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Lifestyle and Risk of Chronic Prostatitis/Chronic Pelvic Pain Syndrome in a Cohort of United States Male Health Professionals

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Abstract

Purpose—Although chronic prostatitis/chronic pelvic pain syndrome is a prevalent urological disorder among men of all ages, its etiology remains unknown. Only a few previous studies have examined associations between lifestyle factors and chronic prostatitis/chronic pelvic pain syndrome, of which most were limited by the cross-sectional study design and lack of control for possible confounders. To address these limitations we performed a cohort study of major lifestyle factors (obesity, smoking and hypertension) and chronic prostatitis/chronic pelvic pain syndrome risk in the HPFS (Health Professionals Follow-up Study), a large ongoing cohort of United States based male health professionals.

Materials and Methods—The HPFS includes 51,529 men who were 40 to 75 years old at baseline in 1986. At enrollment and every 2 years thereafter participants have completed questionnaires on lifestyle and health conditions. In 2008 participants completed an additional set of questions on recent chronic prostatitis/chronic pelvic pain syndrome pain symptoms modified from the NIH (National Institutes of Health)-CPSI (Chronic Prostatitis Symptom Index) as well as questions on approximate date of symptom onset. The 653 participants with NIH-CPSI pain scores 8 or greater who first experienced symptoms after 1986 were considered incident chronic prostatitis/chronic pelvic pain syndrome cases and the 19,138 who completed chronic prostatitis/

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chronic pelvic pain syndrome questions but did not report chronic prostatitis/chronic pelvic pain syndrome related pain were considered noncases.

Results—No associations were observed for baseline body mass index, waist circumference, waist-to-hip ratio, cigarette smoking and hypertension with chronic prostatitis/chronic pelvic pain syndrome risk (each OR ≤1.34).

Conclusions—In this large cohort study none of the lifestyle factors examined was associated with chronic prostatitis/chronic pelvic pain syndrome risk. As the etiology of chronic prostatitis/chronic pelvic pain syndrome remains unknown, additional prospective studies are needed to elucidate modifiable risk factors for this common condition.

Keywords

prostatitis; pain; obesity; smoking; hypertension

Prostatitis is a common condition, accounting for approximately 8% of visits to urologists and 1% to primary care physicians in the United States.[1] In 1995 the NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) revised the definition of prostatitis and categorized it into distinct clinical/pathological entities, including acute bacterial prostatitis, chronic bacterial prostatitis and asymptomatic inflammatory prostatitis.[2] More than 90% of patients with symptomatic prostatitis are believed to have CP/CPPS,[2] a debilitating condition that impairs quality of life to a similar degree as conditions such as myocardial infarction and Crohn's disease.[3] However, even after decades of research the etiology of this condition remains unknown and no established treatment exists.[4]

Although findings from some observational studies suggest that lifestyle factors influence CP/CPPS risk, only a few such studies have been done to date.[5–15] Moreover, many of these studies were limited by small sample size; restricted characterization of lifestyle factors; minimal adjustment for potential confounders; nonspecific definition of prostatitis, which most likely encompassed bacterial prostatitis, CP/CPPS and possibly other conditions; and cross-sectional study design. This last methodological concern is particularly important for studies of CP/CPPS etiology because some patients alter their lifestyle following symptom onset,[16] which may contribute to misleading cross-sectional associations. Therefore, to address some of these limitations, we used lifestyle information collected before CP/CPPS symptom onset from the large, well characterized HPFS to assess associations between several major chronic disease risk factors (obesity, cigarette smoking and hypertension) and CP/CPPS risk.

Materials and Methods

Study Population

The HPFS is an ongoing cohort study of 51,529 United States based male health professionals 40 to 75 years old at baseline in 1986. At enrollment participants provided information on age, ancestry, height and weight, current and past tobacco use, medications, disease history, physical activity and diet. Information on medical conditions and lifestyle factors is updated biennially by followup questionnaires and information on diet is updated

every 4 years by validated semiquantitative food frequency questionnaires. Information on vital status is obtained from the National Death Index.

For the current analysis we excluded from analysis men with cancers (other than nonmelanoma skin cancer) diagnosed before 1986, incomplete dietary data (70 or more food items blank) or implausible calorie intake (less than 800 or greater than 4,200 kcal per day) on the baseline semiquantitative food frequency questionnaire, missing birth year or incomplete CP/CPPS information on the 2008 questionnaire. Additional exclusions are described in the case ascertainment section.

