Influence of Type of Cigarette on Peripheral versus Central Lung Cancer

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Abstract

Objectives: **Adenocarcinoma has replaced squamous cell carcinoma as the most common cell type of lung cancer in the United States. It has been proposed that this shift is due to the increased use of filter and lower-tar cigarettes, resulting in increased delivery of smoke to peripheral regions of the lungs, where adenocarcinoma usually occurs. We reviewed radiologic data to evaluate the hypothesis that tumors in smokers of cigarettes with lower-tar yield are more likely to occur peripherally than tumors in smokers of higher-yield cigarettes.**

Methods: **At two urban academic medical centers, we reviewed computed tomographic scans, chest radiographs, and medical records to assign tumor location (peripheral or central) for 330 smokers diagnosed with carcinoma of the lung between 1993 and 1999. We compared the proportion of tumors in a peripheral versus central location by lifetime filter use and average lifetime tar rating (<21 and ≥21 mg).**

Results: **Tumor location (69% peripheral and 31% central) was unrelated to cigarette filter use. Smokers of cigarettes with lower-tar ratings were more likely than those with higher ratings to have peripheral rather than central tumors (odds ratio, 1.76; 95% confidence interval, 0.89-3.47). When restricted to subjects with adenocarcinoma or squamous cell carcinoma, the odds ratio (95% confidence interval) was 2.31 (1.05-5.08).**

Conclusions: **Among cigarette smokers with lung cancer, use of cigarettes with lower-tar yield was associated with preferential occurrence of tumors in peripheral sites. Our findings support the hypothesis that changes in smoking associated with lower-tar cigarettes have led to a shift in the location of smoking-related lung cancer.** (Cancer Epidemiol Biomarkers Prev 2005;14(3):576–81)

Introduction

In the mid-twentieth century, carcinoma of the lung (''bronchogenic carcinoma'') occurred primarily in the bronchial tree (1-5), and squamous cell carcinoma (SCC) was the predominant cell type (6, 7). Over the past several decades, the incidence of adenocarcinoma increased to the extent that it has now replaced SCC as the most common cell type in the United States and throughout much of the world (8-11). During this period, the types of cigarettes used by smokers have also changed. Fifty years ago, virtually all cigarettes were unfiltered and high in tar. Tar and nicotine ratings of cigarettes, as measured by the Federal Trade Commission (FTC) machine testing procedure, have decreased substantially since that time (12). Today, virtually all smokers in the United States use filter cigarettes, and almost 90% use cigarettes rated as low in tar (≤15 mg/cigarette) and nicotine (≤ 0.8 mg/cigarette; ref. 13).

Investigators have proposed several mechanisms that causally link these two historical trends (14-18). The one most frequently proposed is based on the observation that many smokers compensate for the lower yield of nicotine, the main psychoactive agent in cigarette smoke, by increasing puff frequency, volume, or duration (19-23). This behavior presumably results in deeper inhalation and thereby enhances delivery of carcinogenic compounds to peripheral regions of the lungs, where adenocarcinoma commonly occurs (24).

A second hypothesis suggests that filters reduce the average size of smoke particulates, favoring their deposition in the periphery of the lungs (14, 18). According to either hypothesis, the historical increase in the occurrence of adenocarcinoma is a consequence of the increased delivery of smoke constituents to more distal regions of the lungs. A third proposed mechanism focuses not on the area of the lung to which the smoke is preferentially delivered but rather on changes in the type of tobacco in cigarettes that have resulted in increased nitrosamine content (12). In animal studies, adenocarcinoma is the predominant cell type of lung cancer caused by nitrosamines found in tobacco (25).

Several studies have found that long-term smokers of filter cigarettes are more likely than smokers of nonfilter cigarettes to develop adenocarcinoma compared with SCC (18, 26-30), while, to our knowledge, none have assessed the effect of FTC tar rating on histologic-specific risk. The hypothesized association between type of cigarette and tumor location can be inferred only indirectly from these studies, with cell type acting as a proxy for location. To evaluate directly the hypothesis that carcinoma of the lung is more likely to occur in a peripheral than in a central location among smokers of cigarettes with lower FTC tar ratings compared with smokers of higher-yield cigarettes, we reviewed findings from computed tomographic (CT) scans and chest radiographs of patients with lung cancer who had participated in a study of tobacco-related disease.

