EPIDEMIOLOGY

Increased Risk of Cancer in Men With Peyronie's Disease: A Cohort Study Using a Large United States Insurance Claims Database

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ABSTRACT

Background: Men with Peyronie's disease (PD) may have an increased prevalence of certain comorbidities, including malignancy. We sought to examine the clinical relationship between PD and subsequent diagnosis of malignancy.

Methods: Using data from the IBM Health MarketScan claims database from 2007 to 2013, we compared men with PD to a control group of men without PD or erectile dysfunction matched for age and duration of follow-up. We compared incidence of 18 categories of malignancy between both groups using a Cox regression model.

Results: In total, 48,423 men with PD and 484,230 controls were identified. The mean age within both cohorts was 50 ± 9.4 years old, and mean follow-up time was approximately 4.4 ± 2.1 years. After being controlled for age, year of evaluation, obesity, smoking, number of outpatient visits, number of urologist visits, and duration of follow-up, men with PD had an increased risk of all cancers (hazard ratio = 1.10, 95% CI = 1.06−1.14), stomach cancer (1.43, 1.06−1.14), testis cancer (1.39, 1.05−1.84), and melanoma (1.19, 1.02−1.38) when compared with controls. The strengths in using the MarketScan database are the anonymous nature of the data, accessibility, and the power provided by the large number of patient visits recorded. Limitations include a lack of detail in certain facets of patient clinical data, and the lack of long-term follow-up to assess the impact of time on other potentially associated conditions.

Conclusions: This manuscript is the first to our knowledge to describe a relationship between PD and cancer. Men with PD may be at increased risk for certain malignancies compared with age-matched controls. Further investigation is needed to explore the clinical implications of these findings. **Pastuszak AW, Thirumavalavan N, Kohn TP, et al. Increased Cancer Risk in Men With Peyronie's Disease: A Cohort Study Using a Large US Insurance Claims Database. Sex Med 2019;7:403−408.**

Key Words: Peyronie's Disease; Neoplasms; Cancer; Insurance Claim Reporting

INTRODUCTION

Peyronie's disease (PD) is a progressive fibrotic disorder of the penis, resulting in plaque formation in the tunica albuginea. Men with PD may present with penile deformity such as shortening, curvature, hour-glassing, and pain during intercourse.[1] PD usually occurs during the fifth decade and is currently estimated to affect between 0.4% and 13% of men.[2−5] Although penile trauma is a major risk factor for PD,[6] some cases of PD are postulated to follow an inherited pattern, either through an association of histocompatibility antigens[7−9] or a true autosomal-dominant fashion.[10] In families with PD, 2 related fibrotic diathesis are often seen in combination with PD: Dupuytren's disease (DD), characterized by fibromatosis of the palmar fascia and resulting contracture of the hand, and Ledderhose disease, characterized by fibromatosis of the plantar fascia and resulting nodules present on the soles of the feet.

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Studies have identified associations between PD and several other chronic diseases, such as keloids, lower urinary tract symptoms, and autoimmune diseases.[11,12] However, the clinical association between PD and cancer has not been studied, despite several similarities between PD and malignant neoplasms suggesting a possible association between these pathologies. Fibroblasts derived from both PD and DD lesions are prone to infiltrative growth, proliferation, and decreased apoptosis, mimicking malignancy without apparent metastatic potential.[13–15] In molecular studies, fibroblasts in men with DD share similar quantities and qualities of chromosomal aberrations as have been observed in sarcoma cells in those same men.[16,17] Further studies examining this relationship have demonstrated decreased expression of p53 and the retinoblastoma (Rb) gene in fibroblasts from men with DD, similar to genotypes of many cancers.[18,19] In the first clinical study assessing the relationship between DD and cancer, Żyluk et al[20] found a greater frequency of central nervous tumors, laryngeal cancer, and non-melanoma skin cancer in family members of 508 patients with DD when compared with controls. The clinical association between PD and malignant neoplasms has not been studied to date.

This study sought to examine the relationship between PD and malignant neoplasms following diagnosis of PD with a longitudinal cohort. We hypothesize that a diagnosis of PD is associated with an increased risk of malignancy, given that PD, as well as many malignancies, are genetically influenced conditions. Using data from a commercial insurance claims database to provide a large sample size, we compared the incidence of comorbid conditions in men with a diagnosis of PD and age- and follow-up-matched control men while using a Cox regression model to control for age, smoking, obesity, physician visits per year, urology visits per year, and years of follow-up.

