

Dissociating Fibroepithelioma of Pinkus From Internal Malignancy: A Single-Center Retrospective Study

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PRACTICE POINTS

- Dermatologic reactions may be the initial presentation of an internal malignancy.
- Fibroepithelioma of Pinkus is considered on the spectrum between adnexal neoplasms and a nonaggressive variant of basal cell carcinoma (BCC).
- Fibroepithelioma of Pinkus should be managed similar to nonaggressive variants of BCC such as nodular BCC.
- Fibroepithelioma of Pinkus is not associated with internal malignancy.

Fibroepithelioma of Pinkus (FeP) is a rare skin tumor with a clinical presentation similar to benign neoplasms such as acrochordons and seborrheic keratoses. Our study analyzed if there is an association between FeP and internal tumors, specifically gastrointestinal tract tumors. We retrospectively reviewed the medical records of patients with FeP for other tumors throughout their lives until 2020. Although the quality of documentation for each patient may have differed, this study suggests that the presence of FeP does not indicate the presence of gastrointestinal tract tumors, and

there is no need for altered cancer screening recommendations for those with FeP.

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Fibroepithelioma of Pinkus (FeP), or Pinkus tumor, is a rare tumor with a presentation similar to benign neoplasms such as acrochordons and seborrheic keratoses. Classically, FeP presents as a nontender, solitary, flesh-colored, firm, dome-shaped papule or plaque with a predilection for the lumbosacral region rather than sun-exposed areas. This tumor typically develops in fair-skinned older adults, more often in females.¹

The association between cutaneous lesions and internal malignancies is well known to include dermatoses such as erythema repens in patients with lung cancer, or tripe palms and acanthosis nigricans in patients with gastrointestinal malignancy. Outside of paraneoplastic presentations, many syndromes have unique constellations of clinical findings that require the clinician to investigate for internal malignancy. Cancer-associated genodermatoses such as Birt-Hogg-Dubé, neurofibromatosis, and Cowden syndrome have key findings to alert

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the provider of potential internal malignancies.² Given the rarity and relative novelty of FeP, few studies have been performed that evaluate for an association with internal malignancies.

There potentially is a common pathophysiologic mechanism between FeP and other benign and malignant tumors. Some have noted a possible common embryonic origin, such as Merkel cells, and even a common gene mutation involving tumor protein p53 or *PTCH1* gene.^{3,4} Carcinoembryonic antigen is a glycoprotein often found in association with gastrointestinal tract tumors and also is elevated in some cases of FeP.⁵ A single-center retrospective study performed by Longo et al³ demonstrated an association between FeP and gastrointestinal malignancy by calculating a percentage of those with FeP who also had gastrointestinal tract tumors. Moreover, they noted that FeP preceded gastrointestinal tract tumors by up to 1 to 2 years. Using the results of this study, they suggested that a similar pathogenesis underlies the association between FeP and gastrointestinal malignancy, but a shared pathogenesis has not yet been elucidated.³

With a transition to preventive medicine and age-adjusted malignancy screening in the US medical community, the findings of FeP as a marker of gastrointestinal tract tumors could alter current recommendations of routine skin examinations and colorectal cancer screening. This study investigates the association between FeP and internal malignancy, especially gastrointestinal tract tumors.

Methods

Patient Selection—A single-center, retrospective, case-control study was designed to investigate an association between FeP and internal malignancy. The study protocol was approved by the institutional review board of the Naval Medical Center San Diego, California, in compliance with all applicable federal regulations governing the protection of human subjects. A medical record review was initiated using the Department of Defense (DoD) electronic health record to identify patients with a history of FeP. The query used a natural language search for patients who had received a histopathology report that included *Fibroepithelioma of Pinkus*, *Pinkus*, or *Pinkus tumor* within the diagnosis or comment section for pathology specimens processed at our institution (Naval Medical Center San Diego). A total of 45 patients evaluated at Naval Medical Center San Diego had biopsy specimens that met inclusion criteria. Only 42 electronic medical records were available to review between January 1, 2003, and March 1, 2020. Three patients were excluded from the study for absent or incomplete medical records.

