# The Value of Aspiration Cytologic Examination of the Breast

## A Statistical Review of the Medical Literature

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**The decision to perform surgery in patients with a breast mass usually is made on the basis of combined diagnostic information, with fine-needle aspiration cytologic examination (FNAC) playing a central role. To determine and compare the quality of FNAC of the breast, a search was performed of the English literature for articles with quantitative information about their results. Twenty-nine such articles, containing 31,340 aspirations, were identified and summarized. Required data were extracted from these articles. These numbers were analyzed with the use of a two-by-four contingency table to relate the FNAC result (definitely malignant, suspect, benign, or unsatisfactory cytologic material) with the final diagnosis (malignant or benign breast disease). Test characteristics such as sensitivity, specificity, and the likelihood ratios for the four different FNAC results were derived for each study and compared. There was a striking difference between studies with regard to the probability of a particular FNAC upshot (e.g., in patients with breast cancer, the chance of obtaining definitely malignant cytologic material ranged from 0.35 to 0.92), the sensitivity (range, 0.65 to 0.98), the specificity (range, 0.34 to 1.0), and likelihood ratios. In the opinion of the authors, it is virtually impossible to infer general test characteristics of FNAC of the breast from the medical literature because of differences in methods and different biases. At best, the maximum attainable performance of this test can be described. For the development of a policy for breast mass management, the local test characteristics of this highly operator-dependent test should be established.** *Cancer* **1992; 69:2104–2110.**

The introduction of fine-needle aspiration cytologic examination (FNAC) of the breast has provided a noninvasive way of obtaining cells for establishment of the nature of a breast lump and therefore plays a pivotal role in the preoperative diagnostic process.[1–3] In breast mass management, a prudent diagnostic policy is desired: surgery should be avoided for benign breast disease, but the diagnosis of cancer should not be delayed. This demands proper test evaluation of FNAC findings and knowledge of the prior probability of breast cancer in the referred population.

Diagnostic guidelines often are based on results of the appraisal of this test published in the medical literature.[4,5] Articles on FNAC of the breast therefore must be assessed critically. This includes analysis of patient-related and disease-related variables and details on how these selected patients were examined.

In past years many articles have been published on FNAC of the breast. We have analyzed and compared 29 of such articles for the following reasons: (1) to compare the characteristics of FNAC from these studies and determine how much and possibly why the results vary; (2) to determine whether it was feasible to extract general test characteristics of FNAC; and (3) to assess and analogize the methods of accuracy estimation of FNAC of the breast from each article.

## Methods

### *Data Source Identification and Collection of Information*

A comprehensive search of the English language literature was performed for articles evaluating the accuracy of FNAC of the breast, with the use of a computerized search of MEDLINE (Compact Cambridge, Bethesda, MD) and by bibliographic review of all identified articles. From these potentially acceptable articles, the following information was sought: year of publication, type of institution where the study was conducted (academic *versus* nonacademic), whether the aspiration was performed by the attending clinician or the cytopatho-

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logist, the number of women entering the study, description of mean age and range, the nature of the lesions (cysts or solid lesions), the total number of aspirations, the number of aspirations that actually were evaluated because follow-up information was available, the FNAC diagnosis, the method used to establish the final diagnosis of the breast lump (histologic follow-up only or combined histologic and clinical follow-up), and the final diagnosis.

### *Study Selection*

The FNAC results from all studies selected for analysis had to be classifiable in the following four cytologic outcome categories: definitely malignant, suspect for malignancy, benign, and unsatisfactory specimen for diagnosis (acellular aspirations). When an additional "atypical" category was used, these results were grouped under "suspect." Furthermore, the only studies included are those with full information about the relation between each FNAC diagnostic category (acellular aspirations explicitly included) and the final diagnostic categories (benign or malignant breast disease), which was settled either histologically or by combined histologic and clinical follow-up.

