ASPO Distinguished Achievement Award Lecture

Studies on the Epidemiology and Natural History of Benign Breast Disease and Breast Cancer Using Nipple Aspirate Fluid

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Nicholas L. Petrakis, M.D., was presented the American Society of Preventive Oncology’s Distinguished Achievement Award at the Society’s annual meeting on March 15, 1992, in Bethesda, Maryland. The basis for choosing Dr. Petrakis was his distinguished achievements for over 20 years in research and education concerning the etiology and prevention of cancer, with substantial emphasis on breast cancer.

Dr. Petrakis obtained a Bachelor of Arts degree from Augustana College, Sioux Falls, South Dakota, and his Doctor of Medicine degree from Washington University, St. Louis, Missouri. He has held numerous principal positions at the University of California, beginning with a position with the U.S. Public Health Service, National Cancer Institute Laboratory of Experimental Oncology, and then the Cancer Research Institute, both at the University of California, San Francisco. Dr. Petrakis has held continuing appointments in the Department of Preventive Medicine and Department of Epidemiology and International Health, beginning as an Assistant Professor. He was subsequently promoted to Associate Professor and Professor of Preventive Medicine. During the years from 1978 to 1989, Dr. Petrakis was chair of the Department of Epidemiology and International Health. Since 1981 he has been Professor of Epidemiology, University of California, Berkeley, School of Public Health. In 1989 he became Professor Emeritus of Preventive Medicine and Epidemiology.

Dr. Petrakis’s curriculum vitae includes the following titles and honors: the Eleanor Roosevelt International Cancer Fellowship (1962–63); election in 1979 to the American Epidemiologic Society; a founding member in 1976 the American Society of Preventive Oncology; a member of the Biometry and Epidemiology Contract Review Committee, National Cancer Institute; a member of the Board of Scientific Counselors, Division of Cancer Etiology (1982–86); President of the American Society of Preventive Oncology (1985–86); and recipient of the Lewis C. Robbins Award in 1985 from the Society of Prospective Medicine. Since 1991 he has been a member of the Scientific Advisory Committee of the University of California’s tobacco-related disease research program.

Dr. Petrakis’s research and mentoring career has also been extensive. He began to publish his innovative research on cerumen and its association with disease in 1967. In 1971 he published his first paper on cerumen genetics and human breast cancer. These were followed in 1973 by his participation in a national conference on cancer prevention and detection with the presentation of a paper on the use of breast fluid aspiration in the early diagnosis and epidemiology of breast cancer. These sentinel papers marked the beginning of over 20 years of research and publication on the relationship of breast nipple aspirate fluid, cerumen, and the epidemiology and prevention of breast cancer.

Dr. Petrakis has influenced the career of many scientists by his collaborative research and by serving as their research mentor. One example is the 1977 joint publication by Drs. Petrakis and M-C. King on genetic markers and cancer epidemiology. His scientific investigations of and publications on the etiology and prevention of breast cancer continue with several manuscripts in progress or recently submitted.

Thomas J. Moon
University of Arizona
Tucson, AZ 85724

Introduction

It has been recognized for over 100 years that the adult nonpregnant, nonlactating breast secretes fluid into the breast ductal system. Except during lactation and in the galactorrhea associated with endocrinopathies, the nipple ducts are tightly occluded by keratin plugs, and secretions from the nipple only rarely escape. The presence of stained proteinaceous material and cellular debris within the ducts in histological sections of breast tissue provides microscopic evidence for secretion. Geoffrey Keynes in 1923 wrote: "The breast is a gland which throughout life is exhibiting some secretory activ-
The female breast is unique in that its secretions may be retained for varying periods of time within the alveolar-ductal system, where the various secretory components and exfoliated cells undergo degradation and are metabolized locally and absorbed into the blood and lymphatic systems. Bonser et al. (4) proposed in 1961 that locally formed toxic degradation products or carcinogens, probably derived from the breast ducts from the blood, might be concentrated in relatively static breast secretions and be of significance in the etiology of benign breast disease and breast cancer. However, few if any studies examined this hypothesis.

