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Distribution of PSA Values and Frequency of Very Low PSA Among Transfeminine Individuals and Referent Cis-Gender Males

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2015

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2019

Abstract

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By Ra'ed Hailat

Introduction: Whereas hormone and surgical gender affirmation in transfeminine patients result in profound anatomic and endocrine changes, the prostate usually remains intact. It is not clear if levels of prostate specific antigen (PSA), an important marker of prostate cancer and its aggressiveness, differ in transfeminine people compared to cis-gender men. This was investigated by analyzing clinical data from the Study of Transition, Outcome and Gender (STRONG).

Methods: The current data analyses are limited to transfeminine subjects and cis-gender male controls who were fifty years of age or older, had no history of cancer at baseline, and had at least one PSA test during follow up. All PSA test results were averaged for each participant. The overall distributions of the PSA levels among transfeminine cohort members and their referents were compared using Mann-Whitney test. In addition, the prevalence of low (<0.5 ng/ml) average PSA was compared across the two study groups by multivariable log binomial regression model, which controlled for age, race and frequency of PSA testing.

Results: The eligible study participants included 775 transfeminine cohort members and 9,360 matched subjects. Transfeminine cohort members had significantly lower PSA levels compared to their matched referents (Mann-Whitney p-value <0.001). The multivariable log-binomial model demonstrated that the prevalence of low (<0.5 ng/ml) blood PSA was significantly higher in transfeminine study participants compared with cisgender males (Prevalence ratio = 3.17, 95% confidence interval: 2.92–3.45) after adjusting for other factors.

Conclusions: To the best of our knowledge, this study is the first to compare the distributions of PSA levels among transfeminine people to the corresponding distributions in cis-gender men. These data can be viewed as the initial step towards much needed standardization of laboratory norms for transgender patients.

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Acknowledgments

I would like to express my sincere gratitude to my advisor Dr. Michael Goodman for the continuous support of my master thesis and related research, for his patience, motivation, and immense knowledge. His guidance helped me during research and writing of this thesis. I could not have imagined having a better advisor and mentor.

I must express my very profound gratitude to my parents and a special gratitude to my father for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Table of Contents

Introduction

Transgender and gender non-conforming (TGNC) people comprise a diverse group of individuals whose biological sex does not match their gender identity (1). Typically, gender is assigned at birth based on the appearance of the genitalia, whereas gender identity is one's sense of being a boy/man, girl/woman, neither or both (2). According to one recent estimate there are 1.4 million TGNC adults in the United States (3)**.**

Many TGNC people may not self-identify based on binary definitions; however, a person whose gender identity differs from a male natal sex assignment is often referred to as male-to-female or trans woman, and a person whose gender identity differs from a female natal sex is often referred to as a female-to-male or trans man. More recently, the terms transfeminine and transmasculine have become preferred as they also apply to individuals who do not identify with binary gender categories (4).

To achieve greater congruence between sex characteristic and gender identity some TGNC individuals undergo medical gender affirmation, which involves hormone therapy and/or surgical chest or genital reconstruction. For transfeminine individuals hormone therapy usually includes estrogen, alone or in combination with anti-androgen medications and/or bilateral orchiectomy.

Supplementation with estrogens lowers testosterone concentrations because of negative feedback on the hypothalamic–pituitary–gonadal axis. With the initiation of estrogen therapy

alone, testosterone concentrations decrease into the low-normal range for a man but are still above the normal range for a woman, that is why most patients will require the addition of an anti-androgen medication to further inhibit testosterone production or to block the androgen receptor (5). A successful hormone therapy increases breast growth, softens the skin, and changes the body fat distribution towards a more feminine pattern. Hormones also play a significant role in mood changes and may influence libido (5).

The main surgical gender affirming procedures include orchiectomy, penectomy, and "(neo)vaginoplasty" as well as breast augmentation, through these procedures a person's external sexual features will be changed to the opposite sex. There is no universal pathway that is followed by service providers to undergo surgical gender affirming procedures, usually the decision is taken after multistage complex diagnosis criteria. For example, in the UK, a diagnosis of gender identity disorder should be made by a psychologist or psychiatrist, and a medical consultant may then prescribe the patient with hormones. These patients are required to live and work, full time, in the new gender role for 2 years to obtain real-life experience. After successful completion of this stage, a second professional confirms the diagnosis, and only then can they be referred for surgery (6).