Case Ascertainment

We assessed CP/CPPS pain symptoms on the 2008 questionnaire using a modified set of questions from the validated NIH-CPSI.[17] Specifically we asked participants 1) during the past month how often have you experienced pain or discomfort in any of these areas or circumstances: area between rectum and testicles (perineum), testicles, tip of penis (not related to urination), below waist in pubic or bladder area, pain or burning during urination and pain or discomfort during or after sexual climax (ejaculation: never, rarely, sometimes, often, usually or always); 2) during the past month on a scale of 0 to 10 how would you rate your average severity of pain or discomfort on the days that you had symptoms listed above (no pain—0 to pain as bad as you can imagine—10); and 3) if you had pain related to the areas noted above, when did you first experience this? (before 1960, 1960 to 1970, 1971 to 1985, 1986 to 1990, 1991 to 1995, 1996 to 2000, 2001 to 2004 or after 2004). We calculated a pain score by summing the presence of pain at each of the 6 different areas/circumstances (0—never, 1—rarely to always), the maximum frequency of pain in any of the 6 areas/circumstances (0—never to 5—always) and the average severity of pain (0 to 10) to give a range from 0 to 21.

We defined incident CP/CPPS cases as men with moderate to severe CP/CPPS related pain in the preceding month (8 or greater points on the pain score[18]) who first reported experiencing this pain after 1986. We selected this case definition to allow us to study lifestyle factors before symptom onset and, thus, those uninfluenced by symptoms. To rule out comorbid conditions that might be misperceived as CP/CPPS pain symptoms we further excluded participants with prostate, bladder or urethral cancer; inflammatory bowel disease; and neurological diseases/disorders affecting the bladder (Parkinson disease and multiple sclerosis) through 2008. These exclusions left a total of 19,791 participants in our analysis. Excluded participants tended to be older, currently smoke or have hypertension and be less physically active at baseline than men included in our analysis after age adjustment.

Assessment of Lifestyle Factors

Current height and weight were assessed at baseline. In 1987 a separate questionnaire and tape measure were mailed to each participant to obtain information on waist and hip circumference. Each man was instructed to measure to the nearest quarter of an inch his waist at the umbilicus and his hips at the largest circumference between waist and thighs while standing and avoiding bulky clothing. We used BMI to estimate total adiposity and

waist circumference, and the waist-to-hip ratio to estimate abdominal adiposity. Each of these measures was found to have good validity in a previous HPFS study.[19]

Information on cigarette smoking and hypertension was also collected at baseline. Specifically participants were asked whether they currently smoked or had smoked in the past, their quitting date if applicable, their average number of cigarettes smoked per day and whether they had ever been diagnosed with high blood pressure. This self-reported diagnosis was found to be 81% reproducible, 100% sensitive and 98% specific in a previous HPFS validation/reproducibility study.[20]

Information on BPH, a chronic condition with LUTS overlapping with CP/CPPS (ie urgency, frequency and nocturia), was assessed in several ways. Participants were asked about surgically treated BPH (eg transurethral resection of the prostate) every 2 years since 1988, BPH/LUTS medications every 2 years since 1996 and the I-PSS (International Prostate Symptom Score) in 1992, 1994, 1998, 2000 and 2008. We considered men who reported BPH surgery, medication use or I-PSS 15 or greater at any time during followup to have BPH/LUTS[21] and men who first experienced CP/CPPS related pain after onset of BPH/LUTS to have CP/CPPS with a history of BPH/LUTS.

Statistical Analysis

We calculated the CP/CPPS incidence and the proportions of men who reported pain by location, frequency and intensity. We also calculated age standardized means and proportions of lifestyle factors by CP/CPPS case status. To investigate associations between lifestyle factors and CP/CPPS risk we used logistic regression to calculate the OR and the 95% CI. We performed logistic regression with baseline lifestyle values rather than survival analysis with updated values because of our crude assessment of timing of symptom onset. However, to address the fact that men had varying and in some cases long periods between baseline and symptom onset we also performed stratified analyses by followup time (less than 10 and 10 years or greater) to explore the potential influence of timing of exposure assessment on our findings. Finally, to investigate the possible influence of reverse causation on our findings (ie behavior change following CP/CPPS onset) we performed several sensitivity analyses. First we performed separate analyses for 1) men with CP/CPPS and a history of BPH/LUTS as this condition might also cause men to alter their lifestyle, and 2) men with CP/CPPS related pain only or those in whom LUTS began after CP/CPPS related pain. This analysis also informed independent associations between lifestyle and CP/CPPS related pain vs associated LUTS. We recognize, however, that this analysis was conservative because some BPH medications are used to treat CP/CPPS (ie α-blockers[4]), and because CP/CPPS (or interstitial cystitis/bladder pain syndrome, a similar and possibly equivalent condition[22]) frequently manifests with LUTS. It is also possible that men taking BPH/LUTS medications before 1996 may not have been correctly classified as having BPH/LUTS before 1996 because medication use was only collected from 1996 and thereafter. As a second sensitivity analysis to address reverse causation we excluded men with CP/CPPS who first experienced symptoms between 1986 and 1990 (first 5 years of followup) as well as between 1986 and 1995 (first 10 years).