Study Procedures—Data extracted by researchers were analyzed for statistical significance. All available data in current electronic health records prior to the FeP diagnosis until March 1, 2020, was reviewed for other documented malignancy or colonoscopy data. Data extracted included age, sex, date of diagnosis of FeP, location of FeP, social history, and medical and surgical history to

identify prior malignancy. Colorectal cancer screening results were drawn from original reports, gastrointestinal clinic notes, biopsy results, and/or primary care provider documentation of colonoscopy results. If the exact date of internal tumor diagnosis could not be determined but the year was known, the value “July, year” was utilized as the diagnosis date.

Statistical Analysis—Data were reviewed for validity, and the Shapiro-Wilk test was used to test for normality. Graphical visualization assisted in reviewing the distribution of the data in relation to the internal tumors. The Fisher exact test was performed to test for associations, while continuous variables were assessed using the Student *t* test or the nonparametric Mann-Whitney *U* test. Analysis was conducted with StataCorp. 2017 Stata Statistical Software: Release 15 (StataCorp LLC). Significance was set at $P < .05$.

Results

Patient Demographics—Of the 42 patients with FeP included in this study, 28 (66.7%) were male and 14 (33.3%) were female. The overall mean age at FeP diagnosis was 56.83 years. The mean age (SD) at FeP diagnosis for males was 59.21 (19.00) years and 52.07 (21.61) for females ($P = .2792$) (Table 1). Other pertinent medical history, including alcohol and tobacco use, obesity, and diabetes mellitus, is included in Table 1.

TABLE 1. Patient Demographics (N=42)

Characteristic	Patients With FeP
Sex, n (%)	
Male	28 (66.7)
Female	14 (33.3)
Mean age (SD) at FeP diagnosis, y	
Males	59.21 (19.00)
Females	52.07 (21.61) ^a
Overall	56.83 (19.93)
Social and medical history, n (%)	
Alcohol use	5 (11.9)
Tobacco use	19 (45.2)
Obesity	15 (35.7)
Diabetes mellitus	8 (19.0)
Colorectal adenocarcinoma	3 (7.14)

Abbreviation: FeP, fibroepithelioma of Pinkus.

^a $P = .2792$ (*t* test).

Characterization of Tumors—The classification of the number of patients with any other nonskin neoplasm is presented in Table 2. Fifteen (35.7%) patients had 1 or more gastrointestinal tubular adenomas. Three patients were found to have colorectal adenocarcinoma. Karsenti et al⁶ published a large study of colonic adenoma detection rates in the *World Journal of Gastroenterology* stratified by age and found that the incidence of adenoma for those aged 55 to 59 years was 28.3% vs 35.7% in our study ($P=.2978$ [Fisher exact test]).

Given the number of gastrointestinal tract tumors detected, most of which were found during routine surveillance, and a prior study⁶ suggesting a relationship between FeP and gastrointestinal tract tumors, we analyzed the temporal relationship between the date of gastrointestinal tract tumor diagnosis and the date of FeP diagnosis to assess if gastrointestinal tract tumor or FeP might predict the onset of the other (Figure 1). By assigning a temporal category to each gastrointestinal tract tumor as occurring either before or after the FeP diagnosis by 0 to 3 years, 3 to 10 years, 10 to 15 years, and 15 or more years, the box plot in Figure 1 shows that gastrointestinal adenoma development had no significant temporal relationship to the presence of FeP, excluding any outliers (shown as dots). Additionally, in Figure 1, the same concept was applied to assess the relationship between the dates of all gastrointestinal tract tumors—benign, precancerous, or malignant—and the date of FeP diagnosis, which again showed that FeP and gastrointestinal tract tumors did not predict the onset of the other. Figure 2 showed the same for all nonskin tumor diagnoses and again demonstrated that FeP and all other nondermatologic tumors did not predict the onset of the other.

