Title

Germline Genetic Mutations in a Multi-center Contemporary Cohort of 550 Phyllodes Tumors: An Opportunity for Expanded Multi-gene Panel Testing

Journal

Annals of Surgical Oncology, 27(10)

ISSN

1068-9265

Authors

Rosenberger, Laura H
Thomas, Samantha M
Nimbkar, Suniti N
et al.

Publication Date

2020-10-01

DOI

10.1245/s10434-020-08480-z

Peer reviewed

HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2023 February 22.

Published in final edited form as:

Ann Surg Oncol. 2020 October ; 27(10): 3633–3640. doi:10.1245/s10434-020-08480-z.

Germline Genetic Mutations in a Multi-Center Contemporary Cohort of 550 Phyllodes Tumors; An Opportunity for Expanded Multi-Gene Panel Testing

Laura H. Rosenberger, MD, MS[1,2], **Samantha M. Thomas, MS**[2,3], **Suniti N. Nimbkar, MD**[4], **Tina J. Hieken, MD**[5], **Kandice K. Ludwig, MD**[6], **Lisa K. Jacobs, MD**[7], **Megan E. Miller, MD**[8], **Kristalyn K. Gallagher, DO**[9], **Jasmine Wong, MD**[10], **Heather B. Neuman, MD**[11], **Jennifer Tseng, MD**[12], **Taryn E. Hassinger, MD, MS**[13], **James W. Jakub, MD**[5]

[1]Department of Surgery, Duke University Medical Center, Durham, North Carolina

[2]Duke Cancer Institute, Duke University, Durham, North Carolina

[3]Biostatistics and Bioinformatics, Duke University, Durham, North Carolina

[4]Brigham & Women's Hospital, Dana-Farber Cancer Institute, Boston, Massachusetts

[5]Department of Surgery, Mayo Clinic, Rochester, Minnesota

[6]Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana

[7]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

[8]Department of Surgery, University Hospitals, Case Western Reserve University School of Medicine, Cleveland, Ohio

[9]Department of Surgery, University of North Carolina, Chapel Hill, North Carolina

[10]Department of Surgery, University of California, San Francisco, San Francisco, California

[11]Department of Surgery, University of Wisconsin, Madison, Wisconsin

[12]Department of Surgery, University of Chicago Medicine, Chicago, Illinois

[13]Department of Surgery, University of Virginia Health System, Charlottesville, Virginia

Abstract

BACKGROUND: A paucity data exists regarding inherited mutations associated with phyllodes tumors (PT); however, some are reported (*TP53*, *BRCA1*, and *RB1*). A PT diagnosis does not meet NCCN criteria for testing, including within Li-Fraumeni Syndrome (*TP53*). We sought to determine the prevalence of mutations associated with PT.

METHODS: We performed an 11-institution review of contemporary (2007–2017) PT practice. We recorded multi-generational family history and personal history of genetic testing. We

Corresponding Author: Laura H. Rosenberger MD, MS, FACS, Assistant Professor of Surgery, Duke University Department of Surgery, DUMC 3513, Durham NC, 27710, Laura.Rosenberger@duke.edu, Office: 919-470-8552.

Disclosures: No disclosures

Presentation: Poster presentation, SSO 73rd Annual Cancer Symposium 2020. Boston, MA

identified patients meeting NCCN criteria for genetic evaluation. Logistic regression estimated the association of select covariates with likelihood of undergoing genetic testing.

RESULTS: Of 550 PT patients, 59.8% (N=329) had a close family history of cancer, 34.0% (N=112) had ≥3 family members affected. Only 6.2% (N=34) underwent genetic testing, 38.2% (N=13) of whom had only *BRCA1/BRCA2* tested. Of 34 patients tested, 8.8% had a deleterious mutation (1 *BRCA1*, 2 *TP53*), and 5.9% had a *BRCA2 VUS*. Of women that had *TP53* testing (N=21), 9.5% had a mutation. Selection for testing was not associated with age (OR=1.01, p=0.55) or PT size (p=0.12), but was associated with grade (malignant vs benign: OR=9.17, 95% CI 3.97–21.18), and meeting NCCN criteria (OR=3.43, 95% CI 1.70–6.94). Notably, an additional 86 (15.6%) patients met NCCN criteria, yet had no genetic testing.

CONCLUSIONS: Very few women with PT undergo germline testing; however, in those selected for testing, a deleterious mutation was identified in ~10%. Multi-gene testing of a PT cohort would present an opportunity to discover the true incidence of germline mutations in PT patients.

