Islander; AIAN = American Indian and Alaska Native; NHPI = Native Hawaiian and Pacific Islander. "—" indicates censoring due to low numbers (<5 individuals).

[b]Age at baseline among cohort, age at diagnosis among cases.

[c]Individuals indicating *any* Native Hawaiian, even if also indicating other races or ethnicities, are categorized as Native Hawaiian.

[d]Pacific Islander, not indicating Native Hawaiian.

Patterns of incidence of NSCLC across race/ethnicity resemble those for adenocarcinoma; the majority of cancers within the NSCLC group are adenocarcinomas. Results from sensitivity analyses to account for misclassification of smoking status, potential loss to follow-up, and misclassification of EHR race/ethnicity did not differ substantially from main analyses (Supplementary Tables 4 and 5, available online).

Discussion

Among never-smoking females, all AANHPI female ethnic groups, except for Japanese American females, had substantially elevated risk of lung cancer. These rates (more than 20 per 100 000) make lung cancer among those who never smoked the third most common cancer among Chinese American females (after breast and colon cancer) and the fourth most common

Table 2. Cohort and sociodemographic characteristics among females diagnosed with lung cancer according to smoking status, histologic subtype, and stage at diagnosis in the Sutter Health and Kaiser Hawai'i cohort, 2000-2013

	Lung cancer cases among never-smokers				Lung cancer cases among ever-smokers			
	By histology		By stage		By histology		By stage	
Characteristics	All No. (%)[a]	Adenocarcinoma No. (%)[b]	Localized No. (%)[b]	Regional + Distant No. (%)[b]	All No. (%)[a]	Adenocarcinoma No. (%)[b]	Localized No. (%)[b]	Regional + Distant No. (%)[b]
All	884 (100.0)	570 (64.5)	203 (23.0)	642 (72.6)	2413 (100.0)	1123 (46.5)	498 (20.6)	1828 (75.8)
Age at diagnosis, y								
18-39	27 (3.1)	17 (63.0)	9 (33.3)	16 (59.3)	15 (0.6)	11 (73.3)	5 (33.3)	10 (66.7)
40-49	55 (6.2)	42 (76.4)	12 (21.8)	42 (76.4)	64 (2.7)	34 (53.1)	13 (20.3)	48 (75.0)
50-59	107 (12.1)	73 (68.2)	28 (26.2)	78 (72.9)	300 (12.4)	162 (54.0)	57 (19.0)	235 (78.3)
60-69	217 (24.5)	150 (69.1)	53 (24.4)	155 (71.4)	686 (28.4)	345 (50.3)	138 (20.1)	526 (76.7)
70-79	232 (26.2)	165 (71.1)	54 (23.3)	171 (73.7)	819 (33.9)	368 (44.9)	181 (22.1)	620 (75.7)
≥80	246 (27.8)	123 (50.0)	47 (19.1)	180 (73.2)	529 (21.9)	203 (38.4)	104 (19.7)	389 (73.5)
Baseline year								
2000-2004	460 (52.0)	310 (67.4)	101 (22.0)	339 (73.7)	1264 (52.4)	584 (46.2)	267 (21.1)	954 (75.5)
2005-2009	257 (29.1)	156 (60.7)	60 (23.3)	186 (72.4)	719 (29.8)	332 (46.2)	133 (18.5)	556 (77.3)
2010-2013	167 (18.9)	104 (62.3)	42 (25.1)	117 (70.1)	430 (17.8)	207 (48.1)	98 (22.8)	318 (74.0)
Race/Ethnicity					(0.0)			
Any AANHPI	235 (26.6)	181 (77.0)	56 (23.8)	171 (72.8)	300 (12.4)	140 (46.7)	58 (19.3)	233 (77.7)
Any NHPI	31 (3.5)	22 (71.0)	5 (16.1)	23 (74.2)	147 (6.1)	61 (41.5)	28 (19.0)	115 (78.2)
Native Hawaiian[c]	23 (2.6)	15 (65.2)	—	18 (78.3)	121 (5.0)	52 (43.0)	24 (19.8)	94 (77.7)
Pacific Islander[d]	8 (0.9)	7 (87.5)	—	5 (62.5)	26 (1.1)	9 (34.6)	—	21 (80.8)
Asian (single or multiple)	204 (23.1)	159 (77.9)	51 (25.0)	148 (72.5)	153 (6.3)	79 (51.6)	30 (19.6)	118 (77.1)
Asian (single group)	158 (17.9)	127 (80.4)	41 (25.9)	114 (72.2)	103 (4.3)	50 (48.5)	18 (17.5)	84 (81.6)
Chinese	59 (6.7)	47 (79.7)	15 (25.4)	42 (71.2)	8 (0.3)	—	—	7 (87.5)
Japanese	18 (2.0)	16 (88.9)	6 (33.3)	12 (66.7)	39 (1.6)	18 (46.2)	—	35 (89.7)
Filipinx	42 (4.8)	36 (85.7)	13 (31.0)	29 (69.0)	34 (1.4)	15 (44.1)	10 (29.4)	24 (70.6)
Other Asian	39 (4.4)	28 (71.8)	7 (17.9)	31 (79.5)	22 (0.9)	13 (59.1)	—	18 (81.8)
Asian (multiple group)	46 (5.2)	32 (69.6)	10 (21.7)	34 (73.9)	50 (2.1)	29 (58.0)	12 (24.0)	34 (68.0)
Asian only multiple	12 (1.4)	10 (83.3)	—	8 (66.7)		0 (0.0)	—	—
Asian and non-Asian	34 (3.8)	22 (64.7)	6 (17.6)	26 (76.5)	46 (1.9)	29 (63.0)	11 (23.9)	31 (67.4)
Non-Hispanic White	306 (34.6)	199 (65.0)	89 (29.1)	206 (67.3)	991 (41.1)	507 (51.2)	269 (27.1)	691 (69.7)
Black	13 (1.5)	7 (53.8)	—	8 (61.5)	69 (2.9)	38 (55.1)	21 (30.4)	48 (69.6)
Hispanic	31 (3.5)	20 (64.5)	11 (35.5)	20 (64.5)	41 (1.7)	25 (61.0)	8 (19.5)	33 (80.5)
Non-AANHPI multiple	14 (1.6)	9 (64.3)	5 (35.7)	6 (42.9)	80 (3.3)	42 (52.5)	16 (20.0)	60 (75.0)
Unknown	281 (31.8)	152 (54.1)	38 (13.5)	227 (80.8)	918 (38.0)	362 (39.4)	121 (13.2)	754 (82.1)

