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Gender and lung cancer—SEER-based analysis

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ABSTRACT

Background: Lung cancer remains a major cause of death worldwide. While in the past it was considered to primarily afflict males, in recent decades the number of female patients has risen, such that rates among females are similar to those among males. Nevertheless, it has been found previously (e.g., in cardiovascular disease) that when there is a sex-specific stereotype to a disease, it may remain entrenched in medical diagnostic processes, so as to cause belated diagnosis among the other sex. Gender-based differences in incidence and diagnosis are likely to exist with respect to lung cancer because of smoking habits and stereotypes, geographic and socioeconomic differences, and past epidemiologic differences between the sexes. Here we aim to characterize the effects of gender on lung cancer diagnosis and whether such effects have changed over time.
Methods: The SEER (Statistics, Epidemiology, and End Results) database was used to check for sex-based differences by tumor type and stage at diagnosis and to investigate whether these patterns have changed with time by comparing staging data in different age cohorts over time. Results were stratified by location and analyzed with data regarding possible confounders such as smoking and socioeconomic factors.
Results: We examined 458,132 cases of lung cancer from the years 2004–2012; 243,021 (53%) in males and 215,111 (47%) in females. Lung cancer rates were 73.8 (73.5–74.1) per 100k in males and 51.6 (51.4–51.8) per 100k in females. Of these, 400,800 had the stage listed, 214,479 (54%) in males, and 186,321 (46%) in females. Total lung cancer rates were higher in males than females at all disease stages. Male patients were more likely than female patients to be diagnosed at stage 3–4, consistent across lung cancer types, cancer registries, smoking, and socioeconomic backgrounds. The difference between the percentage of males versus females diagnosed in stages 3–4 correlated negatively with increased female ever-smokers and with squamous and small cell carcinoma and were not correlated with the rate of cancer in females, or the difference between male and female cancer rates.
Conclusions: Our study showed that there is no belated diagnosis of lung cancer in females. Results appear to point to the fact that smoking females are more likely to be diagnosed at later stages, which is consistent with the current literature.

Introduction

Lung cancer is currently the leading cause of cancer death among both males and females, with mortality rates in females greater than the combined mortality of breast, uterine, and ovarian cancers [1,2]. While lung cancer was long considered a “men's disease,” incidence in the United States from 1975 to 2012 increased among females from 25 to 48 per 100k and decreased among males from 102 (in 1984) to 63, so that the difference in incidence reduced significantly from approximately x4 in males to x1.2 [3,4].

While part of the increased incidence of lung cancer in females may be attributed to higher smoking rates [5], it has also been

Micro Abstract: Gender-based differences in incidence and diagnosis are likely to exist with respect to lung cancer. Based on 458,132 cases of lung cancer from the years 2004–2012, this study aims to characterize the effects of gender on lung cancer diagnosis. Our study showed that there is no belated diagnosis of lung cancer in females and that smoking females are more likely to be diagnosed at later stages.

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shown that there is a higher percentage of nonsmokers among female patients [6], compared with their male counterparts [7,8].

While the total lung cancer incidence is similar between males and females, there are differences in the incidence of specific types of lung cancer between the genders, with males having a higher incidence of small cell and squamous cell carcinoma, and females have higher rates of adenocarcinoma [6]. Adenocarcinoma commonly occurs in the outer areas of the lung, which makes it harder to diagnose in its early stages [9]. Despite these gender-based differences, in the recent decades, all forms of lung cancer have been rising among females. While the majority may be attributable to the rise of cigarette smoking among females, the higher rate of lung cancer incidence among females exceeds that expected from the rise of smoking prevalence alone [10,11].

Efforts to investigate gender-based differences relating to lung cancer have focused on hormonal differences and genetic variances [12], which can contribute to differences in susceptibility to, and progression of, various lung cancer types. Another area that has been studied is the gender-related difference in the response to treatment, which appears to be more favorable in females [13].