Methods

The study population was drawn from subjects who had been diagnosed with lung cancer at the Memorial Sloan-Kettering Cancer Center (MSKCC) or Columbia Presbyterian Medical Center (CPMC) in New York City and had participated in the

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American Health Foundation (AHF) case-control study of tobacco-related diseases, which was conducted between 1969 and 1999 at hospitals in several cities throughout the United States. All patients provided written informed consent on forms that were approved by the institutional review boards of the AHF and the two hospitals. The AHF study has been described in detail elsewhere (31, 32).

The current study was restricted to participants between ages 30 and 80 years who had histologically confirmed carcinoma of the lung, had smoked for at least 15 years, and reported no tobacco use other than cigarettes. We included MSKCC patients beginning in 1993 and CPMC patients beginning in 1996 based on the earliest years radiologic studies were available for retrospective review. A total of 490 subjects (372 at MSKCC and 118 at CPMC) met the eligibility criteria, of whom 412 (305 at MSKCC and 107 at CPMC) had sufficient information to characterize use of filter cigarettes or average tar rating as described in the next section.

We attempted to obtain information on tumor location for the 412 subjects with sufficient exposure information. Because of differences in institutional computer systems, we took slightly different approaches at the two hospitals. At MSKCC, we reviewed CT scans for the period within 6 months of diagnosis and before the earliest reported date of surgical therapy. If no CT scan was available, we attempted to locate posteroanterior and lateral chest radiographs (CXR) from the same time period. At CPMC, we first searched the computerized medical record for reports of radiologic, surgical, or pathologic data that might provide information about tumor location. If there was no report or the report contained insufficient information, we obtained the CT scan or CXR for direct review. We located a total of 363 cases: CT scans (n = 211) or CXR (n = 54) for 265 of the 305 (87%) potential subjects at MSKCC and unequivocal medical record reports (41 CT scan, 25 pathology, and 6 additional sources), CT scans (n = 20), or CXR (n = 6) for 98 of the 107 (92%) potential subjects at CPMC.

No standard definition of central and peripheral locations of lung tumors has been employed across different studies. We defined central tumors as those where the center of mass was within the hilar structures and peripheral tumors as those where the center of mass was within the parenchyma and with no or minimal contact with hilar structures. Because we were concerned with etiology rather than treatment outcome, we used the center of geometric mass as a marker for the presumed initial starting point of the tumor. If there were tumors in both central and peripheral locations, we only included cases in which one was clearly larger. We recorded the lobe, location, and size (based on the longest diameter at presentation) of the tumor for each case. Each report or imaging study was reviewed by one of three radiologists, each a subspecialist in thoracic imaging (J.H.M.A., R.T.H., and M.S.G.), who assigned each case to a category of central, peripheral, or ambiguous location. All chest imaging studies of those cases originally judged to be ambiguous (n = 53, 15%) were then reviewed by the three radiologists as a group and resolved by consensus. Radiologists were blinded to subjects' smoking histories throughout the assignment process.

We were able to assign central or peripheral location to the tumors of 330 of the 363 (91%) cases with available clinical data. We were unable to assign 33 cases because (*a*) the location remained ambiguous after review, (*b*) there were multiple lesions with relatively equal components in central and peripheral locations, (*c*) no CT scan was available and the CXR was insufficient, or (*d*) no primary tumor was apparent. We were unable to determine the size of 14 of the 330 tumors with assigned location, because their margins were obscured either by postobstructive atelectasis or by compression atelectasis caused by pleural effusion.

Exposure Assignment. Information for classifying subjects according to filter cigarette use and FTC tar rating was derived from a detailed lifetime smoking history elicited during the original AHF study. Basic smoking information included age at initiation, total duration, current smoking status, number of years temporarily stopped smoking, and number of years since quitting. In addition, participants provided a lifetime cigarette brand history, including name and characteristics (filter/nonfilter, menthol/nonmenthol, regular/light/ultralight, and length), number of years smoked, and average number of cigarettes per day for up to seven brands.

To calculate the average FTC rating of tar level for each subject, we first identified which calendar years subjects reported particular brands, working backward from the most recent brand reported and taking into consideration years in which no smoking occurred due to total or temporary cessation. We then assigned a tar value for each year. Tar ratings were taken from FTC reports, which were generally issued annually beginning in 1967 (33). Before that time, *Reader's Digest* issued an occasional series of reports using a similar methodology between 1957 and 1966 (34-39). Tar ratings for intervening years not covered by FTC or *Reader's Digest* reports were assigned by linear interpolation. Values for years before 1957 were extended back to the release date of each brand based on the assessment that tar levels did not change appreciably before 1957 (40).