Over the past 20 years, my colleagues and I have investigated the epidemiology of the female breast. The central theme of this research has been the study of biochemical, hormonal, and cytological features of breast fluid obtained by nipple aspiration and of the interrelationships of the various constituents of NAF to benign breast disease and the risk of breast cancer. Particularly exciting are the results of our recent analyses of a large cohort of women who underwent nipple aspiration cytology 10 to 18 years ago, the implications for the detection of women at increased risk of breast cancer, and the potential of NAF cytology as a tool for research in the primary prevention of breast cancer.

Working Hypothesis

We have adopted a modification of the now classical views as our working hypothesis. We propose that: (a) the physiological secretory activity of the breast provides a mechanism by which breast epithelium can be exposed to cytotoxic, mutagenic, and carcinogenic substances derived from both endogenous and environmental sources; (b) the secretion and the prolonged retention of weak carcinogens and promoters within the breast ductal system may have greater damaging effects on the epithelium than occasional short-term exposures to high concentrations of substances that are rapidly secreted and reabsorbed from the breast gland; (c) the physiological equilibrium between secretion and reabsorption may be an important determinant of the extent and duration of exposure of breast epithelia to carcinogenic agents; (d) the extent of exposure of the epithelium to these substances is conditioned by genetic, endocrine, reproductive, dietary, and sociocultural factors. In genetically susceptible women, this secretory process may increase the risk of initiation and promotion of breast epithelial cells to proliferative premalignant and malignant stages. Our studies have provided evidence in support of some, but not all, of the elements of this hypothesis.

Technique of Nipple Aspiration

Breast pumps have been used for many years by clinicians for the collection of fluid from women with abnormal nipple secretions for cytological and biochemical study. No systematic large-scale study of the secretions of the normal breast had been reported until the 1950s, when Papanicolaou et al. (5) used the maternal bulb-type breast pump to collect breast epithelial cells for the early detection of breast cancer. However, this type of breast pump is inefficient and yields fluid in only 20% of normal women. More recently, Sartorius devised a simple breast pump with which he obtained nipple aspirate fluid in over 60% of women attending his breast clinic (6). This device consists of a plastic cup that is placed over the cleansed nipple and attached by a short plastic tube to a 15-ml syringe; while the subject compresses her breast between both hands, the plunger of the syringe is withdrawn to 10 ml and held until fluid appears at the nipple surface. If no fluid appears within 15 s, the woman is designated a nonyielder or "nonsecretor." This degree of negative pressure is readily tolerated and will yield usable amounts of NAF in over 50% of non-Asian and in about 30 to 40% of Asian premenopausal women (7, 8). The volume of fluid obtained by nipple aspiration can range from a trace of moisture on the nipple surface to quantities greater than 100 µl. The NAF appearing at the nipple surface is collected into capillary tubes for cytological and biochemical studies. We have used this device to collect fluid from over 8000 women.

Four factors have been consistently associated with our ability to obtain NAF from nonlactating women: age 30 to 55 years; earlier age at menarche; history of parity and/or lactation; and non-Asian versus Asian ethnicity (9). We found no consistent relationship between yield of NAF and a variety of other factors, including serum estrogen levels, exogenous estrogen use, phase of the menstrual cycle, prior abortion, family history of breast cancer, and natural versus surgical menopause. Recent studies indicate that a higher proportion of women consuming more than 50 g of fat/day yield NAF than women consuming less than 50 g of fat/day (10). This influence of dietary fat appears to be independent of the previously mentioned factors. The proportion of women yielding fluid by age and menopausal status is shown in Fig. 1.