### *Methods for Data Abstraction*

To permit uniform handling of data, comparison of categories, and statistical analysis, a two-by-four contingency table was used, relating the FNAC diagnosis to the final diagnosis (Table 1). From each article, the total number of aspirations for any of the eight cells was retrieved.

The sensitivity and specificity of FNAC were determined for each study. Sensitivity was defined as the sum of the probabilities of malignant and suspect test results in patients with cancer (from Table 1: [a + b]/M) and specificity as the probability of an absence of abnormal cells in the aspirate ([g + h]/B). For both indexes, the 95% confidence intervals for binomial parameters were calculated.[6]

In addition, to enable characterization and comparison of the performance of each outcome category separately from FNAC, the likelihood ratio was calculated.[7] For the diagnosis of breast cancer, the likelihood ratio for a particular FNAC upshot was calculated as follows:

$$\text{LR(FNAC} - \text{result for cancer)} = \frac{\text{probability of FNAC} - \text{result given malignancy}}{\text{probability of FNAC} - \text{result given benign lesion}}$$

For the 95% confidence intervals of the likelihood ratios, the same method as was used as described for risk ratios.[7]

**Table 1. Two-By-Four Contigency Table for Relating the Fine-Needle Aspiration Cytologic Examination Outcome to the Final Diagnosis of the Breast Lesion**

| FNAC outcome | Malignant | Suspect | Benign | Unsatisfactory | Total |
|---|---|---|---|---|---|
| Final diagnosis | | | | | |
| Malignant | a | b | c | d | M |
| Benign | e | f | g | h | B |

FNAC: fine-needle aspiration cytologic examination.

## Results

Of 58 identified articles reporting quantitatively on the accuracy of FNAC of the breast, only 29 met the aforementioned inclusion criteria (Table 2).[8–36] The principle reason for exclusion was lack of sufficient primary data. The selected articles were published between 1972 and 1989. All but two studies were from university centers. Pricking had been performed by the cytopathologist in only 6 studies; in the remaining 23 the attending physician was responsible.

Description of patient-related and disease-related variables was scanty. A description of age characteristics was given in only eight articles. In 17 articles, the solid or cystic nature of the breast lesions was not mentioned either qualitatively or quantitatively, although most aspirations seemed to come from solid breast lesions. When the study contained a mixture of both cysts and solid lesions, a separate description of test characteristics was not given for both types of lesions in relation to the final disease category.

As is shown in Table 2, both sample size and breast cancer prevalence vary substantially among articles. Breast cancer prevalence ranged from 10% to 91%, with a mean of 40%. The size of the sample of aspirations in the articles varied between 49 and 4700. The total number of aspirations included in this study was 31,340. Histologic or clinical follow-up data provided a final diagnosis in 20,387 aspirations (65%). Clearly, some authors had the policy to report only those cases in which a final diagnosis was available, whereas others also gave information on all aspirations taken during a certain period. In 22 of the studies, only the available histologic biopsy diagnosis was used for follow-up. In the remainder, both histologic and clinical data were used. The proportion of aspirations with follow-up data differed between 0.20 and 1.0.

As is shown in Table 3, the probability of each of the four FNAC outcome categories given the final diagnosis of benign or malignant breast disease varied considerably. The only exception is a consistently very low probability of "definitely malignant" cytologic findings in benign breast disease. There are striking differences