Whereas hormone and surgical gender affirmation may result in profound anatomic and endocrine changes, the prostate usually remains intact. The prostate is not removed because the operation is cumbersome and comes with possible complications, including urinary incontinence. For this reason, transfeminine individuals remain at risk for prostate cancer even after extensive hormonal and surgical gender affirmation therapy (7).

Although, transfeminine individuals may be at lower risk for prostate cancer (8), the reason behind the lower risk of prostate cancer was not fully understood (7). For example, it is not clear if levels of prostate specific antigen (PSA), an important marker of prostate cancer and its aggressiveness, differ in transfeminine people compared to cis-gender men. The present study addresses this issue by analyzing clinical data from a large study of TGNC and cis-gender individuals enrolled in three integrated health care systems.

Methods

Data used for the present analysis were obtained from the Study of Transition, Outcome and Gender (STRONG). The STRONG is an electronic medical records (EMR)-based retrospective/prospective cohort study of TGNC individuals enrolled in Kaiser Permanente health care plans located in Southern California (KPSC), Northern California (KPNC) and Georgia (KPGA).

The details of cohort ascertainment and data collection were reported elsewhere (4). Briefly, the STRONG cohort was assembled using computerized searches of the EMR and free text validation of eligibility and transfeminine/transmasculine status. The resulting cohort included 6,456 TGNC members with first evidence of transgender status (index date) between 2006 and 2014. Each TGNC study participant was matched to approximately ten cisgender male and ten cis-gender female referents on index date, year of birth, race/ethnicity and study site. Both TGNC and reference cohorts were linked to multiple EMR data sources to ascertain incident and prevalent diagnoses, use of medications and laboratory test results.

For the purposes of the current analyses the data are limited to transfeminine subjects and cis-gender male controls who were 50 years of age or older at the end of follow up and no history of cancer at baseline. Only matched groups that included both the transfeminine and at least one reference subject with at least one PSA test done during follow up were included in the analyses. All PSA test results after the index date were averaged for each

subject; if the subject was diagnosed with prostate cancer during follow up, the PSA test results after the date of diagnosis were excluded from the calculations.

Study participants were characterized with respect to age at the index date (50-59, 60-69 and 70 or more years), health plan site (KPNC, KPSC and KPGA) and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic and Other/Unknown) and frequency of PSA testing during follow up (<0.5/year, 0.5-0.99/year, or 1+/year). Average PSA values were divided into five ordinal categories: <0.5 ng/mL, 0.5 to 0.99 ng/mL, 1 to 1.99 ng/mL, 2 to 4 ng/mL or >4 ng/mL.

The overall distributions of the PSA levels among transfeminine cohort members and their referents were compared by Mann-Whitney test or a chi-square test for trend when blood PSA was expressed as a continuous or an ordinal variable, respectively. In addition, the average PSA level was divided into two groups (<0.5 ng/ml vs. ≥0.5 ng/ml) and the prevalence of low (<0.5 ng/ml) average PSA was compared across the two study groups using multivariable log binomial regression model. In addition to gender identity, the log-binomial model included age category, frequency of PSA testing, and race/ethnicity (defined as non-Hispanic White vs. Other). The results of the multivariable analyses were expressed as adjusted prevalence ratios (PR) and a corresponding 95% confidence intervals (CI). All data analyses were performed using SAS statistical software version 9.4. (SAS Institute, Cary, NC)

Results

Among all study participants aged 50 years or older at the end of follow up and with no history of cancer at baseline, 775 transfeminine cohort members and 9,360 matched subjects had at least one PSA test result. More than 80% of the study participants are less than 70 years of age, more than almost three-quarters were Non-Hispanic Whites, and more than half were in enrolled in KPNC health care plan (Table 1).

