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Search Continues for the Cause of Cervical Cancer



Michele Follen Mitchell

Does human papillomavirus (HPV) really cause cervical cancer? A profusion of research articles has provided considerable evidence of a causal relationship and has directed widespread international media attention to this issue. However, a number of epidemiologically oriented researchers like gynecologist Michele

Follen Mitchell, M.D., take a more conservative stance.

“In some ways, molecular biologists and pathologists are making the same mistakes that were made in the 1970s, when we believed that herpes simplex virus 2 (HSV 2) was the cause,” cautioned Mitchell, assistant professor of gynecology at The University of Texas M. D. Anderson Cancer Center. “We do consider HPV to be a risk factor, but the mechanisms leading to cancer are far more complex than the media would have patients believe.”

The Link Between Cervical Cancer and a Sexually Transmitted Disease

Media attention has focused on the possibility that HPV, usually a sexually transmitted disease, may be the carcinogenic agent for cervical cancer. This is a logical though not necessarily true assumption, Mitchell said. Extensive epidemiological research does pinpoint sexual behavior as a risk factor for cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), and invasive cervical carcinoma. Among the women identified at a higher risk are those who began intercourse at an early age, had many sexual partners, did not use barrier contraception, and had been exposed to sexually transmitted diseases. An increased risk is conferred by the male partner if he has had a previous partner with cervical cancer, many sexual partners, or penile cancer, and possibly if he is uncircumcised.

For over 20 years, HSV-2 was thought to be that sexually transmissible agent. Researchers had found the virus in thousands of cervical biopsies, and a few studies demonstrated higher serum HSV-2 antibody levels in cervical cancer patients than in controls. Those studies proved to be flawed. In 1984, a study published by V. Vonka and colleagues in Prague conclusively disproved that hypothesis; among 10,000 women, no differences were found in HSV-2 antibody levels between patients with no cervical abnormalities and those who developed CIN.

We are on the forefront of an important period when many questions will be answered.

Admittedly, many researchers feel there is a much stronger case for naming HPV the carcinogenic culprit, based on epidemiologic and biologic data, Mitchell said.

HPV exposure is extremely widespread. Statistics provided by The National Disease and Therapeutic Index, a sampling of 10% of diseases treated by general practitioners, indicate that HPV is greatly on the rise, and condyloma acuminatum—a lesion caused by HPV—is the most commonly diagnosed sexually transmitted viral disease in both the United States and the United Kingdom.

Biologic studies have identified HPV in about 90% of the cervical cancers examined; it has also been found in many established cervical cancer cell lines. HPV-6 and -11 are the most prevalent types in benign perineal

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condylomata, while HPV-16 and -18 are more often found in vulvar, vaginal, cervical, and penile intraepithelial neoplasias and carcinomas. The presence of HPV types in cervical squamous cell carcinomas has been demonstrated in samples from the United States, Europe, Africa, Brazil, and Panama.

Further biologic evidence, identified using DNA ploidy analysis, has demonstrated that HPV-associated benign lesions can progress to malignant disease. HPV-16 and -18 possibly target the basal cells of squamous metaplastic epithelium. Manifesting first as condylomatous atypia, the lesion may then progress to CIN and later invasive cancer.

But the epidemiologic and biologic evidence collected thus far, however suggestive, is fundamentally circumstantial and is contradicted by other data, Mitchell said. "We've seen dramatic increases in HPV of at least sixfold over the last decade, but we're not seeing similar increases in CIN or CIS, and we're certainly not seeing cervical cancer increase; in fact, it's definitely decreasing. If HPV is truly a causal mechanism, then we should see it causing precancerous or invasive cancer rates to jump equally. That's just not been the case."

Epidemiologists Remain Unconvinced

For epidemiologists, the link between the two is unproved. Causality requires that five criteria be established: biologic credibility; strong indication of increased relative risk; a compatible time relationship; consistency among many studies; and a dose-response relationship. (Dose-response is not applicable as a criterion in studies of viruses, since number of exposures has no correlation with presence of disease.)

