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Molecular Evidence of *Helicobacter Pylori* Infection in Prostate Tumors

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Key Words
Helicobacter pylori infection • Prostate cancer • Benign prostate hyperplasia • PCR

Abstract
Objectives: To determine whether *Helicobacter pylori (H. pylori)* is detectable in both benign prostatic hyperplasia (BPH) and prostate cancer (PCa). Epidemiological studies have shown significant associations between infective chronic prostatitis and prostatic carcinoma. Many bacteria have been found in the prostate of patients with chronic prostatitis, BPH, and PCa. ***Methods:*** One hundred consecutive patients with prostate diseases were enrolled in the study. Detection of *H. pylori* DNA in prostate tissue from patients with BPH and PCa was performed using both immunohistochemistry and PCR, and the results were confirmed by DNA sequencing. Odds ratios and the Fisher Exact test were used for the analysis of the associations between the variables. ***Results:*** Among the patients, 78% had BPH and 19% had PCa. While immunohistochemistry showed no positive sample for *H. pylori*, PCR combined with sequencing detected *H. pylori* DNA in prostate tissue samples from 5 patients. However, statistical analysis of the data showed that BPH and PCa are not significantly associated with the presence of *H. pylori* DNA in prostate tissue (odds ratio = 0.94, 95% confidence interval = 0.09–23.34, one-tailed Chi-square value = 0.660, $p > 0.05$). The limitation of this study was the small number of PCa patients. ***Conclusions:*** This study provides, for the first time, molecular evidence of the presence of *H. pylori* DNA in prostatic tissue of patients with BPH and PCa. It paves the way for further comprehensive studies to examine the association of *H. pylori* infection with BPH and PCa.

Introduction

Helicobacter pylori (H. pylori) infection is now a rising concern among clinicians and researchers and has been found to cause gastrointestinal [1] and extra-intestinal disorders [2]. According to the World Health Organization *H. pylori* has been classified as a group one (definitive) carcinogen [3]. Various models of gastric carcinogenesis have been developed to describe pathways by which *H. pylori* leads to gastric cancer. One of the models, Correa's multi-step model [4] showed that *H. pylori* infection is a triggering factor in the process of increasingly severe gastric lesions progressing from chronic active gastritis to atrophy, intestinal metaplasia, dysplasia, and gastric cancer. Al-Marhoon et al. [5] proposed a model describing the initial changes induced by *H. pylori* infection that plays a role in protecting the organism and enhancing its colonization in the stomach which can lead to gastric cancer.

There is accumulating evidence relating *H. pylori* infection to urological diseases. The most obvious is the implication of *H. pylori* in inducing chronic cystitis leading to bladder lymphoma [6]. In addition, some

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epidemiological studies have shown significant associations between infective chronic prostatitis and prostatic carcinoma. Al-Marhoon [7] proposed a hypothetical model relating *H. pylori* infection to prostate and bladder diseases. The rationale of this study is based on the following observations: 1) *H. pylori* has been detected in other organs and is associated with other cancers. 2) Evidence has shown certain infectious agents affect specific areas of the body via systemic sequelae. 3) In a mouse model of chronic bacterial prostatitis induced by *Escherichia coli*, chronic inflammation caused severe dysplasia and atypical hyperplasia in the prostate [8]. 4) Epidemiological studies showed significant associations between infection and prostatic carcinoma. Furthermore, 78% of prostatectomy specimens from males suffering from prostate cancer (PCa) or benign prostatic hyperplasia (BPH) were detected to be positive for bacterial DNA [9]. 5) Upon treatment with *H. pylori* eradication therapy, MALT lymphoma of the urinary bladder disappeared [10]. 6) A study conducted where *H. pylori* was transurethrally inoculated into the mouse urinary tract led to the onset of infection and induced inflammation in the urinary bladder and pelvis [11]. These observations led us to make the aim of our study to provide evidence for the presence of *H. pylori* in both BPH and PCa.

Materials and Methods

Patients and Study Design

The study was conducted at Sultan Qaboos University in collaboration between the Department of Urology and Department of Genetics. The study was approved by the local ethics committee, and written informed consent was obtained from each participant. Following a predefined protocol the study recruited 100 consecutive patients with prostatic diseases. Tissue samples were obtained either by transurethral resection or transrectal biopsies of the prostate in the case of BPH and PCa respectively. Infection of *H. pylori* was determined by the presence of *H. pylori* in tissue samples using PCR, histological examination with Giemsa stain, and immunohistochemistry. In addition, *H. pylori* infectivity was determined by the stool antigen test. Exclusion criteria included those patients who were below the age of 18 and above the age of 90 years, those who used proton pump inhibitors and antibiotics within the previous 4 weeks and had severe concomitant diseases, previous gastric surgery, pregnancy or lactation, alcohol abuse, drug addiction, or chronic use of corticosteroids or non-steroidal anti-inflammatory drugs. Patients were diagnosed with lower urinary tract symptoms as defined by the International Continence Society and included irritative and obstructive symptoms.