MATERIALS AND METHODS

Claims Database Population

We analyzed data contained in the IBM (International Business Machines, Armonk, NY, USA) Health Analytics MarketScan Commercial Claims and Encounters database, which contains deidentified data from adjudicated and paid claims filed for the care of privately insured individuals with employment-based insurance. We accessed all available inpatient and outpatient claims data between 2007 and 2013. As MarketScan contains deidentified national data, institutional review board approval was not required.

This study focuses on 2 cohorts of men: one cohort of men with a diagnosis of PD, and another cohort of men without PD or erectile dysfunction (ED) who were matched to PD patients on age and frequency of follow-up visits (controls). Patients without PD or ED were chosen as a control group, given the high incidence of patients with both those conditions simultaneously.

To be eligible for inclusion, subjects had to be male, at least 18 years of age, and enrolled in an insurance plan covered by the database for at least 1 year before and 1 year after the index date (the first date of a diagnostic code for PD). We excluded men whose claims indicated the diagnosis of cancer before the index date or within 1 year after the index date, so that our study could truly assess the incidence of cancer following a diagnosis of PD. Relevant comorbidities were those included in the outcome analysis (see Table 1).

Men with PD were identified by the presence of a PD diagnostic code (*International Classification of Diseases, 9th edition, Clinical Modification* [ICD-9-CM] code 607.95). Lastly, we compiled a control group of age- and follow-up—matched men without PD or ED, obtaining a 10:1 control-to-PD ratio. For each man in the cohort, the number of all outpatient visits after the index date was determined based on the presence of claims with Current Procedural Terminology codes indicating new and follow-up office visits, consultations, or preventative medicine encounters.

Outcome Assessment

For the PD group, we investigated subsequent diagnoses of cancer after the index date, whereas for the control group, we used age matching as a surrogate for an index date. Diagnosis of the following comorbid conditions was assessed using the parenthetical ICD-9-CM codes: hypertension (401), hyperlipidemia (272.0-272.4), diabetes (250), obesity (278.0), and smoking (305.1, V1582).

Cancer diagnoses were identified using diagnosis codes on inpatient and outpatient claims. Diagnosis codes identifying cancer were aligned to definitions from the Surveillance, Epidemiology, and End Results database. We identified men with claims diagnoses indicating the presence of any invasive cancer (ICD-9 140-209 excluding skin squamous cell, skin basal cell, and noninvasive cancers) and identified men with codes indicating the presence of specific cancers such as upper respiratory (140.x-149.x, 160.x, 161.x), stomach (151.x), colorectal (153.x, 154.0, 154.1, 154.8), liver and gallbladder (155.x and 156.x), pancreas (157.x), lung (162.x), melanoma (172.x), breast (175.x), prostate (185.x), testis (186.x), bladder (188.x), kidney (189.0, 189.1), brain and nervous system (191.x, 192.x), thyroid (193.x), non-Hodgkin lymphoma (200.x,202.x), Hodgkin lymphoma (201.x), leukemia (204.x, 205.x, 206.x, 207.x, 208.x), and esophageal (150.x).

Statistical Analysis

All comparisons of health outcomes were performed using a Cox proportional hazard regression model that adjusted for age, year of evaluation, obesity, smoking, number of outpatient visits, number of urologist visits, and duration of follow-up. Effect modification was assessed by entering the term for PD and the covariate of interest (ie, age and follow-up time) in the appropriate regression model. All P values were 2-sided, with $P < .05$ considered statistically significant. Analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics of cohort

	Peyronie's disease (n = 48,423)	Control (n = 484,230)
Age, y		
18–19	255.(0.5%)	2,550 (0.5%)
20–29	2,016.(4%)	20,160 (4%)
30–39	4,466 (9%)	44,660 (9%)
40–50	12,439 (26%)	124,390 (26%)
>50	29,247 (60%)	124,390 (60%)
Mean ± SD	49.8 ± 9.4	49.8 ± 9.4
Follow-up time, y		
1–2	8,043 (17%)	804,430 (17%)
2–3	8,346 (17%)	83,460 (17%)
3–4	8,565 (18%)	85,650 (18%)
>4	23,469 (48%)	234,690 (48%)
Mean ± SD	4.5 ± 2.0	4.4 ± 2.1
Outpatient visits per year		
0 visits	55.(0.1%)	13,730 (3%)
0–1 visit	1,587 (3%)	75,778 (16%)
1–2 visits	4,969 (10%)	94,352 (19%)
>2 visits	41,812 (86%)	300,370 (62%)
Mean ± SD, per person-year	5.6 ± 4.4	3.6 ± 3.5
Comorbidities		
Hypertension	24,942 (52%)	234,788 (48%)
Hyperlipidemia	23,487 (49%)	198,388 (41%)
Diabetes	10,182 (21%)	91,833 (19%)
Lifestyle factors		
Obesity	4,288.(3%)	47,842 (10%)
Smoking	5,788 (7%)	50,512 (10%)
Year of evaluation		
2007	2,581 (30%)	27,890 (32%)
2008	1,476 (17%)	15,193 (17%)
2009	1,102 (13%)	10,873 (12%)
2010	1,011 (12%)	10,056 (12%)
2011	1,231 (14%)	11,182 (13%)
2012	7100 (8%)	6,4210 (7%)
2013	6170 (7%)	5,6650 (6%)