**Table 2. List of Relevant Data From All 29 Publications**

| Investigator | Year | Center | Pricker | Start sample | Follow-up available | Follow-up method | Cancer prevalence | FNAC result given breast cancer | | | | FNAC result given benign disease | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *Malignant* | *Suspect* | *Benign* | *Unsatisfactory* | *Malignant* | *Suspect* | *Benign* | *Unsatisfactory* |
| Linsk[8] | 1972 | A | P | 4700 | 2077 | H | 0.51 | 823 | 156 | 56 | 33 | 1 | 69 | 805 | 134 |
| Furnival[9] | 1975 | A | CL | 239 | 239 | H + C | 0.31 | 51 | 0 | 5 | 17 | 2 | 1 | 121 | 42 |
| Zajdela[10] | 1975 | A | P | 2772 | 2670 | H | 0.64 | 1526 | 43 | 63 | 89 | 3 | 52 | 846 | 48 |
| Wilson[11] | 1978 | A | CL | 1684 | 334 | H | 0.15 | 19 | 16 | 9 | 6 | 2 | 23 | 164 | 95 |
| Thomas[12] | 1978 | A | CL | 255 | 196 | H | 0.36 | 49 | 10 | 4 | 8 | 0 | 4 | 92 | 29 |
| Duguid[13] | 1979 | A | P | 294 | 294 | H + C | 0.20 | 50 | 6 | 2 | 2 | 0 | 18 | 181 | 35 |
| Kline[14] | 1979 | A | CL | 3545 | 3545 | H + C | 0.10 | 240 | 89 | 35 | 4 | 0 | 602 | 2810 | 307 |
| Gardecki[15] | 1980 | NA | CL | 444 | 365 | H + C | 0.39 | 109 | 16 | 6 | 11 | 0 | 10 | 146 | 67 |
| Strawbridge[16] | 1981 | A | CL | 3724 | 861 | H | 0.32 | 141 | 70 | 24 | 39 | 3 | 85 | 326 | 173 |
| Shabot[17] | 1982 | A | CL | 81 | 81 | H | 0.62 | 46 | 3 | 0 | 1 | 0 | 0 | 29 | 2 |
| Azzarelli[18] | 1983 | A | CL | 1498 | 1183 | H | 0.43 | 262 | 74 | 65 | 113 | 3 | 23 | 381 | 262 |
| Bell[19] | 1983 | A | P | 1680 | 1145 | H + C | 0.22 | 119 | 91 | 27 | 15 | 0 | 147 | 615 | 131 |
| Norton[20] | 1984 | A | CL | 49 | 49 | H | 0.39 | 8 | 8 | 1 | 2 | 0 | 5 | 9 | 16 |
| Dixon[21] | 1984 | A | CL | 683 | 683 | H | 0.46 | 222 | 36 | 24 | 29 | 0 | 16 | 275 | 81 |
| Aretz[22] | 1984 | A | CL | 329 | 190 | H | 0.39 | 26 | 30 | 14 | 4 | 0 | 9 | 93 | 14 |
| Ulanow[23] | 1984 | A | CL | 449 | 318 | H | 0.60 | 137 | 25 | 19 | 9 | 1 | 15 | 100 | 12 |
| Wanebo[24] | 1984 | A | CL | 398 | 247 | H | 0.52 | 93 | 23 | 1 | 12 | 0 | 6 | 102 | 10 |
| Wollenberg[25] | 1985 | A | CL | 321 | 321 | H + C | 0.24 | 52 | 13 | 11 | 1 | 0 | 99 | 132 | 13 |
| Somers[26] | 1985 | A | CL | 369 | 187 | H | 0.56 | 81 | 13 | 5 | 5 | 0 | 5 | 37 | 41 |
| Lannin[27] | 1986 | A | CL | 100 | 100 | H | 0.30 | 23 | 3 | 2 | 2 | 0 | 0 | 63 | 7 |
| Eisenberg[28] | 1986 | A | CL | 1942 | 1731 | H + C | 0.91 | 1050 | 268 | 72 | 177 | 0 | 28 | 68 | 68 |
| Barrows[29] | 1986 | A | CL | 1283 | 1283 | H + C | 0.54 | 481 | 88 | 48 | 72 | 2 | 53 | 338 | 201 |
| Watson[30] | 1987 | NA | CL | 350 | 350 | H | 0.18 | 37 | 9 | 13 | 3 | 1 | 0 | 200 | 87 |
| Hammond[31] | 1987 | A | CL | 678 | 159 | H | 0.44 | 59 | 5 | 4 | 2 | 1 | 12 | 61 | 15 |
| Dundas[32] | 1988 | A | CL | 174 | 148 | H + C | 0.29 | 18 | 21 | 2 | 2 | 0 | 1 | 72 | 32 |
| Smith[33] | 1988 | A | P | 787 | 594 | H + C | 0.26 | 110 | 22 | 8 | 12 | 0 | 16 | 307 | 119 |
| Palombini[34] | 1988 | A | P | 1956 | 670 | H | 0.73 | 446 | 24 | 15 | 7 | 0 | 17 | 151 | 10 |
| Langmuir[35] | 1989 | A | CL | 280 | 257 | H | 0.12 | 13 | 15 | 1 | 3 | 0 | 25 | 167 | 33 |
| Wilkinson[36] | 1989 | A | CL | 276 | 110 | H | 0.41 | 29 | 13 | 3 | 0 | 0 | 43 | 21 | 1 |

