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ORIGINAL RESEARCH & CONTRIBUTIONS

Predictors of Lung Cancer: Noteworthy Cell Type Differences

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Abstract

Objective: To study risk factors for cell types of lung cancer.

Methods: Cohort study of 126,293 persons with 1852 subjects with incident cancer. We performed Cox proportional hazards models (8 covariates) to estimate risk of the 4 most numerous specific cell types: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and bronchioloalveolar carcinoma.

Results: Smoking 1 or more cigarette packs per day was a powerful predictor ($p < 0.0001$) of all cell types, with hazard ratios ranging from 5.8 for bronchioloalveolar to 62.7 for squamous cell carcinoma. Other hazard ratio ranges included male/female from 0.6 (bronchioloalveolar, $p < 0.05$) to 2.0 (squamous, $p < 0.001$); black/white from 0.8 (small cell, $p < 0.05$) to 1.7 (squamous, $p < 0.001$); Asian/white from 0.8 (small cell) to 1.9 (bronchioloalveolar); and alcohol intake of 3 or more drinks per day from 1.0 (squamous) to 1.5 (adenocarcinoma, $p < 0.01$). College graduation and increasing body mass index were inversely related to risk of several cell types. Noteworthy sex-specific associations included increased risk of Asian vs white women for adenocarcinoma, squamous cell carcinoma and bronchioloalveolar carcinoma and substantially increased risk of adenocarcinoma in women with alcohol intake of 3 or more drinks per day.

Conclusions: These risk factor disparities for lung cancer cell types presumably reflect biologic differences. Future investigation may contribute to increased understanding of tumorigenesis and optimal treatment.

Introduction

Lung cancer therapy is increasingly targeted to tumor cell type.[1-4] Risk factor associations with specific cell types can help focus research leading to understanding tumorigenesis and refinements in therapy. Epidemiologic observations have revealed several disparities, including the following: 1) smoking and male sex are less dominant as predictors of adenocarcinoma than of squamous cell or of small cell carcinoma;[5] 2) black Americans are at higher risk than whites of several cell types of lung cancer;[6] 3) Asian women are overrepresented among never-smoking women with adenocarcinoma;[7] and 4) women are at greater risk of bronchioloalveolar carcinoma.[8]

Environmental influences are also suggested by longitudinal changes in the incidence of cell type.[5] In men, rates of squamous and small cell carcinoma have decreased in recent decades, whereas adenocarcinoma rates have increased.[5] In women, rates of all cell types of lung cancer have been increasing.[1,5] Although smoking habits may play a major role, the fact that lung cancer does not develop in most smokers indicates that other traits play a role.[2,7,9] The large amount of literature on lung cancer includes few cohort studies that emphasize risk factors for lung cancer cell types.

We have been engaged in studies in a large patient population involving the role of lifestyle habits and race/ethnicity in the risk of several common cancer types. In the course of performing these analyses, we noticed disparities in associations with lung cancer subtypes. Because these disparities had potential implications for etiology and therapy, this led us to perform a more detailed study. We present here the findings of a large cohort study with separate analyses of traits predictive of adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and bronchioloalveolar carcinoma. To our knowledge, there is no prior prospective report of predictors of bronchioloalveolar lung cancer, thus making this analysis the most comprehensive to date of predictors of lung cancer cell type in a single study population.

Methods

Study Population and Data

Study protocols were approved by the institutional review board of the Kaiser Permanente Medical Care Program, Oakland, CA. We studied a multiracial and multiethnic cohort of 129,987 persons who were members of a comprehensive prepaid health care program in Northern California. Baseline data were from questionnaires at voluntary routine health examinations performed from 1978 through 1985. The examination included health measurements; self-classified race/ethnicity; and checksheet queries about sociodemographic status, habits, medical history, and symptoms.[10] The study cohort comprised 79.8% of all examinees; the remainder included mostly persons taking the examination during the absences of a special research clerk.

