

Prostate cancer incidence in men with self-reported prostatitis after 15 years of follow-up

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Abstract. Controversy exists regarding a possible association between prostatitis and prostate cancer. To further evaluate the incidence of prostate cancer following prostatitis, a study of prostate cancer incidence in a cohort of Finnish men was performed. The original survey evaluating self-reported prostatitis was conducted in 1996-1997. A database review was conducted focusing on prostate cancer diagnoses in the cohort. In 2012, there were 13 (5.2%) and 27 (1.8%) prostate cancer cases among men with (n=251) and without (n=1,521) prostatitis symptoms, respectively. There were no significant differences in age, primary therapy distribution, prostate-specific antigen levels, Gleason score, clinical T-class at the time of prostate cancer diagnosis, or time lag between the original survey and prostate cancer diagnosis. The standardized incidence ratio (SIR) of prostate cancer was 1.16 [95% confidence interval (CI), 0.62-1.99] and 0.44 (95% CI, 0.29- 0.64) among men with and without prostatitis symptoms, respectively. After 15 years of follow-up subsequent to self-reported prostatitis, no evident increase in incidence of prostate cancer was detected among Finnish men with prostatitis symptoms. The higher percentage of prostate cancer among men with prostatitis symptoms appears to be due to coincidentally low SIR of prostate cancer among men without prostatitis symptoms, and may additionally be due to increased diagnostic examinations. Further research is required to confirm this speculation.

Introduction

Chronic inflammation is associated with the development of multiple types of cancer, but there are discrepancies between different studies concerning prostate cancer (1). Two previous meta-analyses provided significant evidence of the association between prostatitis and prostate cancer (1,2). There are, however, several studies showing no association or a negative

correlation between prostatitis and prostate cancer (3-7). It has been proposed that chronic inflammatory infiltrate-positive prostatitis may protect against prostate cancer (8). The majority of previous studies included patients with diagnosis of prostate cancer and controls from patients records or interviews (1,2,9). By contrast, the present study used a randomly selected sample of Finnish men surveyed in the 1990s to evaluate the effect of prostatitis on prostate cancer incidence.

Materials and methods

Patients. From April 1996 to February 1997, a survey was conducted in the northern region of Finland to evaluate the prevalence of prostatitis. A total of 2,500 men aged 20-59 years were randomly selected from the population registry (Population Register Centre, Helsinki, Finland) to receive a questionnaire, and 1,832 of them responded. A database review was then performed focusing on prostate cancer diagnoses in the cohort. Respondents were identified via a personal identification number from the Oulu University Hospital registry (Oulu, Finland), based on the name and address information available at the time of the original survey. When present, prostate cancer diagnoses and diagnosis years for the surveyed men were obtained from the Finnish Cancer Registry (Helsinki, Finland). Clinical characteristics [Gleason score, T-class, prostate-specific antigen (PSA) levels and primary therapy] of prostate cancer cases were reviewed from the patients' medical charts.

Ethics statement. The local ethics council of Oulu University Hospital (Oulu, Finland) approved the present study, which was conducted according to the Declaration of Helsinki (10). Written consent from the patients was not obtained, but the volunteers responding to the original survey (11) was considered as consent to participate in the present study. The National Institute for Health and Welfare (Helsinki, Finland), approved the present study and the use of registry data following local ethical approval, according to the Finnish law. Patient data was anonymized and de-identified prior to statistical analysis.

Statistics. Summary statistics included the mean and standard deviation (SD), or the median with the 25th-75th percentile if biased, unless otherwise stated. Comparisons for categorical data were performed using the χ^2 test or the Fisher's exact test. Continuous variables were analyzed

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using the Mann-Whitney U non-parametric test. Prostate cancer incidence and standardized incidence ratio (SIR) with 95% confidence interval (CI) were calculated for the study population and for the whole population of the survey area, which included men aged 41-80 years living at the study area (obtained from the Statistics Finland database) (12) and the number of newly diagnosed prostate cancer cases (obtained from the Finnish Cancer Registry). Data were analyzed using SPSS statistical software version 22.0 (IBM SPSS, Armonk, NY, USA). Two-tailed P-values are reported and $P < 0.05$ were considered to indicate a statistically significant difference.