Prevalence shown as n (%).

RESULTS

Characteristics of the cohort are presented in Table 1. We identified 48,423 men with PD and 484,230 age- and follow-up–matched controls with insurance claims between 2007 and 2013. Men received inpatient and/or outpatient care over an average of 4.4 ± 2.0 years per person. The mean age of men with PD was 49.8 ± 9.4 years, and controls was 49.8 ± 9.4 years; for both groups, approximately one half of the men were younger than 50 years old. Per year, men with PD averaged 5.6 outpatient visits. In contrast, controls averaged only 3.6 outpatient visits per year.

We examined the risk of developing various cancers in men with PD compared with controls without PD or ED (Table 2); we calculated hazard ratios with 95% CIs, and adjusted for age, duration of follow-up, visits per year, urology visits per year, year of entry, hypertension, hyperlipidemia, diabetes, smoking, and obesity. When comparing men with PD with the control men, we found that men with PD were at increased risk for malignancies of the stomach (hazard ratio = 95%, CI = 1.43, 1.06–1.14), testis (1.39, 1.05–1.84), melanoma (1.19, 1.02–1.38), and all malignancies (1.10, 1.06–1.14).

DISCUSSION

In this study, we evaluated the incidence of a large number of common malignant neoplasms among men with a diagnosis of PD to determine whether men with PD may have a greater clinical rate of cancer. We compared a cohort of men with PD to a control cohort of men without PD or ED who were matched by age and duration of follow-up.

We found that men with PD were more likely to be diagnosed with any malignancy, testis cancer, melanoma, and stomach cancer when compared with healthy controls, suggesting an association between PD and malignant neoplasms. Although other benign urologic diseases have been associated with cancer, this is the first report, to our knowledge, to link PD to cancer.[21,22] As an increased risk of testis cancer (and other malignancies) could be secondary to more frequent visits to a urologist or clinician, all analyses were controlled for both number of clinic visits and number of visits with a urologist.

PD is also linked to other fibrosing conditions, including DD, characterized by fibromatosis of the palmar fascia and resulting in contracture of the hand, and Ledderhose disease, characterized by fibromatosis of the plantar fascia and resulting in nodules on the soles of the feet. Żyluk et al[20] observed a tendency toward a greater frequency of central nervous system tumors, laryngeal cancer, and non-melanoma skin cancer in family members of 508 patients with DD when compared with controls.

The exact mechanism linking a subsequent diagnosis of cancer to a diagnosis of PD has not been understood to date. Multiple studies have demonstrated that fibroblasts derived from PD plaques contained chromosomal abnormalities and display genomic instability.[23–25] Elevated levels of transforming growth factor beta 1 are present in PD, possibly resulting from heritable mutations.[26] Transforming growth factor beta 1 promotes tumor growth and survival by decreasing proinflammatory signaling and extracellular matrix remodeling.[27] In vitro studies of fibroblasts derived from PD plaques revealed abnormalities in p53, a proapoptotic cell-cycle regulator associated with multiple cancers.[28] Similarly, Zorba et al[29] demonstrated that tunica albuginea plaque cells from patients undergoing surgical repair of PD exhibit lower levels of apoptotic gene expression. Genes implicated in PD have also been implicated in malignancies. For example, c-myc, found in PD, is also highly expressed in testicular cancer, melanoma, and gastric cancer, among other cancers.[26,30–32] These studies

Table 2. Prevalence and risk of malignancy in men with PD compared with control men