A: academic; NA: nonacademic; P: pathologist; CL: clinician; H: histologic follow-up only; H + C: combined clinical and histologic follow-up; FNAC: fine-needle aspiration cytologic examination.

**Table 3. Ranges of Conditional Probabilities, Given the Final Diagnosis, for Different Fine-Needle Aspiration Cytologic Tests Results**

| Test result | Malignant | Suspect | Benign | Unsatisfactory |
|---|---|---|---|---|
| Final diagnosis | | | | |
| Malignant | 0.35–0.92 | 0.00–0.48 | 0.00–0.21 | 0.00–0.23 |
| Benign | 0.00–0.002 | 0.00–0.62 | 0.30–0.93 | 0.01–0.53 |

between the 29 studies for the proportions of definitely malignant and suspect findings among the patients with breast cancer. The sensitivity of FNAC ranged from 0.65 to 0.98. The specificity ranged from 0.82 to 1.00, with two outliers of 0.34 and 0.59. In Figures 1 and 2, the sensitivity and specificity for all 29 studies are presented graphically.

The range of likelihood ratios for each FNAC result is given in Table 4. In 19 of the 29 studies, there were no false-positive results in the malignant category, resulting in an infinite likelihood ratio. In 26 of the 29 studies, the likelihood ratio for unsatisfactory outcome was well below 1, indicating that this test result lowered the pretest probability of breast cancer. In Figure 3, the likelihood ratios for definitely malignant and suspect cytologic results are given for all 29 articles.

## Discussion

Our study of the 29 articles reporting the relationship between FNAC result and final diagnosis shows striking dissimilarities in the probability of a particular FNAC outcome category given the diagnosis of benign or malignant breast disease and their discriminating power (Tables 2, 3, and 4, and Figs. 2, 3, and 4). For the

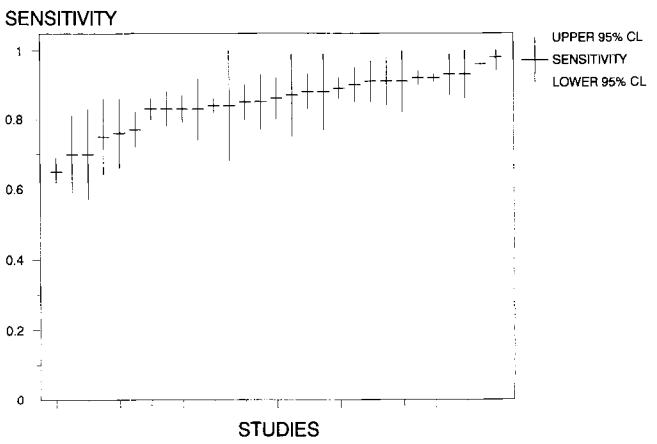


Figure 1. Sensitivity of FNAC (definitely malignant and suspect results) with upper and lower 95% confidence limits for the 29 studies.