Though some may feel that the biologic evidence has been ample, the other criteria have not been satisfied, said Mitchell, who listed several reasons for the lack of convincing data. For one, studies have been complicated by the fact that HPV is not considered a reportable disease by epidemiologic surveys, and CIN—a precancerous lesion—is not reported to cancer registries.

Second, HPV may well be just one of several cofactors. The long latency period between HPV infection and the development of cervical malignancy, Mitchell said, is one significant indication that cofactors are involved: it takes an average of 10 years for most of the precancerous cells to develop into cervical cancer.

Third, the difficulties involved in viral testing further complicate investigation efforts: A growing, maturing squamous epithelial surface is required for the virus to grow, so efforts to develop a papillomavirus culture system have failed. As the surface becomes more neoplastic, less virus can be extracted. The virus is thought to incorporate into the DNA, making it impossible to obtain viral bodies from the cytoplasm; DNA must therefore be extracted for study.

Improved Tests May Soon Provide the Key

While Pap tests, colposcopy, cervicography, and magnification with a hand lens are extremely useful in detecting and monitoring abnormal epithelium, they do not differentiate the various viral types to provide the information that researchers need. Other methods, such as improved immunohistochemical stains, polymerase chain reaction, and antibody response level assays, are being developed.

More sophisticated methods of testing serum antibody response levels may also provide conclusive proof, Mitchell said. In addition to elucidating the immune response to HPV, serum antibody response levels would allow researchers to prove whether HPV type-specific antibodies are present in the blood of cervical cancer patients. "We are on the forefront of an important period when many questions will be answered," Mitchell feels. (Thus far, however, Mitchell said that tests of HPV-16 and -18 antibody levels and corresponding epitope assays in cancer patients have provided conflicting data.)

Epidemiologic Conclusions Slowed by Flaws in Research

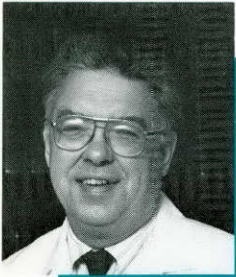
Sophisticated laboratory procedures can contribute to the data base, but only when used in a well-designed study. Mitchell sees many flaws in studies she reads. "We're seeing articles based on research that was simply conducted too quickly before adequate information was gathered or before the long-term results were in. The really carefully done studies are slow-going. Unfortunately, they are also expensive because of the facilities and expertise necessary."

Generally, she finds that many studies lack in several areas: careful consideration of the study population's characteristics (failure to control for certain factors, such as age and sexual behavior, might weaken the study's findings); lack of rigid controls of certain clinical and laboratory testing procedures; inadequate facilities or equipment; or improperly trained personnel. Statistical analyses are often not as thorough as they should be. "Medical schools simply do not provide much training in research design," she said. "Yet physicians are expected, once they enter academic medicine, to also be researchers." (Mitchell, a clinical gynecologist, is on the M. D. Anderson faculty as a lecturer in research design.)

For the past year, she has been preparing the framework of a case-control study designed to determine the relative risk of HPV in causing cervical cancer. Her study, which she will conduct through her clinical practice, will analyze a variety of possible risk factors: nutrition, smoking, sexual behavior, HPV type, and immunologic function. Assembling the appropriate study team members, identifying

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Breast Conservation Should Be the Patient's Choice



David C. Hohn

In the wake of mounting data, many physicians have come to believe that breast conservation is a legitimate treatment option for patients with early stage breast cancer. But some physicians are reluctant to let go of tradition and believe that total mastectomy, the traditional treatment, is still the treatment of choice.

For David C. Hohn, M.D., there is no controversy. He regularly presents both options to eligible patients so that they can choose. But Hohn, professor of surgery at The University of Texas M. D. Anderson Cancer Center, recognizes that treatment dogma is best changed not by polemic but by data.

Panel Reaches Consensus

Last June, Hohn attended the National Institutes of Health (NIH) Treatment of Early Stage Breast Cancer Conference, which was convened to develop an official position based on the most recent data. Hohn was a member of a panel of 15 physicians and scientists who were charged with drafting the NIH Consensus Development Panel statement. During the four-day conference, data from prospective, randomized studies, some of which had a decade or more of follow-up, were presented by investigators from all over the world.