We were unable to assign tar values for all years for some subjects, because they reported either insufficient detail, brands for which no tar information was available, or using particular brands before they were actually on the market. We calculated the mean FTC tar rating for each subject by averaging the assigned tar ratings across all years with an assigned value. We did not include the 3 years before diagnosis in calculation of tar means, because exposure within this timeframe was unlikely to have had an impact on the occurrence of lung cancer (31). We excluded all subjects for whom tar ratings were available for <60% of their smoking history. In preliminary analyses, we found that estimates based on ≥60% information were very similar to those with ≥80% information; thus, we chose the 60% cutoff point to increase the number of subjects available for analysis. All 330 subjects with assigned tumor location could be classified according to extent of filter cigarette use (nonfilter only, filter only, or mixed); 272 (82%) had sufficient information to calculate average FTC tar rating.

Statistical Analysis. We dichotomized average FTC tar ratings at <21.0 and ≥21.0 mg to provide approximately equal numbers of subjects in each category. We used unconditional logistic regression to estimate the likelihood of having a tumor in a peripheral location for lower-tar compared with higher-tar smokers as well as for lifetime filter and mixed filter/nonfilter compared with lifetime nonfilter smokers. Because this study is restricted to subjects with lung cancer, the odds ratio (OR) does not represent an estimate of the effect of tar level on the occurrence of disease but can appropriately be interpreted as the effect of FTC tar rating on the distribution of tumor location (41, 42).

Estimates were adjusted for sex, age (<55, 55-59, 60-64, 65-69, or ≥70 years), and cell type (adenocarcinoma, SCC, small cell carcinoma, large cell carcinoma, or other/unknown). Cell type was determined at the time of the original AHF study from surgical pathology reports or cytologic findings. We also conducted analyses restricted to adenocarcinoma and SCC, because the primary hypotheses regarding tumor location have focused specifically on historical changes in the distribution of these two cell types (16-19). Finally, because prior studies have assessed the association between type of cigarette and cell type instead of location, we evaluated whether smokers with lower FTC tar ratings were more likely than those with higher ratings to develop adenocarcinoma than SCC.

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Results

Tumors were in the periphery of the lung in 69% of subjects and in the hilar region in 31%. Adenocarcinoma was the most common cell type (50% of all tumors), whereas SCC accounted for 28%; 132 of the 166 (80%) adenocarcinomas and 51 of the 93 (55%) SCCs were peripheral (χ^2 = 17.51; P = 0.00003). The mean size of the 228 peripheral tumors was 4.4 cm (SD = 2.5; range, 0.8-17.0) and the mean size of the 102 central tumors was 5.4 cm (SD = 2.3; range, 1.0-12.7; t = 3.33; P = 0.001). Subjects who were ages <55 years (n = 65) were less likely than those age ≥55 years (n = 265) to have peripheral tumors; otherwise, there were only minor differences in tumor location by demographic or smoking-related characteristics (Table 1).

Differences in type of cigarette use were extensive but consistent with the introduction of filter and lower-tar cigarettes during the 1950s to 1970s: smokers with lower average FTC tar ratings were much more likely to be female, to be younger, to have smoked for fewer years, and to smoke currently or to have recently quit. The demographic characteristics of those who exclusively smoked filter cigarettes were similar to those of lower-tar smokers.

There was no association between tumor location and either extent of filter use or average tar rating as measured by the crude OR (Table 2). Use of filter cigarettes remained unassociated with tumor location after adjustment. However, after adjusting for sex, age, and cell type, smokers of lower-tar brands were more likely to have tumors in a peripheral than a central location [OR, 1.76; 95% confidence interval (95% CI), 0.89-3.47]. There was little evidence of any difference between men and women in the relationship between FTC tar rating and tumor location (P for interaction = 0.54). The association between lower-tar ratings and peripheral tumors was similar among current (OR, 1.81; 95% CI, 0.66-4.98) and former (OR, 2.09; 95% CI, 0.72-6.08) smokers.

When the analysis was restricted to subjects with adenocarcinoma and SCC only, the adjusted association between lower-tar rating and peripheral location was even stronger (OR, 2.31; 95% CI, 1.05-5.08; Table 2). Lower-tar smokers were also more likely to have a tumor in a peripheral location whether the cell type was adenocarcinoma (OR, 2.85; 95% CI, 0.82-9.95) or SCC (OR, 2.29; 95% CI, 0.77-6.87).