The lower proportion of NAF yielders found among Asian women compared with white and African-American women may be related, in part, to a dimorphic mendelian apocrine trait affecting secretion by the breast, axillary, cerumenous, and other apocrine glands (11). With an otoscope, the two phenotypes can be classified by the appearance of cerumen (earwax) as "wet" or "soft" and as "dry" or "hard." The dry cerumen phenotype is highly prevalent among Japanese, Chinese, and Native American populations; the wet type is characteristic of Caucasian and African-American populations (11, 12). Women with the dominant wet-type cerumen are reported to have greater quantities of axillary apocrine secretion than those with homozygous recessive dry-type cerumen (13). We found that women with wet cerumen are more likely to yield NAF, and of higher volume, than women with dry cerumen (14) (Fig. 2).

Biochemical Components of Nipple Aspirate Fluid

Of Endogenous Origin

Nipple aspirate fluid contains a variety of biochemical constituents of endogenous origin, including lactose, α-
lactalbumin, protein, immunoglobulins, lipids, fatty acids, cholesterol and cholesterol oxidation products, and steroid hormones, including estrogens, androgens, progesterone, dehydroepiandrosterone sulfate, prolactin, growth hormone, and the peptide growth factors epidermal growth factor and transforming growth factor \( \alpha \) (15–32). Our biochemical findings on estrogens, cholesterol, and cholesterol epoxides in NAF may have potential etiological significance in breast disease. Information on other substances studied by us and by others can be found in several earlier reviews (15, 16).

**Estrogens.** Our studies have examined the relation of menstrual, reproductive, and other risk factors to the concentrations of estradiol and estrone in the NAF and serum of women with and without breast disease. Nipple aspirate fluid commonly contains estrogens, estrone, and estradiol at levels far exceeding those found in plasma (22, 23). We found that concentrations of estradiol and estrone in NAF from women with normal breasts or with benign breast disease were 10 to 40 times higher than corresponding serum levels. There was no significant relationship of the levels of estrogens in NAF with day in the menstrual cycle, pre- and postmenopausal status, or benign breast disease and breast cancer. The most striking finding was the marked and sustained decrease in estrogen levels in NAF that persisted for several years following pregnancy or the cessation of lactation (22). This decrease in estrogen levels, and the likely decrease in other hormones and constituents of NAF such as cholesterol (see below), in the breast ductal system following pregnancy offers a physiological mechanism for the protective effect of parity against breast cancer, i.e., a prolonged period of reduced exposure of breast epithelia to estrogen and other potentially harmful chemical substances of endogenous and exogenous sources that, prior to the pregnancy, have accumulated in the NAF.

The mechanisms responsible for the high concentrations of these hormones in NAF are not clear. Possibly, as the result of a normal physiological uptake from the blood by the breast epithelium, estrogens are transported across and secreted by the epithelium and, because of a low rate of reabsorption, they slowly accumulate in NAF. Alternatively, estrogens may be actively synthesized by the breast epithelium and secreted into NAF (24). The finding of the enzyme aromatase in breast cancer tissue and of extremely high concentrations of dehydroepiandrosterone in NAF compared with plasma suggests that DHA-S, an androgenic steroid, may serve as a precursor in the synthesis of estrogen and other steroid hormones by breast tumors (20, 28, 29). Possibly this also occurs in the normal breast.

**Cholesterol and Cholesterol 5,6α-Epoxide.** A wide range of cholesterol concentrations occurs in NAF, ranging from 0.013 to 25.7 mmol/liter (30–32). Similar to the steroid hormones, the levels of cholesterol in the NAF are elevated above plasma levels. NAF also contains significant concentrations of the 5,6α- and β-epoxides of cholesterol (30–32). These peroxidation products of cholesterol, which likely arise within the relatively stagnant secretions in the breast ducts, have been reported to damage DNA and to induce breaks in chromosomes (33), to cause sarcomas when injected into experimental animals (34), and to transform hamster kidney cells in tissue culture (35). Also similar to estrogen, the concentrations of cholesterol in NAF fall to markedly low concentrations following pregnancy and lactation and only
Table 1  Breast cancer incidence and adjusted relative risks of breast cancer by cytological diagnosis in nipple aspirates of breast fluid from white volunteer women in the San Francisco Bay Area, 1973-1991

