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The incidence of primary fallopian tube cancer in the United States

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Abstract

Objective. The objective of this study was to report the incidence of primary fallopian tube carcinoma (PFTC) in the United States population and to describe associated demographic and clinical factors.

Methods. A total of 3051 PFTC cases diagnosed from 1998 to 2003, reported from population-based cancer registries, were analyzed. Registries contributing data represent 83.1% of the U.S. population. Data are presented by age, race/ethnicity, U.S. census region, stage, histology, grade, and laterality. Trends in incidence over time from 1998 to 2003 are also presented.

Results. The incidence rate was 0.41 per 100,000 women from 1998 to 2003. White, non-Hispanic women and women aged 60–79 had the highest incidence rates ($p<0.0001$). The majority (88%) of PFTCs were adenocarcinomas; serous adenocarcinomas accounted for 44% and endometrioid adenocarcinomas for 19% of adenocarcinoma diagnoses. Essentially half (49.9%) of PFTCs were poorly differentiated; 89% were unilateral at diagnosis. Stage at diagnosis was fairly evenly distributed among localized (36%), regional (30%), and distant (32%). Overall, rates of PFTC remained stable over time. Among women aged 65–69, incidence rates increased significantly by 3.8% per year from 1998 to 2003 ($p<0.05$).

Conclusions. This report provides characteristics of PFTC using the largest number of cases assembled in one study to date. Although the demographic characteristics of PFTC are similar to those of ovarian cancer, stage at diagnosis and the stable trend observed in PFTC are in contrast to ovarian cancer. Future studies should focus on examining the increasing trend of PFTC among 65- to 69-year-old women.
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Keywords: Fallopian tube; Cancer; Surveillance; Incidence

Introduction

Primary fallopian tube cancer (PFTC) is rare, accounting for less than 0.2% of cancer diagnoses among women annually [1], and little is known about its etiology. Various studies have linked mutations in the *BRCA1* and *BRCA2* genes to PFTC [2–4], and alterations in p53 have been shown to be common in the disease; it has been suggested that these alterations may reduce survival [5,6]. Advanced stage [7,8], age [7], and the presence of residual tumor after initial surgery [7] have also been associated with decreased survival. Although the prognosis of PFTC patients is generally poor [9], those with endometrioid adenocarcinomas may have relatively better prognoses [10]. The histologic and biologic features of PFTC are similar to those of ovarian cancer [7], and these two tumor types appear identical under light microscopy [11]. Some reports suggest that PFTC may be underestimated because advanced cases are often incorrectly diagnosed as primary ovarian cancer [12]; a correct diagnosis of PFTC requires close attention by a pathologist to the macroscopic and histological findings in resection specimens [13]. Clinically, tubal carcinomas are generally treated with surgical staging, debulking, and adjuvant chemotherapy according to guidelines for treating epithelial ovarian cancer [11,14].

Because of its rarity, the incidence of PFTC in the United States has not been well-defined. A study published in the 1980s, representing approximately 9% of the U.S. population, indicated an incidence of 0.36 per 100,000 women from 1973 to 1984 [15]. While this study is an important contribution because it is one of the only population-based studies of PFTC to date, the small sample led to the presentation of limited demographic data, and no information was presented on the tumor charac-

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Table 1
Demographic characteristics of women diagnosed with primary fallopian tube cancer in the United States, 1998–2003 [a]

	Count (%)	Rate [b] (95% CI)	*p*-value
Total	3051 (100)	0.41 (0.38–0.41)	
Race			
White	2747 (90)	0.41 (0.40–0.43)	REF
Black	190 (6)	0.27 (0.23–0.31)	<0.0001
American Indian/Alaska Native	11 (0.4)	0.26 (0.12–0.48)	0.1758
Asian or Pacific Islander	73 (2.4)	0.25 (0.20–0.32)	<0.0001
Other/Unknown	30 (0.9)	–	–
Ethnicity [c]			
Non-Hispanic/Latino	2893 (94.8)	0.41 (0.39–0.42)	REF
Hispanic/Latino	158 (5.2)	0.27 (0.23–0.32)	<0.0001
Region			
Northeast	780 (26)	0.43 (0.40–0.46)	REF
Midwest	808 (26)	0.39 (0.36–0.42)	0.0603
South	738 (24)	0.35 (0.32–0.37)	<0.0001
West	725 (24)	0.44 (0.41–0.48)	0.526
Age (years)			
0–39	66 (2.2)	0.02 (0.01–0.02)	<0.0001
40–49	347 (11.4)	0.32 (0.29–0.35)	<0.0001
50–59	755 (24.7)	0.93 (0.86–1.0)	<0.0001
60–69	813 (26.6)	1.48 (1.38–1.59)	0.0579
70–79	764 (25.0)	1.63 (1.52–1.75)	REF
80+	306 (10.0)	0.97 (0.87–1.09)	<0.0001