We evaluated the reasons for the substantial difference between the crude (0.96) and adjusted (1.76) OR estimates for the effect of tar level on tumor location. Age had the strongest effect on the estimate; adjusting for age alone raised the OR to 1.43, which accounted for two thirds of the difference between crude and fully adjusted estimates. Adjusting for cell type, in addition to age, further increased the OR to 1.71. Age was not simply a proxy for smoking duration; adjusting for duration alone only increased the OR to 1.14, and substituting duration for age in the full model produced an estimate of 1.34.

Because almost all (97%) subjects ages <55 years (n = 58) were in the lower-tar category, we repeated analyses limited to subjects who were ages ≥55 years (n = 272). For this subgroup, the crude OR for the likelihood of peripheral tumors among smokers of lower-tar cigarettes was 1.35, which was

Table 1. Smoking history by type of cigarette and location of lung tumors by subject characteristics

	Smoking history*				Tumor location†	
	Lifetime filter use		Average FTC tar rating (mg)		Peripheral, n (%)	Central, n (%)
	Filter only, n (%)	Mixed and nonfilter, n (%)	<21, n (%)	≥21, n (%)		
Overall	138 (42)	192 (58)	139 (51)	133 (49)	228 (69)	102 (31)
Cell type						
Adenocarcinoma	73 (44)	93 (56)	69 (53)	63 (47)	132 (80)	34 (20)
SCC	32 (34)	61 (66)	35 (45)	42 (55)	51 (55)	42 (45)
Small cell	6 (46)	7 (54)	7 (64)	4 (36)	3 (23)	10 (77)
Large cell	5 (56)	4 (44)	2 (29)	5 (71)	7 (78)	2 (22)
Other‡	22 (45)	27 (55)	26 (58)	19 (42)	35 (71)	14 (29)
Size (cm)§						
≤3	43 (47)	48 (53)	40 (52)	37 (48)	77 (85)	14 (15)
>3-6	60 (38)	99 (62)	66 (52)	62 (48)	102 (64)	57 (36)
>6	28 (42)	38 (58)	28 (50)	28 (50)	40 (61)	26 (39)
Sex						
Male	60 (33)	123 (67)	68 (43)	91 (57)	126 (69)	57 (31)
Female	78 (53)	69 (47)	71 (63)	42 (37)	102 (69)	45 (31)
Age (y)						
<55	49 (75)	16 (25)	56 (97)	2 (3)	38 (58)	27 (42)
55-59	23 (40)	35 (60)	29 (60)	19 (40)	41 (71)	17 (29)
60-64	21 (35)	39 (65)	23 (44)	29 (56)	43 (72)	17 (28)
65-69	23 (31)	51 (69)	16 (28)	42 (72)	54 (73)	20 (27)
≥70	22 (30)	51 (70)	15 (27)	41 (73)	52 (71)	21 (29)
Years smoked						
<40	88 (56)	70 (44)	87 (66)	44 (34)	104 (66)	54 (34)
≥40	50 (29)	122 (71)	52 (37)	89 (63)	124 (72)	48 (28)
Cigarettes/d‖						
<25	67 (46)	80 (54)	52 (46)	61 (54)	100 (68)	47 (32)
≥25	71 (39)	110 (61)	87 (55)	72 (45)	126 (70)	55 (30)
Years quit smoking						
0 (current)	81 (59)	94 (41)	88 (60)	58 (40)	118 (67)	57 (33)
1-5	18 (36)	32 (64)	24 (56)	19 (44)	36 (72)	14 (28)
6-15	26 (43)	34 (57)	24 (46)	28 (54)	42 (70)	18 (30)
>15	13 (29)	32 (71)	3 (10)	28 (90)	32 (71)	13 (29)

*Information was sufficient to determine extent of filter cigarette use for 330 subjects and average tar rating for 272 subjects.
†As determined by review of imaging studies or other information in the medical record.
‡Includes other miscellaneous types and nonclassified.
§Size was not determined for 14 subjects. See text for details.
‖Information was insufficient to determine the number of cigarettes per day for two subjects.