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>No. with breast cancer/ no. of women</th>
<th>Percentage with breast cancer</th>
<th>Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted relative risk*</td>
</tr>
<tr>
<td>No breast fluid</td>
<td>9/352</td>
<td>2.6</td>
<td>1.0*</td>
</tr>
<tr>
<td>Specimen unsatisfactory</td>
<td>15/315</td>
<td>4.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Normal</td>
<td>56/1291</td>
<td>4.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>18/327</td>
<td>5.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>6/58</td>
<td>10.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Total</td>
<td>104/2343</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

* Relative risks adjusted by Cox regression for age and year of specimen collection.

Studies of the Cytology of Nipple Aspirate Fluid

In the early 1950s, Papanicolaou et al. (5) studied both healthy women and women with breast cancer to learn if nipple aspiration cytology could be used to detect breast cancer. More recently, King et al. (41-43), Sartorius et al. (8), and Buehning (44) have investigated the cytology of NAF from patients with benign breast disease or breast cancer and from women without known breast disease. Detailed descriptions of the preparatory techniques and the cytological characteristics of NAF are given in the papers by King et al. The normal cellular components of NAF include ductal epithelial cells, colostral (foam) cells, lymphocytes, neutrophils, and necrotic cells (41). NAF specimens from normal women without symptoms of breast disease contain mostly foamy cells, and ductal epithelial cells are scarce or absent. In contrast, a significant proportion of NAF specimens obtained from women with evidence of benign breast disease are cellular and almost always contain foamy cells, apocrine metaplastic cells, normal ductal epithelial cells, and, less frequently, ductal epithelial cells that may have nuclear changes characteristic of hyperplasia and severe atypia (42, 43). As used here, the term "atypia" is the NAF equivalent of histological "atypical hyperplasia" (43). About 25% of nipple aspirates from premenopausal women contain proliferative epithelium, i.e., hyperplasia and atypia. Malignant cells are rarely found in NAF, even when they are obtained from breasts containing cancer. Possibly this is due to the obstruction of the breast ducts by the tumor which prevents the cells from reaching the nipple.

Examples of Exogenous Substances in NAF

It is well recognized that nursing mothers will secrete many medications and food-derived substances into their milk. Since nipple aspirate fluid closely resembles colostrum and milk in composition, we attempted to determine if the nonlactating breast also secretes chemical substances of exogenous origin into breast fluid. We found that nicotine and cotinine are secreted into breast fluid soon after a woman begins to smoke a cigarette (38). Similarly, following its i.v. injection, technetium (¹⁹⁵Tc) promptly appears in the NAF. Using the Ames Salmonella mutagenicity test, we detected mutagens of unknown nature in 6 to 10% of random samples of the NAF of apparently healthy women (39). Of 44 pregnant farm workers environmentally exposed to pesticides, the precociously obtained by nipple aspiration was positive for mutagenicity by the Ames test in 26 (59.1%), whereas only 7 (17.4%) of 55 pregnant women seen in our clinics were positive (40). It is of interest that in a patient with cancer who was treated with the alkylating drug thiotepa, the NAF became strongly mutagenic within 12 h after i.v. injection. These and other findings support the hypothesis that potentially toxic and mutagenic substances from the environment can reach the breast epithelium.

Gradually increase in concentration, taking several years to reach the levels comparable to those of nulliparous women (28). In a recent study of the relation of NAF cholesterol and 5,6-epoxide to breast cancer risk factors we measured the concentrations of these substances in NAF samples from 68 women with biopsied benign breast disease and 135 control women without a history of benign breast disease (31, 32). Significant associations were found of both NAF cholesterol and 5,6-epoxide with age and ethnicity (i.e., higher with advancing age, higher in white than in nonwhite women, and higher in current or past smokers). When controlled for the various risk factors, strong associations were found of proliferative benign breast disease (hyperplasia with or without atypia), with NAF cholesterol and particularly with 5,6-epoxide in breast biopsies compared with controls (odds ratio = 2.5 and 8.5, respectively). These findings support an etiological role for cholesterol 5,6-epoxide in proliferative breast disease.