In this study, we aim to characterize the effects of gender on lung cancer diagnosis and whether such effects have changed over time. We presume that if a higher percentage of female patients are diagnosed in later stages as a result of bias relating to societal norms regarding the prevalence of lung cancer, than the difference between the percentage of men and women diagnosed in later stages should be influenced by factors which would contribute to said biases, such as smoking rates, lung cancer incidence, and socioeconomic status. Additionally, we would expect the difference between the percentages of men and women diagnosed in later stages to be greater in histologic subtypes more commonly associated with smoking.

The question being addressed is whether there is a difference between the percentage of males and females diagnosed with early-stage (stage 1–2) versus Late-stage (stage 3–4) lung cancer, and whether such differences are affected by cancer rates in men and in women. Additionally, we investigate whether such differences vary by histologic cancer type and the age of patient at diagnosis and whether they have changed over time.

Methods

The SEER database

The Surveillance, Epidemiology, and End Results Program 18 (SEER18) database consists of 18 cancer registries, of which 9 existed since 1973 [14]. The SEER database currently includes over 6 million cases, approximately 28% of all US cancer cases [15], from geographically and socioeconomically diverse backgrounds. The population covered by SEER is comparable with the general US population with regard to measures of poverty and education. The SEER population tends to have a higher proportion of foreign-born persons than the general US population [16].

The SEER database contains per case information, such as site, staging, histology, age at diagnosis, gender, race, type of therapy offered, and mortality information. Moreover, it offers regional (county) level data pertaining to socioeconomic factors, such as smoking, education, poverty, and unemployment.

*The SEER*Stat program*

The SEER*Stat program is a software program that allows the user to access the SEER database and perform analyses. The user may analyze the data using the variables provided or create user-defined variables within the data provided or with variables and parameters exported from other databases. The SEER*Stat allows calculation of age-adjusted incidence and mortality rates. When calculating an age-adjusted rate, the user may define the *P*-value for statistical significance and calculation of confidence intervals (CIs). The SEER*Stat output for a rate session contains the number of cases, the age-adjusted rate per 100k, and the referent population, as well as the standard error and confidence levels.

County data in the SEER database

Smoking data and socioeconomic information, such as poverty levels, education, immigration, and median income are present in the SEER database as county attributes, meaning that this information is not available on a per-patient basis, but rather on the county level only. County data are updated periodically, but not on an annual basis. Socioeconomic data in this study use the 2000's county data, the county attribute variables for 2000 are calculated using the Census 2000 SF files [17]. The Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS) were used to develop estimates for current smoking prevalence and ever-smoking prevalence. The data were combined based on the approach of Raghunathan et al. [18] The most recent smoking data available are from the years 2000–2003, and these were used for the entire study period. Per-patient smoking data are not available in the SEER database [19,20].

Table 1
Baseline characteristics of age and diagnosis

Patient characteristics			
Sex	Total	Male	Female
	458,132	243,021	215,111
Age			
>50	21,043	10,232	10,811
50–59	66,822	36,698	30,124
60–69	128,297	70,508	57,789
70–79	146,444	78,041	68,403
80+	95,526	47,542	47,984
Histology			
Squamous cell	88,196	55,710	32,486
Adenocarcinoma	163,750	79,391	84,359
Small cell	62,020	31,085	30,935
Large cell	36,769	19,889	16,880
Other	107,397	56,946	50,451

Table 2
Percentage of male and female lung cancer patients diagnosed in stage 3–4, by SEER registry