Cancers	PD (n = 48,423)	Control (n = 484,230)	PD vs control
All malignancies	3,269 (6.8)	33,699 (7.0)	1.10 (1.06–1.14)*
Upper aerodigestive tract	72 (0.15)	955 (0.20)	1.10 (0.86–1.39)
Esophagus	28 (0.06)	375 (0.08)	1.29 (0.88–1.90)
Stomach	36 (0.07)	402 (0.08)	1.43 (1.02–2.00)*
Colon and rectum	110 (0.23)	1,893 (0.39)	0.88 (0.73–1.07)
Liver and gallbladder	47 (0.1)	698 (0.14)	0.98 (0.74–1.32)
Pancreas	44 (0.09)	464 (0.10)	1.35 (0.997–1.83)
Lung	92 (0.19)	1,473 (0.30)	0.94 (0.76–1.16)
Melanoma	179 (0.37)	2,088 (0.43)	1.19 (1.02–1.38)*
Breast	9 (0.02)	78 (0.02)	1.32 (0.67–2.60)
Prostate	804 (1.7)	5,010 (1.0)	0.94 (0.87–1.01)
Testis	52 (0.11)	309 (0.06)	1.39 (1.05–1.84)*
Urinary bladder	124 (0.26)	1,034 (0.21)	1.15 (0.96–1.38)
Kidney	82 (0.17)	1,069 (0.22)	0.90 (0.72–1.12)
Brain + other nervous system	33 (0.07)	465 (0.1)	0.91 (0.64–1.29)
Thyroid	34 (0.07)	427 (0.09)	1.00 (0.71–1.41)
Non-Hodgkin's lymphoma	105 (0.22)	1,448 (0.3)	0.99 (0.81–1.20)
Hodgkin's lymphoma	16 (0.03)	236 (0.05)	0.97 (0.59–1.61)
Leukemia	74 (0.15)	803 (0.17)	1.20 (0.95–1.52)

Prevalence shown as n (%), whereas risk comparison is shown as hazard ratio (95% CI).
CI = confidence interval; PD = Peyronie's disease.
*Denotes statistical significance.

provide an in vitro basis for a mechanism underlying our findings, but further work is necessary to understand their clinical implications.

Although our results are significant, their applicability in daily clinical practice remains to be determined. Other benign urologic conditions, such as infertility, are linked with increased risk of malignancy, but urologists do not routinely counsel their patients regarding this risk. Relaying a possible future cancer risk to patients diagnosed with PD, in the absence of confirmatory clinical and basic research data, is not advocated at this time.

Several strengths and limitations of the present work are worth discussing. As with all large database research, the strengths in these efforts lie in the anonymous nature of the data, accessibility, and the power provided by the large number of patient visits recorded.[33] The need for large datasets is more significant when looking at the intersection of relatively rare diseases, as the present work does. However, our work is limited by the lack of more detailed data on each individual patient, including race, severity and duration of PD, histology, or details regarding the diagnosed cancer, such as grade, stage, and pathology. Further, there is no way to obtain tissue or genomic information from affected individuals using the MarketScan database to further explore the mechanisms underlying this association. The outcomes of this work are also dependent on accurate coding of patient diagnoses, procedures, and visits. For example, the results could be clouded if control patients had PD but were not diagnosed and billed for it. Large insurance databases are representative of the payer mix that they represent—in this case, private insurers in the United States. Thus, they may not reflect the entire United States population, both socioeconomically and geographically, and are unlikely to represent the global population. The average age in both study groups was approximately 49 years, with follow up of approximately 4 years. Some of the cancers evaluated, such as prostate cancer, traditionally present at a later age than PD and may present significantly later than a diagnosis of PD. Malignancies that present earlier in life and are more likely to be fatal may also be missed, given the inability to examine the subject cohort for long time frames before and after a diagnosis of PD. As such, a relationship between PD and other conditions may have been missed. Previous work using the IBM MarketScan database has acknowledged that rates of cancer in this database are greater than those observed in the Surveillance, Epidemiology, and End Results data.[21]

CONCLUSIONS

The present study is the first to assess the clinical relationship between a diagnosis of PD and a subsequent diagnosis of malignancy, finding an increased rate of several malignancies in men with PD. Given these findings, and in the absence of data that causally link PD to malignancy, men with PD should be counseled that although a risk may exist, it remains to be definitively proven. Patients' long-term health concerns with respect to increased risk of cancer should also be evaluated in the context of other risk factors for malignancy. Further work

should focus on molecular mechanisms that may further explain this relationship, toward the goal of a molecular risk-stratification tool, as well as whether an increased risk of malignancy in men with PD is significant enough to routinely counsel patients and/or recommend altered screening protocols for these patients.

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