Keywords

Phyllodes Tumor; Genetic Testing; Germline Mutations; BRCA; PT53; RB1

INTRODUCTION

Incidence and Classification

Phyllodes tumors (PT) are rare fibroepithelial breast neoplasms, first described in 1838 as "cystosarcoma phyllodes", and represent 0.3 – 1.0% of all primary breast tumors. [1–3] These rare tumors exhibit a unique histology, and are classified by the World Health Organization (WHO) as benign, borderline, or malignant, which have diverse biological behavior. [4, 5] Although these tumors can occur at any age, they are most typically identified in younger women, with a median age of 40 years. [6–13] Primary management for all grades of PT are limited, and consist almost exclusively of surgical excision. [14] Moreover, when these tumors are found to be metastatic, there are limited data on additional treatment options and prognosis is dismal.

There are currently no tools available to identify those women at highest risk for developing PT, representing a significant knowledge gap in the field of breast cancer screening and treatment. However, recent literature suggests there may be an underlying genetic susceptibility for PT, opening up the potential for identification of germline mutations associated with their development and progression. Validation of a germline predisposition would allow for the identification of women at the highest risk for PT and potentially lead to a change in recommendations for screening.

Inherited Germline Mutations

The genomic landscape of PT has been rapidly expanding in terms of *somatic* mutations; however, there remain sparse data with regards to *germline* genetic susceptibility mutations. For women with a history of a PT, no study has systematically evaluated inherited germline mutations, and as such, the prevalence and types of mutations associated with PT are currently unknown. There are reports that indicate the possibility of genetic susceptibility to

these rare breast tumors. One publication describes both a mother and daughter (each with a benign PT tumor) [15], while another identifies two affected sisters (one borderline and one malignant PT) [16]. Neither report indicates that any genetic testing had been performed.

While these prior case series did not have genetic testing to confirm a suspected genetic susceptibility, some published series *have* identified specific germline mutations in patients with PT including (1) a deleterious *BRCA1* germline mutation (missense C5214T, R1699W), [17] (2) multiple cases of malignant PT in patients with hereditary retinoblastoma (*RB1* gene) [18, 19], and (3) a plethora of cases associated with *TP53* mutations. [20–23] The strongest data in the literature indicating a genetic predisposition for the development of PT comes from a study evaluating 28 families with Li-Fraumeni syndrome (germline *TP53* mutation). [20] This syndrome is a rare disorder, which greatly increases the risk of rare cancers in young adults including: osteosarcomas and other soft tissue sarcomas, breast carcinoma, brain tumors, leukemia, adrenocortical carcinomas, Wilms' tumors, and malignant PTs. The authors found the greatest increase in cancers for patients with *TP53* mutations relative to the general population rates were in adrenocortical carcinoma and malignant PT. [20]

With no known environmental risk factors for PT development, the expanding recent literature suggests a heritable mutation, which may increase women's risk of developing PT. However, a PT diagnosis does not meet any National Comprehensive Cancer Network (NCCN) criteria for genetic referral or testing, including within the Li-Fraumeni Syndrome criteria. [24] Currently, the prevalence and types of germline mutations for women with a history of PT are unknown. *We aimed to describe family cancer history, personal genetic testing rates for women with PT, and estimate the incidence and types of germline mutations in a large multi-institutional contemporary cohort of women with PT.*

METHODS

We performed an 11 institution review of the contemporary management of PT from 2007 to 2017. Patient demographics and genetic testing characteristics were recorded and summarized with N (%) for categorical variables, and median (interquartile range, IQR) for continuous variables for all patients and by PT grade (benign, borderline, or malignant). A multi-generational family cancer history was abstracted from patients' records specifically identifying all 1st- (parents, siblings, children), 2nd- (grandparents, aunts/uncles, nieces/nephews, grandchildren), and *select* 3rd-degree relatives (first cousins), including maternal or paternal lineage. Additional 3rd-degree relatives (e.g. great-aunt/uncle, great-grandparents) were not reliably identified and/or recorded, as there was not a separate designation for such in the multi-center database. For the index patient with a PT we also recorded personal history of genetic testing, specific genes tested, as well as any mutations and/or variants of unknown significance (VUS) identified. Specific genes recorded included: *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, and TP53.*

We identified patients that met criteria for further breast and ovarian genetic risk evaluation based on the NCCN "Genetic/Familial High-Risk Assessment: Breast and Ovarian" guidelines (March, 2019), for which we had data available. [24] Utilizing the "Breast and/or Ovarian Cancer Genetic Assessment" criteria, women with a PT would be considered an unaffected individual, who would meet criteria for further genetic risk evaluation based on separate specific criteria. These include those who had a 1st or 2nd-degree relative with ovarian cancer, pancreatic cancer, or a male breast cancer. Additionally these criteria included women with a 1st-, 2nd-, or 3rd-degree family history of three or more of the following on the same side of the family (including multiple primary cancers in the same individual): brain, breast, colon or rectal, kidney/renal or bladder, leukemia, lymphoma, ovarian, pancreatic, prostate, sarcoma, stomach, thyroid, and uterine (endometrial). As we did not have age of diagnosis abstracted for the family cancer history, or specifically if prostate cancer was metastatic, we could *not* include the following criteria; 1st- or 2nd-degree relative with the following (1) breast cancer ≤45 y, (2), ≥2 individuals with breast cancer primaries on the same side of the family with at least one diagnosed ≤50 y, or (3) metastatic prostate cancer.