SEER registry			
Registry	Percentage diagnosed in stage 3–4		
	Male (CI)	Female (CI)	Significance
San Francisco	70.2% (69.3%–71.1%)	66.0% (65.1%–67.0%)	$P < .0001$
Connecticut	64.2% (63.3%–65.1%)	60.6% (59.7%–61.5%)	$P < .0001$
Detroit	68.6% (67.8%–69.3%)	65.5% (64.7%–66.3%)	$P < .0001$
Hawaii	67.6% (66.2%–69.1%)	63.6% (61.9%–65.4%)	$P < .001$
Iowa	67.4% (66.6%–68.3%)	63.1% (62.1%–64.1%)	$P < .0001$
New Mexico	59.7% (58.3%–61.1%)	55.7% (54.2%–57.3%)	$P < .001$
Seattle	66.7% (65.9%–67.5%)	62.5% (61.6%–63.3%)	$P < .0001$
Utah	68.1% (66.4%–69.9%)	62.0% (60.0%–64.0%)	$P < .0001$
Atlanta	69.9% (68.8%–71.1%)	63.7% (62.5%–65.0%)	$P < .0001$
San Jose–Monterey	70.2% (68.8%–71.5%)	65.9% (64.5%–67.3%)	$P < .0001$
Los Angeles	67.0% (66.3%–67.7%)	61.2% (60.5%–62.0%)	$P < .0001$
Alaska Natives	74.2% (69.3%–79.1%)	65.2% (59.4%–71.0%)	$P < .01$
Rural Georgia	68.3% (64.6%–71.9%)	62.1% (57.1%–67.2%)	$P < .05$
California (excl. SF/SJ/LA)	53.4% (53.0%–53.9%)	61.8% (61.3%–62.2%)	$P < .0001$
Kentucky	66.7% (66.1%–67.3%)	63.3% (62.6%–64.0%)	$P < .0001$
Louisiana	68.9% (68.2%–69.6%)	65.4% (64.5%–66.2%)	$P < .0001$
New Jersey	64.0% (63.4%–64.6%)	59.3% (58.7%–59.9%)	$P < .0001$
Greater Georgia	67.3% (66.7%–67.9%)	63.5% (62.8%–64.3%)	$P < .0001$

Study population

The population used in this study is the complete population of lung and bronchus cancer patients as per the International Classification of Diseases for Oncology of the World Health Organization (ICD-O-3/WHO) 2008 Criteria, contained within the SEER 18 database in the years 2004–2012. The total population consists of approximately 540,000 cases from 18 registries (Table 1 and Table 2).

Research methods

Age-adjusted rates and number of cases by stage were calculated for males and females. The percentage of cases of males versus females diagnosed in stage 3 and 4 were calculated, and statistical significance was determined.

Patients included in this study were stratified by sex, age (SEER*Stat 5-year age groups were combined into 10-year age groups), SEER registry, and county level data regarding smoking prevalence and socioeconomic status.

Stratification by histologic type

The AJCC (American Joint Committee on Cancer) sixth edition was used for defining disease stage.

Patients were stratified by histology according to ICD-O-3 codes, based on the histologic grouping of the International Agency for Research on Cancer (IARC) into adenocarcinoma (codes 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576), squamous cell carcinoma (8050–8078, 8083–8084), large cell carcinoma (8010–8012, 8014–8031, 8035, 8310), and small cell carcinoma (8041–8045, 8246). All other malignancies have been grouped as "Other." The percentage difference between male and female patients diagnosed in stages 3–4 was calculated, and the statistical significance was determined.

Stratification by smoking prevalence

Patients were grouped by county percentage of female ever-smokers divided into seven groups: <30%, 30–35%, 35–40%, 40–45%, 45–50%, 50–55%, and >55% smokers. The percentage difference between male and female patients diagnosed in stages

Table 3
Lung cancer rates and percentage diagnosed in stage 3–4 stratified by county percent in poverty, by histologic type and by age at diagnosis