The item "What is your race?" identified white persons as comprising 55.7% of the population (n = 72,345); blacks, 26.9% (n = 34,938); Asian Americans (Asians), 10.6% (n = 13,719); Hispanics, 4.5% (n = 5834); and other races, 2.2% (n = 2908). The largest subgroups among Asians were 6062 Chinese (44%),

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4308 Filipinos (31%), and 1722 Japanese (13%). The proportions of these subgroups born in the US varied from 7% of Filipinos to 79% of Japanese.

Baseline smoking was categorized in most models as "never smokers" (62,258; 47.9%), ex-smokers (28,822; 22.2%), current smokers of less than 1 pack per day of cigarettes (21,783; 16.8%), current smokers of 1 or more packs per day (11,935; 9.2%), and unknown (5189; 4.0%).

Baseline alcohol drinking was categorized as nondrinkers (abstainers plus those who consumed less than 1 alcoholic drink per month (42,788; 32.9%); drinkers of less than 1 drink per day (47,805; 33.0%), 1 to 2 drinks per day (23,342; 18.0%), or 3 or more drinks per day (10,489; 8.1%); and unknown (1402, 1.1%). Drinkers received separate questions about the number of days per week that they drank wine, liquor, or beer, which was strongly correlated with number of drinks per week in a 10% subgroup.[11] Wine, liquor, or beer "preponderance" was defined among current drinkers as exclusive intake or drinking the type more often than the other 2; this enabled categorization as "preponderantly" wine (16.4%), liquor (8.5%), beer (10.9%), or none (ie, 2 or 3 types equally frequently [64.2%]).

Subjects with Lung Cancer

Cancer ascertainment and data about cancer cell type were from the Health Care Program's Cancer Registry, which covers all subscribers and which contributes to the local Surveillance, Epidemiology and End Results (SEER) program.[12] There were 1852 subjects with Code 162 of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We present data about the 4 most numerous specific cell types: 631 subjects with adenocarcinoma (34.1%), 455 with squamous cell carcinoma (25.0%), 256 with small cell carcinoma (13.8%), and 73 with bronchioloalveolar carcinoma (3.9%). Of the remaining 437 cancer-affected subjects, 114 consisted of small numbers with other specific cell types (30 carcinoid tumors were the most numerous) and 323 had cancer of unspecified cell type. Table 1 details data about selected traits of the study population by cancer cell type.

Table 1. Selected baseline traits of study population and lung cancer subjects by cell type

	Number of subjects (%)[a]				
Trait	**Study population**	**Adenocarcinoma**	**Squamous cell Ca**	**Small cell Ca**	**Bronchioloalveolar Ca**
Crude rate per 1000 person-years	8.52	2.94	2.12	1.19	0.32
Sex and baseline age					
Total	129,987 (100)	631 (100)	455 (100)	256 (100)	73 (100)
Men	57,272 (44.1)	304 (48.2)	286 (62.9)	135 (52.7)	28 (38.4)
Women	72,715 (55.9)	327 (51.8)	169 (37.1)	121 (47.3)	45 (61.6)
< 50 years	92,639 (71.3)	220 (35.9)	103 (22.6)	99 (38.7)	31 (42.5)
≥ 50 years	37,348 (28.7)	411 (65.1)	352 (77.4)	157 (67.3)	42 (57.5)
Race/ethnicity					
White	72,345 (55.7)	362 (57.4)	250 (55.0)	166 (64.8)	44 (60.3)
Black	34,938 (26.9)	187 (29.6)	173 (38.2)	64 (25.0)	16 (21.9)
Asian	13,719 (10.6)	56 (8.9)	22 (4.8)	16 (6.3)	11 (15.1)
Chinese	6062 (4.7)	32 (5.1)	11 (2.4)	7 (2.7)	6 (8.2)
Filipino	4308 (3.3)	18 (2.9)	2.2 (4.0)	4 (1.6)	4 (5.5)
Japanese	1722 (1.3)	5 (0.8)	1 (0.2)	4 (1.6)	1 (1.4)
South Asian	721 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Other Asian	906 (0.7)	1 (0.2)	0 (0)	1 (0.4)	0 (0)
Hispanic	5834 (4.5)	18 (2.9)	4 (0.9)	5 (2.0)	2 (2.7)
Other	2908 (2.2)	8 (1.3)	6 (1.3)	5 (2.0)	0 (0)
Baseline smoking					
Never	62,258 (47.9)	93 (14.7)	20 (4.4)	18 (7.0)	21 (28.8)
Ex-smoker	28,822 (22.2)	152 (24.1)	1.3 (22.6)	49 (19.1)	17 (23.3)
< 1 pack per day	21,783 (16.8)	168 (26.6)	130 (28.6)	80 (31.3)	14 (19.2)
≥ 1 pack per day	11,935 (9.2)	187 (29.6)	181 (39.8)	100 (39.1)	13 (17.8)
Baseline alcohol intake					
Nondrinker	42,788 (32.9)	171 (27.6)	115 (25.3)	68 (26.6)	21 (28.8)
Ex-drinker	4163 (3.2)	25 (4.0)	29 (6.4)	19 (7.4)	4 (5.5)
< 1 drink per day	47,805 (33.0)	187 (29.6)	127 (27.9)	67 (26.2)	19 (26.0)
1-2 drinks per day	23,342 (18.0)	129 (20.4)	105 (23.1)	57 (22.3)	19 (26.0)
≥ 3 drinks per day	10,489 (8.1)	104 (16.4)	70 (15.4)	41 (16.0)	8 (10.1)

