BRIEF COMMUNICATION

Lung Cancer Histologic Type in the Surveillance, Epidemiology, and End Results Registry Versus Independent Review

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Because few studies have assessed the accuracy of lung cancer histologic diagnoses reported by state cancer registries, we examined whether the Iowa Surveillance, Epidemiology, and End Results Cancer Registry (i.e., the Iowa Cancer Registry)–reported lung cancer histologic diagnoses were reliable. We investigated agreement between lung cancer histologic types reported for 413 patients with lung cancer by the Iowa Cancer Registry and those obtained through an independent review of diagnostic slides. Among lung cancer histologic types, small-cell carcinoma had the highest sensitivity (94.1%, 95% confidence interval [CI] = 85.6% to 98.4%), positive predictive value (94.1%, 95% CI = 85.6% to 98.4%), negative predictive value (98.8%, 95% CI = 96.9% to 99.7%), and highest percent exact agreement (98.0%, 95% CI = 96.6% to 99.4%). The lowest sensitivity (21.9%, 95% CI = 9.3% to 40.0%) and positive predictive value (23.3%, 95% CI = 9.9% to 42.3%) were noted for large-cell carcinoma, probably because other more specific features of adenocarcinoma or squamous carcinoma were absent. Adenocarcinoma had the lowest specificity (84.4%, 95% CI = 79.0% to 88.9%), negative predictive value (85.2%, 95% CI = 79.9% to 89.6%), and percent exact agreement (82.9%, 95% CI = 79.2% to 86.6%). Samples collected by cytologic examination (odds ratio [OR] = 2.4, 95% CI = 1.1 to 5.2) or biopsy examination (OR = 2.2, 95% CI = 1.1 to 4.2) were more likely to be misclassified than samples obtained via resection. Thus, the histologic type obtained by the Iowa Cancer Registry is reasonably reliable, but independent slide review is needed for precise histologic typing of lung cancer. [J Natl Cancer Inst 2004;96:1105–7]

Lung cancer has been the leading cause of cancer death among U.S. women since 1987. Inaccuracy in reporting the histologic type of lung cancers can affect estimates of 1) histologic type-specific incidence trends, 2) survivorship by histologic type, and 3) risk estimates associated with various etiologic factors. Surprisingly few studies have been performed, even within National Cancer Institute–supported Surveillance, Epidemiology, and End Results (SEER[1]) Cancer Registries comparing the agreement between registry and independently reviewed lung cancer histologic types *(1–3).* To determine whether SEER-reported lung cancer histologic diagnoses were reliable for use in epidemiologic analyses, we compared agreement between data from the Iowa Cancer Registry, a member of the SEER program since data collection commenced on January 1, 1973 *(4),* and those obtained through an independent review of diagnostic slides.

The Iowa Radon Lung Cancer Study was a population-based, case–control epidemiologic study conducted between October 1, 1992, and December 31, 1997, that examined the relationships of smoking status, residential radon exposure, and lung cancer in Iowa women. A component of the Iowa Radon Lung Cancer Study included the expert review of pathology samples obtained from patients with lung cancer who participated in the study *(5).* Existing data from the Iowa Cancer Registry reported lung cancer histologic types and the follow-up expert consensus review of slides of lung cancer tissue from the Iowa Radon Lung Cancer Study provided a rare opportunity to 1) compare the agreement between the lung cancer histologic types reported in the Iowa Cancer Registry with that of the histologic types from an independent review, 2) determine whether the histologic sample collection method affected the agreement between histologic types reported by the Iowa Cancer Registry and by the independent review, and 3) determine whether the two methods of histologic identification (Iowa Cancer Registry–reported versus independent blinded review) produced similar estimates of histologic type–specific lung cancer survival. The study, which included collection and review of archived tissue and block samples, received human subject approval from the University of Iowa's Institutional Review Board.

Four hundred thirteen female patients with lung cancer from the Iowa Radon Lung Cancer Study served as the study population. Patients with lung cancer met the following inclusion criteria for the study: 1) newly diagnosed with a primary invasive (not *in situ*) lung carcinoma without any prior primary invasive lung carcinoma, 2) female Iowa resident at time of diagnosis, 3) age ranging from 40 to 84 years, 4) microscopically confirmed primary lung carcinoma, and 5) residence for 20 consecutive years or more in the current home. Case patients that met these eligibility criteria were identified via a rapid-reporting mechanism by the Iowa Cancer Registry between May 1, 1993, and October 30, 1996. Information concerning the Iowa Cancer Registry is presented elsewhere *(5).* Eight patients did not have slides available, and another eight patients (or their next of kin) refused to sign the consent form granting release of these materials, leaving diagnostic slide materials available from 397 (96%) of the 413 patients enrolled in the Iowa Radon Lung Cancer Study. Signed consent for release of pathologic materials was obtained from all other participants.