Comment

Malignancy Potential—The malignant potential of FeP—characterized as a trichoblastoma (an adnexal tumor) or a basal cell carcinoma (BCC) variant—has been documented.¹ Haddock and Cohen¹ noted that FeP can be considered as an intermediate variant between BCC and trichoblastomas. Furthermore, they questioned the relevance of differentiating FeP as benign or malignant.¹ There are additional elements of FeP that currently are unknown, which can be partially attributed to its rarity. If we can clarify a more accurate pathogenic model of FeP, then common mutational pathways with other malignancies may be identified.

Screening for Malignancy in FeP Patients—Until recently, FeP has not been demonstrated to be associated with other cancers or to have increased metastatic potential.¹ In a 1985 case series of 2 patients, FeP was found to be specifically overlying infiltrating ductal carcinoma of the breast. After a unilateral mastectomy, examination of the overlying skin of the breast showed a solitary, lightly pigmented nodule, which was identified as an FeP after histopathologic evaluation.⁷ There have been limited investigations of whether FeP is simply a solitary tumor

TABLE 2. Breakdown of Non-FeP Tumors in the Study Population (N=42)

Non-FeP tumor type	Patients, n (%)
Adenoma (gastrointestinal)	15 (35.7)
Carcinoma	10 (23.8)
Leukemia	3 (7.1)
Any type	21 (50.0)

Abbreviation: FeP, fibroepithelioma of Pinkus.

or a harbinger for other malignancies, despite a study by Longo et al³ that attempted to establish this temporal relationship. They recommended that patients with FeP be clinically evaluated and screened for gastrointestinal tract tumors.³ Based on these recommendations, textbooks for dermatopathology now highlight the possible correlation of FeP and gastrointestinal malignancy,⁸ which may lead to earlier and unwarranted screening.

Comparison to the General Population—Although our analysis showed a portion of patients with FeP have gastrointestinal tract tumors, we do not detect a significant difference from the general population. The average age at the time of FeP diagnosis in our study was 56.83 years compared with the average age of 64.0 years by Longo et al,³ where they found an association with gastrointestinal adenocarcinoma and neuroendocrine tumors. As the rate of gastrointestinal adenoma and malignancy increases with age, the older population in the study by Longo et al³ may have developed colorectal cancer independent of FeP development. However, the rate of gastrointestinal or other malignancies in their study was substantially higher than that of the general population. The Longo et al³ study found that 22 of 49 patients developed nondermatologic malignancies within 2 years of FeP diagnosis. Additionally, no data were provided in the study regarding precancerous lesions.

In our study population, benign gastrointestinal tract tumors, specifically tubular adenomas, were noted in 35.7% of patients with FeP compared with 28.3% of the general population in the same age group reported by Karsenti et al.⁶ Although limited by our sample size, our study demonstrated that patients with FeP diagnosis showed no significant difference in age-stratified incidence of tubular adenoma compared with the general population ($P=.2978$). Figures 1 and 2 showed no obvious temporal relationship between the development of FeP and the diagnosis of gastrointestinal tumor—either precancerous or malignant lesions—suggesting that diagnosis of one does not indicate the presence of the other.

Relationship With Colonoscopy Results—By analyzing those patients with FeP who specifically had documented