[a] Percentages do not total to 100% for smoking and alcohol categories because of missing data and for other categories because of rounding.
Ca = carcinoma.

Analytic Methods

Subjects were followed up through 2008, lung cancer diagnosis, or termination of their Health Plan membership. Mean follow-up was 18.2 years, yielding an estimated 2,365,000 person-years of follow-up. Analyses used the Cox proportional hazards model separately for the 4 cell types. These yielded hazard ratio (HR) estimates, 95% confidence intervals (CI), and p values. Covariates in most models were age (continuous), race/ethnicity (white referent, black, Asian, Hispanic, others), education (no college referent, some college, college graduate), body mass index (BMI; < 25 kg/m^2 referent, 25 to 29 kg/m^2, ≥ 30 kg/m^2), marital status (married referent, never married, formerly married), cigarette smoking (never smokers referent, ex-smokers, smokers < 1 pack per day, smokers ≥ 1 packs per day, unknown), total alcohol (abstainers referent, ex-drinkers, < 1 drink per day, 1 to 2 drinks per day, ≥ 3 drinks per day, unknown). Only fully adjusted data are presented in Tables 2 to 5.

The role of beverage choice was studied as the relationship of the categories of daily total alcohol intake within strata of drinkers according to their preponderant beverage choice (wine, liquor, beer, none). Separate models yielded estimates of the risk of lung cancer (vs whites as referent) for Asian subgroups. Stratified models were performed for smoking and racial/ethnicity strata in 3 racial groups (white, black, Asian) within each specific cell type. We use the term *significant* for p values < 0.05.

Estimates of population-attributable risk (or attributable fraction) for smoking were calculated by $AF_p = I_p - I_u / I_p$, where AF was the attributable fraction, I_p the incidence in the total population, and I_u the incidence in the unexposed (never smoker) group.

Table 2. Adjusted relationships of sex and ethnicity to risk of lung cancer by cell type