CI=confidence interval; REF=referent.
– Rate not calculated due to lack of denominator data.
[a] Data are from population-based statewide cancer registries covering 83.1% of U.S. population.
[b] Rates are age adjusted to the 2000 U.S. standard population.
[c] Hispanic ethnicity is not mutually exclusive from race categories.

teristics associated with the cases reported. Most studies that have examined the clinical and pathologic factors of PFTC have been based on single cases or groups of cases reported from individual institutions. The current study uses combined data from statewide cancer registries participating in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR), and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program to analyze PFTC in the United States. This combined dataset forms the basis for the calculation and dissemination of annual official federal government statistics on cancer incidence in the United States [1]. Population-based statistics on current PFTC incidence, as well as demographic, clinical, and pathologic factors associated with diagnoses of fallopian tube cancer, are provided. Comparisons are made with ovarian cancer because of its similarity to PFTC.

Materials and methods

A total of 3051 malignant primary PFTC cases diagnosed from 1998 to 2003 were included from population-based cancer registries affiliated with the NPCR or SEER programs. Of these, 2891 cases were reported to CDC/NPCR as of January 31, 2006, and the remaining 160 were reported to NCI/SEER as of December 2005 and made available through a public-use data file in April 2006. PFTC cases were collected by trained tumor registrars using uniform and standardized methodology and practices to abstract information from medical records [16]. PFTC cases were coded according to third edition of the World Health Organization *International Classification of Diseases for Oncology* [17]. Only cases with the primary site of origin coded as the fallopian tube (C57.0) were included in the analysis [17]. All other cases were excluded; these exclusions included cases that were coded to other parts of the female genital system and related sites (e.g., ovary, uterus, peritoneum, broad ligament) and those that were classified as overlapping lesions of fallopian tube, ovary and/or endometrium.

Data from 38 states and the District of Columbia, representing 83.1% of the U.S. population, were considered of high quality according to the publication criteria of *United States Cancer Statistics* [1] and were included in these analyses. State data were organized and presented by regions defined by the U.S. Census Bureau (http://www.census.gov/popest/counties); population coverage by U.S. census region was as follows: 97.7% for the Northeast; 97.8%, Midwest; 63.0%, South; and 87.8%, West. All statistical calculations were performed using SEERStat version 6.1 software (http://www.seer.cancer.gov/seerstat/). Rates and corresponding 95% confidence intervals were calculated for demographic factors (race, ethnicity, age, U.S. census region). Population estimates used as denominators in the rate calculations were obtained from the U.S. Census Bureau and modified slightly by SEER in order to produce potentially more accurate rates [1]. All rates were age adjusted by 19 age groups (<1 year, 1–4 years, 5–9 years etc.) to the 2000 U.S. standard population by the direct method [1]. Confidence intervals were calculated using the gamma method [18]. All rates are presented as per 100,000 women. Significant

Table 2
Clinical and pathologic characteristics of primary fallopian tube cancer diagnosed in the United States, 1998–2003 [a]

	Count	Percentage
Histology		
Adenocarcinoma	2695	88.3
Serous adenocarcinoma	1179	
Endometrioid adenocarcinoma	499	
Other adenocarcinoma	1017	
Carcinoma	272	8.9
Sex cord tumors and sarcomas	67	2.2
Lipid cell tumors	15	0.5
Other	2	0.07
Laterality		
Unilateral, origin in right tube	1282	42
Unilateral, origin in left tube	1386	45.4
Unilateral, unspecified origin	41	1.3
Bilateral	236	7.7
Unknown	106	3.5
Grade		
Well differentiated	141	4.6
Moderately differentiated	559	18.3
Poorly differentiated	1521	49.9
Undifferentiated	267	8.8
Unknown	563	18.5
Stage [b]		
Total	1570	100
Localized	565	36
Regional	468	29.8
Distant	496	31.6
Unstaged	41	2.6

Because of rounding, percentages in each category may not total to 100.0%.
[a] Data are from population-based statewide cancer registries covering 83.1% of U.S. population.
[b] Stage analyses are limited to diagnosis years 2001–2003 (1570 cases) and are presented as SEER Summary Stage 2000 [14].

differences between rates were detected using the rate ratio test, with the significance level set at $p<0.05$. The group with the highest rate was used as the referent group for race, ethnicity, and age. The Northeast region was used as the referent group for regional analyses because it has the highest cancer rates overall in the United States [1].