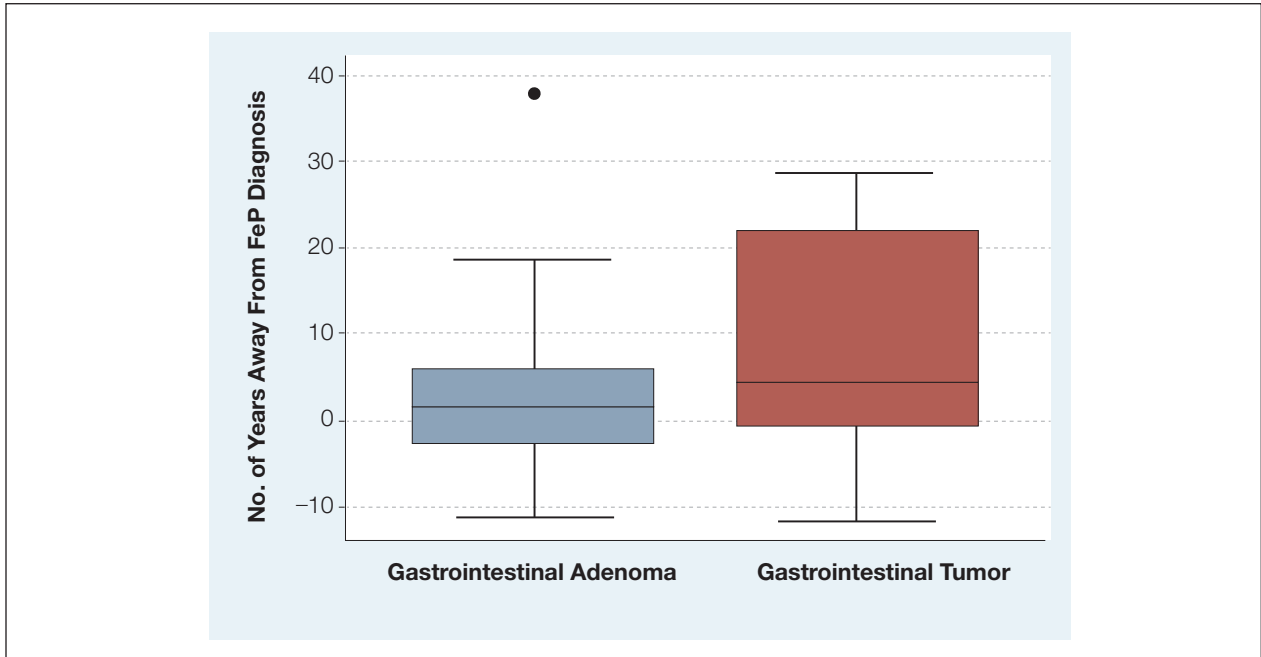


FIGURE 1. The temporal relationship between fibroepithelioma of Pinkus (FeP) and gastrointestinal adenoma and gastrointestinal tract tumors. The dates of gastrointestinal tumor diagnoses are represented in the box plot according to their temporal relationship to the patient's date of FeP diagnosis. Positive values indicate that a diagnosis of FeP occurred after the tumor. Negative values indicate that a diagnosis of FeP occurred before the tumor. The horizontal bar inside the boxes indicates the median, and the lower and upper ends of the boxes are the first and third quartiles. The whiskers indicate the upper and lower ranges, and the data more extreme than the whiskers are plotted as outliers (shaded circles). The data in this figure show that FeP diagnosis occurs both before and after a diagnosis of gastrointestinal tract tumors without a statistically significant trend.