	Adjusted hazard ratio[a] (95% confidence interval)			
Group	Adenocarcinoma (n = 631)	Squamous cell Ca (n = 455)	Small cell Ca (n = 256)	Bronchioloalveolar Ca (n = 73)
Sex (vs women as referent)				
All	1.1 (0.9 – 1.3)	2.0 (1.6-2.5)[b]	1.3 (1.0-1.7)[c]	0.6 (0.4-1.0)[c]
White	1.0 (0.9 -1.5)	2.0 (1.5-2.6)[b]	1.2 (0.9-1.7)	0.7 (0.4-1.4)
Black	1.5 (1.0-1.9)[c]	2.2 (1.5-3.0)[b]	1.6 (0.9-1.7)	0.5 (0.4-1.0)[c]
Asian	0.7 (0.4-1.3)	0.7 (0.3-1.9)	0.9 (0.3-1.7)	0.6 (0.2-1.5)
Race/ethnicity (vs white as referent)				
All blacks	1.3 (1.1-1.6)[d]	1.7 (1.4-2.1)[c]	0.9 (0.6-1.1)	1.0 (0.6-1.9)
Black men	1.4 (1.1-1.9)[c]	1.8 (1.4-2.3)[c]	0.9 (0.6-1.4)	0.9 (0.3-2.6)
Black women	1.2 (0.9-1.5)	1.7 (1.2-2.4)[d]	0.6 (0.4-1.0)[c]	1.1 (0.5-2.4)
All Asians	1.3 (1.0-1.8)	0.9 (0.6-1.5)	0.8 (0.5-1.4)	1.9 (0.9-4.0)
Asian men	1.0 (0.7-1.6)	0.6 (0.3-1.1)	0.8 (0.4-1.7)	1.5 (0.5-4.9)
Asian women	1.8 (1.2-2.7)[d]	2.2 1.2-4.2)[c]	0.9 (0.4-1.9)	2.3 (0.9-5.7)

[a] Controlled for age, sex, race/ethnicity, smoking, alcohol, body mass index, education, and marital status.
[b] p < 0.001; [c] p < 0.05; [d] p < 0.01.
Ca = carcinoma.

Table 3. Adjusted relationships of cigarette smoking and alcohol intake to risk of lung cancer by cell type

	Adjusted hazard ratio[a] (95% confidence interval)			
Baseline	Adenocarcinoma (n = 631)	Squamous cell Ca (n = 455)	Small cell Ca (n = 256)	Bronchioloalveolar Ca (n = 73)
Smoking				
Never	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Ex-smoker	2.9 (2.5-3.8)[b]	7.8 (4.8-12.7)[b]	4.5 (2.6-7.9)[b]	2.6 (1.4-5.1)[c]
< 1 pack per day	6.4 (4.9-8.3)[b]	22.4 (13.9-36.1)[b]	16.7 (9.9-28.2)[b]	3.2 (1.5-6.7)[c]
≥ 1 pack per day	13.2 (10.1-17.2)[b]	59.1 (36.8-94.9)[b]	34.5 (20.5-58.1)[b]	5.8 (2.7-12.4)[b]
Population-attributable risk (%)[d]	69	91	85	50
Alcohol intake				
Nondrinker	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Ex-drinker	1.0 (0.6-1.4)	1.0 (0.6-1.4)	1.5 (0.9-2.5)	1.8 (0.0.6-5.2)
< 1 drink per day	1.0 (0.8-1.2)	0.9 (0.7-1.2)	0.8 (0.6-1.1)	1.0 (0.5-1.9)
1-2 drinks per day	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.9 (0.6-1.3)	1.5 (0.8-3.1)
≥ 3 drinks per day	1.5 (1.2-1.9)[c]	1.0 (0.7-1.4)	1.1 (0.7-1.7)	1.5 (0.6-3.6)

[a] Controlled for age, sex, ethnicity, smoking, alcohol, body mass index, education, and marital status.
[b] p < 0.001; [c] p < 0.01; [d] Exposed is defined as current smokers plus ex-smokers.
Ca = carcinoma.

Results

Sex and Race/Ethnicity

Adjusted data (Table 2) indicated a substantially higher risk among men (vs women) for squamous cell carcinoma and a modestly increased male risk of small cell carcinoma. These sex differences were strongest for black men, who were also at increased risk of adenocarcinoma. Except for blacks, there was little sex difference in the risk of adenocarcinoma, and women were at greater risk of bronchioloalveolar carcinoma. Asian women were at higher risk of all cell types of carcinoma, but this was not statistically significant. Compared with the data in Table 2 for all subjects, the male/female comparisons were not much different in never smokers with HRs of 1.2 for adenocarcinoma, 2.0 for squamous cell, 0.6 for small cell, and 0.6 for bronchioloalveolar (all $p > 0.05$).