Frequency calculations are shown for clinical and pathologic factors (histology, stage, laterality, grade). In order to accommodate the presentation of histology, only microscopically confirmed cases of primary PFTC were included in all analyses. Histology groupings were devised following the selection of primary PFTC cases and were based on the World Health Organization criteria for gynecologic cancers [19]. Lymphomas originating in the fallopian tube were excluded. Stage is presented as SEER Summary Stage, a system routinely used by cancer registries, incorporating information from the FIGO (International Federation of Obstetricians and Gynaecologists) and AJCC (American Joint Committee on Cancer) staging systems [20]. Trained cancer registrars use all clinical and pathological information available from medical records (physical exam, radiologic procedures, tumor markers, pathologic exams, surgical reports) to code SEER Summary Stage [20,21]. For PFTC, SEER Summary Stage incorporates information obtained from medical records of surgical staging, including lymph node assessment and inspection of the peritoneal cavity [20]; however, the detailed outcomes of the procedures and the staging physician specialty are not reported. Because the rules for staging in the SEER Summary Stage system changed significantly with 2001 diagnoses [20], all figures analyzing stage were limited to diagnoses occurring from 2001 to 2003 (1570 cases). In SEER Summary Stage, localized stage refers to FIGO stage I and is defined as cancer confined to the fallopian tube or tubal serosa or malignant ascites/peritoneal washings only; regional stage is either direct extension to proximal organs (FIGO stage II) or involvement of a regional lymph node (FIGO stage IIIC); distant stage is pelvic extension with malignant cells in ascites or peritoneal washings or peritoneal implants outside the pelvis (FIGO stages IIIA, IIIB, III NOS [not otherwise specified], and IV) [20].

Trends in the incidence of PFTC are shown as annual percentage change (APC) over the study period (1998–2003). APCs were calculated using the weighted least squared method, and significant differences in trends were calculated with a significance level of $p<0.05$.

Results

The age-adjusted incidence rate of PFTC in the United States was 0.41 per 100,000 women from 1998 to 2003 (Table 1). The rate among white women (0.41) was significantly higher than that among black women (0.27) and Asians/Pacific Islanders (0.25) ($p<0.0001$). Non-Hispanic women had a higher rate of PFTC (0.41) than Hispanic women (0.27) ($p<0.0001$). Rates of PFTC were similar among the four regions of the United States; however, the South had a significantly lower rate than the Northeast (0.35 for South and 0.43 for Northeast, $p<0.0001$). Rates differed significantly by age, ranging from 0.02 among those aged 0–39 to 1.63 among those 70–79. The rate among 70- to 79-year olds was significantly higher ($p<0.0001$) than in every other age group except 60–69.

In all, 88.3% of the PFTCs were adenocarcinomas (Table 2). Serous adenocarcinomas accounted for 44% of the adenocarcinomas, and endometrioid carcinomas accounted for another