"We rigorously reviewed the data and then issued a statement that we hoped had the capacity to clarify misconceptions and change attitudes," Hohn said. "We concluded that breast conservation should be considered equivalent in terms of survival to any other treatment, and in many cases cosmetic concerns make it preferable. If a woman wants to keep her breast and is eligible for breast conservation, she should have that option. Absolutely no data indicate that survival is reduced by opting for breast conservation instead of mastectomy."

It is important to stress, however, that the panel's statement was not categorical. "Some panel members wanted to come out and say that breast conservation is the treatment of choice, but most of us agreed that it isn't always. A variety of factors enter into the decision," Hohn said. "We simply said that breast conservation is appropriate and often preferable. We did not say that mastectomy is wrong."

Breast conservation therapy consists of local tumor excision and axillary dissection followed by several weeks of radiotherapy. Hohn stressed that two rigid require-

ments must be followed if the procedure is to be effective. "First, the tumor has to be removed with adequate margins of at least one centimeter in all directions, and it is also preferable that the incision be directly over the tumor to optimize the cosmetic result. Second, patients also must undergo axillary node dissection, which is necessary to stage disease, assess risk of recurrence, and plan further treatment. Axillary dissection also minimizes risk of nodal recurrence," Hohn said.

If a woman wants to keep her breast and is eligible for breast conservation, she should have that option.

Contraindications to Breast Conservation

Breast conservation, however, may not be an option for patients with multifocal disease or extreme breast size (very small or very large). In regard to breast size, "local excision has a much greater impact on the size of a small breast, and radiotherapy may shrink it further still. With current techniques, breast reconstruction after total mastectomy can often achieve a cosmetically superior result, so it may be best for these patients to elect total mastectomy followed by breast reconstruction," Hohn said. Breast conservation may also not be advisable for women with very large breasts, since a higher radiation dose is needed and mastectomy with reconstruction and contralateral reduction mammoplasty may yield superior cosmesis.

Even in the absence of contraindications, however, physicians should not assume that patients will automatically choose breast conservation. Keeping the breast is very important to most patients, but each patient has specific circumstances that may lead her to choose mastectomy. "Often it's logistics, often it's expense, often it's fear of radiotherapy," according to Hohn. "Physicians should be very sensitive to patient preference."

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The Uncertain Role of Adjuvant Systemic Therapy



Aman U. Buzdar

How much should a patient endure to improve the outcome of an already successful therapy? Local therapy for early stage breast cancer cures 70% of patients. The 30% recurrence rate can be decreased to 15–20% by adjuvant systemic hormone therapy or combination chemotherapy, but are the

financial costs and the physical side effects worth the 10–15% decrease in recurrence?

Last June, the National Institutes of Health (NIH) Early Stage Breast Cancer Conference was convened in Bethesda, Maryland to address several issues in early stage (node-negative) breast cancer therapy. The Consensus Development Panel—a task force of 15 conference attendees—was made the voice of the conference. (See “Breast Conservation Should Be the Patient’s Choice” for the panel’s statement on breast conservation treatment.) Their conclusion: Because of the treatment’s toxicity, its potential long-term side effects, and the restriction of its benefit to a small percentage of the patient population, systemic treatment cannot be recommended as the treatment of choice for all patients. However, patients should still have the option of choosing systemic therapy: “The many unanswered questions in the adjuvant systemic treatment of node-negative breast cancer make it imperative that all patients who are candidates for clinical trials be offered the opportunity to participate,” according to the panel’s report.

Systemic therapy for early breast cancer raises difficult questions.

No Accurate Assessment of Risk is Available

Underlying the panel’s conclusion are two issues: subjective assessment of risk and lack of precise prognostic factors. For some patients, the risks of systemic therapy

may far outweigh the potential benefit, whereas others will want any chance, however slim, of reducing the possibility of recurrence, according to Aman U. Buzdar, M.D., who attended the NIH conference. Buzdar is professor of medicine at The University of Texas M. D. Anderson Cancer Center.

This issue is nothing new to physicians, and it usually poses no difficulties when the physician knows that a recommended treatment has a good chance of benefiting the patient. But systemic therapy for early breast cancer raises difficult questions. It is *likely* that one in ten patients will benefit; it is *certain* that all ten patients will have to deal with the treatment’s toxicity.