Univariate logistic regression was used to estimate the association of four selected covariates (determined *a priori*) with likelihood of undergoing genetic testing including; (1) age at diagnosis, (2) PT grade, (3) pathologic tumor size, and (4) eligibility for genetic risk evaluation. Covariates with univariate *p*-value of <0.10 were selected for inclusion in a subsequent multivariate model. All logistic models were built in the generalized estimating equations framework, and an exchangeable correlation structure was incorporated to account for the correlation of patients treated at the same facility. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC). This study had institutional review board approval from each collaborating site.

RESULTS

We identified a total of 550 patients with PT from 11 institutions (N=91, 71, 62, 58, 55, 51, 47, 41, 34, 31, 9). Median age at diagnosis was 44 years (IQR 36–53), BMI was 27 (IQR 23–33), the majority were white (59.3%, N=326), and non-Hispanic (72.0%, N=396). Less than 1% (N=4) reported Ashkenazi Jewish heritage, and there were no reported cases with a history of Mantle radiation (100%, N=550). Despite the young age of the cohort, 24.9% (N=137) had a prior benign breast biopsy, and 2.5% (N=14) had a personal history of breast cancer. (Table 1) Of these 14 women with a *prior* breast cancer history and a current PT diagnosis, only a single woman (7.1%) underwent genetic testing (who had not met the breast and ovarian NCCN criteria for further genetic assessment).

The majority of women (59.8%, N=329) had at least one close (1st-, 2nd-, or 3rd-degree) relative with a reported history of cancer. Of these 329 patients, a third (34.0%, N=112) had ≥3 family members affected on the same side of the family. (Table 2) The most commonly identified familial cancers were breast (56.2%, N=185), colon or rectal (14.6%, N=48), lung (13.7%, N=45), ovarian (11.6%, N=38), prostate (11.2%, N=37), pancreatic (5.2%, N=17), lymphoma (5.2%, N=17), and stomach (4.3%, N=14). Using the breast and ovarian NCCN criteria (3.2019) for which we had data available, as described in the methods, 18.5%

(N=102) of the total cohort met criteria for further genetic risk evaluation; however, only 13.7% (N=14) of these 102 patients had documented genetic testing. Notably, this leaves a total of 15.6% (N=86) of the entire cohort that met criteria for genetic risk evaluation, yet *had no genetic testing completed*. An additional 2 patients met criteria; however, genetic testing status was unknown.

Of the total cohort, 6.2% (N=34) underwent germline testing for at least a single gene. 58.8% (N=20) of these women who were tested, did *not* meet any NCCN breast and ovarian criteria for genetic testing. Of these 34 patients that completed testing, 38.2% (N=13) had *only BRCA1/BRCA2* testing, whereas 50% (N=17) had *TP53* included in their testing. A total of 8.8% (N=3) had a deleterious mutation identified, including a *BRCA1* (*BRCA1*:c.213–11T>G, previously *BRCA1*:IVS5–11T>G), and two *TP53* mutations (*TP53*:c.375G>A and *TP53*:c.586C>T (p.Arg196Ter), previously *TP53*:13346 C>T (arg196stop). In addition, two patients (5.9%) were identified to have a *BRCA2 VUS* (IVS9+5G>A and *BRCA2*:c.6225A>C (p.Lys2075Asn), previously *BRCA2* K2075N (6453A>C)). Of the three patients who tested positive for a pathogenic mutation, 33% (N=1) did *not* meet NCCN criteria for testing.

Selection for genetic testing was not associated with age at diagnosis (Odds Ratio (OR)=1.01, 95% Confidence Interval (CI) 0.99–1.03, p=0.56) or PT size (OR=1.00, 95% CI 1.00–1.01, p=0.12), but was significantly associated with PT grade (malignant vs benign OR=9.19, 95% CI 4.09–20.67, p<0.001), and meeting NCCN criteria (OR=3.39, 95% CI 1.69–6.77, p=0.001). (Table 3) Malignant grade (OR=8.40, 95% CI 3.25–21.68, p<0.001) and meeting NCCN criteria (OR=3.18, 95% CI 1.40–7.27, p=0.006) remained significantly associated with genetic testing on multivariate analysis. (Table 4)

DISCUSSION

We describe a very large contemporary cohort of PT patients, which represents the largest series in the literature from the United States, compiled from 11 institutions. This series reveals that each contributing major academic center is only managing roughly 5 PT annually, highlighting the critical need for multi-institutional collaboration regarding this rare tumor. Within this contemporary and academic PT cohort, we found that very few women with PT undergo genetic testing (6.2% overall), even when they met independent breast and ovarian NCCN criteria to do so (e.g. family history of ovarian, pancreatic, or male breast cancer). Nearly 20% of the total cohort met criteria for further genetic risk evaluation; however, only 14% *of these* had documented testing. This under testing is likely multi-factorial including (1) NCCN criteria do not include PT as a specific criteria for any Genetic / Familial High Risk Assessment categories, (2) genetic counselors do not consider PT as a soft tissue sarcoma, precluding inclusion within the sarcoma criteria, (3) providers are unaware of the association between *TP53* and PT, (4) and the association with various other germline mutations and PT are currently unknown, leading providers to potentially overlook standard indications for genetic referral and evaluation.