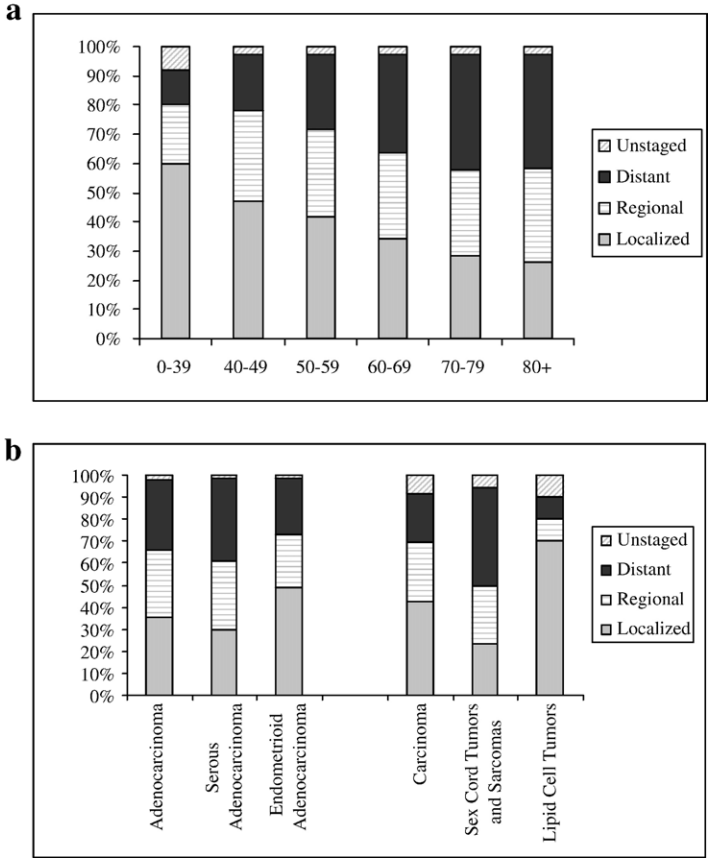

Fig. 1. (a) Stage of primary fallopian tube cancer at diagnosis by age group, United States, 2001–2003. (b) Stage of primary fallopian tube cancer at diagnosis by histology, United States, 2001–2003. Serous and endometrioid adenocarcinoma subtype data are included in the overall adenocarcinoma data. (a, b) Data are from population-based statewide cancer registries covering 83.1% of U.S. population. Stage analyses are limited to diagnosis years 2001–2003 (1570 cases) and are presented as SEER Summary Stage 2000 (14).

19%. Other histologic subtypes diagnosed included carcinomas (9% of cases; most were not further specified), sex cord/stromal tumors and sarcomas (2%), and lipid cell tumors (0.5%). Overall, 88.7% of PFTCs were unilateral at diagnosis, with a slightly higher percentage originating in the left tube than in the right tube. A small percentage of tumors were bilateral at diagnosis (8%). Essentially half (49.9%) of women with PFTC presented with poor differentiation at diagnosis, and another 9% were undifferentiated. Only 4.6% of cases were well differentiated at diagnosis. Stage at diagnosis was fairly evenly distributed among localized, regional, and distant stages, with a slightly higher percentage of localized cases than of regional and distant (36%, 30%, and 32%, respectively).

Although there was generally an even distribution with regard to stage at diagnosis, the percentage of advanced-stage cases increased with advancing age (Fig. 1a). When examining stage and histology, there was a fairly even distribution of stage among adenocarcinomas (Fig. 1b). Serous adenocarcinomas, however, were diagnosed at distant stages slightly more often than were all adenocarcinomas. Additionally, approximately 50% of endometrioid adenocarcinomas were diagnosed at a localized stage (versus 36% of all PFTCs). Sex cord tumors and sarcomas were diagnosed more often at a distant stage than were adenocarcinomas.

Rates of PFTC remained stable over time, with an APC of 0.4% per year from 1998 to 2003 (Fig. 2). This slight increase in PFTC rates was not statistically significant. In comparison, the rates of ovarian cancer decreased significantly (2.0% per year). Additionally, combined rates of other gynecologic cancers (mainly uterine, vulvar, vaginal, and cervical) declined significantly (1.8% per year). Examination of PFTC trends by age group revealed nonsignificant increases or decreases among most ages (Table 3), with the exception of women aged 65–69, for whom a significant increase of 3.8% per year was seen.

Table 3
Recent trends of primary fallopian tube cancer by age, United States, 1998–2003 [a]

Age	APC	*p*-value
0–59	−0.39	0.79
60–64	4.38	0.38
65–69	3.76 [b]	0.04
70–74	−1.37	0.52
75–79	−0.55	0.87
80+	−3.45	0.07

[a] Data are from population-based statewide cancer registries covering 83.1% of U.S. population.
[b] Annual percentage change (APC) is significantly different from 0 ($p<0.05$).