More Prognostic Factors Needed

The crux of the problem is that current prognostic factors cannot adequately define the degree of risk of many subgroups. Reliable correlations have been found for prognostic factors like tumor size, nuclear grade, and histologic grade, and researchers are studying the potential of others like estrogen receptor status, cell proliferation rate, cathepsin D, the HER-2/neu oncogene, and epidermal growth factor. These factors can help in defining subgroups with high or low risk of recurrence, Buzdar said, but a large proportion of patients fall into a prognostic gray area.

“If we could accurately assess the risk of all subgroups, we could be more confident recommending systemic therapy for those with a statistically higher chance of benefiting,” Buzdar said. “Currently, we can accurately assess risk only in a small subgroup of patients based on three prognostic factors: tumor size, nuclear grade, and histologic subtype. For patients with favorable characteristics in all three categories (tumor less than one centimeter in diameter, low nuclear grade, and tubular, colloid, or papillary histologic subtype), we can safely recommend that they not have systemic therapy, since their chance of cure with just local therapy alone is very good (above 90%). The risks of systemic therapy would outweigh the benefits.”

Treatment Options: Tamoxifen or Chemotherapy

Patients with unfavorable or mixed prognostic factors, on the other hand, have to make the difficult decision of whether to receive tamoxifen therapy or receive combination chemotherapy.

Both regimens have proved effective in reducing recurrence rates, but premenopausal women or women with estrogen receptor–negative tumors usually are not

candidates for tamoxifen. The alteration of endocrine function caused by tamoxifen has been tenuously linked to endometrial cancer. Though not proved, this potential side effect becomes all the more significant as treatment periods are revised from two to five or ten years, as the newer protocols now call for. (The growth-stimulatory effects of estrogen are inhibited by tamoxifen, in effect inactivating, though not killing, tumor cells. It is therefore thought that longer periods of treatment will reduce recurrence by prolonging tumor cells' inactivation.)

If we could accurately assess the risk of all subgroups, we could be more confident recommending systemic therapy.

Even without the possible connection between this agent and endometrial cancer, the long-term administration of any drug raises legitimate concerns about its effects. "We simply have no data on the long-term effects of tamoxifen," Buzdar said.

More Survival Data Needed

A final issue to be resolved by future research is the question of systemic therapy's effect on overall survival. Reducing the rate of recurrence does not necessarily improve final outcome. Over five years, disease may recur in fewer patients, but what if treatment is merely delaying, rather than preventing, recurrence?

It is clear that before a definitive statement on systemic therapy can be made, researchers must determine its effect on overall survival. Central to this objective is developing an array of prognostic factors that can accurately assess risk. In the meantime, Buzdar said, "the best we can do is outline to the patient the risk and benefits of systemic therapy." In the absence of definitive data, the decision, for most patients, is solely theirs. ■

Physicians who desire additional information may write Aman U. Buzdar, M.D., Department of Medical Oncology, Box 78, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-2817.

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Many Patients Still Choose Total Mastectomy

"I still do more mastectomies than breast conservation, and I'd like to believe I'm enlightened," Hohn said. "Many patients listen to the pluses (of breast conservation) and simply say no. They may not want to commit themselves to four to five weeks of daily radiation treatments. I had a patient from central Texas who recently opted for mastectomy. She said 'Look, I've got canning to do, I've got kids at home to look after, and I'm going to be working in the fall, and there's no radiation therapy close by (her home town). I don't want to spend three weeks recovering from surgery and spend five weeks getting radiation in Houston.'"

For this patient, the issues dealt with her responsibility to her family, but cost can also be a reason for refusing breast conservation. "For patients without insurance, cost is a legitimate concern. The expense of local excision and axillary dissection is about the same as that of mastectomy, but then you add the cost of radiation, which is considerable."

Physicians should be very sensitive to patient preference.

Hohn stressed that patients who choose breast conservation must also make a commitment to long-term surveillance. "If the patient chooses to retain her breast, she is obligated to monitor it carefully," Hohn said. "This is very important, especially in light of the fact that recurrent tumors in a treated breast may be harder to detect. Patients need to understand that there is a small possibility (probably less than one person in ten) of local recurrence, which will require mastectomy. But basically the message should be positive: 90% of patients can keep their breast without concern for jeopardizing survival." ■

Physicians who desire additional information may write David C. Hohn, M.D., Department of General Surgery, Box 112, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-6927.