Consistent with prior literature documenting germline mutations associated with PT, we identified two *TP53* mutations[20–23] and a *BRCA1* mutation[17] in our PT cohort. Of the

women that underwent *TP53* testing (N=21), 9.5% (N=2) were identified as having a mutation, both of whom had malignant PT. This *TP53* mutation prevalence exceeds the published baseline mutation rate of 2% in the general population of women with a diagnosis of breast adenocarcinoma. [25] No population-based study has been conducted to determine the prevalence, and types, of mutations in a cohort of PT. In our cohort, specific to the potential discovery of additional *TP53* mutations, 46 additional women with malignant grade PT did not undergo germline testing.

Of the women that underwent genetic testing, 40% had only *BRCA1/BRCA2* testing and 6% had only *TP53* gene testing. Limiting testing to the *BRCA1/BRCA2* mutation may simply be a reflection of the time period during which testing was performed (i.e. broad panel testing not readily available), that testing was performed based on family history alone without additional consideration of how the PT diagnosis contributed, and that these patients are being managed by providers whose scope of practice lends them to consider breast cancer associated genes and not sarcoma associated genes. However, 50% of women tested did have an inclusion of the *TP53* gene suggesting some provider knowledge of the association between *TP53* mutations and PT. This concept is supported by the observation that 100% of those tested for *TP53 alone* had malignant phyllodes, and of all the malignant PT that underwent testing, >90% had *TP53* included in their selected panel. Furthermore, genetic testing was nearly 10 times more likely for those with a malignant PT as compared to those with a benign PT. Including *TP53* into the risk evaluation for women with malignant PT may reflect providers' consideration of malignant PT as within the sarcoma spectrum.

The majority of women in our series with PT have a family history of cancer, and a third of these had at least 3 relatives affected on the same side of the family. The top three cancers reported are consistent with national cancer statistics from the CDC's (Centers for Disease Control and Prevention) Cancer Data and Statistics reports, [26] including breast, colon or rectal, and lung. However, while we would expect the subsequent tumors to include prostate/uterine, thyroid, melanoma, lymphoma, renal, and bladder, our PT cohort identified ovarian, pancreatic, and gastric in the top ten most commonly reported cancers. While this may be due to a collection or reporting bias in the family histories taken for the PT of the breast, this may also reflect underlying germline predisposition or cancer syndromes that were not identified, due to lack of germline testing.

Identification of a genetic predisposition to developing PT would 1) direct enhanced screening to screen both women at risk, as well as affected women, 2) facilitate conversations regarding risk-reducing strategies for known cancer syndromes (e.g. Li-Fraumeni), and 3) potentially have significant implications for direct relatives, with an opportunity for cascade testing. Since 7–24% of *TP53* mutation carriers are identified as *de novo* mutations, genetic testing for PT associated gene mutations should not be based solely on family history, as is current standard. [27, 28] This concept is supported by one of the two identified *TP53* mutation carriers having had *no TP53*-associated cancers in their family history.

Identification of a *TP53* mutation, or other cancer susceptibility gene mutations, may have critical consequences as certain germline mutations have well documented susceptibility

to radiation-induced secondary malignancies. Multiple studies have identified *TP53* and *RB1* mutations as being associated with increased risk of radiation-induced secondary malignancy. The use of adjuvant radiation for PT has increased over time, in an attempt to reduce local recurrence and prevent future mastectomy, with current rates of radiation use between 10–15%. [29–33] Multiple retrospective series and a meta-analyses have evaluated the use of radiation for PT, revealing that while adjuvant radiation reduces local recurrence rates, it has no effect on disease-free or overall survival. [29–32, 34] These retrospective series are notably biased in patient selection, have no appropriate control arm, and there are no prospective randomized trials to validate these findings. Identification of a *TP53* or *RB1* gene mutation may have significant implications, for weighing the benefits and risks of treatment decisions, such as use of radiation for this patient cohort.