Discussion

The U.S. incidence rate for PFTC (0.41 per 100,000) was similar to those reported in Denmark and Finland of 0.3 and 0.5 per 100,000, respectively [22,23]. White women in the United States had significantly higher rates of PFTC than other women, a finding consistent with ovarian cancer. In a report covering diagnoses from 1992 to 1997, rates of malignant ovarian cancer among white women were about 1.5 times greater than among black or Asian/Pacific Islander women [24]. Nulliparity is a risk factor for ovarian cancer [25] and may explain some of the observed racial variability in risk of ovarian cancer according to a case–control study that compared differences in the obstetric experiences of white and black women [26]. Case–control studies probing PFTC and parity have yet to be published,

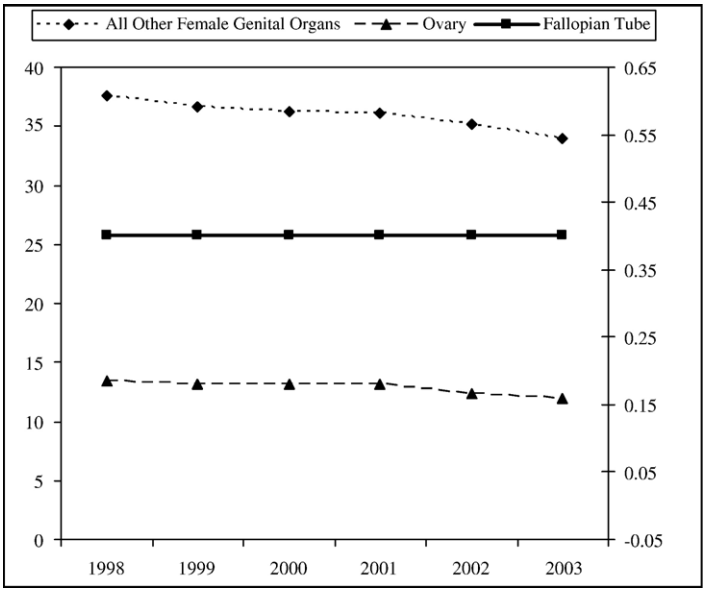

Fig. 2. Recent trends of gynecologic cancers, United States, 1998–2003. Annual percentage change (APC): all other female genital organs = −1.8*; fallopian tube = 0.4; ovary = −2.0*. Asterisk (*) indicates that APC is significantly different from 0 ($p<0.05$). Trends for all other female genital organs and ovary are plotted on the primary *y*-axis (values 0–40); fallopian tube trends are plotted on the secondary *Y*-axis (values −0.05 to 0.65). All other female genital organs group contains: cervix, uterus, vulva, vagina, broad ligament, round ligament, parametrium, uterine adnexa, placenta, and female genital tract not otherwise specified. Data are from population-based statewide cancer registries covering 83.1% of U.S. population.

however, a study linking registry data to census data in a Finnish population suggested that variations in PFTC incidence might be correlated with variations in parity [22]. Incidence rates were highest in urban areas and among higher social classes in Finland, and parity was low among these populations [22]. In contrast to a previous study showing variable PFTC rates by geography [15], PFTC rates were generally similar among census regions in our study. The lower rate calculated for the South may be due to less population coverage of that region than for the others (63% for South, 88–-98% for other regions). Most individual state rates, including states in the South, were similar and ranged from 0.3 to 0.5 per 100,000 (data not shown). Incidence rates peaked at an older age (70–79) in our study, but most previous studies reported peak incidence occurring in the early 60s [15,22,27]. Population-based registries contributing data to these studies included cases diagnosed 10–50 years ago [15,22]; however, while our study included diagnoses from the last 4–9 years. The age difference observed between these studies and ours may be a reflection of the recent longer life expectancy of Americans, resulting in a greater number of cancer diagnoses among older people [28]. In addition, previous reports that examined cases from hospital-based registries [27] may have included only those PFTC patients receiving surgery, and they may not represent older women who received palliative or hospice care. These patients could account for a large portion of the cases occurring among older women in our study, although it has been reported that typically a small percentage of PFTC patients are diagnosed outside of surgery [29].