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M. D. Anderson Fine Needle Aspiration clinic. Of the 1,995 cases, 1,147 were suitable for follow-up. Her study focused on determining the specificity (the true positives) and sensitivity (the true negatives) of cytological tests of tissue aspirated by FNA. The specificity, 99%, was equivalent to that of most other studies, but the sensitivity was 96%—higher than that of most other reports (78–96%)—and the percentage of inconclusive cases was very low (2.7%).

“From a clinician’s standpoint, these values are very significant,” Sneige said. “High sensitivity means a very low incidence of false negatives, and the very low percentage of inconclusive results means that fewer patients had to undergo surgery for biopsy. False positive reports occur even in the most experienced centers. However, the false positive rate with FNA cytology is similar to that reported with histological analysis of frozen section samples (0–4%), so FNA cytology of breast tissue, if performed by an experienced practitioner, is just as good as the traditional technique.”

FNA cytology of breast tissue, if performed by an experienced practitioner, is as good as the traditional technique.

FNA Proves Accurate for B Cell Lymphoma

Sneige and her colleagues have also shown that FNA cytology combined with immunocytochemical techniques can be used to accurately diagnose B cell lymphomas. Of 220 aspirates recently studied, 173 (79%) were correctly diagnosed as one of seven subtypes of B cell lymphoma, based on their expression of specific surface markers (*Acta Cytol* 34:311–323, 1990). The remaining samples were classified as suspicious for lymphoma (7%), benign (10%), or inadequate for diagnosis (4%). (The FNA diagnoses were confirmed by histological analysis of tissue sections.)

“Immunocytochemical techniques have been applied to histological analysis of lymph tissue for some time,” Sneige said, “but their application to FNA cytology is fairly new, so it was important to establish that FNA cytology is just as accurate and reliable.”

FNA an Excellent Alternative to Diagnostic Procedures for Screening Thyroid Cancer

Thyroid tissue is also being examined with FNA cytology. Compared with the number of breast and lymph node aspirates, the number of thyroid aspirates is very low. But for those patients who require thyroid biopsy, FNA cytology provides a vast improvement over traditional methods, Sneige said.

“Generally, to identify a thyroid cancer, you have to take into account a combination of factors: patient history, physical examination, radioisotope imaging, and ultrasound, but this method is very inefficient. Usually, patients must undergo surgery for confirmatory biopsy, which means that many patients with benign nodular goiter have unnecessary surgery. Even with frozen section, the false negative rate can range from 5 to 50%. FNA biopsy, however, can accurately identify malignancy before surgery (with a false-negative rate of 5 to 10%). It’s a far more efficient and cost effective method,” Sneige said.

The major limitation of FNA of thyroid tissue lies in separating follicular/Hürthle cell adenoma from follicular/Hürthle cell carcinoma. The diagnosis of the latter depends on the demonstration of capsular or vascular invasion by the tumor, which can only be evaluated by examination of several histological sections of tumor capsule.

Skill and Experience Essential for Accurate FNA Diagnoses

In fact, skill and experience with FNA affect diagnostic accuracy for any type of tissue, Sneige said. “FNA is by no means new, nor is it complicated, but as with any technique, accuracy improves with practice. In our clinic, accuracy of diagnosis is one of the highest in the country, which is no doubt attributable to the experience our pathologists have gained by performing these procedures daily. Researchers at the University of California, San Francisco (Cohen et al., *Arch Pathol Lab Med* 111:518–520, 1987), the University of Louisville (Barrows et al., *Cancer* 58:1493–1498, 1986), and the University of Vermont College of Medicine (Lee et al., *Acta Cytol* 31:281–284, 1986) have demonstrated that experience and skill, both in performing the biopsy and in interpreting the results, improve diagnostic accuracy. Our clinic was established in 1985; since then, we’ve performed about 8,000 aspirations and now average about 200 per month. The variability in accuracy from institution to institution is probably due to the setting in which FNAs are performed. At some institutions, the technique may be performed infrequently or by a variety of personnel, such that it is difficult for any one person to develop a breadth of experience.”