We found no history of Mantle radiation in this cohort, which is notable as Mantle field radiation for childhood cancers such as Hodgkin lymphoma, is known to greatly increase the risk of breast cancer. [35] While it remains unknown whether there is any association between chest irradiation and PT development, we did not identify any women with prior Mantle radiation in this cohort. While we did not identify any unexpected demographic factors, we did find 24.9% of women had a prior breast biopsy, which is markedly higher than expected. Of these women with a prior history of a benign breast biopsy, roughly 60% had a diagnosis of a fibroadenoma or fibroepithelial lesion. In breast cancer screening programs, only 10 breast biopsies should be performed per 1000 women screened (1%), indicating our cohort of women with PT may have more proliferative breast tissue or predilection for fibroepithelial tumor development. Additionally, 2.5% of women in this cohort had a prior personal history of adenocarcinoma of the breast, a higher than expected rate for this relatively young cohort of women with a median age two decades younger than the average woman with breast cancer. Only *one* woman with a PT and a prior *personal* history of breast cancer underwent genetic testing, consistent with the very low rates of genetic testing identified in this PT cohort.

Our study has a number of strengths and a few limitations. As with any rare tumor or disease, an engaged network of investigators must facilitate tremendous coordination to pool cases and data for discovery and direct evidence based decision making. This study collated 550 cases from a contemporary time period, which is unique to the literature, where most series >100 cases have required multiple decades of data from a single institution. This engaged network now has in place multiple additional studies underway for this rare tumor. One limitation to this rare tumor is that there is no specific WHO ICD (International Statistical Classification of Diseases) code for PT, and as such, cases may have been missed during retrospective case identification. Family cancer histories are noted to be variably reported in the medical record, potentially worsened in this younger cohort of women with a tumor that is not currently considered heritably associated by current NCCN guidelines. This study likely *underestimated* the family history of other cancers as we only recorded “cousins”, excluding potential additional 3rd-degree relatives, which may have omitted cancers from great-grandparents, great-aunts/uncles, and great-grandchildren in our NCCN criteria definition. Similarly, we were not able to identify additional patients who met strict NCCN criteria with any *age* component (e.g. family member with breast cancer age <45), or *metastatic* prostate cancer. Notably, this potential for missed family history of cancers would

only strengthen the findings of this study, which reveal an under testing of women with PT, even when meeting NCCN criteria for genetic risk evaluation.

CONCLUSION

Currently, the NCCN practice guidelines *do not include* PT as criteria for genetic counseling, or as testing criteria for any of the known heritable cancer syndromes. Even within the Li-Fraumeni (*TP53*) Syndrome Testing Criteria, PT are not specifically listed with the other syndrome-associated Li-Fraumeni tumors, and therefore very few women with PT currently undergo germline testing, including those who meet criteria based on family history alone. Furthermore, PT may be the presenting tumor in these young women and may represent a *de novo* mutation, which would not be predicted based on their family history alone. Were women with PT found to have an increased prevalence of germline mutations, there could be significant clinical implications.

In conclusion, our study identified that roughly 10% of PT patients tested for germline cancer predisposition genes carried a deleterious mutation, similar to that seen among women with breast adenocarcinoma. We are currently working on multi-gene testing of a PT cohort with the intent to discover the true incidence of germline mutations in PT patients. This presents an opportunity to expand research into correlations with known *somatic* PT mutations, provide cascade testing, and immediately improve patient counseling regarding future cancer risk.

ACKNOWLEDGEMENTS

This publication was made possible (in part) by philanthropic funds through the generosity of Sara and Bruce Brandaleone. Statistical support was funded by the Duke Cancer Institute through NIH grant P30CA014236 (PI: Kastan).

Funding:

This publication was made possible (in part) by philanthropic funds through the generosity of Sara and Bruce Brandaleone. Statistical support was funded by the Duke Cancer Institute through NIH grant P30CA014236 (PI: Kastan).

REFERENCES

1. Muller J Uber den feineran Bau and die Formen der krankhaften art Geschwulste. Berlin, Germany: G Reimer. 1838(54).
2. Rosen PP, Oberman HA. Tumors of the Mammary Gland. Washington, DC: Armed Forces Institute of Pathology, 1993.
3. Rosen PP. Rosen's Breast Pathology. Lippincott William Wilkins, New York, NY, USA. 2001. 2nd edition.
4. Tan PH, Ellis IO. Myoepithelial and Epithelial-Myoepithelial, Mesenchymal and Fibroepithelial Breast Lesions: Updates from the WHO Classification of Tumours of the Breast 2012. J Clin Pathol, 2013; 66:465–470. [PubMed: 23533258]
5. Zhang Y, Kleer CG. Phyllodes Tumor of the Breast: Histopathologic Features, Differential Diagnosis, and Molecular/Genetic Updates. Arch Pathol Lab Med. 2016; 140:665–671. [PubMed: 27362571]
6. Yom CK, Han W, Kim SW, Park SY, Park IA, Noh Dy. Reappraisal of Conventional Risk Stratification for Local Recurrence Based on Clinical Outcomes in 285 Resected Phyllodes Tumors of the Breast. Ann Surg Oncol. 2015; 22:2912–2918. [PubMed: 25652050]