DNA Extraction

Post-surgery, the fresh tissue obtained was immediately frozen in liquid nitrogen and then stored at -80ºC prior to testing. DNA was extracted from each tissue sample using the QIAamp tissue DNA isolation mini kit (Qiagen, Valencia, CA) as recommended by the manufacturer. Briefly, up to 25 mg of tissue was cut into small pieces, placed in a 1.5 ml microcentrifuge tube, and processed by following the steps described by the manufacturer (Qiagen, Valencia, CA).

PCR and Sequencing

DNA was directly extracted from each tissue sample and used as a template for the specific detection of the *H. pylori* 16S rRNA gene. Nested PCR reactions were performed for the 16S rRNA (product size 423 and 110, respectively) in an Eppendorf Mastercycler Gradient using the following primers: Hp1 (5'- CTG GAG AGA CTA AGC CCT CC - 3'), Hp2 (5'- ATT ACT GAC GCT GAT TGT GC - 3'), and Hp3 (5'- AGG ATC AAG GTT TAA GGA TT - 3') (Metabion, Germany) as previously reported by Ho et al. [12]. A positive control was used in each run (ATCC Helicobacter Pylori 26695, genomic DNA) in addition to a negative control (no DNA). For the first PCR involving Hp1 and Hp3 primers, the following conditions were used: an initial denaturation of 95ºC for 5 min, then 25 cycles (95ºC: 30 s, 55ºC: 30 s, 72ºC: 30 s, and final extension 72ºC for 10 min).

The PCR was carried out in 25 µl containing 2.5 µl of 10×PCR buffer (Promega, Madison, WI), 1.5 µl of the 25 mM $MgCl_2$, 0.3 µM of each primer (Hp1 and Hp3), and 0.5 U of taq DNA polymerase (Ampli Taq Gold, Applied Biosystem, UK). Approximately 100 ng of the isolated DNA was used as a template. For the second PCR including Hp1 and Hp2 primers, the PCR conditions were similar to the first PCR except that the annealing temperature was 60°C and 2 µl from the first PCR product was used as a template for the second PCR reaction. The PCR products were analyzed by electrophoresis on a 2% (w/v) agarose gel (Promega V3121) at 100 V for 40 min. Gels were stained with ethidium bromide and photographed.

To identify *H.pylori* in the samples, the PCR product from the second PCR (Hp1 and Hp2, 110 bp) was sequenced in an Eppendorf Mastercycler Gradient using the ABI BigDye® Terminator v3.1 Cycle Sequencing Kit and run on the ABI Genetic Analyzer 3130xl as recommended by the manufacturer. The conditions of the sequencing reaction included 25 cycles at 96ºC (10 s), 60ºC (5 s), 60ºC (4 min), and 4ºC (holding temperature). Sequencing data analysis was performed using the ChromasPro version 1.41 software, a powerful bioinformatic tool to interpret the sequencing results by comparing the normal sequence of the targeted gene CFTR to the tested sequence.

Immunohistochemistry

Immunohistochemistry was carried out as previously described [13]. Briefly, 5 mm paraffin sections were predigested with proteinase K (Dako, S3020, Denmark), and incubated with the specific Polyclonal Rabbit anti-helicobacter primary antibody (Dako, B0471, Denmark) diluted 1:50. After further incubation with the biotinylated anti-rabbit secondary antibody (Envision Dual link system HRB, K4061, Dako, Denmark) they were washed in Tris-buffered saline (pH 7.6), and the standard horseradish peroxidase immunohistochemical method was used. The rabbit anti-*H. pylori* specific polyclonal antibody raised against heat-stable antigens of *H. pylori* strain CH-20429 is highly specific for *H. pylori* and has a sensitivity of 100% and specificity of 94% in distinguishing *H. pylori* from other curved bacteria present in the tissues. Heat-stable antigens of *H. pylori* are responsible for a specific humoral immune response in patients infected by this strain.

Table 1. Demographic data of the 100 patients included in the study

Characteristics	No. of patients
Presentation	
LUTS	66
Urinary retention	31
Hematuria	3
Comorbidities	
No comorbidities	29
DM	7
HTN	27
DM & HTN	13
Others	18
Unknown	7
Pathological diagnosis	
BPH	42
Prostate cancer	19
Prostatitis	1
BPH and Prostatitis	36
PIN high grade	1
Lymphoma	1

LUTS = Lower urinary tract symptoms; DM = diabetes; HTN = hypertension.