Results

Of the 1,832 men responding to the original survey, 261 had prostatitis symptoms, leading to a lifetime prevalence of 14.2% (13). In the present study, detailed data were available for 251 and 1,772 out of 261 and 1,832 men with prostatitis symptoms and the total number of men responding to the original survey, respectively. Missing cases ($n=60$) were due to incomplete identification data recorded following the original survey. According to the Finnish Cancer Registry, there were a total of 40 prostate cancer cases diagnosed among men in the cohort in 2012. The incidence of prostate cancer was more than double among men reporting prostatitis symptoms in the original survey (Table I).

There was no significant difference in the ages of men at the time of prostate cancer diagnosis between the groups. Mean ages (SD, range) were 64.8 years (3.7, 58-73 years) and 62.7 years (6.2, 51-73 years) for subjects with and without prostatitis symptoms, respectively ($P=0.26$). PSA values at prostate cancer diagnosis were available for 13 and 24 subjects with and without prostatitis symptoms, respectively. Median PSA values (25th-75th percentile, range) were 8.1 $\mu\text{g/l}$ (5.2-13.2, 0.4-26.0 $\mu\text{g/l}$) and 9.2 $\mu\text{g/l}$ (5.9-18.9, 0.9-1,759.0 $\mu\text{g/l}$) for subjects with and without prostatitis symptoms, respectively ($P=0.33$). The Gleason score at diagnosis was available for 13 and 25 subjects with and without prostatitis symptoms, respectively. The median Gleason scores (25th-75th percentile, range) were 6 (6-7, 4-8) and 6 (6-8, 4-9) for subjects with and without prostatitis symptoms, respectively ($P=0.55$).

Table II contains the distribution of clinical T-class (tumor-node-metastasis classification) (14) among men with prostate cancer. Although there was a tendency for an increased number of subjects with locally advanced disease (T3-T4) among men with prostatitis symptoms, the difference was not significant ($P=0.63$). There were no data available for one subject. The distribution of different primary treatment modalities did not differ between the groups ($P=0.61$). There were no data available for one subject. Furthermore, there was no significant difference between the groups in the time lag between the survey and the diagnosis of prostate cancer ($P=0.79$).

The present study further evaluated the incidence of prostate cancer in the present cohort compared with that observed during 15 years in the geographical area where the original survey was conducted. Despite the seemingly high incidence of prostate cancer among men with prostatitis symptoms, the incidence was not higher than that reported among men in the age groups of 61-70 and 71-80 years in the aforementioned

Table I. Incidence of prostate cancer among Finnish men with and without self-reported prostatitis symptoms.

Patients	Prostatitis symptoms		Total, n
	No, n (%)	Yes, n (%)	
Prostate cancer diagnosis			
No	1,494 (98.2)	238 (94.8)	1,732
Yes	27 (1.8)	13 (5.2) ^a	40
Total	1,521	251	1,772

^a $P=0.001$.