Analyses were performed using SAS®, release 9.2. All p values were 2-sided and $p < 0.05$ was considered statistically significant. This study was approved by the Harvard School of Public Health institutional review board.

Results

We identified 653 CP/CPPS cases in which the condition began after 1986 (3.3% of 19,791 participants or 1.55/1,000 person-years). Incidence was similar by decade of age (range 3.2% in men younger than 50 years to 3.7% in men 60 years old or older at baseline). Pain in the pubic region in 73.9% of cases and pain during urination in 66.9% were the most frequently reported pain symptoms (table 1). Of the cases 52.9% reported pain sometimes, 23.8% reported pain often, 5.8% reported it usually and 3.7% reported it always. Approximately half of the cases reported a pain intensity of less than 4, 40.4% reported an intensity of between 4 and 6, and 9.6% reported an intensity of 7 or greater.

CP/CPPS cases were similar to noncases by age, race/ethnicity, BMI, waist circumference, waist-to-hip ratio, smoking, and intake of fish, red meat, fruit and vegetables (table 2). They differed by alcohol intake, hypertension and physical activity. Specifically cases drank less alcohol, were more likely to have a diagnosis of hypertension and exercised less than noncases.

In multivariable adjusted analyses no associations were observed for overall or abdominal obesity, or for smoking (table 3) with the exception of a nonsignificant trend for smoking pack-years (p-trend = 0.12, supplementary table 1, http://jurology.com/). This trend appeared to be stronger among men who had smoked within the past 10 years (p-trend = 0.07). No association was observed for a clinical diagnosis of hypertension (table 3).

Although our study design was prospective, we further addressed the possibility of reverse causation by performing analyses stratified by BPH/LUTS history and by excluding 61 and 128 cases who first experienced pain within the first 5 and 10 years of followup, respectively. In analyses stratified by BPH/LUTS history generally similar null results were observed for obesity and smoking. Hypertension was associated with an increased risk but only among participants without a BPH/LUTS history (OR 1.36, 95% CI 1.02–1.81, p-interaction = 0.06, supplementary table 2, http://jurology.com/). Generally similar results were observed in analyses stratified by followup time, age, BMI (for smoking and hypertension) and smoking status (for obesity and hypertension). Finally no differences were observed when men who first experienced pain within the first 5 or 10 years of followup were excluded.

Discussion

In this large cohort of middle-aged to older United States male health professionals we observed a crude cumulative incidence of CP/CPPS of 3.3% during 22 years of followup (or 1.55/1,000 person-years). No associations were observed for overall or abdominal obesity, or for smoking whereas a positive association was observed for hypertension but only among men without a BPH/LUTS history.

To our knowledge only 1 previous study has estimated the CP/CPPS incidence.[23] This study showed an incidence rate of 3.3 new type III prostatitis physician diagnoses per 1,000 person-years (2.8/1,000 person-years when limited to pain symptoms) in male Kaiser Permanente® Northwest members 25 to 85 years old. Differences between this estimate and our estimate likely reflect differences in the definition of CP/CPPS used in each study. Considering pain characteristics among cases, our observed mean modified NIH-CPSI pain score (9.6) and the distribution of pain location are generally similar to those observed in the NIH Chronic Prostatitis Research Network cohort study.[24]

As mentioned previously, the literature on CP/CPPS risk factors is generally inconclusive to date. For obesity all studies that examined body size measures as continuous variables revealed null associations.[12–14] However, studies that investigated categories of overweight and obesity in relation to self-reported history of prostatitis showed protective findings[7,9] and those that examined overweight/obesity in relation to CP/CPPS or pain/discomfort with ejaculation showed mixed findings.[10,11,15] While reasons for these conflicting results are unclear, each of these studies was cross-sectional and several were small with minimal to no adjustment for covariates associated with metabolism or weight, such as physical activity, diet and smoking. In our large cohort study we observed no association between obesity and CP/CPPS risk before and after adjusting for other lifestyle factors.