Sneige said that having a clinic dedicated solely to FNA and staffed by pathologists has another advantage: The pathologist has direct contact with the patient. This is helpful when choosing the appropriate number of aspirates and the preparatory technique, and it allows the pathologist to integrate the physical characteristics of the tumor with its cytologic appearance.

FNA is less traumatic than surgery, much less expensive and requires no special preparation.

Patient Contact Results in Better Assessments

“All these factors contribute to a more accurate assessment,” Sneige said. “By feeling the mass and noting its consistency (tumor resistance) as the needle is inserted, we can get an idea of whether the mass is malignant. The characteristic ‘gritty’ consistency of malignant tumor, for example, differs from the ‘rubbery’ feel of fibroadenoma. This distinction can be useful if, for instance, we feel a hard tumor in a patient whose first aspirate was negative for malignancy. We’ll therefore sample multiple areas of tumor, since it’s possible that the first aspirate might have been taken from a sclerotic area devoid of tumor cells.”

In addition to breast, lymph node, and thyroid tissue, pathologists in the Fine Needle Aspiration clinic can perform aspirations on any superficial mass. (For deep tumors, aspirations are performed by a radiologist using fluoroscopy, computed tomography, or sonography.) Sneige said that over the years the clinic has added a number of prognostic and diagnostic tests to its armamentarium (flow cytometry, estrogen and progesterone assays, lymphoma surface marker studies) and hopes to offer other tests in the future. Sneige added that use of the clinic is not restricted to M. D. Anderson patients.

“Patients can be referred specifically for aspiration only, so if a patient is being treated by his or her community oncologist, the patient can use the clinic and still be treated closer to home. For breast studies, however, we advise that mammograms be performed before referral, since aspirations can cause minor bleeding and distort subsequent mammograms.” ■

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a valid study population, and developing all the components of the testing process has taken a year. The long-term study—which involves over 400 patients—began entering patients this fall. Similar studies are being conducted at some of the major cancer research institutions, but more tests throughout the United States are necessary to truly determine the causes of cervical cancer, Mitchell said.

Mitchell recommends that physicians treat the symptoms and conduct a biopsy to determine whether the abnormal cells are an indication of either preinvasive or invasive cancer. She advises her patients that while there is some evidence that HPV may contribute to both preclinical and clinical cancer, she does not think that it is strong enough across the board. “I don’t get them worried about it,” she emphasizes. “I tell them simply that we should follow the condition.” ■

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Clinical Applications of Fine Needle Aspiration Increase



Nour Sneige

Although cutting biopsy has been the standard technique for tissue diagnosis, fine needle aspiration (FNA) is rapidly gaining popularity among physicians as a less invasive alternative. FNA is most often used to examine breast, lymph node, and thyroid tissue, which is aspirated through a 22- or 25-gauge needle. Diagnoses

can be obtained within 30 minutes of aspiration and are just as accurate as those obtained from surgical biopsy.

FNA is less traumatic than surgery, is much less expensive, and requires no special preparations, except for local anesthesia for patients who request it, according to Nour Sneige, M.D., chief of the Fine Needle Aspiration service and operations director of Cytopathology at The University of Texas M. D. Anderson Cancer Center.

Because of these advantages, FNA is increasingly being used in the United States. But it first had to be proved that cytological analysis of FNA-derived tissue was just as accurate as histological analysis of tissue derived from cutting biopsy. The primary difference between cutting biopsy and FNA lies in the nature of the sample and the processing technique. With cutting biopsy, a larger tissue sample is obtained, which is then fixed in formalin and embedded in paraffin for histological staining. In FNA, however, the aspirated samples are smeared on slides, stained, and examined in a few minutes. For the latter, an experienced pathologist is needed for accurate interpretation.

The data of Sneige and coworkers at the M. D. Anderson Cancer Center and those of other investigators around the country indeed confirm that cytological analysis of tissue obtained by FNA is just as accurate.

Sneige recently analyzed the data from 1,995 breast tissue aspirates performed between 1985 and 1989 in the

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