[a]Column percentages are provided. AANHPI = Asian American, Native Hawaiian, and Pacific Islander; AIAN = American Indian and Alaska Native; NHPI = Native Hawaiian and Pacific Islander. "—" indicates censoring due to low numbers (<5 individuals).
[b]Row percentages are provided.
[c]Individuals indicating *any* Native Hawaiian, even if also indicating other races or ethnicities, are categorized as Native Hawaiian.
[d]Pacific Islander, not indicating Native Hawaiian.

among Filipinx females (after breast, colon, and thyroid cancer) (28). Among females who ever smoked, NHPI have higher risk of lung cancer. Our 2007 study summarized lung cancer incidence among never-smoking females in 4 large cohort studies and found published rates from 15.2 per 100 000 (95% CI = 9.1 to 24.5) to 20.8 (95% CI = 13.5 to 31.2). The rate we observed among all females in our cohort 13.1 (95% CI = 12.2 to 14.0) is within this range, and our study provides much needed stratification of rates by detailed race/ethnicity, particularly for AANHPI ethnic groups (4).

Among never-smoking females, we also examined incidence of the adenocarcinoma histologic subtype, the most common histologic subtype among those who never smoked (29). In our cohort, adenocarcinoma accounted for 64.5% of lung cancers among females who never smoked compared to 46.5% among those who ever smoked. In our 2010 SEER study, increasing incidence rates for adenocarcinoma among some AANHPI groups suggested higher rates of lung cancer among AANHPI who never smoked, an observation confirmed here (26).