As shown in Figure 1, transfeminine cohort members had significantly lower PSA levels compared to their matched referents (Mann-Whitney p-value <0.001). The proportions of persons in the lowest PSA category (<0.5 ng/ml) were 52% among transfeminine persons and 16% among cis-gender males. The corresponding proportions in the highest category (>4 ng/ml) were 2% and 7%, respectively (Table 2). The overall test for trend in the analyses that examined average PSA as an ordinal variable was statistically significant (p <0.001).

The multivariable log-binomial model demonstrated that the prevalence of low (<0.5 ng/ml) blood PSA was significantly higher in transfeminine study participants to cisgender males (PR = 3.17, 95% CI: 2.92–3.45) after adjusting for other study factors. The same model also, showed that participants of more advanced age, racial/ethnic minority patients and those with more frequent PSA testing were less likely to have average PSA lower than 0.5 ng/ml (Table 3).

Discussion

Results of this study revealed that transfeminine cohort members had significantly lower PSA levels compared to their matched referent cis-gender males. These observations are likely explained by the influence of hormone therapy. Following hormonal gender affirmation transfeminine people experience a sharp decrease in blood testosterone levels and often achieve normal female concentrations of blood estradiol.

These findings are consistent with the expectation that prostate tissue responds to cross sex hormone in a manner that may delay or prevent the development of prostate cancer (9, 10). Although the data on prostate cancer incidence are sparse, a previous analysis of the STRONG cohort indicated that the risk of prostate cancer among transfeminine people was about half the risk of cisgender referents (8). In another study that used cancer registry data from 46 states and the District of Columbia the proportion of prostate cancers among transgender patients were significantly lower than the corresponding proportion in the general population of male cancer patients (11).

Other findings in our studies were in the expected direction and in agreement with the current literature. As expected, participants of more advanced age were more likely to have higher PSA levels than their younger counterparts. These observations confirm previous studies that reported that PSA levels were positively correlated with advancing age (12). Similarly, the differences in PSA levels among Non-Hispanic whites and racial/ethnic minority participants were also consistent with the previous data. This

difference is most likely attributable to the high PSA levels among African Americans (13); however relatively sparse data prevented us from comparing data for African Americans separately from other groups.

The limited ability to analyze the data for specific racial/ethnic groups is only one limitation of our study. Another, perhaps more important, methodological limitation is the inability to investigate the relation between hormone therapy and PSA levels in a longitudinal fashion. Addressing this research question would require a more detailed history of gender affirmation with specific data on temporal changes in hormone doses, routes of administration and combination of medications. It is also important to point out that the endpoint of interest in the current analysis is total PSA. Other more sensitive measures such as free PSA and PSA velocity (i.e., changes in levels over time) may offer additional insight into the specific effects of cross sex hormone therapy on prostate function.

Conclusions

Despite methodological limitations, the present analysis should be viewed as an important step towards closing the knowledge gaps regarding prostate health in transfeminine people. To the best of our knowledge, this study is the first to compare the distributions of PSA levels among transfeminine people and in cisgender men with similar demographic characteristics. These data can also be viewed as the initial step towards much needed standardization of laboratory norms for transgender patients.

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Tables and Figure

Table 1: Characteristics of the study population.

Patient Characteristics	Transfeminine cohort N (%)	Referent cisgender males N (%)
Age at index		
50-59 years	345 (44.52)	3,996 (42.69)
60-69 years	314 (40.52)	3,986 (42.59)
70+ years	116 (14.97)	1,378 (14.72)
Health plan site		
KPNC	456 (58.84)	5,567 (59.48)
KPSC	304 (39.23)	3,612 (38.59)
KPGA	15 (1.94)	181 (1.93)
Race/ethnicity		
Non-Hispanic White	571 (73.68)	6,836 (73.03)
Non-Hispanic Black	31 (4.00)	419 (4.48)
Hispanic	85 (10.97)	1,008 (10.77)
Other/unknown	88 (11.35)	1,097 (11.72)
TOTAL	775	9,360

Table 2: Distribution of average PSA tests among transfeminine cohort and referent cisgender males during follow-up.