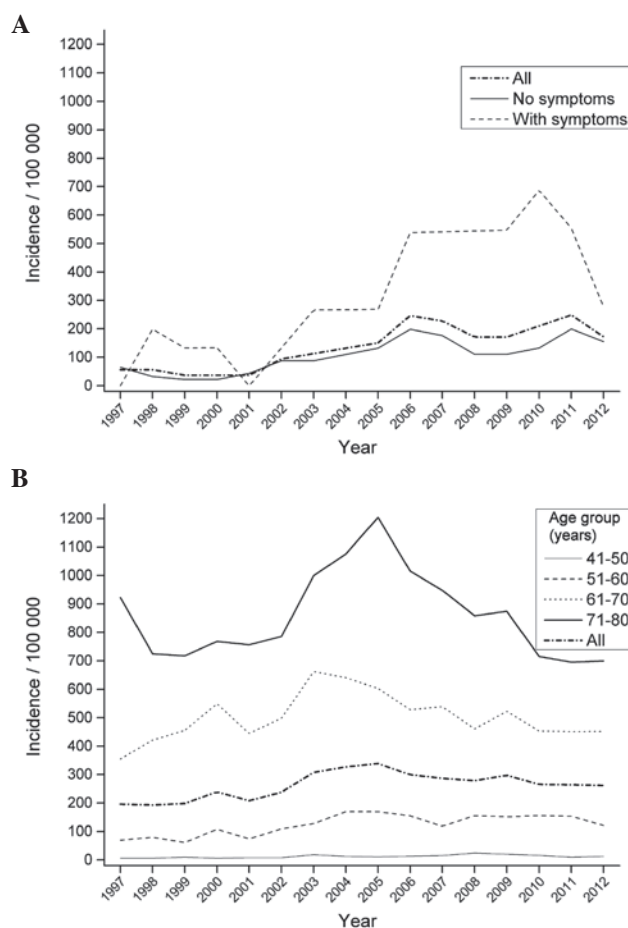


Figure 1. (A) Incidence of prostate cancer among the study cohort. Annual incidence of prostate cancer (number of cases/100,000) among a cohort of Finnish men ($n=1,772$) with or without self-reported symptoms of prostatitis. The time series was smoothed by calculating the 3-year moving average for each year. (B) Annual incidence of prostate cancer in the geographical area of the original survey. Curves for different age groups and the combined curve for all presented age groups are shown.

geographical area (Fig. 1). Furthermore, the analysis of SIR of prostate cancer revealed that the SIR was slightly increased among men with prostatitis symptoms, but the 95% CI covered 1.0, indicating no significant difference compared with the population. The SIR of prostate cancer among men with no prostatitis symptoms was lower than expected (Table III).

Table II. Clinical T-class, primary prostate cancer therapy and year of prostate cancer diagnosis among Finnish men with prostate cancer with or without a history of self-reported prostatitis.

Characteristics	Prostatitis symptoms		Total
	No, n (%)	Yes, n (%)	
Clinical T-class			
T1a-T1c	6 (22.2)	3 (25.0)	9
T2	10 (37.0)	6 (50.0)	16
T3-T4	11 (40.7)	3 (25.0)	14
Primary prostate cancer therapy			
Active surveillance	1 (3.7)	2 (16.7)	3
Permanent seed implantation radiation therapy	5 (18.5)	1 (8.3)	6
Androgen deprivation therapy	5 (18.5)	3 (25.0)	8
Radical prostatectomy	6 (22.2)	2 (16.7)	8
External beam radiation therapy	10 (37.0)	4 (33.3)	14
Year of prostate cancer diagnosis			
1997	1 (3.7)	0 (0.0)	1
1998	0 (0.0)	1 (7.7)	1
2000	1 (3.7)	0 (0.0)	1
2001	1 (3.7)	0 (0.0)	1
2002	2 (7.4)	1 (7.7)	3
2003	1 (3.7)	1 (7.7)	2
2004	2 (7.4)	0 (0.0)	2
2005	3 (11.1)	1 (7.7)	4
2006	4 (14.8)	3 (23.1)	7
2007	1 (3.7)	0 (0.0)	1
2008	0 (0.0)	1 (7.7)	1
2009	4 (14.8)	3 (23.1)	7
2010	2 (7.4)	1 (7.7)	3
2011	3 (11.1)	0 (0.0)	3
2012	2 (7.4)	1 (7.7)	3

Table III. SIRs of men with and without prostatitis symptoms in different age groups in the geographical area of the study.

Age group, years	Prostate cancer cases in the study population, n		Expected cases in the study population, n		SIRs			
	Prostatitis symptoms	No symptoms	Prostatitis symptoms	No symptoms	Prostatitis symptoms		No symptoms	
					1/100,000	95% CI	1/100,000	95% CI
41-50	0	0	0.08	1.03	0.00	0.00-46.40	0.00	0.00-3.57
51-60	1	10	1.84	14.20	0.55	0.01-3.04	0.70	0.34-1.29
61-70	11	13	6.87	35.30	1.60	0.80-2.87	0.37	0.20-0.63
71-80	1	4	2.40	11.30	0.42	0.01-2.32	0.35	0.10-0.91
Total, n	13	27	11.20	61.90	1.16	0.62-1.99	0.44	0.29-0.64

SIR, standardized incidence ratio.

Discussion

To the best of our knowledge, the present study is the first to evaluate a large cohort of randomly selected men for several

years following the report of prostatitis symptoms in order to measure the risk of developing prostate cancer. The prevalence of self-reported prostatitis in the present cohort was 14.2% (11), which is consistent with a previous survey conducted by health

professionals in the USA, where the prevalence of prostatitis was 16% (13), thus supporting the validity of the present cohort. Previously, an association between self-reported prostatitis and self-reported prostate cancer was documented (15); however, that study was not longitudinal, in contrast to the current study. Additionally, a previous retrospective study among men with prostate cancer revealed an elevated incidence of history of any type of prostatitis compared with matched control men (9). On the contrary, histological prostatitis has been reported to be significantly more prevalent in benign prostatic hyperplasia than in prostate cancer (16). However, it is well known that histological prostatitis does not correlate with clinical symptoms (17).