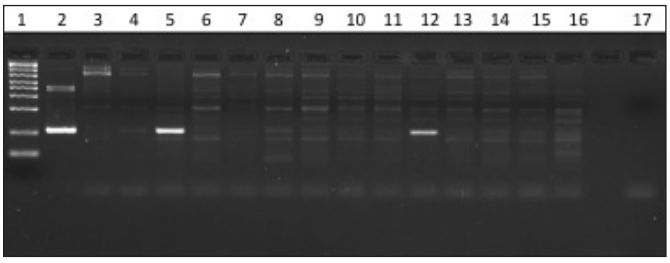

Fig. 1. Nested PCR analysis of prostate tissues. DNA was isolated from prostate tissue samples and analyzed by Nested PCR. **Lane 1**: 50-2000 bp Ladder; Lane 2: Positive control (H. pylori genomic DNA, 26695), Lane 3: DNA sample from peripheral blood; Lane 5, 12: positive samples, 110 bp; Lane 17: Negative control (No DNA); Lane: 4, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16: Negative samples.

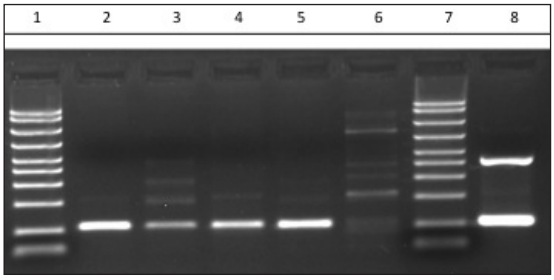

Fig. 2. Confirmation of 4 positive prostate tissue samples by nested PCR. From the 5 positive samples, DNA was analyzed by nested PCR for only 4 samples, because of non-availability of the DNA for further studies. Lane 1, 7: 50-2000 bp Ladder; Lane 2: Positive sample (110 bp); Lane 3: Positive sample (110 bp); Lane 4: Positive sample (110 bp); Lane 5: Positive sample (110 bp); Lane 6: Negative sample; Lane 8: Positive control (H. pylori genomic DNA, 26695).

H. Pylori Stool Antigen Test

The *H. pylori* antigen rapid test in human fecal specimens (Bioline, SD H. pylori Ag, Standard Diagnostic Inc., Korea) was used to detect *H. pylori* infection as previously described [14].

Statistical Analysis

Data were analyzed using SPSS (version 15) (SPSS, Chicago, IL, USA). In order to examine the association between the presence of *H. pylori* infection and the type of prostate disease (BPH or PCa), odds ratios (ORs) and their 95% confidence intervals (CI) were estimated and the Fisher Exact test was used. Values of $p < 0.05$ were considered to be statistically significant.

Results

One hundred consecutive patients with prostate diseases were enrolled in the study. The mean age (mean ± SD) was 68.7 ± 8.3 years. Clinical data and pathological diagnoses are presented in table 1. The details of the 5 patients positive for *H. pylori* are presented in table 2. Among the patients, 78% were diagnosed with BPH and 19% with PCa. We initially used immunohistochemistry to examine all the tissue samples for *H. pylori*, and none of the samples were positive for *H. pylori* (data not shown). In contrast, when we used a more sensitive technique such as PCR, *H. pylori* DNA was detected in 5 samples (fig. 1, 2). Since 1 of the 5 tissue samples did not generate enough DNA for sequencing, nested PCR and subsequent sequencing analysis were performed for only 4 of the 5 positive samples. The results confirmed the presence of *H. pylori* DNA sequences in these 4 patients (fig. 3). However, statistical analysis of the data showed that BPH and PCa are not significantly associated with the presence of *H. pylori* DNA in prostate tissue (OR = 0.94, 95% CI = 0.09–23.34, one tail Chi-square value = 0.660, $p > 0.05$). Interestingly, the *H. pylori* stool antigen test was positive for these 5 patients.

Table 2. The details of the 5 patients positive for *H. pylori*

Patient	Pathological diagnosis	Age (years)	Presentation	PSA (ng/ml)	PCR	Stool antigen test
1	BPH & prostatitis	66	LUTS	0.6	+	+
2	BPH	71	hematuria	8.9	+	+
3	Prostate cancer	81	LUTS	10	+	+
4	BPH	79	LUTS	10.4	+	+
5	BPH & prostatitis	79	LUTS	3.8	+	+

PSA = Prostate specific antigen; PCR = polymerase chain reaction.