We found that PFTCs were most often unilateral and diagnosed slightly more often at a localized stage than at regional or distant stages. This is in contrast to ovarian cancer, where over 50% of malignant tumors are diagnosed at a distant stage [30]. The difference between PFTC and ovarian cancer in stage at diagnosis may be primarily due to the fact that signs and symptoms such as abnormal vaginal bleeding or discharge and abdominal pain together with an abdominal mass are largely present for women with PFTC, while this is not the case for many women with ovarian cancer, allowing for an earlier stage at diagnosis for PFTC [27]. We also considered the possibility that the relatively higher percentage of localized cases compared to ovarian cancer in this study may be due to lack of complete and accurate surgical staging of PFTC patients. However, a study examining PFTC diagnoses from 1990 to 1997 in 14% of the U.S. population found that a little more than half (53%) of women diagnosed with FIGO stage I/II PFTC underwent surgical evaluation of the lymph nodes in order to rule out a higher stage [11]; this was higher than the percentage of stage I/II ovarian cancer patients receiving lymph node sampling in the same population in 1996 (42%) [31]. Stage was found to be an important prognostic factor in several PFTC studies [7,8,11,32]. In the United States, 5-year survival for FIGO stage I disease was reported to be 95%, but it was only 45% for FIGO stage IV disease [11]. Our finding that advanced PFTC cases were more common among older women is consistent with Alvarado-Cabrero et al., who reported an association of FIGO stage I tumors with younger age [8]. The Alvarado-Cabrero et al. study also found that older age had a significant adverse prognostic effect for women with tumors FIGO Stage II or lower, but this age effect was not present for more advanced tumors [8].

In the present study, PFTCs were histologically similar to ovarian cancer in that a large percentage were adenocarcinomas of the serous type. We also found that almost one-fifth of adenocarcinomas (16% of total PFTCs) were endometrioid carcinomas. Reports suggest that endometrioid carcinomas should be distinguished from serous adenocarcinomas, in part due to a more favorable prognosis [8,10] and the large portion of early-stage disease among these tumors [10], a finding consistent with our study. It has also been suggested that endometrioid carcinomas of the fallopian tube represent an intermediate entity between endometrial carcinoma and endometrioid ovarian carcinoma [33]. Examinations of grade showed that about half of the tumors in this study were poorly differentiated at diagnosis. The prognostic relevance of grade is unknown for PFTC. Some studies have reported grade to be a strong prognostic factor [5], but others have found no association [34] or just a weak association [7] between grade and survival.

Unlike other gynecologic cancers whose incidence rates are decreasing, we found that PFTC incidence rates have been stable over time in the United States, with a significant increase among women aged 65–69. In contrast, studies in U.K. [13] and Finnish [22] populations demonstrated overall increases in PFTC over time. In the U.K. study, it was suggested that the increasing trends could be a result of small chance variations in annual cases, variations that could exert a large overall effect due to the rarity of PFTC [13]. Because we examined over 3000 cases of PFTC, it seems unlikely that minor variations in reported cases could account for the lack of a decrease in the current study. Another possible explanation for the lack of a decreasing trend in incidence is a possible reduction in the misclassification of PFTC [22]. Distinguishing between PFTC and ovarian cancer can be difficult due to the proximity of the organs and the similarities in tumor presentation and histologies [14]. Generally, all clinical evidence, including history of symptoms, age, CA125 levels, and patterns of cancer spread, is used to make the diagnosis of PFTC [14,29]. In cases where the evidence does not favor a diagnosis of tubal or ovarian cancer, a diagnosis of tubo-ovarian cancer may be made [14,29,34,35]. Alternatively, a diagnosis of ovarian cancer may be made because these tumors occur more frequently than tubal cancers [22,29]. Over time, increased knowledge of the presentation and behavior of PFTC could have led to better diagnostic practices and less misclassification as ovarian cancer. While our study was not designed to specifically address this issue, our finding that rates of ovarian cancer were decreasing over the same time period is consistent with this explanation. The age-specific increase in PFTC among 65- to 69-year olds could be a reflection of the aging U.S. population; in 2002, it was estimated that the overall number of cancers occurring in persons aged 65 years would double in the next 30 years [28].

In summary, this report provides demographic and clinical characteristics of PFTC using the largest number of cases assembled in one study to date. While data were not presented from every state, this analysis covers the vast majority of the United

States population and is one of the only population-based studies on PFTC. The rarity of PFTC makes the discovery of underlying causes and new treatments through case–control studies and clinical trials very difficult. The information presented in this study may aid in the development of hypotheses regarding the etiology of PFTC, its diagnosis in clinical settings, and the monitoring of incidence in the United States population. Future studies should continue to examine the increasing trend of PFTC diagnoses among women aged 65–69 in the United States.

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