In the present study, the time lag between the original survey and the diagnosis of prostate cancer was long (Table I), which further challenges the connection between prostatitis symptoms and prostate cancer. However, in another study, the mean time from the most recent episode of acute prostatitis and the diagnosis of prostate cancer was 12.2 years among a cohort of prostate cancer patients (9). Based on the present data, it is possible to suggest that the increased incidence of prostate cancer among men with prostatitis symptoms compared with that among men with no symptoms may be due to a larger number of prostate cancer diagnostic examinations based on the patients symptoms. Data supporting this hypothesis have been published recently (18). In that study, the increased lower urinary tract symptoms were not associated with the intensity of prostate cancer diagnosis, but the diagnostic intensity increased when symptoms were brought to the attention of physicians (18). However, the present data do not enable the reliable evaluation of this aspect. The current results demonstrated that prostatitis symptoms did not lead to a higher incidence of prostate cancer in the geographical area evaluated after 15 years of follow-up, compared with that in the general population. Furthermore, despite the seemingly higher prostate cancer incidence among men with prostatitis symptoms, the 95% CIs of SIRs revealed that the differences were not significant, which may be due to the low amount of prostate cancer cases and the limited number of men with prostatitis symptoms in the present study. The current cohort was obtained by random sampling from a population registry. Therefore, the low SIR of prostate cancer among men with no symptoms is likely to be coincidental.

Although there was a significant difference in the number of cancer cases between men with and without a history of prostatitis, the limited number of cancer cases included in the present study prevents any firm conclusions. In the present cohort, a remarkable amount of men were young at the time of the original survey, and were not in the highest risk group for prostate cancer, as estimated by age 15 years later, despite the fact that ~1/3 of the men were 50-59 years old at the time of the original survey (11).

There are several limitations in the present study. Firstly, there was no differentiation between the various types of prostatitis. Therefore, it could not be concluded whether the risk of cancer is different in patients with chronic prostatitis compared with that in men with 1-2 acute episodes of prostatitis. Secondly, the diagnosis of prostatitis was based on a questionnaire, and it has been reported that self-reported genitourinary diseases such as benign prostatic hyperplasia and prostatitis are poorly concordant with data from medical records (19). However, the

respondents provided the details of the health care professional (general practitioner or hospital doctor/urologist) who established the diagnosis of prostatitis; thus, the diagnosis was not based solely on patient self-evaluation (11). Possible symptoms at the time of prostate cancer diagnosis were not collected from the patients charts, as the retrospective evaluation of symptoms is likely to be misleading, due to the lack of systematic recording of the presence or absence of symptoms.

The incidence of prostate cancer in the present study was based on data from the Finnish Cancer Registry, which automatically receives notification of each suspected or diagnosed cancer directly from every pathology laboratory (20). However, despite the estimated high consistency of the Finnish Cancer Registry (diagnosed and registered prostate cancer cases, 99%), a number of prostate cancer diagnoses may be missed (21).

It is challenging to draw conclusive deductions regarding the connection between prostatitis and prostate cancer. Chronic prostatitis is a symptom with no objective diagnostic test. In certain men, chronic pelvic pain may mimic prostatitis with no inflammation of the prostate (22). Thus, including these men will produce bias in similar studies.

To conclude, after 15 years of follow-up subsequent to self-reported prostatitis, no evidently increased incidence of prostate cancer was detected in the present cohort of Finnish men. Despite the higher percentage of prostate cancer among men with prostatitis symptoms compared with that among men with no symptoms, the SIR of prostate cancer among men with prostatitis symptoms was within the expected range of values. It may be suggested that the higher percentage of prostate cancer among men with prostatitis symptoms compared with that among men without symptoms is due to the low SIR of prostate cancer cases among men without prostatitis symptoms, and it may also be due to more frequent prostate cancer diagnostic examinations based on symptoms. The present results do not support extensive diagnostic interventions in order to detect possible prostate cancer among men with prostatitis symptoms, considering that the clinical characteristics of prostate cancer did not differ between men with and without prostatitis symptoms.

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