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Phyllodes Tumors of the Female Breast

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FOREWORD

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Stanley H. Weiss September 30, 1997  
PI - Signature Date

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## INTRODUCTION

**BACKGROUND:** Phyllodes (formerly termed Cystosarcoma phyllodes) tumors of the breast are uncommon breast neoplasms, accounting for about 0.5% of primary breast neoplasms<sup>1</sup>. These tumors are fibroepithelial tumors composed of an epithelial and a cellular stromal component. This tumor typically occurs in women from 30-69, peaking at age 40-49.

The age-adjusted annual incidence rate of malignant phyllodes tumors is 2.1 per million women. In one of the largest reported case series from the United States, over a period of 78 years (1913 to 1990), 60 patients (59 women, 1 man) who were treated at the Mayo Clinic were confirmed to have phyllodes tumors. This represents an average of only about one case per year. A recent study in California of malignant phyllodes tumors found that the incidence rates were substantially higher in the 1980's than in the 1970's with the highest rates in Latino whites.<sup>2</sup> They noted that the epidemiology was strikingly different from that of the more common histologic types of breast cancer.<sup>2</sup> In the largest case series published, from Poland, none of 170 phyllodes patients had multiple primary tumors.<sup>3</sup>

The differentiation of benign phyllodes tumors from benign fibroadenomas can be uncertain based on cytopathology alone,<sup>4</sup> so follow-up biopsy is recommended if a phyllodes tumor is suspected. In our current study, we have tabulated as cases only women who have had biopsy-confirmed diagnoses of a phyllodes tumor; since some women did not have biopsies despite fine-needle aspirates suggestive of a phyllodes tumor, our data will somewhat underestimate the benign cystosarcoma phyllodes tumors.

This study represents a collaboration between the New Jersey Medical School (NJMS) of the University of Medicine and Dentistry of New Jersey (UMDNJ) and Englewood Hospital and Medical Center (EHMC).

This project has financial support for some of its activities from agencies other than the U.S. Army. These sources of support are the Englewood Hospital and Medical Center Research Fund, the Foundation of UMDNJ (PI = Dr. Joan Skurnick), an NCI Cancer Education grant (PI = Dr. Elizabeth Alger) which helps support student summer research and UMDNJ-NJ Medical School

research funds.

During the first two years of this project, the U.S. Army grant funds were utilized exclusively for activities that meet the criteria for an "exempt" review under DHSS human use guidelines. This work included study design issues, forms design, data base design and programming, systems programming, entry of collected data without personal identifiers, and data analysis.

In the original scope of work, it was proposed by us that interviews would be conducted using U.S. Army funds, including during the first year. As noted above, it was necessary to modify this. No Army funds were utilized for this activity, and only very limited funds were allocated in the budget towards this proposed activity.

The scope of work has been modified twice, as approved by the U.S. Army on June 6, 1997 (concerning request dated February 2, 1996) and on August 28, 1997 (concerning request dated August 14, 1997). The grant Performance Period is 15 August 1994 through 30 September 1998.

As per the approved 2 February 96 modification, the "interviews" were deleted from the original required Scope of Work. The remainder of activities in the grant were in the "exempt" category. We also added a new component, which received Human Use approval prior to implementation related to the development of a Tissue Repository.

#### **PURPOSE OF THE CURRENT WORK**

The purposes of this grant subsequent to the initial year are to:

- 1) conduct standard epidemiologic analyses of data to characterize potential risk factors
- 2) summarize findings in appropriate forums
- 3) continue to assess the geographic bounds of phyllodes cases in our region of New Jersey
- 4) solicit written consent to enable the development of a tissue repository.

**BODY**

At Englewood Hospital and Medical Center (EHMC, located in Englewood, Bergen County, New Jersey), 110 women have been diagnosed with new cystosarcoma phyllodes tumors by Drs. Miguel Sanchez, Rosalyn Stahl and colleagues from 1987 through June 1997. An outside breast pathologist (Paul Peter Rosen, M.D., Sloan Kettering Memorial Cancer Center, New York) formally reviewed the slides in a subset of the initial cases prior to the initiation of this grant and confirmed the diagnosis of cystosarcoma phyllodes. Thus, our current series at EHMC is among the largest to date in the United States, representing diagnoses at a single local medical center over a relatively short period of time. This accumulation of cases provides a unique opportunity to better characterize and understand this rare tumor.

We presented our initial epidemiologic findings from the 110 women (ages 16-69 y/o) with phyllodes tumors from this single institution in Bergen County over only 10.5 years, 1987-1997, at the U.S. Army Era of Hope meeting in 1997. All cases were documented by review of biopsy histology according to the criteria of Rosen and Rosai.<sup>5</sup> Clinical follow-up data were reviewed to determine rates of phyllodes tumor recurrence and of new tumors in the case series. The data in this report supersede the preliminary data included in the Era of Hope extended abstract.<sup>6</sup>

Hospitals in the five county region have been systematically surveyed to ascertain phyllodes tumor rates in other neighboring institutions and for the counties over an 11.5 year period (1986-1997); data collection remains in progress so that the summary below is not complete. In particular, case counts from some hospitals remain pending, so that the county rates can be expected to change.

In depth information collected from 73 women with phyllodes tumors and age- and time-matched controls (without breast cancer or fibroadenomas) as part of a case-control study are under analysis. Data from additional interviews are anticipated to become available over the course of the next year, and will lead to revised analyses (and greater study statistical power).

Our cases occurred primarily among caucasians (78%). The 11 women with malignant tumors (mean 40.2 y/o) were significantly older than the 99 with benign tumors (mean 33.4 y/o),  $p < .03$  (ANOVA). Marital status at the time of diagnosis was 36% never married, 56% married, 8%

divorced.

