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14. ABSTRACT

Nipple aspiration, ductal lavage and ductography are methods of obtaining breast fluids from women who are neither pregnant or lactating. Breast cells in these fluids can be classified as either normal or as showing various abnormalities including hyperplasia, atypical hyperplasia and cancer. In previous follow-up studies of women who participated in breast fluid and tissue studies, it was shown that women with proliferative cytology (hyperplasia or atypical hyperplasia) were significantly more likely to develop breast cancer than women with normal cytologic findings in breast fluids or than women from whom fluid could not be obtained. (Fabian et al., 2000; Wrensch et al., 2001) This study followed an additional cohort of women from Santa Barbara, CA that had fluids drawn between 1970-1990. Statistical methods of association were used to determine if women with abnormal ctyologic findings developed breast cancer at a higher rate than women with normal cytologic findings or women from whom fluid could not be obtained. Overall, 10% (93) of the 946 women developed breast cancer during the follow-up period.

15. SUBJECT TERMS
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INTRODUCTION:

Nipple aspiration, ductal lavage and ductography are methods of obtaining breast fluids from women who are neither pregnant or lactating. Breast cells in these fluids can be classified as either normal or as showing various abnormalities including hyperplasia, atypical hyperplasia and cancer. In previous follow-up studies of women who participated in breast fluid and tissue studies, it was shown that women with proliferative cytology (hyperplasia or atypical hyperplasia) were significantly more likely to develop breast cancer than women with normal cytologic findings in breast fluids or than women from whom fluid could not be obtained. (Fabian et al., 2000; Wrensch et al., 2001) This study followed an additional cohort of women from Santa Barbara, CA that had fluids drawn between 1970-1990. Statistical methods of association were used to determine if women with abnormal ctyologic findings developed breast cancer at a higher rate than women with normal cytologic findings or women from whom fluid could not be obtained.

BODY:

The stated goals (including Steps 1-3) in the Statement of Work were addressed in the 2006 annual summary report. The completion of Steps 4-5 will be outlined in this report:

Step 4 – The study pathologist, Dr. Eileen King, completed review of various cytologic diagnoses from the original study data abstraction. She ranked cytology from least to most severe. Cytologic categories were defined as 1) no fluid 2) insufficient specimen 3) normal epithelial cells 4) hyperplasia and 5) atypia. We eliminated cytologic categories from the original database that could not have been from nipple aspiration in order to ensure that all of the results were obtained from the techniques analyzed for this study.

Step 5 – Final data analysis has been completed at this time. A presentation abstract was developed, submitted and accepted for presentation at the Dr. Susan Love Research Foundations' Intraductal Symposium on March 3, 2007. In addition, the P.I. will be doing a podium presentation on an earlier manuscript published from this data on February 8, 2007 at the ONS Research Conference in Hollywood, CA .

From the 3,204 members of the original cohort (total of alive and deceased), we have completed data from 950 members of the original cohort. 946 were eligible for use in the final model, and another 1,534 had vital statistics and address information confirmed. We did not include these subjects in the final model due to lack of confirmed breast cancer status. This was a limitation of the study given that California Cancer Registry (CCR) has only been collecting breast cancer data since 1988. We have completed all second mailings and linkage with DMV for updated addresses. Phone calls were completed to all remaining subjects who did not respond. All phone contact

attempts were completed by June 15, 2006. Our data has been merged with California mortality tapes (years 1970-1999) and we purchased tapes from years 1999-2004 to complete a final merge in July 2006. All follow up contact attempts and linkages were completed by July, 2006. Analysis of collected data began in July/August, 2006 with final study results completed in December, 2006.

KEY RESEARCH ACCOMPLISHMENTS:

-Study objective achieved: P.I. determined breast cancer incidence and mortality in cohort

-P.I. participated in multi-disciplinary effort to achieve specific aims of the study

-Cohort of breast clinic patients followed from 1970-2006

-Statistical models of association between categories of breast fluid cytology were constructed

REPORTABLE OUTCOMES:

-P.I. received Ph.D. in Nursing – June 2005, University of California San Francisco

-poster presentation: Oncology Nursing Society – Anahem, CA, April 2004

-poster presentation: DOD Era of Hope meeting – Philadelphia, PA, June 2005

-podium presentation: ONS Research Conference – Hollywood, CA, February 2007

-podium presentation: Dr. Susan Love Research Conference – Santa Monica, CA, March 2007

- article – *Breast Carcinogenesis – Can the Examination of Ductal Fluid Enhance Our Understanding?* ONF, January 2005

- article – *Strengths and Limitations of Breast Cancer Risk Assessment.* ONF, May 2005

- article – *Variables Associated with Obtaining Nipple Aspirate Fluid in a Cohort of Non-Lactating Women.* BMC Women's Health, May, 2006.

- Teaching opportunity - the grant recipient was co-faculty of record in fall quarter, 2005 & 2006 for N265 – Cancer Prevention and Early Detection at UCSF Department of Physiological Nursing and has been asked to teach the course again in Fall, 2007

- Employment opportunity – Grant recipient has accepted a position as adjunct assistant professor at UCSF Department of Physiological Nursing (7/06) based on experience supported by this grant

CONCLUSIONS:

Overall, 10% (93) of the 946 women developed breast cancer during the follow-up period. Breast cancer incidence was 9% (63 of 714) in women from whom no fluid could be obtained, 11% (2 of 19) in women with insufficient specimens, 12 % (11 of 89) in women with normal epithelial cells, and 28% (17 of 124) in women with hyperplasia/atypia. Age-adjusted relative risks and 95% confidence intervals (C.I.) compared to those with no fluid were 1.4 (0.3 to 6.4), 1.7 (0.9 to 3.5), and 2.0 (1.1 to 3.6) for women with insufficient specimens, normal epithelial cells and hyperplasia/atypia, respectively. Comparing solely the presence or absence of epithelial cells in NAF, women with epithelial cells present in NAF were more likely to develop breast cancer than women with no fluid or insufficient specimens (RR = 1.8, 1.1 to 3.0).