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Table 2. Association among filter cigarette use, average FTC tar rating, and tumor location

	All cell types				SCC and adenocarcinoma only			
	No. peripheral	No. central	Crude OR	Adjusted OR* (95% CI)	No. peripheral	No. central	Crude OR	Adjusted OR* (95% CI)
Filter usage								
Only nonfilter†	32	14	1	1	27	11	1	1
Mixed	103	43	1.05	1.19 (0.55-2.58)	79	34	0.95	0.91 (0.39-2.15)
Only filter	93	45	0.90	1.16 (0.52-2.63)	73	30	0.99	1.12 (0.44-2.83)
Mean tar level (mg)								
≥21†	91	42	1	1	67	35	1	1
<21	94	45	0.96	1.76 (0.89-3.47)	72	30	1.25	2.31 (1.05-5.08)

*Adjusted for sex, age, and cell type.
†Reference group.

substantially higher than the crude OR for all ages (OR, 0.96). The adjusted OR (95% CI) among subjects ages ≥55 years was 1.75 (0.87-3.53), virtually identical to the estimate based on subjects of all ages. When restricted to subjects with adenocarcinoma or SCC, the adjusted OR (95% CI) was 2.53 (1.12-5.73).

We did not find a greater occurrence of adenocarcinoma than SCC for lower-tar compared with higher-tar smokers (OR, 0.66; 95% CI, 0.33-1.35) nor for lifetime filter compared with lifetime nonfilter smokers (OR, 1.26; 95% CI, 0.55-2.91).

Discussion

The main result of the present study is that smokers of cigarettes with lower average FTC tar ratings who developed carcinoma of the lung were more likely to develop tumors in a peripheral rather than in a central location compared with smokers of cigarettes with higher average tar ratings. This result is consistent with the theory that the altered inhalation pattern observed in smokers of cigarettes that are lower in tar and nicotine as measured by machine smoking results in increased delivery of carcinogens to the periphery of the lungs and thereby in an associated shift in the distribution of location of origin of smoking-related lung cancers (11, 17-19).

Prior evidence for this theory has relied primarily on the general relationship between tumor histology and location. First, there has been a shift in the predominant cell type of lung cancer from SCC (which tends to occur centrally) to adenocarcinoma (which commonly occurs peripherally) during the same time period that filter use has been increasing and average FTC tar ratings have been falling (8-11). Second, some studies have found that long-term filter smokers were more likely to develop adenocarcinoma than SCC compared with smokers of nonfilter cigarettes (18, 26-30). In the present study, we were able to show a direct association between cigarette tar yield and tumor location, which was strongest among patients with adenocarcinoma or SCC.

It is interesting to note that we did not find an association between FTC tar ratings and cell type despite the relationship between tar rating and location. One possible explanation for this apparent paradox is that the correlation between tumor cell type and location may not be as strong as sometimes assumed. In our study, 80% of the adenocarcinomas occurred peripherally, but only 45% of the SCCs occurred in a central location. Although the relationship between tumor histology and location may have been straightforward in the mid-twentieth century (43, 44), more recent studies have described considerable proportions of SCC in a peripheral location (39-59%; refs. 45-47) as well as adenocarcinoma in a central location (41-60%; refs. 48-50). In addition, studies may differ due to different definitions and methodologies for determining central and peripheral locations.

Although the mechanism for the increased occurrence of peripheral lung tumors in smokers of lower-yield cigarettes is presumed to be the enhanced delivery of smoke to peripheral regions of the lung, we are not aware of any studies that directly demonstrate this phenomenon. Numerous experimental and observational studies have shown that smokers of lower-yield cigarettes as measured by machine smoking use a variety of strategies that maximize the inhalation of nicotine and tar from each cigarette, including covering filter ventilation holes with lips or fingers, taking more puffs, and increasing puff size (19-23). Although it perhaps may be inferred that the larger puff volumes observed among smokers of low-yield cigarettes imply deeper inhalation, the dynamics of deposition of cigarette smoke in the lung are complex and do not necessarily follow simple predictive models (51, 52).

Cigarette filters trap larger particles in smoke, thereby reducing the median diameter of the particles inhaled (14, 18), which should favor peripheral particulate deposition among filter compared with nonfilter cigarette smokers (53). Therefore, it is perhaps surprising that we did not find any association between lifetime filter use and tumor location. However, laboratory simulations suggest that the mass of particles in inhaled cigarette smoke behaves as a single, larger entity rather than according to their constituent characteristics (54). Therefore, particle size may be a less important determinant of deposition site than predicted by models that are based on the diameter of individual particles. The design characteristics of lower-yield cigarettes may also offset to some degree the effect of filters in reducing particle size of inhaled smoke. Lower-yield cigarettes partially rely on ventilation holes in the filter, which allow ambient air to dilute the smoke, to reduce their standardized machine ratings (22). Increased ventilation increases the particle size of smoke, which would counteract the effect of the filter in reducing particle size (55).