Factor	Male		Female		Male–female percentage of stage 3–4 diagnosis	
	Rate mean (CI)	Pct. stage 3–4	Rate mean (CI)	Pct. stage 3–4	% (CI)	*P*-value
County percent in poverty						
<10%	70.9 (70.5–71.3)	66.6%	52.3 (52–52.6)	62.1%	4.5% (4.1%–4.8%)	<.0001
10%–15%	72.8 (72.3–73.4)	66.6%	49.1 (48.7–49.5)	62.5%	4.0% (3.6%–4.6%)	<.0001
15%–20%	87.6 (86.3–88.3)	67.8%	52 (51.2–52.9)	62.9%	5.0% (3.9%–5.9%)	<.0001
>20%	111.2 (109–113.4)	67.6%	63.6 (62.1–65.1)	64.5%	3.1% (1.7%–4.5%)	<.0001
Cancer histologic type						
Squamous cell	16.9 (16.8–17.1)	60.7%	7.9 (7.8–8)	56.1%	4.7% (3.9%–5.3%)	<.0001
Adenocarcinoma	23.8 (23.6–24)	66.7%	20.3 (20.1–20.4)	60.6%	6.1% (5.6%–6.6%)	<.0001
Small cell	9.1 (9–9.2)	86.4%	7.4 (7.4–7.5)	84.7%	1.7% (1.1%–2.3%)	<.0001
Large cell	6.3 (6.2–6.3)	67.8%	4 (3.9–4)	64.6%	3.2% (2.2%–4.2%)	<.0001
Patients by age (y)						
<50	3.8 (3.8–3.9)	75.4%	4 (3.9–4.1)	69.9%	5.5% (4.3%–6.7%)	<.0001
50–60	75.2 (74.4–76)	74.8%	58.8 (58.2–59.5)	69.9%	4.9% (4.2%–5.6%)	<.0001
60–70	240.5 (238.7–242.3)	68.9%	176.9 (175.4–178.3)	64.4%	4.5% (4.0%–5.0%)	<.0001
70–80	473.1 (469.8–476.4)	64.0%	325.9 (323.5–328.4)	60.4%	3.5% (3.1%–4.0%)	<.0001
>80	516.8 (512.2–521.5)	60.1%	301.3 (306.5–313.7)	56.3%	3.8% (3.2%–4.4%)	<.0001