7. Jang JH, Choi MY, Lee SK, et al. Clinicopathologic Risk Factors for the Local Recurrence of Phyllodes Tumors of the Breast. Ann Surg Oncol. 2012; 19:2612–2617. [PubMed: 22476816]
8. Cheng SP, Chang YC, Liu TP, Lee JJ, Tzen CY, Liu CL. Phyllodes Tumor of the Breast: The Challenge Persists. World J Surg. 2006; 30:1414–1421. [PubMed: 16865317]
9. Ben Hassouna J, Damak T, Gamoudi A, et al. Phyllodes Tumors of the Breast: A Case Series of 106 Patients. Am J Surg. 2006; 192:141–147. [PubMed: 16860620]
10. Barrio AV, Clark BD, Goldberg JI, et al. Clinicopathologic Features and Long-Term Outcomes of 293 Phyllodes Tumors of the Breast. Ann Surg Oncol. 2007; 14:2961–2970. [PubMed: 17562113]
11. Tan PH, Thike AA, Tan WJ, et al. Predicting Clinical Behaviour of Breast Phyllodes Tumours: A Nomogram Based on Histological Criteria and Surgical Margins. J Clin Pathol. 2012: 65:69–76. [PubMed: 22049216]
12. Rajan PB, Cranor ML, Rosen PP. Cystosarcoma Phyllodes in Adolescent Girls and Young Women: A Study of 45 Patients. Am J Pathol. 1998; 22:64–69.
13. Salvadori B, Cusumano F, Del Bo R, et al. Surgical Treatment of Phyllodes Tumors of the Breast. Cancer. 1989; 63:2532–2536. [PubMed: 2541890]
14. National Comprehensive Cancer Network. NCCN, Clinical Practice Guidelines in Oncology: Breast Cancer, Version, 3.2019. Accessed 12/9/2019, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
15. Foucar CE, Hardy A, Siziopikou KP, et al. A Mother and Daughter with Phyllodes Tumors of the Breast. Clinical Breast Cancer. 2012; 12:373–377. [PubMed: 22981939]
16. Wang Y, Zhu J, Gou J, Xiong J, Yang X. Phyllodes Tumors of the Breast in 2 Sisters: Case Report and Review of Literature. Medicine. 2017; 96: e8552. [PubMed: 29145261]
17. Rhiem K, Flucke U, Engel C, et al. Association of the BRCA1 Missense Variant R1699W with a Malignant Phyllodes Tumor of the Breast. Cancer Genetics and Cytogenetics. 2007; 176; 76–79. [PubMed: 17574969]
18. Shearer DD, et al. Malignant Phyllodes Tumor in a Patient with Hereditary Retinoblastoma: a Case Report and Literature Review. Proceedings in Obstetrics and Gynecology. 2013; 3(2):5.
19. Mak J Two Cases of Malignant Phyllodes Tumor in Patients with History of Bilateral Retinoblastoma – A Possible Novel Association with RB1 Germline Mutations. ASHG American Society of Human Genetics Annual Meeting; October 23–27, 2007; San Diego, CA. Available at: http://www.ashg.org/genetics/ashg07s/f21566.htm. Accessed on October 27, 2019.
20. Birch JM, Alston RD, McNally RJ, et al. Relative Frequency and Morphology of Cancers in Carriers of Germline TP53 Mutations. Oncogene. 2001; 20: 4621–4628. [PubMed: 11498785]
21. Giacomazzi J, Koehler-Santos P, Palmero EI, et al. A TP53 Founder Mutation, p.R337H, is Associated with Phyllodes Breast Tumors in Brazil. Virchows Arch. 2013; 463: 17–22. [PubMed: 23794094]
22. Bot FJ, Sleddens HF, Dinjens WN. Molecular Assessment of Clonality Leads to the Identification of a New Germ Line TP53 Mutation Associated with Malignant Cystosarcoma Phyllodes and Soft Tissue Sarcoma. Diagnostic Molecular Pathology. 1998; 7:295–301. [PubMed: 10207667]
23. Prochazkova K, Foretova L, Sedlacek Z. A Rare Tumor and an Ethical Dilemma in a Family with a Germline TP53 Mutation. Cancer Genetic Cytogenet. 2008; 180:65–69.
24. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 3.2019. Accessed at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf on October 27th, 2019.
25. Beitsch PD, Whitworth PW, Hughes K, et al. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? J Clin Oncol. 2019; 37:453–460. [PubMed: 30526229]
26. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999–2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Accessed at: https://gis.cdc.gov/Cancer/USCS/DataViz.html on December 30, 2019.
27. Chompret A, Brugieres L, Ronsin M, et al. P53 Germline Mutations in Childhood Cancers and Cancer Risk for Carrier Individuals. Br J Cancer. 2000; 82:1932–7. [PubMed: 10864200]