Average value of PSA tests during follow-up	TF Cohort N (%)	Reference cisgender males* N (%)
<0.5 ng/mL	400 (51.6)	1,353 (15.8)
0.5 to 0.99 ng/mL	173 (22.3)	2,908 (33.9)
1 to 1.99 ng/mL	130 (16.8)	2,519 (29.3)
2 to 4 ng/mL	56 (7.2)	1,230 (14.3)
> 4 ng/mL	16 (2.1)	577 (6.7)
Total	775	8,587

*Only includes referents whose matched TF cohort member had PSA test results.

Figure 1: Distribution of PSA values among transfeminine cohort and referent cisgender males during follow-up.

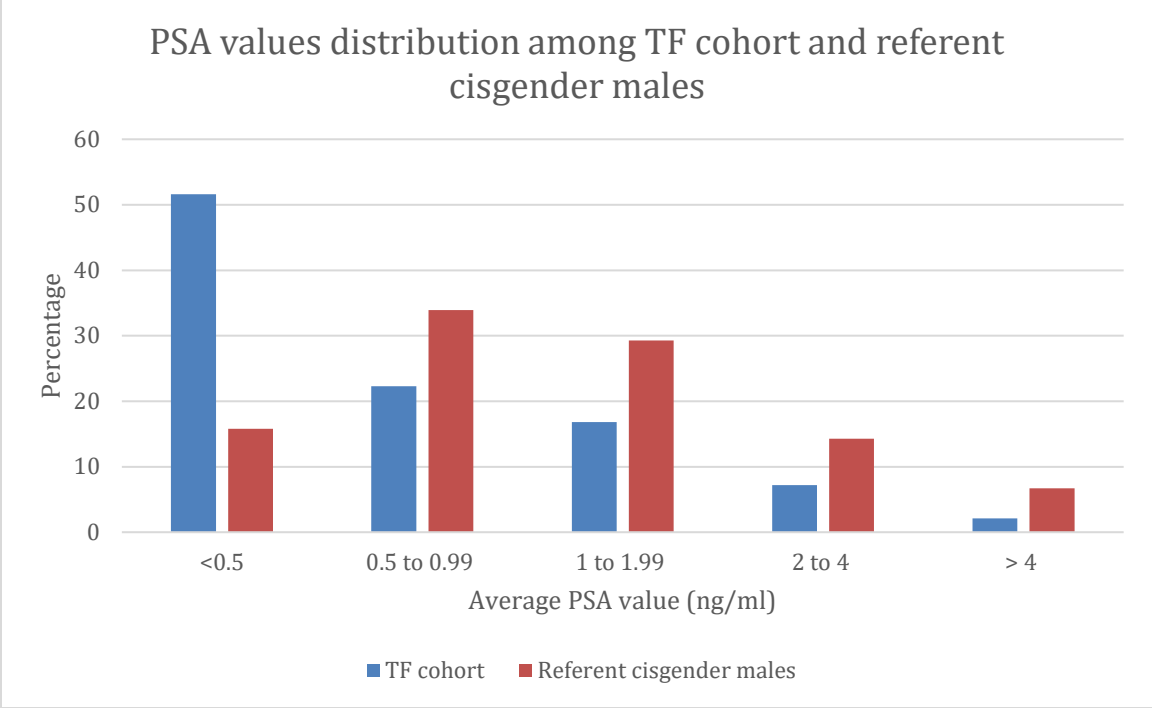

Table 3: Log binomial regression analysis for low PSA test (<0.5 ng/ml).

Parameter	Prevalence Ratio	95% CI	P-value
Gender identity			
Cisgender	1.0	(ref)	
Transgender	3.17	2.92 – 3.45	<0.001
Age			
<55	1.0	(ref)	
56-65	0.90	0.82 - 0.99	0.038
66+	0.72	0.63 - 0.81	<0.001
PSA frequency			
<0.5/year	1.0	(ref)	
0.5-0.99/year	0.84	0.76 - 0.92	<0.001
1+ year	0.80	0.72 - 0.88	<0.001
Race			
Non-Hispanic White	1.0	(ref)	
Other	0.90	0.82 – 0.98	0.022