We found an overall rate of 9.6 phyllodes tumors (6.2 benign, 3.4 malignant) per million women per year (MWY) in Passaic, Essex, Hudson and Morris counties, comparable to expectations. In contrast, the Bergen County [our index county, where EHMC is located] rate was significantly higher, 34.3 (28.7 benign, 5.6 malignant) per MWY. The rate ratios were 3.6 (95% CI 2.8-4.7) overall, 4.6 (95% CI 3.5-6.4) for benign and 1.7 (95% CI 0.93-2.9) for malignant tumors. Preliminary analysis of the addresses at the time of diagnosis from our case-control data suggests that the cases are more highly clustered geographically than age- and time-matched controls.

Six women (5.5%) in our series had bilateral, simultaneous phyllodes tumors and five women (4.5%) developed new primary tumors at 0.66, 1.79, 1.79, 2.10 and 2.22 years of follow-up. Seven women have had recurrent tumors, including one woman who developed metastatic disease.

Whereas only 4.5% (3/66) tumors with adequate surgical margins recurred, 6.1% (2/33) with "other" margins recurred (relative risk 1.3,  $p=NS$ ). However, if two instances of ambiguous recurrences were reclassified as primary tumors, and a possible recurrence documented only by FNA was counted, the risk rises to 6.0 ( $p=.11$ ).

Cases were significantly more likely to be non-white and non-Jewish compared to the matched controls. Cases tended to develop physically somewhat later than controls, with older ages for menarche and full height.

Cases had a significantly greater history of reported male relatives with cancer ( $p=.009$ ,  $OR=3$ ), and specifically males with lung cancer ( $p=.06$ ,  $OR = 2.9$ ). The fathers of seven cases had lung cancer compared to none of the fathers of controls ( $p=.01$ ). Although many case families presented unremarkable cancer history genograms, in some families there may be an inherited pattern.

Phyllodes tumors can occur within the spectrum of "classic" Li-Fraumeni syndrome.<sup>7</sup> Specific **p53** mutations in phyllodes tumors have been reported. An expanded Li-Fraumeni-like syndrome may include lung cancers. Laboratory based studies will help further define these issues within our case



series. Further analyses concerning possible spatial-temporal clustering and of genetic factors are anticipated during the next, and final, year of this grant.

### DEVELOPMENT OF TISSUE REPOSITORY

We have been contacting, primarily by mail (but including telephone contact when necessary to update last known addresses), women who have had a confirmed diagnosis of a phyllodes tumor to obtain written consent for the use of their stored specimens. No new specimens and no clinical procedures are proposed as part of this grant. An introductory letter is sent along with the consent form. We have two versions of the letter, depending upon whether or not we have interviewed the woman. For the women previously interviewed, we simultaneously also request return of a form in which they acknowledge their prior voluntary telephone interview, since this places a minimal added burden on the respondent yet provides a written record of their prior consent. Army grant resources in soliciting the consent are being utilized.

If written permission is received, then we would be able to retain linkage, as stated in the consent form, in developing a tissue repository. If written permission for linked testing is not given, then we shall code existing data, including such steps as the exclusion of personal identifiers. This would enable us to perform unlinked testing of residual biologic material while retaining some critical information. Prior to sending any such specimen to a laboratory, identified by a unique repository code number, we would irrevocably break linkage by destroying the link between the personal identifier and the new code number. Some specimens would be linked to each other (but not to the woman) in cases where multiple specimens from a single woman exist to enable assessment of sequential data and ensure that a given woman is not multiply counted in statistical analyses. No grant resources will be used for actual laboratory testing, which is outside the scope of the Scope of Work.

For some of the cases from EHMC, the women have moved and contact between them and their EHMC physicians has not occurred recently. Thus, it will not be possible to contact some of these women. Our EHMC collaborators are assisting with checking of records to ensure that any updated location information will be provided.

Through August 15, 1997, 40 cases had returned consent forms. 38 women (95%) agreed to participate in the linked laboratory study, a very high acceptance rate. Analysis of the return process indicates that personal follow-up by telephone has been helpful in leading to the return of forms and that this will likely lead to significantly more responses, many of which are likely to be agreement for linked study. We have performed power calculations which indicate that continued, enhanced effort to this follow-up process remains warranted to develop a tumor registry large enough to initiate subsequent laboratory assessments. Each positive response to the consent forms is an important contribution to statistical power. For example, if the prevalence of a factor X is 50% among cases and laboratory test T carries a 4-fold increase in risk, then if 36 women are studied,  $p=0.047$  for a 1-tailed analysis (Fischer's exact test) but  $p=0.094$  for a 2-tailed analysis. When the study size is increased by 33% to 48 women, both 1-tailed ( $p=.02$ ) and 2-tailed analyses ( $p=0.04$ ) would be significant.

## CONCLUSIONS

We are developing important descriptive epidemiologic data concerning the phyllodes tumor cases, both in terms of patient profile and natural history. Our evolving data suggest relatively localized clustering with some individual women at particular biologic risk. One in seven cases (14.5%, 16/110) had multiple phyllodes tumors diagnosed either simultaneously or over our limited period of follow-up. This is significantly more frequent than in the Polish series in which this phenomena apparently did not occur ( $p < 10^{-6}$ ). Adequate surgical resection margins were associated with a low tumor recurrence rate.

The elevated relative incidence in Bergen county may in part reflect under-ascertainment as well as under-diagnosis of cases in the surrounding hospitals. Both environmental and genetic factors may potentially place women at risk for phyllodes tumors.

Given our findings already of intriguing, statistically significant differences, we are optimistic that this project will provide a better understanding with important new information about this rare tumor. Further efforts to develop a larger tumor repository will be worthwhile.

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