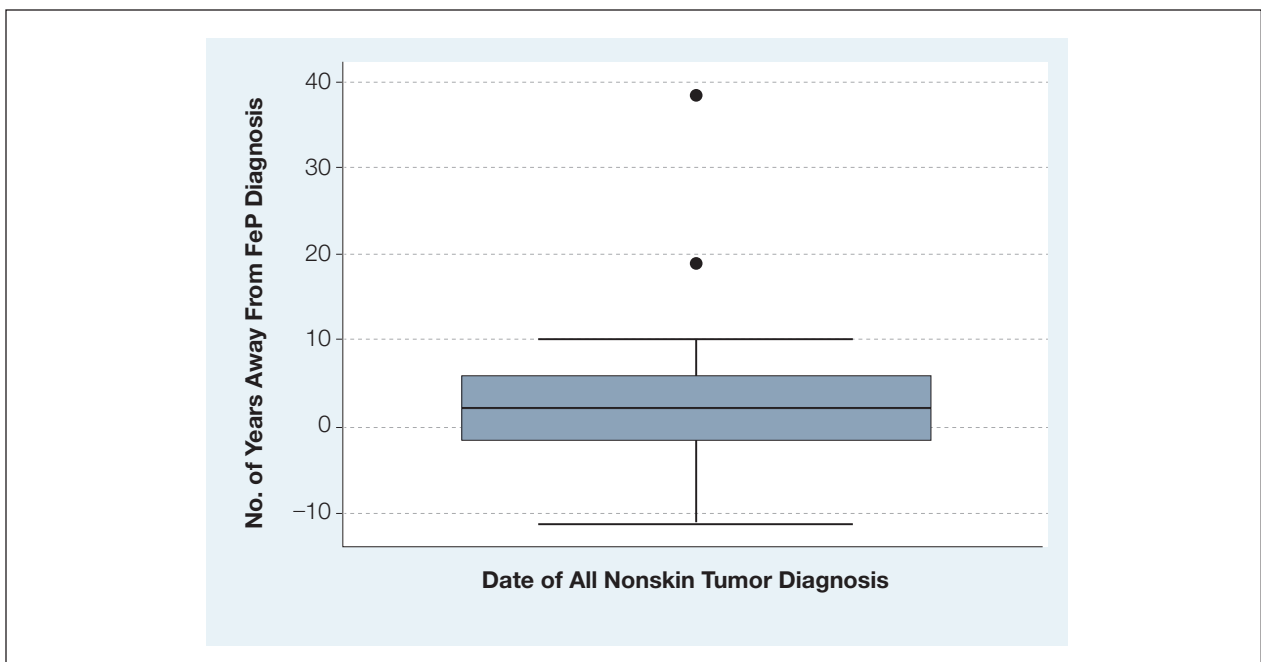


FIGURE 2. The temporal relationship between fibroepithelioma of Pinkus (FeP) and all nonskin tumors. The dates of all nonskin tumor diagnoses are represented in the box plot according to their temporal relationship to the patient's date of FeP diagnosis. Positive values indicate that FeP diagnosis occurred after the tumor. Negative values indicate that FeP diagnosis occurred before the tumor. The horizontal bar inside the box indicates the median, and the lower and upper ends of the box are the first and third quartiles. The whiskers indicate upper and lower ranges, and the data more extreme than the whiskers are plotted as outliers (shaded circles). The data in this figure suggest that FeP diagnosis occurs both before and after diagnosis of nonskin tumor types without a statistically significant trend.

colonoscopy results, we did not find a correlation between FeP and gastrointestinal tubular adenoma or carcinoma at any time during the patients' available records. Although some patients may have had undocumented colonoscopies performed outside the DoD medical system, most had evidence that these procedures were being performed by transcription into primary care provider notes, uploaded gastroenterologist clinical notes, or colonoscopy reports. It is unlikely a true colorectal or other malignancy would remain undocumented over years within the electronic medical record.

Study Limitations—Because of the nature of electronic medical records at multiple institutions, the quality and/or the quantity of medical documentation is not standardized across all patients. Not all pathology reports may include FeP as the primary diagnosis or description, as FeP may simply be reported as BCC. Despite thorough data extraction by physicians, we were limited to the data available within our electronic medical records. Colonoscopies and other specialty care often were performed by civilian providers. Documentation regarding where patients were referred for such procedures outside the DoD was not available unless reports were transmitted to the DoD or transcribed by primary care providers. Incomplete records may make it more difficult to identify and document the number and characteristics of patients' tubular adenomas. Therefore, a complete review of civilian records was not possible, causing some patients' medical records to be documented for a longer period of their lives than for others.

Conclusion

Our data demonstrated no statistically significant temporal relationship between the development of FeP and other benign or malignant tumors. Additionally, the

prevalence of tubular adenoma or gastrointestinal malignancy is not substantially higher in those with FeP than the age-adjusted population. Current guidelines recommend that patients with FeP should be treated and return for follow up at regular intervals, similar to patients with a history of BCC. This study does not establish FeP as a risk factor for development of any type of cancer that would require earlier or more frequent intervals beyond the established age-appropriate screening guidelines.

Given the discrepancies in our findings with the previous study,³ future investigations on FeP and associated tumors should focus on integrated health care systems with longitudinal data sets for all age-appropriate cancer screenings in a larger sample size. Another related study is needed to evaluate the pathophysiologic mechanisms of FeP development relative to known cancer lines.

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