Females with unknown or missing race/ethnicity according to our EHR data, especially those who ever smoked, have a particularly high risk of lung cancer. This observation led us to examine the possibility of misclassification of race/ethnicity among cases: although we were only able to extract EHR data
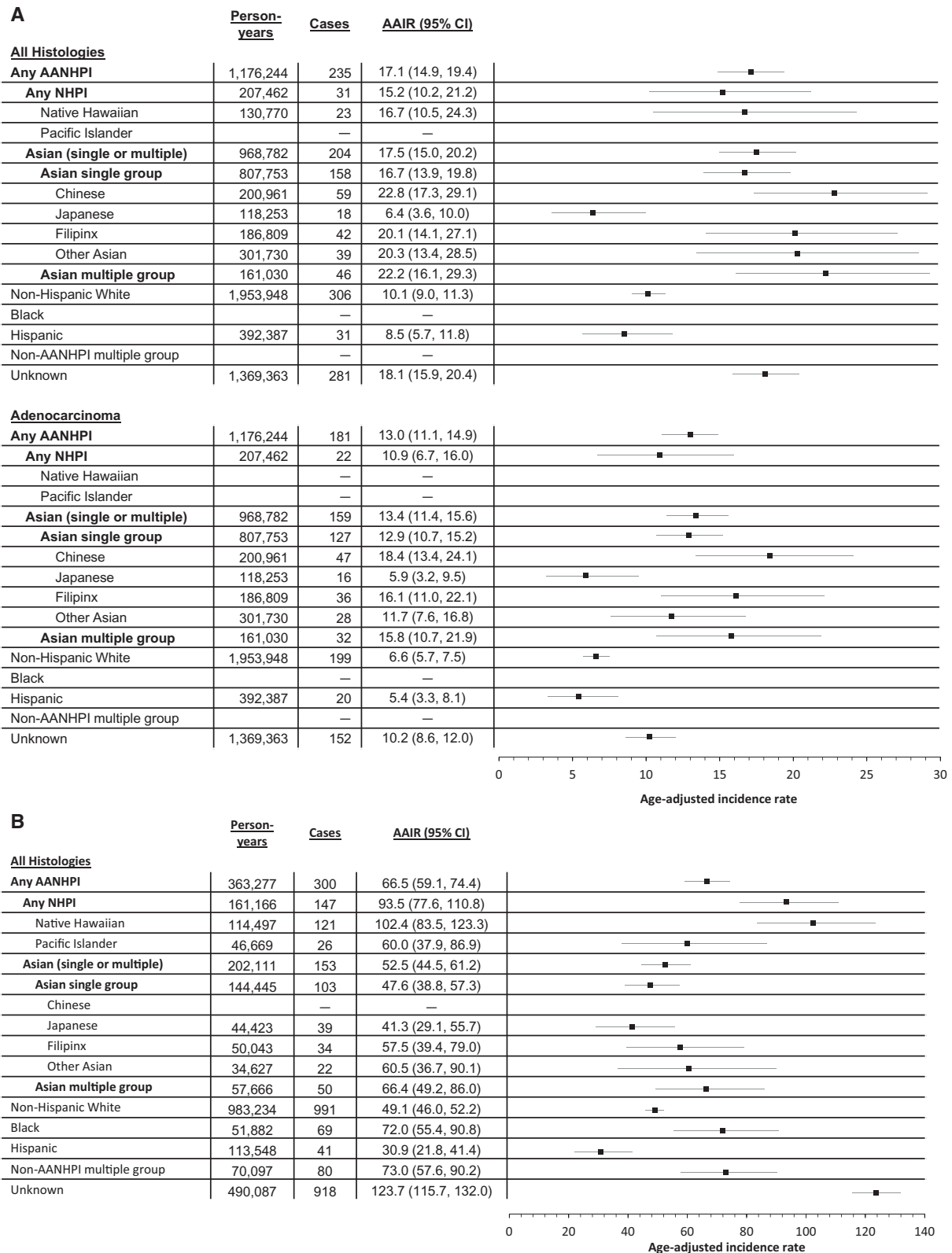
A