28. Gonzalez KD, Buzin CH, Noltner KA, et al. High Frequency of De Novo Mutations in Li-Fraumeni Syndrome. J Med Genet. 2009; 46:689–93. [PubMed: 19556618]

29. Macdonald OK, Lee CM, Tward JD, Chappel CD, Gaffney DK. Malignant Phyllodes Tumor of the Female Breast: Association of Primary Therapy with Cause-Specific Survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer. 2006; 107:2127–2133. [PubMed: 16998937]

30. Kim YJ, Kim K. Radiation Therapy for Malignant Phyllodes Tumor of the Breast: An Analysis of SEER Data. Breast. 2017; 32:26–32. [PubMed: 28013032]

31. Gnerlich JL, Williams RT, Jaskowiak N, Kulkarni SA. Utilization of Radiotherapy for Malignant Phyllodes Tumors: Analysis of the National Cancer Data Base, 1998–2009. Ann Surg Oncol. 2014; 21:1222–1230. [PubMed: 24306659]

32. Belkacemi Y, Bousquet G, Marsiglia H, et al. Phyllodes Tumor of the Breast. Int J Radiat Oncol Biol Phys. 2008; 70:492–500. [PubMed: 17931796]

33. Barth RJ Jr, Wells WA, Mitchell SE, Cole BF. A Prospective, Multi-Institutional Study of Adjuvant Radiotherapy after Resection of Malignant Phyllodes Tumors. Ann Surg Oncol. 2009; 16:2288–2294. [PubMed: 19424757]

34. Zeng S, Zhang X, Yang D, Wang X, Ren G. Effects of Adjuvant Radiotherapy on Borderline and Malignant Phyllodes Tumors: A Systemic Review and Meta-Analysis. Mol Clin Oncol. 2015; 3:663–671. [PubMed: 26137284]

35. Moskowitz CS, Chou JF, Wolden SL, et al. Breast Cancer after Chest Radiation Therapy for Childhood Cancer. J Clin Oncol. 2014; 32:2217–2223. [PubMed: 24752044]

Synopsis:

Very few women with phyllodes undergo germline testing, even when they meet NCCN criteria. However, in those selected for testing, deleterious mutations are identified in ~10%. This presents an opportunity to discover the incidence of germline mutations in phyllodes patients.

Table #1:

Multi-Center Phyllodes Tumor Patient Demographics and Personal Breast History, 2007 – 2017.

	OVERALL N=550	Benign N=379 (68.9%)	Borderline N=108 (19.6%)	Malignant N=58 (10.5%)
Race				
- Asian	47 (8.5%)	28 (59.6%)	16 (34.0%)	2 (4.3%)
- Native Hawaiian/Pacific Islander	1 (0.2%)	1 (100%)	0 (0%)	0 (0%)
- American Indian	5 (0.9%)	1 (20.0%)	1 (20.0%)	3 (60.0%)
- Black /African American	85 (15.5%)	61 (71.8%)	13 (15.3%)	10 (11.8%)
- White	326 (59.3%)	227 (69.6%)	64 (19.6%)	34 (10.4%)
- Other	39 (7.1%)	25 (64.1%)	8 (20.5%)	6 (15.4%)
Ethnicity				
- Hispanic or Latino	37 (6.7%)	28 (75.7%)	8 (21.6%)	1 (2.7%)
- Not Hispanic or Latino	396 (72.0%)	258 (65.2%)	84 (21.2%)	50 (12.6%)
Family History of Ashkenazi Jewish Descent				
- Yes	4 (0.7%)	4 (100%)	0 (0%)	0 (0%)
Body Mass Index (BMI) – Median (IQR)	27 (23 – 33)	26 (23 – 33)	28 (24 – 34)	29 (24 – 34)
Personal History of Mantle Radiation				
- Yes	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Personal History of Benign Breast Biopsy				
- Yes	137 (24.9%)	101 (73.7%)	24 (17.5%)	10 (7.3%)
Atypia (ALH, ADH, LCIS, etc.)	7 (5.1%)	3 (42.9%)	1 (14.3%)	2 (28.6%)
Fibroadenoma, Fibroepithelial Lesion	81 (59.1%)	60 (74.1%)	17 (21.0%)	3 (3.7%)
Other Benign Lesion	48 (35.0%)	38 (79.2%)	5 (10.4%)	5 (10.4%)
Personal History of Breast Cancer				
- Yes	14 (2.5%)	8 (57.1%)	2 (14.3%)	3 (21.4%)

Data presented as N (%) unless otherwise specified. Column percentages are presented for variables overall, and row percentages are presented for all subgroups. Percentages may not add up to 100 due to rounding or missing values.

Table #2.