It is noteworthy that NAF occurs in different colorations, ranging from colorless to white, pale yellow, dark yellow, brown, green and black (36). Higher NAF concentrations of the lipid-soluble steroids cholesterol, cholesterol 5,6-epoxide, estrogens, and fluorescent products of lipid peroxidation were positively associated with the concentrations of the lipid-soluble steroids cholesterol, cho-

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Atypical NAF Cytology and Risk of Breast Cancer

In the pathogenesis of breast cancer, epithelial changes in the breast ductal system are believed to change from the normal nonproliferative epithelium through proliferative stages of hyperplasia, atypical hyperplasia, and carcinoma in situ to cancer. It is now generally accepted that the histological changes of hyperplasia and atypical hyperplasia of the breast epithelium found in breast biopsies represent precursor or "marker" lesions that are indicative of an increased risk of breast cancer (45–51).

When diagnosed in surgical biopsies of suspicious breast masses, these cellular alterations provide information on the natural history of breast cancer, and they alert both patient and physician to the necessity of continuing clinical and mammographic surveillance.

Although the evidence that proliferative epithelial changes within the breast are useful as markers of increased risk, breast biopsy can be made only when clinically indicated. Studies indicate that less than 15% of women with breast symptoms or physical findings have ever undergone a breast biopsy and that only about 5% of these biopsy specimens show evidence of atypical hyperplasia (52). Further, fewer than 15% of women who develop breast cancer have a history of a benign breast biopsy (52). These data indicate that the great majority of women who develop breast cancer have never undergone breast biopsy and that the status of their breast epithelia during the prolonged earlier preclinical phases of proliferative breast disease is unknown (53).

For epidemiological studies of the natural history and risk of breast cancer, it is important to determine the prevalence of these proliferative precursor or marker lesions and the subsequent risk of breast cancer in women without clinical breast findings and for whom breast biopsy is not warranted. Nipple aspirate cytology provides a clinically acceptable technique for this purpose, but the evaluation of NAF cytology as a prognostic marker requires that a large cohort of women be followed for a sufficient period of time until an adequate number of breast cancers has developed so that breast status can be correlated with earlier cytological findings.

Table 2  Breast cancer incidence and adjusted relative risks of breast cancer by cytological diagnosis in nipple aspirates of breast fluid from white volunteer women in the San Francisco Bay Area, for women 25–54 years, and 55 years of age and older, 1971–1991

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>No. with breast cancer/no. of women</th>
<th>Percentage with breast cancer</th>
<th>Adjusted relative risk*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women 25–54 years of age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast fluid</td>
<td>1/178</td>
<td>(0.6)</td>
<td>1.0b</td>
<td></td>
</tr>
<tr>
<td>Specimen unsatisfactory</td>
<td>8/168</td>
<td>(4.8)</td>
<td>6.7</td>
<td>0.8–53.4</td>
</tr>
<tr>
<td>Normal</td>
<td>41/1031</td>
<td>(4.0)</td>
<td>6.4</td>
<td>0.9–46.3</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>16/281</td>
<td>(5.7)</td>
<td>9.5</td>
<td>1.3–71.7</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>5/51</td>
<td>(9.8)</td>
<td>16.3</td>
<td>1.9–139.3</td>
</tr>
<tr>
<td>Total</td>
<td>71/1709</td>
<td>(4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women ≥55 years of age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast fluid</td>
<td>8/144</td>
<td>(5.6)</td>
<td>1.0b</td>
<td></td>
</tr>
<tr>
<td>Specimen unsatisfactory</td>
<td>7/132</td>
<td>(5.3)</td>
<td>0.8</td>
<td>0.3–2.2</td>
</tr>
<tr>
<td>Normal</td>
<td>152/244</td>
<td>(6.7)</td>
<td>1.0</td>
<td>0.4–2.3</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>2/41</td>
<td>(4.9)</td>
<td>0.7</td>
<td>0.1–3.3</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>1/6</td>
<td>(16.7)</td>
<td>2.6</td>
<td>0.3–20.9</td>
</tr>
<tr>
<td>Total</td>
<td>33/547</td>
<td>(6.0)</td>
<td></td>
<td></td>
</tr>
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* Relative risks adjusted by Cox regressions for age and year of entry.