All Histologies	Person-years	Cases	AAIR (95% CI)
Any AANHPI	1,176,244	235	17.1 (14.9, 19.4)
Any NHPI	207,462	31	15.2 (10.2, 21.2)
Native Hawaiian	130,770	23	16.7 (10.5, 24.3)
Pacific Islander		—	—
Asian (single or multiple)	968,782	204	17.5 (15.0, 20.2)
Asian single group	807,753	158	16.7 (13.9, 19.8)
Chinese	200,961	59	22.8 (17.3, 29.1)
Japanese	118,253	18	6.4 (3.6, 10.0)
Filipinx	186,809	42	20.1 (14.1, 27.1)
Other Asian	301,730	39	20.3 (13.4, 28.5)
Asian multiple group	161,030	46	22.2 (16.1, 29.3)
Non-Hispanic White	1,953,948	306	10.1 (9.0, 11.3)
Black		—	—
Hispanic	392,387	31	8.5 (5.7, 11.8)
Non-AANHPI multiple group		—	
Unknown	1,369,363	281	18.1 (15.9, 20.4)

Adenocarcinoma	Person-years	Cases	AAIR (95% CI)
Any AANHPI	1,176,244	181	13.0 (11.1, 14.9)
Any NHPI	207,462	22	10.9 (6.7, 16.0)
Native Hawaiian		—	—
Pacific Islander		—	—
Asian (single or multiple)	968,782	159	13.4 (11.4, 15.6)
Asian single group	807,753	127	12.9 (10.7, 15.2)
Chinese	200,961	47	18.4 (13.4, 24.1)
Japanese	118,253	16	5.9 (3.2, 9.5)
Filipinx	186,809	36	16.1 (11.0, 22.1)
Other Asian	301,730	28	11.7 (7.6, 16.8)
Asian multiple group	161,030	32	15.8 (10.7, 21.9)
Non-Hispanic White	1,953,948	199	6.6 (5.7, 7.5)
Black		—	—
Hispanic	392,387	20	5.4 (3.3, 8.1)
Non-AANHPI multiple group		—	—
Unknown	1,369,363	152	10.2 (8.6, 12.0)

Age-adjusted incidence rate (0 to 30)

B

All Histologies	Person-years	Cases	AAIR (95% CI)
Any AANHPI	363,277	300	66.5 (59.1, 74.4)
Any NHPI	161,166	147	93.5 (77.6, 110.8)
Native Hawaiian	114,497	121	102.4 (83.5, 123.3)
Pacific Islander	46,669	26	60.0 (37.9, 86.9)
Asian (single or multiple)	202,111	153	52.5 (44.5, 61.2)
Asian single group	144,445	103	47.6 (38.8, 57.3)
Chinese		—	—
Japanese	44,423	39	41.3 (29.1, 55.7)
Filipinx	50,043	34	57.5 (39.4, 79.0)
Other Asian	34,627	22	60.5 (36.7, 90.1)
Asian multiple group	57,666	50	66.4 (49.2, 86.0)
Non-Hispanic White	983,234	991	49.1 (46.0, 52.2)
Black	51,882	69	72.0 (55.4, 90.8)
Hispanic	113,548	41	30.9 (21.8, 41.4)
Non-AANHPI multiple group	70,097	80	73.0 (57.6, 90.2)
Unknown	490,087	918	123.7 (115.7, 132.0)

Age-adjusted incidence rate (0 to 140)