Risk estimates for racial/ethnic groups (see Table 2) used whites as the referent. Black men and women had greater risk of squamous cell carcinoma and of adenocarcinoma (not statistically significant among black women). Asian women, but not Asian men, had greater risk of both adenocarcinoma and squamous cell carcinoma. This was seen for Chinese and Filipino women, but not for Japanese women (data not shown). Asian women were at increased risk of bronchioloalveolar carcinoma, with a wide CI ($p = 0.08$).

Smoking

Smoking was a powerful predictor of all cell types (Table 3), with HRs for smokers of 1 or more packs per day ranging from 5.8 for bronchioloalveolar carcinoma to 59.1 for squamous cell carcinoma. The strength of the smoking association was generally strongest for blacks and weakest for Asians. For smokers of 1 or more packs per day, HRs for adenocarcinoma were 13.9 for whites, 20.9 for blacks, and 3.4 for Asians. For squamous cell carcinoma, the HRs were 69.8 for whites, 115.7 for blacks, and 6.5 for Asians. Population-attributable risks for smoking in this cohort (see Table 3) ranged from 50% for bronchioloalveolar to 91% for squamous cell carcinoma.

Alcohol Drinking

Alcohol intake of fewer than 3 drinks per day was unrelated to the risk of any tumor cell type, but intake of 3 or more drinks per day carried an increased risk of adenocarcinoma (see Table 3). This was concentrated in women with an HR of 2.1 (95% CI = 1.4-3.1, $p = 0.0002$), compared with men whose HR was 1.0 (95% CI = 0.7-1.5). The risk of alcohol-associated adenocarcinoma in women was concentrated in white women and in heavy smokers, and among the latter it was of borderline significance at 1 to 2 drinks per day (Table 4). The HR for squamous cell carcinoma among women reporting 3 or more drinks per day was 1.2 (95% CI = 0.7-2.0, $p = 0.6$), and there was no significant relationship in any stratum (data not shown). Increased risk of adenocarcinoma in heavy-drinking women was not related to any preponderant beverage choice (see Table 4).

Education and Body Mass Index

Higher educational attainment was inversely related to risk of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma (Table 5). These inverse relationships were concentrated in smokers. For college graduates the HRs among never smokers were 1.3, 1.0, and 0.9 for the 3 respective cell types, whereas the corresponding HRs for smokers of 1 or more packs per day were 0.6, 0.7, and 0.7. The inverse BMI relationship was substantially stronger for adenocarcinoma than for squamous cell carcinoma (see Table 5) and was consistent in multiple strata, including smoking categories (Table 6). The adenocarcinoma association was stronger after 10 years than earlier in follow-up, whereas for squamous cell carcinoma the inverse BMI relationship was entirely concentrated in the earlier years of follow-up (see Table 6).

Table 4. Adjusted hazard ratio for adenocarcinoma for daily drinkers in women[a]