These results support previous findings that 1) women with abnormal epithelial cells in NAF have an increased risk of breast cancer when compared to women with no NAF or normal epithelial cells in NAF and 2) women with epithelial cells present in NAF have an increased risk of breast cancer when compared to women with no NAF fluid or NAF without epithelial cells present

REFERENCES:

See attached.

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Wrensch, M. R., Petrakis, N. L., Miike, R., King, E. B., Chew, K., Neuhaus, J., et al. (2001). Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. *Journal of the National Cancer Institute, 93*(23), 1791-1798.

ABNORMAL CYTOLOGY IN NIPPLE ASPIRATE FLUID AND SUBSEQUENT BREAST CANCER RISK

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Background: Past studies have shown that women with abnormal cytology in nipple aspirate fluid (NAF) have an increased relative risk (RR) of breast cancer when compared to women with normal cytology in NAF and women from whom NAF was attempted but not obtained (Wrensch et al., 1992, 2001). In addition, a recent study (Buehring et al., 2006) found that women with epithelial cells present in NAF, regardless of cytological category, were more likely to develop breast cancer than women without NAF. This study analyzed NAF results from a group of women seen by Dr. Otto Sartorius in his Santa Barbara breast clinic between 1970-1990 (N= 2480). Our analysis presented here is an aggregate of two sub-groups: women with questionnaire data (n=712) and those with NAF visits beginning in 1988 (n=238), the year in which cancer case information was uniformly collected in the state of California.

Methods: Cytological classification was determined for a group of 946 women using the most severe epithelial cytology observed in fluid specimens. Classifications included no fluid obtained, insufficient specimen, normal cell cytology, hyperplasia, and atypical hyperplasia. Breast cancer incidence and mortality status was determined through June 2006 using data from the California Cancer Registry, California Vital Statistics and self-report. We estimated RRs for breast cancer using logistic regression analysis, adjusting for age. We analyzed breast cancer risk related to severity of NAF cytology using no fluid as the referent group and breast cancer risk related to the presence or absence of epithelial cells in NAF, using no fluid/insufficient specimen as the referent group. All statistical tests were two-sided.

Results: Overall, 10% (93) of the 946 women developed breast cancer during the follow-up period. Breast cancer incidence was 9% (63 of 714) in women from whom no fluid could be obtained, 11% (2 of 19) in women with insufficient specimens, 12 % (11 of 89) in women with normal epithelial cells, and 28% (17 of 124) in women with hyperplasia/atypia. Age-adjusted relative risks and 95% confidence intervals (C.I.) compared to those with no fluid were 1.4 (0.3 to 6.4), 1.7 (0.9 to 3.5), and 2.0 (1.1 to 3.6) for women with insufficient specimens, normal epithelial cells and hyperplasia/atypia, respectively. Comparing solely the presence or absence of epithelial cells in NAF, women with epithelial cells present in NAF were more likely to develop breast cancer than women with no fluid or insufficient specimens (RR = 1.8, 1.1 to 3.0).

Conclusions: These results support previous findings that 1) women with abnormal epithelial cells in NAF have an increased risk of breast cancer when compared to women with no NAF or normal epithelial cells in NAF and 2) women with epithelial cells present in NAF have an increased risk of breast cancer when compared to women with no NAF fluid or NAF without epithelial cells present.

VARIABLES ASSOCIATED WITH OBTAINING NIPPLE ASPIRATE FLUID IN A COHORT OF NON-LACTATING WOMEN

Kimberly Baltzell, R.N., Ph.D., Margaret Wrensch, Ph.D., Jennette Sison, M.P.H.

Background

The search for biologic endpoints and biomarkers in the study of breast cancer risk assessment and risk reduction strategies has led to an interest in obtaining cytologic information and other biomarkers from nipple aspirate fluid (NAF).

Methods

This descriptive study examined factors associated with an increased ability to obtain NAF in a cohort of 3043 women between the ages of 15 and 89 years of age. The majority of women were between the ages of 30-49 (N=1529/50.2%). Variables examined in relation to obtaining fluid include: age, marital status, age at menarche, menopausal status, a history of pregnancy, a history of breast-feeding, estrogen use, oral contraceptive use, endocrine disorders and tranquilizer use.

Results

On average, women from whom breast fluid was obtained were younger than women from whom breast fluid was attempted but not obtained (mean = 41.9 years versus 46.5 years, $p<0.0001$). In unadjusted and age-adjusted comparisons, being married, a history of pregnancy, younger age at menarche (12 years of age or younger), tranquilizer use, oral contraceptive pill (OCP) use and endocrine problems were associated with an increased ability to obtain breast fluid. Post-menopausal status and exogenous estrogen use were associated with a decreased ability to obtain breast fluid. After age-adjustment, oral contraceptive use was no longer significantly associated with an increased ability to obtain fluid and post-menopausal status was no longer associated with a decreased ability to obtain breast fluid. After multivariate adjustment, age, being married, a history of pregnancy, tranquilizer use and a history of endocrine problems remained positively associated with the ability to obtain breast fluid. In addition, menopausal women who took estrogen were less likely to yield fluid than premenopausal women.