Figure 1. Person-years of follow-up, lung cancer case frequencies, age-adjusted incidence rates (AAIRs) per 100 000, and corresponding forest plots for (**A**) females who have never smoked (all histologies combined and adenocarcinoma) and (**B**) females who ever smoked, by detailed race/ethnicity, Sutter Health and Kaiser Hawai'i cohort, 2000-2013. AAIRs are not reported for Pacific Islander, Black, and non-AANHPI females who never smoked or Chinese females who smoked because of low case frequencies (<16). Because of low case frequencies among Asian Indian, Vietnamese, and Korean females, these groups were aggregated with the "Other Asian" group. AANHPI = Asian American, Native Hawaiian, or Pacific Islander; AIAN = American Indian or Alaska Native; CI = confidence interval; NHPI = Native Hawaiian or Pacific Islander.
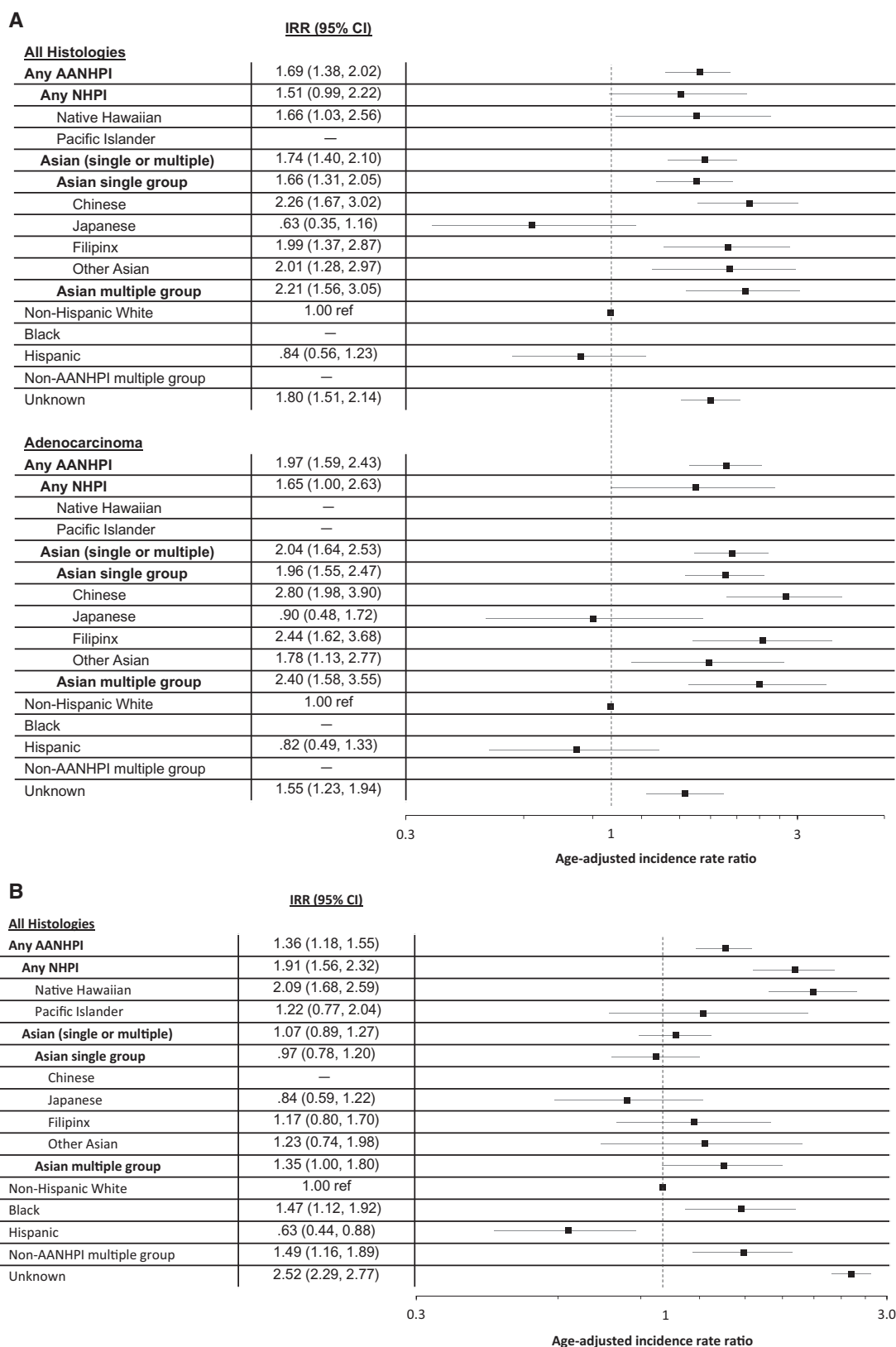
A