Group	Number with adenocarcinoma	≥ 3 drinks per day		1 to 2 drinks per day	
		HR (95% CI)	p value	HR (95% CI)	p value
All women	327	2.1 (1.4-3.1)	< 0.001	1.2 (0.9-1.7)	0.3
White	194	3.1 (1.9-5.1)	< 0.001	1.5 (1.0-2.4)	0.06
Black	91	1.1 (0.5-2.6)	0.9	1.0 (0.5-1.9)	1.0
Asian	56	—[b]	—[b]	0.4 (0.1-3.4)	0.4
Never smoker	56	2.4 (0.6-10.3)	0.2	0.8 (0.3-2.3)	0.4
Ex-smoker	60	1.4 (0.5-4.4)	0.5	1.1 (0.5-2.4)	0.8
Smoker < 1 pack per day	104	1.5 (0.7-3.4)	0.3	0.9 (0.5-1.6)	0.8
Smoker ≥ 1 pack per day	90	3.6 (1.9-7.1)	< 0.001	1.8 (1.0-3.7)	0.06
Diagnosis ≤ 10 years	81	3.7 (1.7-8.2)	0.006	1.4 (0.9-2.2)	0.1
Diagnosis > 10 years	246	1.8 (1.1-2.8)	0.01	1.0 (0.7-1.4)	0.9
Baseline age < 50 years	120	1.4 (0.9-2.2)	0.2	1.2 (0.9-1.7)	0.3
Baseline age ≥ 50 years	206	2.3 (1.4-3.6)	< 0.001	1.1 (0.7-1.7)	0.6
Prefer wine	77	1.9 (0.9-4.2)	0.1	0.9 (0.4-1.8)	0.9
Prefer liquor	89	1.4 (0.6-3.1)	0.4	0.8 (0.4-1.7)	0.6
Prefer beer	54	0.6 (0.2-2.6)	0.5	1.1 (0.4-3.0)	0.8
No preference	200	1.8 (1.0-3.4)	0.05	0.9 (0.5-1.7)	0.8

[a] Separate Cox models with 8 covariates; referent is never drinkers.
[b] Insufficient data.
CI = confidence interval; HR = hazard ratio.

Discussion

Sex and Race/Ethnicity

Our data confirm the male preponderance of squamous cell and small cell carcinoma. Although this has been historically attributed to increased prevalence of smoking in men,[1,5] its presence in studies that controlled for smoking amount, like ours, could indicate increased susceptibility in men to smoking-related carcinogens. Among never smokers, lung cancer has been reported to affect a relatively larger proportion of women for several cell types,[13] but our analysis did not confirm this.

We also confirm the increased risk of black men and women for squamous cell carcinoma. It has been suggested that variation in nicotine metabolism with greater inhalation of nicotine could play a role in this risk by also increasing tar inhalation.[1,14] Another factor might be the preference of many black smokers for mentholated cigarettes,[15] which might promote greater inhalation or absorption of tars.[16] However, a recent review concluded that mentholating had little effect on lung cancer risk but also pointed out that the available data were mostly nonspecific for cancer cell types.[17]

We cannot readily explain our finding that Asian women, particularly Chinese and Filipinos, are at increased risk of both adenocarcinoma and squamous cell carcinoma. Possible environmental explanations include secondhand smoke exposure, exposure to carcinogenic cooking oil vapors, and infections such as papillomavirus.[18] Potential genetic factors in Chinese women with lung cancer include human leukocyte antigens, K-ras activation, p53 mutation, and epidermal growth factor (EGFR) related to EGFR mutations.[18,19] Targeted therapy related to EGFR mutations has been tried in Asian women with adenocarcinoma and bronchioloalveolar carcinoma.[8,9,20]

Smoking

Smoking behaviors, including intensity and cessation, have been the most studied risk traits with respect to cell type disparities.[1,21] Our data (see Table 3) confirm previous reports, indicating that the most powerful smoking relation is to squamous and small cell cancers compared with a less powerful association with adenocarcinoma.[1,21] Data about bronchioloalveolar carcinoma are sparse, but our data are roughly compatible with those in a recent report.[22]

Lung cancer cell type preponderance has shifted toward a greater proportion of adenocarcinoma than squamous cell carcinoma.[5] This shift may be due partially to cessation of smoking, which results in greater reduction in incidence of squamous cell and small cell carcinoma than of adenocarcinoma.[21] Lessened tar yield and introduction of filtered cigarettes are possible additional factors in the shift in cell types.[6] Because smoking is a less powerful predictor of adenocarcinoma and bronchioloalveolar carcinoma, additional risk factors presumably play a larger role for these types.[22,23]