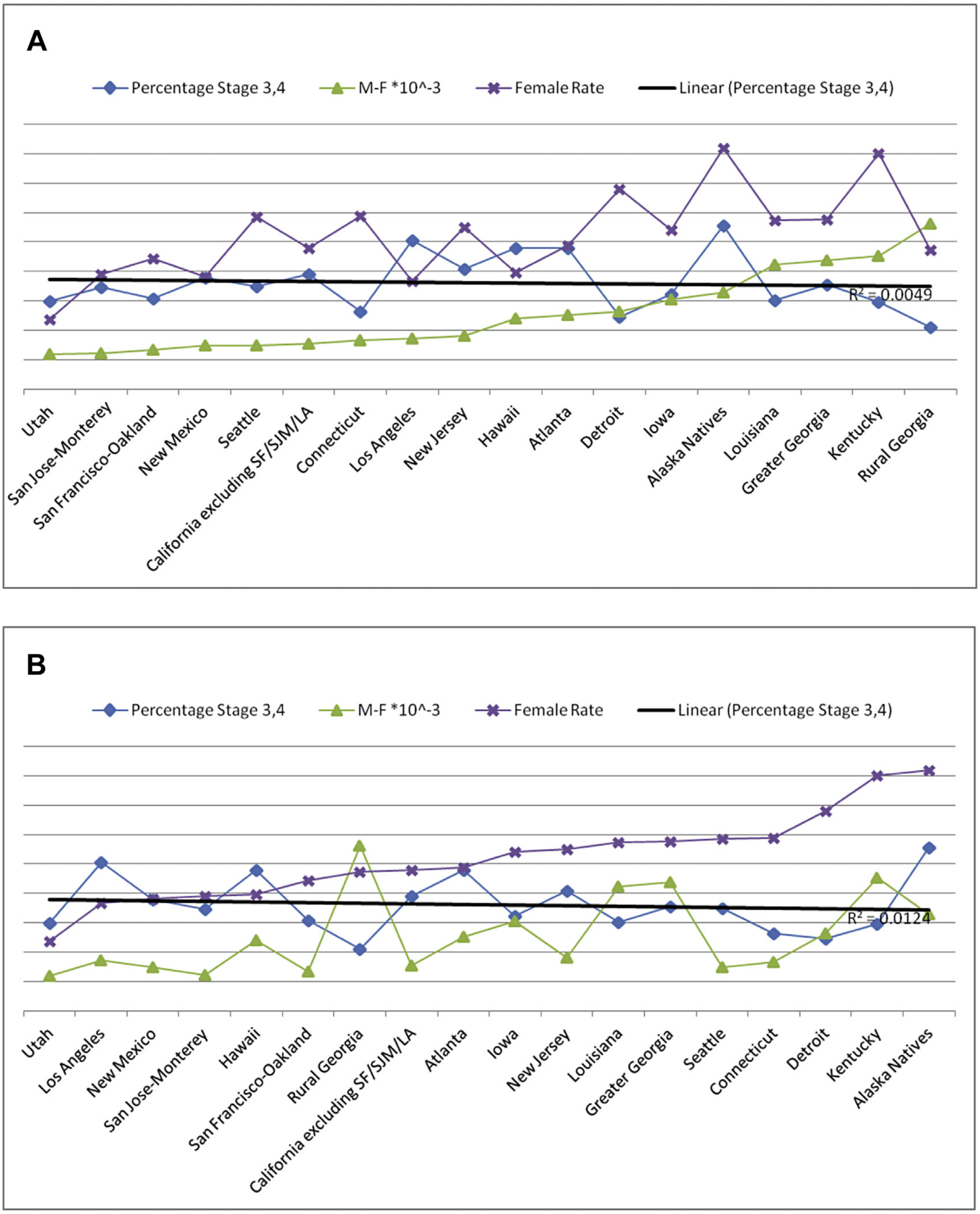

Fig. 1. The correlation between the percentage of females diagnosed with stage 3–4 lung cancer, and (A) greater differences between lung cancer rates in men and women, and (B) higher lung cancer rates in women correlate to a higher percentage of female patients being diagnosed later (stage 3–4). (M-F*10ˆ3—the difference between lung cancer rated in men and women).

3–4 was calculated and examined for correlation with the percentage of female smokers.

Stratification by socioeconomic status

The effect of socioeconomic status on belated diagnosis was calculated by stratifying the SEER data based on county level data of the percentage of county individuals below the poverty line. County data were divided into four groups: 0–15%, 15.01–30%, 30.01–45%, and >45.01%; and the percentage difference between male and female patients diagnosed in stages 3–4 was calculated and examined for correlation with the county poverty level (Table 3).

Stratification by age

Existing age groups in the SEER database were combined into 10-year brackets, with the lowest bracket containing patients age <50, owing to the low incidence of lung cancer in younger patients. Age-adjusted cancer rates in the SEER database were calculated based on US 2000 census data.

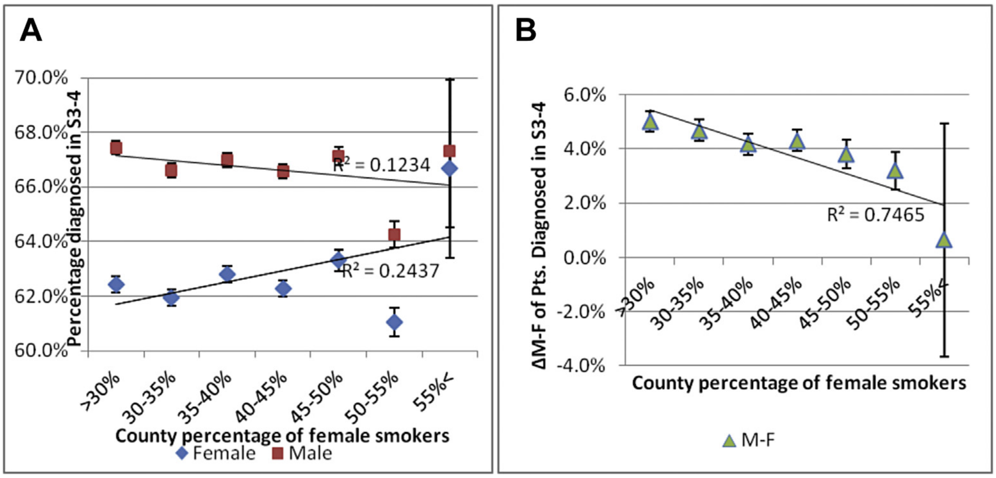

Fig. 2. (A) The percentage of male and female lung cancer patients diagnosed at stages 3–4, stratified by percentage of female smokers. (B) The difference between percentages of male and female lung cancer patients diagnosed at stages 3–4 by stratified by the percentage of female smokers.