IRR (95% CI)

	IRR (95% CI)
All Histologies	
Any AANHPI	1.69 (1.38, 2.02)
Any NHPI	1.51 (0.99, 2.22)
Native Hawaiian	1.66 (1.03, 2.56)
Pacific Islander	—
Asian (single or multiple)	1.74 (1.40, 2.10)
Asian single group	1.66 (1.31, 2.05)
Chinese	2.26 (1.67, 3.02)
Japanese	.63 (0.35, 1.16)
Filipinx	1.99 (1.37, 2.87)
Other Asian	2.01 (1.28, 2.97)
Asian multiple group	2.21 (1.56, 3.05)
Non-Hispanic White	1.00 ref
Black	—
Hispanic	.84 (0.56, 1.23)
Non-AANHPI multiple group	—
Unknown	1.80 (1.51, 2.14)
Adenocarcinoma	
Any AANHPI	1.97 (1.59, 2.43)
Any NHPI	1.65 (1.00, 2.63)
Native Hawaiian	—
Pacific Islander	—
Asian (single or multiple)	2.04 (1.64, 2.53)
Asian single group	1.96 (1.55, 2.47)
Chinese	2.80 (1.98, 3.90)
Japanese	.90 (0.48, 1.72)
Filipinx	2.44 (1.62, 3.68)
Other Asian	1.78 (1.13, 2.77)
Asian multiple group	2.40 (1.58, 3.55)
Non-Hispanic White	1.00 ref
Black	—
Hispanic	.82 (0.49, 1.33)
Non-AANHPI multiple group	—
Unknown	1.55 (1.23, 1.94)

Age-adjusted incidence rate ratio

B

IRR (95% CI)

	IRR (95% CI)
All Histologies	
Any AANHPI	1.36 (1.18, 1.55)
Any NHPI	1.91 (1.56, 2.32)
Native Hawaiian	2.09 (1.68, 2.59)
Pacific Islander	1.22 (0.77, 2.04)
Asian (single or multiple)	1.07 (0.89, 1.27)
Asian single group	.97 (0.78, 1.20)
Chinese	—
Japanese	.84 (0.59, 1.22)
Filipinx	1.17 (0.80, 1.70)
Other Asian	1.23 (0.74, 1.98)
Asian multiple group	1.35 (1.00, 1.80)
Non-Hispanic White	1.00 ref
Black	1.47 (1.12, 1.92)
Hispanic	.63 (0.44, 0.88)
Non-AANHPI multiple group	1.49 (1.16, 1.89)
Unknown	2.52 (2.29, 2.77)

Age-adjusted incidence rate ratio

Figure 2. Incidence rate ratios (IRRs) and corresponding forest plots for lung cancer among females who have (**A**) never smoked (all histologies combined and adenocarcinoma) and who have (**B**) ever smoked, Sutter Health and Kaiser Hawai'i cohort, 2000-2013. Rate ratios are displayed on a logarithmic scale. The **vertical dotted line** indicates the reference IRR among non-Hispanic White females (IRR =1.00). **Bolded IRRs** and confidence interval (CIs) indicate those results are statistically significant. IRRs are not reported for Pacific Islander, Black, and non-AANHPI females who never smoked or Chinese females who smoked because of low case frequencies (<16). AANHPI = Asian American, Native Hawaiian, or Pacific Islander; AIAN = American Indian or Alaska Native; NHPI = Native Hawaiian or Pacific Islander.

on race/ethnicity from specific fields, the cancer registries have race and ethnicity data informed through more extensive chart review. We found that proportionally more individuals with lung cancer who were missing EHR race/ethnicity were NH White (82.9%) compared to those with known EHR race/ethnicity (61.8%). Thus, AAIRs for the NH White group may be slightly underestimated because of misclassification of EHR race/ethnicity. Because incidence rate ratios rely on NH White as the reference group, we also calculated standardized incidence rate ratios as a relative measure of incidence across race/ethnicity (Supplementary Table 5, available online). Incidence rate ratios and standardized incidence rate ratios show similar patterns of risk across race/ethnicity, so bias in the group with unknown or missing EHR race/ethnicity is not substantially affecting our observations.