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An overview of the pathology laboratories serving Iowa is provided elsewhere *(6)*. The Iowa Radon Lung Cancer Study adhered to the confidentiality policy of the Iowa Cancer Registry for research protocols and collection of tissue slides and blocks. Two board-certified surgical pathologists (CEP, RAR) provided independent and consensus histologic diagnoses for the 397 patients studied; these diagnoses were based on the 1981 World Health Organization's histologic typing of lung tumors, which was in place at the time of the study, and included the major categories of small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma (including bronchioloalveolar carcinoma), and large-cell carcinoma *(7)*. To ensure comparability of findings, we based criteria for diagnosis on light-microscope observation only. The reviewers were blinded to the diagnosis on the pathology report (Iowa Cancer Registry–reported histology) and to each other's review diagnosis. Six subjects with carcinoid tumors were not included in the study because the clinicians of the patients did not always view these tumors as malignant.

When the designated histologic type of tumor differed between the two reviewers, they reviewed the slides simultaneously and rendered a consensus diagnosis. In some cases, special stains such as mucicarmine, periodic acid–Schiff, and periodic acid–Schiff after diastase were requested for the tissue blocks by the reviewing pathologists to resolve a diagnostic question. Sensitivity, specificity, and the predictive values were calculated for each cell type, with the consensus diagnosis serving as a reference. Specimen type was categorized as to resection, biopsy (transbronchial or fine-needle aspiration), or cytology (sputum, bronchial brushings, and/or washings) specimen. Prior biopsy and/or cytology material was not reviewed for all patients for whom resected tumor tissue was available.

Linkage of data from patients with the mortality database from the Iowa Department of Public Health allowed determination of the survival status for 100% of the patients between diagnosis and December 31, 2002. For each histologic type, percent agreement, sensitivity, specificity, predictive value–positive, and predictive value–negative values were computed by dichotomizing histologic diagnosis as either the type of interest or any of the remaining types, for which the cross-classification of the Iowa Cancer Registry and independent review results in a 2×2 table. The independent histologic review served as the reference diagnoses for the analyses. McNemar's test was performed to test for differential misclassification. Multivariable logistic regression was used to study the effect of histology and tissue collection method on the probability of misclassifying subjects. The logistic model was used to estimate the odds of misclassification for each tissue collection method compared with that of tissue resection. Main effects for the histologic types and collection methods were included in the regression model. Results of a global test for interaction were not statistically significant ($P = .70$). The Kaplan–Meier estimator was used to construct survival plots and to estimate the median survival times within histologic types. All statistical tests were two-sided. All computations were performed at the 5% level of statistical significance with the SAS software package (SAS Institute, Cary, NC).

No statistically significant difference (Pearson's χ^2 statistic = 5.56, $df = 6$; $P = .47$) was found between the distribution of histologic types in the 397 patients from the Iowa Radon Lung Cancer Study compared with the Iowa SEER Cancer Registry for 2593 females 40–84 years old with lung cancer diagnosis dates between May 1, 1993, and October 30, 1996 (November 2002 SEER submission). The percent exact initial agreement between the two blinded expert observers was 74.7%. Not surprisingly, similar demographic information (e.g., age, education, previous lung disease, and smoking history) was obtained for the 397 patients who had an independent histologic type review and the total study population of 413 patients (data not shown). General demographic information for the subjects is presented elsewhere *(5)*.

A cross-classification of lung cancer histologic types reported to the Iowa Cancer Registry versus the independent pathology review is presented in Table 1. The high relative percentage of adenocarcinoma was expected in females. The overall percent exact agreement was 71.5% (95% CI = 67.1% to 76.0%). Table 2 summarizes the measures of agreement for the individual histologic types. Sensitivity and positive predictive value provide the clearest indication of agreement in the cross-classification of lung cancer histologic types reported to the Iowa Cancer Registry and the consensus diagnosis from independent histologic type review because they measure the probability of correctly classifying one specific cell type. Among lung cancer histologic types, small-cell carcinoma had the highest sensitivity (94.1%, 95% CI = 85.6% to 98.4%), positive predictive value (94.1%, 95% CI = 85.6% to 98.4%), negative predictive value (98.8%, 95% CI = 96.9% to 99.7%), and percent exact agreement (98.0%, 95% CI = 96.6%

Table 1. Cross-classification of histologic types of lung cancer reported to the Iowa Cancer Registry (ICR) and expert consensus diagnosis from independent histologic type review*

ICR-reported histologic type	Consensus diagnosis from independent histologic type review, No.						
	Adenocarcinoma	Adenosquamous	Large cell	Small cell	Squamous	Other†	Not reviewed
Adenocarcinoma	139	5	11	3	7	9	3
Adenosquamous	3	6	0	0	1	0	1
Large cell	12	2	7	0	5	4	0
Small cell	0	0	2	64	0	2	6
Squamous	3	2	4	0	56	3	3
Other†	15	1	8	1	10	12	3
Total	172	16	32	68	79	30	16

*The percent exact agreement is 71.5% (95% confidence interval = 67.1% to 76.0%).