Statistical analysis

Statistical significance was defined in the SEER*Stat analysis results as *P* value < 0.05. CIs for database rates given based on Tiwari et al. [21] Proportional results were compared statistically using the χ^2 test, with CIs calculated according to the methods of Altman et al. [22] Some statistical calculations performed using the MEDCALC statistical calculator (MedCalc for Windows, version 17.2. MedCalc Software, Ostend, Belgium). Correlation was determined using linear regression (r^2).

Results

In this study, 458,132 cases of lung cancer were examined, 243,021 (53%) in males and 215,111 (47%) in females. Lung cancer mean rates were 73.8 (CI 73.5–74.1) per 100k in males, and 51.6 (51.4–51.8) per 100k in females. Of these, 400,800 had the stage listed, 214,479 (54%) in males, and 186,321 (46%) in females. Total lung cancer rates were higher in males than females at all disease stages. Of all lung cancers in males, 75.6% were diagnosed in stages 3 and 4, versus 72% of lung cancers in females ($p < 0.001$).

When results were examined by SEER registry, lung cancer rates were higher in males than females in all 18 SEER registries. The percentage of patients diagnosed in later stages was higher in males than females in all SEER registries (Table 2), with the exception of California (excluding Los Angeles, San Francisco), where 62% of cancers in females and 53% in males were diagnosed at stages 3 or 4.

Age-adjusted lung cancer rates in females were between 23.8 (22.8–24.8, Utah) and 82 (72.2–92.7, Alaska natives) per 100k. The difference in lung cancer rates between males and females was between 11.9 (Utah) and 56.1 (Rural Georgia) per 100k. No correlation was found in the rate difference between males and females or between the age-adjusted rate in females and the percentage of females diagnosed at stages 3–4 (Fig. 1).

When patients were stratified by county female ever-smoker incidence, lung cancer rates rose from 25.2 (24.9–25.5) per 100k in counties with <30% female ever smokers to 49.1 (42.6–56.4) in counties with over 55% female ever smokers. Increased percentage of female ever smokers was not strongly correlated with a decrease in the percentage diagnosed in stages 3–4 ($r^2 = 0.25$). There was, however, a stronger correlation with a decrease in the difference between the percentage of male and female patients diagnosed in stages 3–4 ($r^2 = 0.75$) (Fig. 2).

When patients were stratified by county percentage in poverty, increased poverty levels correlated with an increased rate of lung cancer in men ($r^2 = 0.88$) and women ($r^2 = 0.55$). The percentage diagnosed in stage 3–4 was higher in males than females across poverty levels (Table 3). The difference in percent diagnosed in