There are few previous studies in the United States reporting incidence of lung cancer among females who have never smoked, and none, to our knowledge, that report these rates by detailed race/ethnicity. Our linkage of EHR with cancer registry data allowed calculation of lung cancer incidence by race/ethnicity and smoking status, which was not possible with registry data alone. Moreover, with more recent research focusing on the disaggregation of the AANHPI population, there is growing evidence of substantial health and exposure inequalities that debunk the perception that they are at lower risk for developing cancer (11,30,31). Our study sites, Hawai'i and Northern California, are among the nation's largest and most diverse AANHPI populations (7,8). This focus on geographies with a substantial and diverse AANHPI population and the large size of our cohort made possible the disaggregation of AANHPI groups and allowed us to document, for the first time, the high burden of lung cancer among most never-smoking AANHPI female ethnic groups.

Known risk factors for lung cancer among females in the United States who have never smoked include second-hand tobacco smoke, family history of lung cancer, air pollution, cooking oil fumes, and radon (32–35), but the degree to which these risk factors contribute to higher risk among AANHPI females is not known (36,37). There is evidence of high levels of air pollution exposures among AANHPIs, including high traffic volume, fine particulate matter ($PM_{2.5}$), and exposure to volcanic smog in Hawai'i, but robust studies to address these exposures in regard to lung cancer among AANHPI are not available (38–40). No studies of cooking oil fumes and lung cancer risk have been conducted in the United States (35). Body size, reproductive factors such as hormone therapies, and certain infectious diseases may also have etiologic significance, but so far, results from previous studies have been mixed and not specific to AANHPI groups (41–51). Genetic ancestry and the mutational landscapes of lung cancers among AANHPI females who have never smoked may also provide insights into the etiology and increased burden of lung cancer among this group.

Our study was made possible with an innovative approach to data integration, including pooling EHR data across healthcare systems and linkage to cancer registries. We note some limitations. EHR data often contain a high degree of missingness. The 2 EHR systems had remarkably complete smoking information and, with our approach to extraction of smoking status, yielded smoking status classification for more than 95% of the cohort (18). Health care utilization might contribute substantially to completeness of EHR data; however, the proportion of individuals with race/ethnicity and smoking status data did not change substantially when we considered a subset of the population from Sutter Health with a designated primary care physician (43% of the Sutter Health cohort). There is a potential for loss to follow-up for individuals who were diagnosed with lung cancer in another state; to mitigate this, we required a California (for Sutter Health) or Hawai'i (for Kaiser Permanente Hawaii) address during the follow-up period. A relatively small proportion (2.5%) of the cohort had an out-of-state address at the last follow-up date, and sensitivity analyses to censor these individuals at that date did not indicate bias because of loss to follow-up. The systematic use of EHR data also requires careful consideration of the introduction of measurement bias. Thus, as previously noted, we also conducted sensitivity analyses to account for potential differential misclassification of smoking or race/ethnicity by lung cancer status; these analyses showed our results to be robust.

Among never-smoking females, most AANHPI ethnic groups experience a high burden of lung cancer incidence. Continuing studies are needed to determine risk factors for lung cancer among females who have never smoked and why the burden of this disease is greater for AANHPI females.

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Notes

Data Availability

The data underlying this article were provided by Sutter Health, Kaiser Permanente Hawai'i, the California Cancer Registry, and the Hawai'i Tumor Registry by permission. Data will be shared on request to the corresponding author with permission of these parties.

ARTICLE

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