We have recently published the findings from the first prospective study of breast cancer risk in relation to NAF cytology (54). This study involved 2701 white women volunteers from the San Francisco Bay Area in whom a single nipple aspiration had been attempted 10–18 years earlier. The women had not been pregnant or lactating and were free of breast cancer within 6 months of entry into the study. Follow-up was complete for 87% of this cohort, representing an average of 12.5 years of follow-up. The results of this cohort study provide strong support for our hypothesis that cytological epithelial hyperplasia and atypia in NAF are associated with an increased risk for breast cancer. The incidence and the relative risk of breast cancer by cytological diagnosis for women of all ages are shown in Table 1. Compared with nonsecretors of NAF who had the lowest risk, a stepwise increase in risk was found for both the incidence and the relative risk of breast cancer with increasing severity of cytological change. Women with NAF atypia and a first-degree family history of breast cancer were 6 times more...
likely to develop breast cancer than women with atypia but without a family history of breast cancer. Even greater risks of breast cancer were found for hyperplasia and for atypia in women under 55 years of age (Table 2). It is of particular interest that women whose nipple aspirates were either unsatisfactory for cytology or contained normal cytology had elevated relative risks of breast cancer compared with women who yielded no fluid. These findings provide support for our hypothesis that secretion, per se, may be associated with an increased risk of breast cancer. At the date of closure of the last follow-up (April 1991), only a small proportion of the women, 20 (7.6%) of 265, whose NAF specimens had been diagnosed as hyperplasia or atypia developed breast cancer, indicating that additional factors are likely to be involved in susceptibility to the disease.

As seen in Fig. 3, the cumulative risk of breast cancer at 17 years since aspiration in women with NAF atypia is almost identical to that found for atypical hyperplasia in biopsy by Dupont and Page (49). This suggests that epithelial atypical hyperplasia, whether diagnosed in benign breast biopsy or in nipple aspirate fluid, is a cytological marker of increased risk for breast cancer. This reasoning led us to compare the sensitivity, specificity, and positive predictive value of our nipple aspirate diagnosis of atypia with those calculated from data in several recent reports on atypical hyperplasia diagnosed by biopsy. The positive predictive values for the two modalities of atypical hyperplasia in biopsies and NAF atypia are comparably low (Table 3). Of additional interest is the finding that the positive predictive value in the Canadian mammographic study was similar (55). Lee et al. reported a strong association of proliferative epithelial cells in NAF with mammographic pattern and density. In the most recent analyses of our cohort, we found that NAF atypia in women who had previously undergone a benign breast biopsy was associated with a significantly increased risk of breast cancer compared with women without this history. These findings suggest that NAF cytology may be a useful ancillary technique for identifying those women undergoing mammographic screening, who have a prior history of benign breast biopsy and who are truly at increased risk for breast cancer.