Alcohol

Most reports about alcohol and lung cancer involve all lung cancers combined and show no consensus about the existence of any association independent of smoking.[1,24,25] We know of no previous reports indicating a link between alcohol intake and adenocarcinoma in women specifically (see Table 4). One analysis suggested an increased risk of squamous cell cancer, but not of adenocarcinoma.[24] The few published reports with beverage choice data involve all cell types combined and suggest increased risk primarily with beer or liquor intake, with wine drinking being protective.[26-28]

The concentration of alcohol-associated risk in white women could represent a genetic predisposition, but we have no genetic data. Possible residual confounding by smoking might be involved in the concentration of risk in heavier smokers; yet this might plausibly be a larger issue for squamous cell cancer, which was unrelated to alcohol in our data. Our data do not support an important role of beverage type, thus pointing to alcohol as the possible responsible factor. Validity of our data requires confirmation by others, but it is noteworthy that estrogen and estrogen receptor proteins have been implicated in the genesis and promotion of non-small cell lung cancer[29] and in adenocarcinoma of the lung in particular.[30,31] Alcohol is thought to increase breast cancer risk via enhancement of estrogen levels or synergy with estrogen effects and, in this population, is related to increased risk only in estrogen receptor-positive tumors.[32] We hypothesize that a similar phenomenon might exist for adenocarcinoma of the lung. Unfortunately, we have no data about hormone replacement therapy in these subjects.

Table 5. Relationships of body mass index and education to risk of lung cancer by cell type

	Adjusted hazard ratio[a] (95% confidence interval)			
Group	Adenocarcinoma (n = 631)	Squamous cell Ca (n = 455)	Small cell Ca (n = 256)	Bronchioloalveolar Ca (n = 73)
BMI				
< 25 kg/m^2	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
25-29 kg/m^2	0.7 (0.6-0.9)[b]	0.8 (0.7-1.0)	0.9 (0.6-1.1)	0.8 (0.5-1.4)
≥ 30 kg/m^2	0.5 (0.4-0.7)[b]	0.7 (0.5-1.0)[c]	0.8 (0.5-1.2)	0.4 (0.1-1.1)
Education				
No college	1.0 [Reference]	1.0 [Reference]	1.0 [Reference	1.0 [Reference]
Some college	0.9 (0.7-1.1)	0.8 (0.6-1.0)[c]	0.6 (0.5-0.8)[d]	0.9 (0.5-1.7)
College graduate	0.7 (0.6-0.9)[c]	0.6 (0.5-0.8)[b]	0.5 (0.4-0.7)[b]	0.8 (0.4-1.4)

[a] Controlled for age, sex, race/ethnicity, smoking, alcohol, BMI, education, and marital status.
[b] $p < 0.001$; [c] $p < 0.05$; [d] $p < 0.0101$.
BMI = body mass index (referent <25 kg/m^2); Ca = carcinoma.

Finally, with respect to the alcohol association, we point out that the absence of a relation of light-moderate drinking to any lung cancer cell type in our data is reassuring to light-moderate drinkers, the majority in our study population.

… the absence of a relation of light-moderate drinking to any lung cancer cell type in our data is reassuring to light-moderate drinkers …

Education and Body Mass Index

It is likely that the inverse relationship of higher educational attainment to risk of several types of lung cancer is due to confounding. Concentration in smokers suggests possible residual confounding by aspects of active smoking, but it could also represent the effects of smoking-related traits such as passive smoking exposure, occupational factors, diet, and exercise. We speculate that the most likely explanation is that college graduates were more likely to quit smoking after baseline data intake.

An inverse obesity-lung cancer relationship has been previously reported, but residual confounding by smoking or by baseline illness has been the suspected explanation.[33-35] These reports included no data about specific cell types, and, to our knowledge, the relative specificity we found for adenocarcinoma has not previously been presented. Because we found an inverse relationship to squamous cell cancer only in the earlier follow-up years, that relationship might be caused by baseline illness, but the strong relationship after 10 years for incident adenocarcinoma makes this explanation unlikely. The similar strength of the inverse BMI-adenocarcinoma relationship in smoking categories, albeit without statistical significance in several strata, lessens the likelihood that residual confounding by smoking is responsible. It is relevant that data about BMI as a predictor of severe chronic obstructive pulmonary disease in this population[36] showed a much weaker relationship of BMI of 30 kg/m^2 or above, with HR of 0.9 (CI = 0.7-1.1). We can offer only speculative explanations for this aspect of our data; these include confounding by dietary factors, a common genetic predilection, or protection by some obesity-related trait.