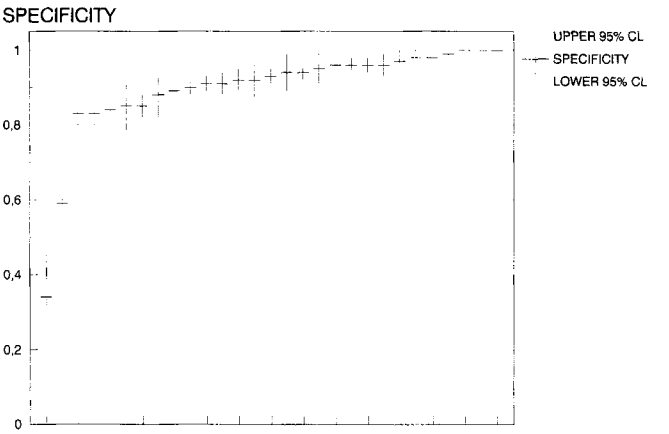


Figure 2. Specificity of FNAC (normal and unsatisfactory results) with upper and lower 95% confidence limits for the 29 studies.

following reasons, this casts at least some doubt on the validity of any generalization regarding test characteristics: First, the literature is bound to be biased because, for this particular type of test, poor performance is less likely to be published. Secondly, outcome assessment may be biased in several different ways. Thirdly, many articles lack specific essential data desired for review and assessment of comparability.

Because the quality of FNAC is highly operator dependent (the act of aspiration and the microscopic examination), this provides a simple psychologic reason for publication bias: poor test quality indicates poor human performance. Although this study includes only those articles that permit retrieval of the primary data for the two-by-four cell contingency table, and with awareness of the publication bias, there is still an impressive range of values for the different test characteristics. This operator dependency stresses the importance of determining the effectiveness of FNAC in a particular (local) diagnostic setting.

The second class of problems lies with the methods of accuracy assessment. Several types of bias may distort the evaluation in different stages of the work-up.[37] The disease spectrum of benign and malignant breast lesions may vary because of demographic and referral factors. Most articles were from academic centers. Little information was provided regarding whether FNAC

**Table 4. Likelihood Ratios for Malignancy of Different Fine-Needle Aspiration Cytologic Results**

| Test result | Range |
|---|---|
| Malignant | 777–infinite |
| Suspect | 51–infinite |
| Benign | 0–0.31 |
| Unsatisfactory | 0–1.09 |

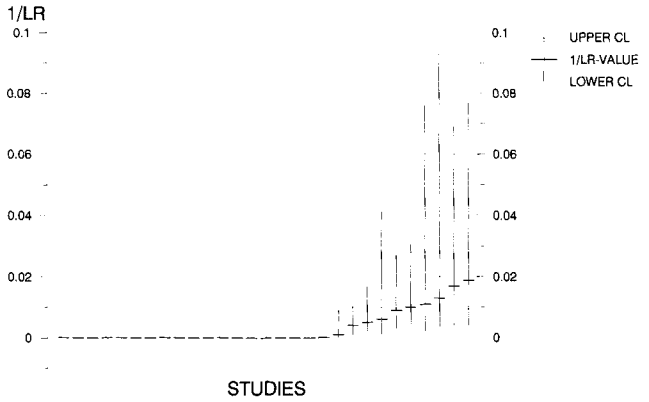


Figure 3. Likelihood ratios from all 29 studies for the outcome category definitely malignant. For scaling purposes, the inverse value of the likelihood ratio is represented.

was being used systematically on all patients with a breast mass or not. In some articles it was indicated that multiple aspirations were performed in numerous women, but in the process of evaluation all punctures were taken together.

All studies were retrospective in nature. This implies that the cases included were selected, first, on the basis of performance of FNAC and, second, on the availability of clinical and/or histologic follow-up data. The proportion of the population with adequate follow-up information was sometimes as low as 0.2! Furthermore, two distinct methods were used: histologic examination only, or the combination of biopsy diagnosis and clinical follow-up information. The duration of that follow-up ranged from 3 months to several years.

Another major problem concerning comparability is demonstrated in Table 2. There is a tremendous variation in sample size and cancer prevalence. This high variation in these factors is one of the reasons that, in our opinion, it does not make sense to derive overall test characteristics from these data. Because of the patient selection and biased ascertainment of the disease state, not all studies are equally comparable.