In 1954, Papanicolaou et al. (5) reported their studies with nipple aspiration in over 2000 women, in which a small number of unsuspected cancers were diagnosed in women without clinical findings. They suggested that NAF cytology might be used as a screening test in the physician’s office, particularly in women from whom nipple fluid can be manually expressed, but they noted that as a screening method for breast cancer, the widespread use of nipple aspiration was limited by the method for nipple aspiration available. Our current findings suggest that Papanicolaou’s proposal has merit. This simple collection procedure could be quickly carried out with the more efficient Sartorius-type breast pump during the physical examination. Its use should be of greatest value in premenopausal women from whom NAF is most readily obtained and in whom we found the highest risks to be associated with NAF atypia. However, to implement a widespread application of NAF cytology would require additional training of physicians, pathologists, and cytotechnologists in the nuances of nipple aspiration cytology. In addition, the receipt of large numbers of NAF specimens would likely swamp the nation’s already overburdened cytopathology laboratories. The development of automated cytologic technologies promises to alleviate this potential bottleneck in the near future.

Because our studies of breast cancer risk by NAF cytology have been made almost entirely on white women, it is desirable to obtain risk data for African-American, Asian, and Hispanic women in whom breast cancer incidence rates are increasing. Emphasis should be given to immigrant populations from countries of low breast cancer incidence risk to help identify host and environmental factors of possible etiological significance. NAF cytology might also be used to identify high-risk women with NAF atypia for use in proposed low-fat, tamoxifen, and other prevention trials. Finally, it will be possible in the near future to apply some of the newer molecular and immunologic methods for nipple aspirates of breast fluid and history of biopsy on the risk of breast cancer (Abstract). Presented at the 25th Annual Meeting of the Society for Epidemiologic Research, Minneapolis, MN, June 9–12, 1992, manuscript in preparation.

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### Table 1: Risk of breast cancer: a comparison of the sensitivity, specificity, and positive predictive value of a biopsy diagnosis of atypical hyperplasia versus nipple aspirate cytology diagnosis of atypia

<table>
<thead>
<tr>
<th></th>
<th>Biopsy</th>
<th>NAF cytolgy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Dupont and Page (49)</td>
<td>Carter et al. (50)</td>
</tr>
<tr>
<td>No. of women</td>
<td>1,303</td>
<td>16,692</td>
</tr>
<tr>
<td>Years of follow up</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Control group</td>
<td>Atlanta TNCS</td>
<td>No BBID</td>
</tr>
<tr>
<td>Percentage atypical hyperplasia</td>
<td>3.6</td>
<td>8</td>
</tr>
<tr>
<td>NAF atypia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of breast cancer</td>
<td>4.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Percentage sensitivity</td>
<td>49.2</td>
<td>28.4</td>
</tr>
<tr>
<td>Percentage specificity</td>
<td>90.0</td>
<td>95.0</td>
</tr>
<tr>
<td>Percentage positive predictive value</td>
<td>12.9</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* TNCS, Third National Cancer Survey; BBG, benign breast disease.

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munological techniques to the cells and fluid obtained by nipple aspiration. This should increase our ability to more precisely identify those women with NAF atypia who are at increased risk and who might benefit from more intensive surveillance and, when developed, from new effective preventive modalities.

Acknowledgments

The author is deeply indebted to the following colleagues and staff members for their collaboration and contributions to this program—project grant: Eileen B. King; Virginia L. Ernster; Margaret R. Wrensch; Marion M. Lee; Rei Miike; Larry D. Gruenke; John C. Craig; Pentti Siteri; Brian Mayall; Lynn Mason; Karen L. Chew; John K. Wieczer; John Horn; Thomas K. Hunt; Robert Schweitzer; William H. Goodson, III; Walter Hauck; Joan Hilton; Christopher Maack; Mary-Claire King; Edward Sickles; Diana Barrett; James Murai; Mulan Lim; Maureen Morris; Linda Lee; Susan Sacks; Michael Lyon; LeeAnn Duarte; Stella Petrakis-Pawson; Betty Chang Lee. He wishes to specially acknowledge the sustained assistance and support given to this project by Nathaniel I. Berlin, Genrose Copley, and Elizabeth Anderson of the National Cancer Institute.

References

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N L Petrakis

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