†Category, for the most part, includes carcinoma, not otherwise specified lung cancer histologic types.

Table 2. Agreement between lung cancer histologic types reported to the Iowa Cancer Registry (ICR) and expert consensus diagnosis from independent histology review

Histologic type	Sensitivity, %	Specificity, %	% positive predictive value	% negative predictive value	% exact agreement (95% CI)*	*P*†
Adenocarcinoma	80.8	84.4	79.9	85.2	82.9 (79.2 to 86.6)	.808
Adenosquamous	37.5	99.0	60.0	97.4	96.5 (94.7 to 98.3)	.109
Large cell	21.9	93.7	23.3	93.2	87.9 (84.7 to 91.1)	.773
Small cell	94.1	98.8	94.1	98.8	98.0 (96.6 to 99.4)	1.000
Squamous	70.9	96.2	82.4	93.0	91.2 (88.4 to 94.0)	.063
Other‡	40.0	90.5	25.5	94.9	86.6 (83.3 to 90.0)	.020

*CI = confidence interval.

†Two-sided McNemar test.

‡Category, for the most part, includes carcinoma, not otherwise specified lung cancer histologic types.

to 99.4%). The lower sensitivity (21.9%, 95% CI = 9.3% to 40%) and positive predictive value (23.3%, 95% = 9.9% to 42.3%) found for large-cell carcinoma results in part from the absence of other more specific features that would permit a diagnosis of adenocarcinoma or squamous carcinoma. Sample size becomes a factor when the pathologist is looking for infrequent indicators of differentiation. Ultrastructural or immunohistochemical characteristics may permit further separation, but these are infrequently used because in many cases treatment is not different or is based on the stage of disease. Adenocarcinoma had the lowest specificity (84.4%, 95% CI = 79.0% to 88.9%), negative predictive value (85.2%, 95% CI = 79.9% to 89.6%), and percent exact agreement (82.9%, 95% CI = 79.2% to 86.6%). McNemar's test results indicated that there was a statistically significant nonrandom misclassification for the "other" histologic category ($P = .02$). The corresponding cross-classification of "other" histologic type between the Iowa Cancer Registry and independent histology review is presented in Table 3. The disproportionately large number of consensus pathologically determined "not other" (squamous, small cell, adenocarcinoma, large cell, or adenosquamous) cancers that were reported as "other" to the Iowa Cancer Registry represent original diagnoses of non–small-cell carcinoma for which the independent reviewers were able to make a more specific diagnosis.

Relative to resection, the odds of misclassification were similar for samples collected by cytologic examination (odds ratio [OR] = 2.4, 95% CI = 1.1 to 5.2) and biopsy examination (OR = 2.2, 95% CI = 1.1 to 4.2). No interaction was noted between collection method and histologic type (data not shown). Survival associated with both the Iowa Cancer Registry histologic type classifications and the independent review classifications was estimated with the Kaplan–Meier method, and as expected from their relatively lower positive predictive value, large-cell carcinoma and adenosquamous cancers visually showed more divergence of the survival curves than other histologic types (data not shown).

A major strength of this study was the high percentage of patients for which tissue was available for review. In addition, the distribution of histologic types for study patients in the Iowa Radon Lung Cancer Study was population based and not statistically significantly different from the distribution of histologic types from the Iowa SEER Cancer Registry for females 40–84 years old with dates of lung cancer diagnosis between May 1, 1993 and October 30, 1996. Overall, the results of the study suggest that, at least for Iowa, the histologic type diagnosis obtained by the Iowa Cancer Registry from the various pathology laboratories is reasonably reliable. However, if accurate histologic typing of lung cancer is critical to activities involving cancer surveillance program data, independent slide review should be performed.

Table 3. Comparison of other histologic classification between the Iowa Cancer Registry (ICR) and expert consensus diagnosis from independent histologic-type review

ICR-reported histologic type	Consensus diagnosis from independent histologic type review, No.		Total No.
	Other	Not other*	
Other	12	35	47
Not other*	18	332	350
Total	30	367	397

*This category includes adenocarcinoma, adenosquamous, large-cell, squamous, small-cell, or squamous-cell histologic types (*see* Tables 1 and 2).

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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