A striking feature was that, in the process of calculating sensitivity and specificity, unsatisfactory specimens usually were discarded in most studies because it was not known whether they were normal or abnormal. This, together with the biased outcome assessment, will tend to lead to overestimation of the sensitivity of FNAC.

The third problem is that too little information was provided to associate differences between studies with patient-related or disease-related variables. In recent studies, the patient age and the size and type of tumor were determinants of the probability of a positive test result in patients with cancer.[38,40,41] In the reviewed articles, age characteristics were scanty, as were details on size and type of tumors. In a recent review of the results of our own institution, we found an essential difference between the test characteristics for solid and cystic breast lesions.[39] This implies that FNAC test characteristics should be reported separately for both categories.

These points indicate that there are several constraints on an integrative literature review. It is essentially impossible to infer the general test characteristics of FNAC from the literature. At best, the maximum attainable performance of this test can be described as detailed to each of the four outcome categories. Because such striking differences are seen between laboratories, "local" test characteristics should be established to provide data for the optimal practice policy.

A methodologically sound evaluation of FNAC of the breast demands that all factors pertaining to the outcome be recorded and reported to allow for generalization of findings. For the evaluation of a diagnostic test, a two-by-two table usually is used, which enables the calculation of test performance characteristics such as sensitivity and specificity. For tests that have a "natural" binary test outcome (the presence or absence of a finding), or when a single cutoff point demarcates between normal and abnormal, this method is appropriate.

However, when test results are expressed as multiple categories (*e.g.*, in diagnostic cytology) this approach is less desirable. In the process of dichotomization, imperative for calculation of sensitivity and specificity, outcome categories such as suspect and malignant must be lumped together. It is tricky to determine where to place unsatisfactory outcomes. Because these are regarded as neither normal nor abnormal, often they are discarded. The inclusion of all outcomes in

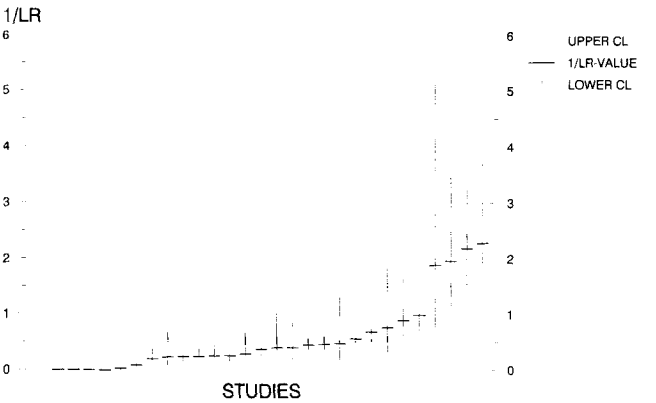


Figure 4. Same plot as Figure 3, but now for the outcome category suspect. Notice that the inverse value of the likelihood ratio is represented and the scale of the y-axis is different.

a two-by-four cell contingency table circumvents these problems but requires a different statistical approach.

Recently, use of the likelihood ratio was recommended for characterization of FNAC.[6] The likelihood ratio of a defined FNAC outcome category is simply the quotient of the proportion of patients with breast cancer who have that particular outcome to the proportion of people without cancer who also have that outcome. With this method, every diagnostic category can be evaluated separately, which is much more realistic because the clinician must decide what has to be done on the basis of each outcome. Additionally, it allows for better comparison of different studies, as is shown in Figures 3 and 4.

Another essential element is the thoroughness with which follow-up data are collected. Ideally, follow-up data should be available for every aspiration. The availability of computerized databases in most hospitals and pathologic laboratories should facilitate the collection of the necessary data.

FNAC has become an indispensable diagnostic tool in breast mass management. Knowledge of its characteristics allows for optimal decision making, resulting in a minimum of unnecessary breast biopsies. This can be achieved only when the results from a particular laboratory are evaluated.

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