Similar to obesity, the literature on smoking and CP/CPPS is also conflicting. Two previous studies demonstrated positive associations for smoking status[5,14] whereas the remaining 7 studies showed no associations for smoking status[7,8,11,13,25,26] or pack-years smoked.[12] However, like the aforementioned studies of body size, each of these studies was cross-sectional and many were small, did not adjust for potential confounders and considered fairly crude definitions of smoking (eg ever vs never). In our cohort study we did not observe associations for any definitions of smoking and CP/CPPS risk before or after adjustment. Although we found a suggestion of a positive association for increasing smoking pack-years, this association was not statistically significant.

Finally, with respect to hypertension only a few previous studies have examined this condition in relation to CP/CPPS. Hypertension is of interest because of emerging evidence that the nervous system, particularly the autonomic nervous system, has a role in CP/CPPS development.[27,28] The prostate gland is highly innervated and the extensive presence of adrenergic and cholinergic receptors suggests that autonomic nerves may be involved in prostatic function.[29] One previous study identified specific metabolomic patterns associated with symptom severity and autonomic nervous system dysfunction in patients with CP/CPPS,[26] another showed a positive association for greater supine and standing blood pressure,[27] and a third demonstrated a positive association for a diagnosis of hypertension.[15] However, this latter association may have been influenced by differences in health care use by CP/CPPS status. In contrast, a fourth study revealed no associations for systolic or diastolic blood pressure.[13] Our observation of a generally null association between clinically diagnosed hypertension and later CP/CPPS risk is consistent with this latter finding, although our positive finding among men without BPH/LUTS history may warrant further investigation.

The major strengths of the HPFS include its large sample size, long followup, high participant retention (with over 90% follow-up per each 2-year questionnaire cycle), assessment of lifestyle factors before CP/CPPS pain onset, ability to control for numerous potential confounders and accuracy of self-reported health information because of the medical background of participants. However, the HPFS also has several limitations. Exclusive enrollment of well educated health professionals and assessment of CP/CPPS related pain only once later in followup (ie in 2008) likely limited the number of participants with extreme lifestyle values (eg morbid obesity) because well educated health professionals are less likely to have these values, and because those who did at baseline were less likely to survive/remain under followup until 2008. Therefore, if CP/CPPS risk is only associated with extreme lifestyle values, we may have missed these associations. Some misclassification may have also been introduced by our self-reported assessment of CP/CPPS related pain and retrospective assessment of symptom onset. We attempted to limit the influence of these factors by excluding men who had conditions with similar pain symptoms as CP/CPPS and by performing sensitivity analyses excluding cases that developed in the first 5 and 10 years of followup to increase the likelihood of studying pre-symptom onset lifestyle values. Finally, because followup began when men were in the fifth to eighth decades of life, we cannot comment on risk factors for younger onset CP/CPPS.

Conclusions

We observed no associations for obesity, smoking and hypertension with CP/CPPS risk. As the etiology of CP/CPPS remains unknown, further studies are needed to determine modifiable risk factors for this common condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

BMI	body mass index
BPH	benign prostatic hyperplasia
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
LUTS	lower urinary tract symptoms

Table 1

CP/CPPS pain symptom incidence, location, frequency and intensity in 19,791 HPFS participants from 1986 to 2008

	No. NIH-CPSI Pain Score (%)*		
	1–3†	4–7‡	8 or Greater§
Totals	2,386 (12.1)	3,060 (15.5)	653 (3.3)
Pain location or type:‖			
Perineum	259 (10.9)	874 (28.8)	372 (58.2)
Testicles	328 (13.9)	917 (30.3)	355 (55.2)
Penis tip	140 (6.0)	491 (16.3)	224 (35.1)
Pubic region	451 (19.2)	1,487 (49.4)	470 (73.9)
During urination	846 (35.9)	1,441 (47.7)	428 (66.9)
During/after ejaculation	304 (13.3)	836 (28.5)	330 (53.1)
Pain frequency:‖			
Never	241 (10.1)	69 (2.3)	1 (0.2)
Rarely	2,020 (84.8)	1,695 (55.4)	89 (13.7)
Sometimes	120 (5.0)	1,187 (38.8)	345 (52.9)
Often	0	101 (3.3)	155 (23.8)
Usually	0	2 (0.1)	38 (5.8)
Always	0	4 (0.1)	24 (3.7)
Pain intensity:‖			
0–3	2,343 (100.0)	2,853 (93.9)	326 (49.9)
4–6	0	180 (5.9)	264 (40.4)
7–10	0	5 (0.2)	63 (9.6)