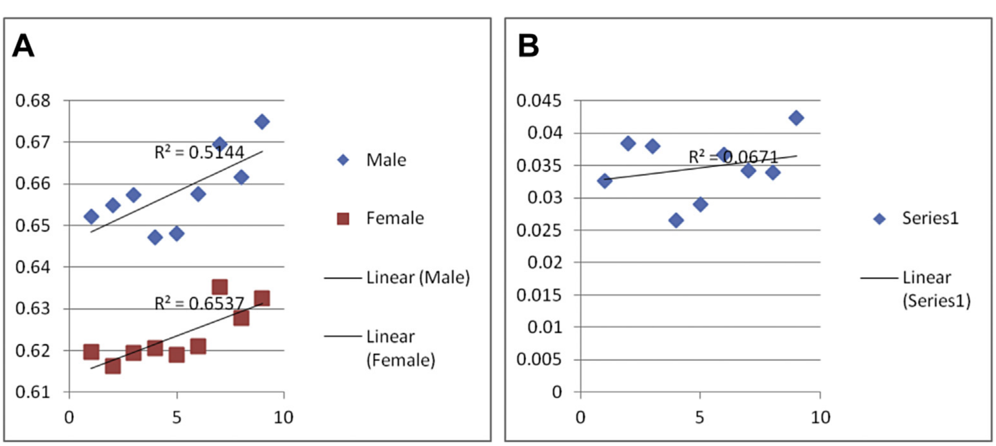

Fig. 3. Correlation between patient age at diagnosis: (A) The percentage of male and female lung cancer patients diagnosed at stages 3–4. (B) The difference between the percentages of male and female lung cancer patients diagnosed at stages 3–4.

stage 3–4 showed a low negative correlation to increased poverty levels ($r^2 = 0.26$).

When stratified by lung cancer histology, cancer rates and the percentage of patients diagnosed in stage 3–4, rates were higher in males than in females for all cancer types (Table 3).

Analysis of the yearly trend showed that while lung cancer rates have decreased since 2004, the percentage of patients diagnosed in stages 3–4 has increased in the years studied. However, the percentage difference between males and females diagnosed at stages 3–4 was not correlated with this increase ($r^2 = 0.07$) and has remained unchanged (Fig. 3).

When patients were analyzed by age, the percentage of patients diagnosed in stages 3–4 was significantly greater in males in all age groups (Table 3). The difference between males and females in percent diagnosed in stage 3–4 showed a strong negative correlation to increased age ($r^2 = 0.89$).

Discussion

This study shows that there is no belated diagnosis of lung cancer in females. On the contrary, the results have consistently shown that a higher percentage of lung cancers in males are diagnosed in later stages than in females. These results were consistent among all 18 SEER registries. A greater difference in lung cancer rates between males and females does not appear to have any effect on the diagnosis of cancer in females.

A higher percentage of county female smokers was correlated with a higher percentage of patients being diagnosed in later stages. Additionally, a high percentage of female smokers correlated with a lower difference between males and females, with regard to the proportion of patients being diagnosed in later stages. This may reflect the fact that smokers are less likely to seek medical care than nonsmokers for lung cancer–related symptoms [11,23]. Moreover, it would explain the higher percentage of male patients diagnosed in later stages.

While there was an increased incidence of lung cancer in counties with a higher percentage of households in poverty, there was shown to be only a modest increase in the percentage of patients diagnosed in later stages both among males and females, as well as a modest decrease in the difference between males and females diagnosed in later stages, with a low degree of correlation with the increase in poverty levels.

While cancer rates and percentage of patients diagnosed in stage 3–4 varied greatly by cancer histologic types, the percentage of patients diagnosed in stages 3–4 was higher among males than females in all lung cancer types. However, the difference between the percentage of male and female patients diagnosed in stages 3–4 was lower in squamous cell carcinoma and small cell carcinoma, which are more strongly associated with smoking (Table 3). This result is consistent with the higher percentage of females diagnosed in later stages in counties with a higher proportion of female smokers, as discussed previously.

Yearly trends showed no evidence that the percentage difference between males and females diagnosed in stages 3–4 has changed during the study period, despite changes in both the overall cancer rate and the percentage diagnosed at stages 3–4. The reasons for this are unclear and bear further investigation.

The percentage of patients diagnosed in stages 3–4 increased with the patients age, and the percentage difference between males and females diagnosed in stages 3–4 decreased significantly with age. The reason for this is unclear and bears further investigation.

The primary limitation of this study is that the SEER database does not contain per-patient information regarding smoking and socioeconomic factors, making it difficult to differentiate between gender and smoking or socioeconomic effects. Despite this limitation, the fact that the percentage of patients diagnosed in later stages was higher among males in the lung cancer subtypes linked most strongly to tobacco smoking appears to show that the lack of per patient smoking data does not significantly confound these results.

In conclusion, aside from differences related to smoking habits, there does not appear to be a delay in the diagnosis of lung cancer among females compared with males.

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