Multi-Center Phyllodes Tumor Distribution of National Comprehensive Cancer Network Criteria, Genetic Testing, and Mutations Identified, 2007–2017.

	OVERALL N = 550	Benign N=379 (68.9%)	Borderline N=108 (19.6%)	Malignant N=58 (10.5%)
Any Family History of Cancer *	329 (59.8%)	220 (58.0%)	70 (64.8%)	39 (67.2%)
≥3 Family Members with Cancer †	112 (34.0%)	71 (32.3%)	22 (31.4%)	19 (48.7%)
Met Any NCCN Criteria for Genetic Referral ‡	102 (18.5%)	70 (18.5%)	18 (16.7%)	14 (24.1%)
- Close relative with pancreatic ca§	17 (16.7%)	9 (12.9%)	3 (16.7%)	5 (35.7%)
- Close relative with ovarian ca	36 (35.3%)	25 (35.7%)	8 (44.4%)	3 (21.4%)
- Close relative with male breast ca	4 (3.9%)	3 (4.3%)	0 (0%)	1 (7.1%)
- ≥3 close relatives with any cancer	68 (66.7%)	48 (68.6%)	11 (61.1%)	9 (64.3%)
Genetic Testing Performed	34 (6.2%)	14 (3.7%)	7 (6.5%)	13 (22.4%)
Type of Genetic Testing¶				
- *TP53* only	2 (5.9%)	0 (0%)	0 (0%)	2 (15.4%)
- *BRCA1* & *BRCA2* only	13 (38.2%)	9 (64.3%)	3 (42.9%)	1 (7.7%)
- *BRCA1, BRCA2, & TP53* only	5 (14.7%)	1 (7.1%)	0 (0%)	4 (30.8%)
- ≥5 Genes Tested	10 (29.4%)	2 (14.3%)	3 (42.9%)	5 (38.5%)
- ≥10 Genes Tested	9 (26.5%)	2 (14.3%)	3 (42.9%)	4 (30.8%)
- ≥15 Genes Tested	6 (17.6%)	1 (7.1%)	1 (14.3%)	4 (30.8%)
- ≥25 Genes Tested	4 (11.8%)	0 (0%)	1 (14.3%)	3 (23.1%)
- Included *TP53* in *any* testing type	17 (50.0%)	2 (14.3%)	3 (42.9%)	12 (92.3%)
Gene Mutations Identified	3 (8.8%)	1 (7.1%)	0 (0%)	2 (15.4%)
- *TP53*	2 (5.9%)	0 (0%)	0 (0%)	2 (15.4%)
- *BRCA1*	1 (2.9%)	1 (7.1%)	0 (0%)	0 (0%)
- *BRCA2 VUS***	2 (5.9%)	2 (14.3%)	0 (0%)	0 (0%)

*Including at least one 1st-, 2nd-, or 3rd-degree relative on either maternal or paternal side

†Including ≥3 close relatives on maternal *or* ≥3 close relatives on paternal side, percentages out of those with *any* family history (N=329)

‡Percentages for all variables in this section are out of the number of patients who were eligible for genetic testing

§Close relative as defined by NCCN, 1st-, 2nd-, or 3rd-degree relative

¶All percentages are out of the total that underwent testing in each group

**One patient with benign phyllodes had both a *BRCA1* mutation and a *BRCA2* VUS

Data presented as N (%) unless otherwise specified. Percentages may not add up to 100 due to rounding or missing values.

Table 3.

Univariate Logistic Regression Predicting Likelihood of Undergoing Genetic Testing.

Model	Model N	Predictor	Odds Ratio (95% CI)	P-Value	Overall P-Value
1	**541**	**Age at Diagnosis**	1.01 (0.99–1.03)	0.56	0.56
2	**513**	**Pathologic Tumor Size**	1.00 (1.00–1.01)	0.12	0.12
3	**539**	**Grade**			**<0.001**
		1 (Benign)	REF		
		2 (Borderline)	2.20 (0.91–5.28)	0.08	
		3 (Malignant)	9.19 (4.09–20.67)	<0.001	
4	**542**	**NCCN Criteria**			**0.001**
		Ineligible	REF		
		Eligible	3.39 (1.69–6.77)	0.001	

Each model was fit separately, and all models account for the correlation of patients treated at the same facility.

Table 4.

Multivariate Logistic Regression Predicting Likelihood of Undergoing Genetic Testing.

Model	Model N	Predictor	Odds Ratio (95% CI)	P-Value	Overall P-Value
1	**539**	**Grade**			**<0.001**
		1 (Benign)	REF		
		2 (Borderline)	2.07 (0.71–5.99)	0.18	
		3 (Malignant)	8.40 (3.25–21.68)	<0.001	
		NCCN Criteria			**0.006**
		Ineligible	REF		
		Eligible	3.18 (1.40–7.27)	0.006	

Model accounts for the correlation of patients treated at the same facility.