Limitations and Strengths

Our analyses have limitations. One is possible residual confounding by incomplete control for smoking intensity or amount within categories. Another is measurement of smoking and other nonfixed covariates only at baseline; similarity of risk estimates in models stratified by interval to diagnosis indicates that this may not be a major factor. A third drawback is the inability to control for some potential confounders such as diet, history of infections, occupation, and family history. Another limitation is potential bias introduced by lack of cell type data among 323 subjects with lung cancer. Hypothetically, these subjects with unspecified cell type might include a disproportionate number in 1 of the 4 specific cell types we studied, but this seems unlikely to us. We believe that most subjects with unspecified cell type either had no entry of the histologic findings or had no histologic diagnosis at all.

Strengths of our study include the size of the cohort with follow-up over three decades, diagnosis of lung cancer via tumor registry, good control for several important confounders, and self-identification of race/ethnicity including Asian ethnic subsets. An additional strength is the analysis of the bronchioloalveolar carcinoma cell type. This subset of adenocarcinoma has specific features with respect to prognosis and therapy,[37] but to our knowledge, prospective studies have not been previously reported.

Table 6. Adjusted hazard ratio for adenocarcinoma and squamous cell carcinoma for body mass index 30 kg/m^2 or higher in various groups

	Adenocarcinoma		Squamous cell carcinoma	
Group[a]	HR (95% CI)	p value	HR (95% CI)	p value
All subjects	0.5 (0.4-0.7)	< 0.001	0.7 (0.5-1.0)	0.03
Men	0.5 (0.3-0.7)	0.001	0.6 (0.4-0.9)	0.02
Women	0.6 (0.4-0.9)	0.008	0.9 (0.6-1.4)	0.6
White	0.5 (0.3-1.8)	0.005	0.9 (0.6-1.4)	0.6
Black	0.5 (0.3-0.8)	0.003	0.6 (0.4-1.0)	0.05
Asian	—[b]	—[b]	—[b]	—[b]
Never smoker	0.4 (0.2-1.1)	0.1	0.4 (0.04-2.9)	0.3
Ex-smoker	0.6 (0.4-1.1)	0.1	0.7 (0.3-1.3)	0.3
Smoker < 1 pack per day	0.4 (0.2-0.8)	0.008	0.8 (0.5-1.4)	0.5
Smoker ≥ 1 pack per day	0.6 (0.4-1.1)	0.09	0.8 (0.5-1.3)	0.3
Diagnosis ≤ 10 years	0.7 (0.4-1.1)	0.1	0.4 (0.2-0.7)	< 0.001
Diagnosis > 10 years	0.5 (0.3-0.7)	< 0.001	1.0 (0.7-1.4)	1.0
Baseline age < 50 years	0.3 (0.2-0.6)	< 0.001	0.7 (0.4-1.4)	0.3
Baseline age ≥ 50 years	0.6 (0.4-0.8)	0.002	0.6 (0.4-0.9)	0.03

[a] Separate Cox models with 8 covariates; referent is BMI < 25 kg/m^2.
[b] Insufficient data.
BMI = body mass index; CI = confidence interval; HR = hazard ratio.

Conclusion

We present data that cast light on several disparities in risk factors for lung cancer cell types. This may be the most comprehensive analysis yet reported. Noteworthy features include the data about Asian-American ethnic groups, the positive association of heavy alcohol intake with risk of adenocarcinoma, and the inverse association of high BMI with risk. The cell type disparities are likely to be related to biologic differences, and we hope that future research will contribute to understanding of tumorigenesis and delivery of optimal treatment. ❖

Disclosure statement

The author(s) have no conflicts of interest to disclose.

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