*Range 0 to 21, calculated by summing pain at 6 areas or circumstances (perineum, testicles, penis tip, pubic area, urination and ejaculation never—0 and rarely to always—1), pain maximum frequency in 6 areas/circumstances (never—0, rarely—1, sometimes—2, often—3, usually—4 and always—5) and pain average severity (0 to 10), and denominator of each pain location or type, frequency and intensity calculation may differ from total due to missing values.

†Including 143, 937 and 1,306 men who reported score of 1, 2 and 3, respectively.

‡Including 1,083, 906, 616 and 455 men who reported score of 4, 5, 6 and 7, respectively.

§Including 232, 148, 116 and 157 men who reported score of 8, 9, 10 and 11 or greater (mean modified NIH-CPSI pain score 9.6).

Table 2

Baseline characteristics of participants by later development of CP/CPPS symptoms in HPFS in 1986

	CP/CPPS (NIH-CPSI pain score)*	
	Noncases (0–7)	**Cases (8 or greater)**
No. participants	19,138	653
Mean age	50.7	51.1
No. race/ethnicity (%):		
White	94.3	93.6
Black	0.6	0.4
Asian	1.5	1.5
Other	3.6	4.5
Mean BMI (kg/m^2)	25.3	25.5
Mean waist circumference (in)	37.0	37.3
Mean waist-to-hip ratio	0.93	0.94
No. cigarette smoking (%):		
Current	7.5	7.1
Past	40.7	43.0
Never	51.8	49.9
Mean daily dietary intake:		
Alcohol (gm)	11.1	10.2
Red meat (No. servings)	0.6	0.6
Fish (No. servings)	0.4	0.4
Vegetables (No. servings)	3.7	3.6
Fruit (No. servings)	2.4	2.2
% Hypertension	15.9	17.8
Physical activity (MET-hrs/wk)	22.1	18.0

*All variables except age are standardized to age.

Table 3
Association of lifestyle factors with CP/CPPS risk in HPFS from 1986 to 2008

Lifestyle Factors	CP/CPPS*		
	No. Cases	OR (95% CI)†	p Value‡ (trend)
BMI (kg/m^2):			
Less than 25.0	306	1.00	
25.0–27.4	212	1.03 (0.86–1.23)	
27.5–29.9	84	1.06 (0.82–1.36)	
30.0 or Greater	51	1.06 (0.77–1.44)	0.62
Waist circumference (in):§			
Less than 34.50	95	1.00	
34.50–36.00	92	1.24 (0.93–1.67)	
36.25–37.75	130	1.19 (0.90–1.57)	
38.00–40.00	83	1.13 (0.83–1.54)	
40.25 or Greater	88	1.09 (0.80–1.48)	0.87
Waist-hip ratio:§			
Less than 0.90	123	1.00	
0.90–0.92	99	0.87 (0.67–1.14)	
0.93–0.94	84	1.24 (0.93–1.65)	
0.95–0.98	127	1.22 (0.94–1.58)	
0.99 or Greater	55	0.84 (0.60–1.18)	0.77
Smoking:			
Never	327	1.00	
Former			
Quit 10 yrs or greater	181	1.04 (0.86–1.26)	
Quit less than 10 yrs	99	1.34 (1.06–1.70)	
Current			
Current, less than 15 cigarettes/day	18	0.95 (0.58–1.54)	
Current, 15 cigarettes/day or greate	28	1.01 (0.68–1.50)	0.29
Hypertension:			
No	532	1.00	
Yes	121	1.15 (0.93–1.42)	0.19

*NIH-CPSI pain score 8 or greater.

†Multivariable model adjusted for age (5-year intervals), race/ethnicity (white, African-American, Asian and other), BPH/LUTS history (yes or no), physical activity (MET-hours per week in quintiles), total calorie intake (kcal per day in quintiles) and alcohol intake (0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9 and 30.0 gm per day or greater), including other lifestyle factors simultaneously, for waist circumference and waist-to-hip ratio models did not include BMI and for lifestyle factors other than obesity measurements models were adjusted for BMI and not waist circumference or waist-to-hip ratio.

‡Median of each exposure category was used.

§Cases do not sum to total because of missing values.