Because our study was limited to cases only, it would be erroneous to conclude that the results necessarily mean that smokers of cigarettes with lower FTC tar ratings have a higher risk of peripheral lung cancer than do higher-tar smokers. Rather, the results indicate that smokers who do develop lung cancer are more likely to have a peripheral than a central tumor if they smoked cigarettes with lower average tar rating compared with the distribution of location among higher-tar smokers.

We suggest that the clarification of etiologic mechanisms may be a more important result of this study than clinical implications for individual patients. Overall 5-year survival remains very poor for lung cancer, and there is little difference in 5-year survival rates between patients with central and peripheral tumors (56, 57). At the same time, survival is better for early-stage tumors which are ≤3 cm compared with >3 cm in diameter (58), and 35% of peripheral tumors in our study were ≤3 cm compared with 14% of tumors in a central location.

Other cigarette constituents might play an important role in determining tumor location. Although our analyses were based on filter use and FTC tar ratings, the amount of smoke delivered to the peripheral region of the lung may be determined in

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greater measure by nicotine than by tar. However, nicotine and tar ratings are generally highly correlated and have tracked closely over time; therefore, use of either FTC tar or nicotine ratings would likely produce very similar results. The average nicotine/tar ratios within categories of brands rated as high, low, and ultralow in tar in 1984 were 14, 12.6, and 11.4, respectively (12). We also found an extremely high correlation ($r = 0.98$) among a representative group of U.S. brands based on 1996 ratings (59).

Inreased levels of nitrosamines in lower-tar cigarettes might also be at least partly responsible for changes in tumor histology and, indirectly, location (12, 25). Nitrosamine levels in cigarettes are not necessarily correlated with tar or nicotine ratings (12) and therefore might produce different results. However, analysis of nitrosamines has never been required by the FTC, and publicly available data are very sparse, making it impossible to reconstruct brand-specific nitrosamine levels over time.

Some limitations of the present study need to be considered. Information on FTC tar ratings came from self-reported recall of a lifetime history of brand names, associated characteristics, and number of years each brand was smoked. Interviewers at both hospitals were trained and supervised by the same AHF personnel, and similar quality control procedures for data collection and management were in place at both institutions. Nevertheless, we did not specifically measure the reliability of recall of lifetime brand history and there is bound to be some degree of misclassification in our exposure measure. However, misclassification should be nondifferential (i.e., not associated with tumor location) and so should bias our estimate toward the null.

There is also likely to be some misclassification in determining tumor location. Fifteen percent of cases were sufficiently ambiguous to require review, and a greater percentage of these were assigned to peripheral location (89%) than among cases not requiring review (66%). However, when we excluded cases requiring review, the OR for peripheral tumors among lower-tar smokers increased (2.24 versus 1.76). We also had to use CXR instead of CT scans for 16% of cases. Cases based on review of CXR were somewhat less likely to be assigned to peripheral location (60%) than were cases assigned by CT scans or other sources (71%). However, when we excluded cases assigned by CXR, the estimates for the effect of FTC tar rating on location were virtually the same as when all cases were included.

The substantial difference between crude and adjusted analyses of FTC tar ratings and tumor location is also a cause for concern. The confounding effect of age, particularly among those ages <55 years, was the main contributor to this difference. As expected, younger smokers were much more likely than older smokers to have had a lower average FTC tar rating, but (counterintuitively) they were also more likely to have central rather than peripheral tumors. Our results did not change when the analysis was restricted to those ages ≥55 years, but additional studies would help determine the reason for the age-related change in estimate.

In summary, we found that smokers of cigarettes with lower FTC tar ratings had relatively more tumors in a peripheral location than did smokers of cigarettes with higher-tar levels. These results provide support for the theory that the decrease in nicotine and tar levels as measured by machine smoking over time has caused smokers to adopt a pattern of deeper inhalation, which has resulted in increased exposure of peripheral lung tissue to tobacco smoke and a consequent shift to the periphery in the site of origin of lung cancers.

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