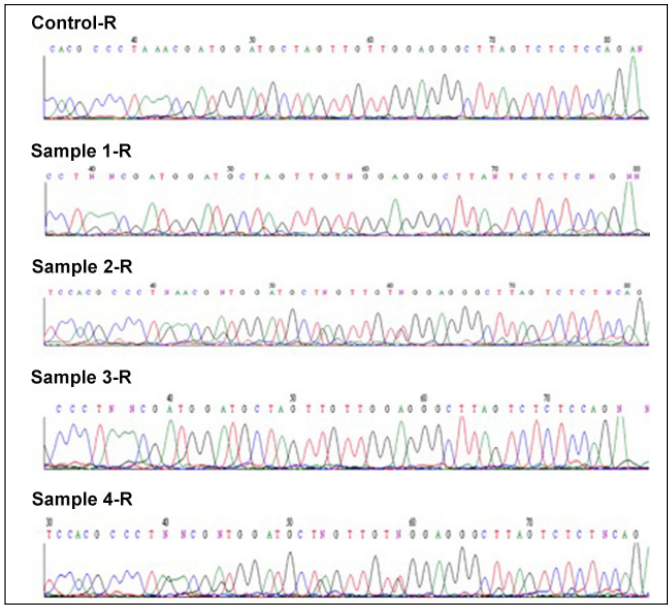

Fig. 3. Sequencing analysis of the DNA from the 4 *H. pylori* positive prostate tissue samples. The DNA from the 4 *H. pylori* positive prostate tissue samples (shown in fig. 2), was subsequently examined by sequencing analysis to confirm the presence of *H. pylori*. Analyzing DNA sequencing results of positive samples (Sample 1–4), and the positive control (using Hp2 primer).

Discussion

Accumulating evidence suggests an association of *H. pylori* infection and urological diseases. Our study is the first to show evidence of the presence of *H. pylori* DNA in the prostatic tissue of patients with BPH and PCa. We employed 2 different approaches: while immunohistochemistry results were negative, PCR allowed us to detect *H. pylori* infection in 5% of the prostate tissue analyzed from patients with BPH and PCa. One possible explanation for the discordance between PCR and immunohistochemistry might be the fact that samples were embedded in paraffin, however, in situ hybridization which was not done in the present study may have improved *H. pylori* detection in the tissues using immunohistochemical methods.

The link between chronic inflammation and cancer has been recognized for many years [15]. However, the underlying mechanism of the interaction between inflammatory cells and their elaborated factors and tumor cells still remains nascent. Originally, inflammation was assumed to be principally a beneficial host response, representing the body's fight against invading tumor cells. However, in contrast, recent data suggests inflammation to be a cause for the onset of certain cancers and a powerful trigger for tumor growth and invasion [15]. Interestingly, there are numerous data supporting the association of chronic long-standing inflammation and increased risk of tumors of the gastrointestinal tract [16]. In addition, systemic non-steroidal anti-inflammatory drug use has been found to be linked with a significant loss of tumor growth in the bowel, lung, liver, and prostate [17]. A recent study showed that *Propionibacterium acnes* was detected in 35% of radical prostatectomy specimens [18] thus indicating that along with genetic factors, environmental factors (e.g. lifestyle, microbial infection, and underlying subclinical prostatitis) also tend to play a role in prostate carcinogenesis.

Various reviews have highlighted the role of infections as a cause of cancer [19]. The major infectious agents trigger cancer by the following mechanisms which demonstrate that inflammation is a crucial aspect of oncogenesis attributable to infection: 1) infect and transform lymphoid cells e.g. Epstein-Barr virus leading to Burkitt's lymphoma [19], 2) transformation e.g. human papillomavirus leading to cervical cancer [20], 3) inflammation and partial integration e.g. hepatitis B vi-

rus leading to hepatocellular carcinoma [20], 4) chronic inflammation and oncogenic proteins e.g. hepatitis C virus leading to hepatocellular carcinoma [19], 5) chronic stimulation of lymphocytes by pathogen antigens and/or autoantigens e.g. *H. pylori* leading to gastric lymphoma [21], 6) chronic inflammation e.g. *H. pylori* leading to gastric and esophageal adenocarcinoma [22] and Schistosomiasis leading to bladder cancer [20], 7) chronic inflammation possible associations e.g. *Propionibacterium acnes* leading to PCa [18] and *Mycoplasma* species leading to PCa [23], and 8) immunosuppression e.g. HIV leading to Epstein-Barr virus + central nervous system lymphomas [19]. As mentioned above, it is known that certain infectious agents tend to affect specific areas of the body through systemic sequelae. Karatas et al. [24] investigated the possible relationship between *H. pylori* infection and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and found the seropositivity for the antibody against *H. pylori* to be higher in the CP/CPPS group than in the control group ($p < 0.05$), thus concluding that *H. pylori* is involved in CP/CPPS. It was further recommended that *H. pylori* must be investigated in prostate biopsy material.

One of the major drawbacks of molecular-based techniques for microbial detection is the persistent threat of artifact and/or false-positive results due to highly sensitive methods for detection as well as the constant threat of potential contamination. A very recent and relevant example of this concern involves the controversy surrounding the discovery of a novel murine retrovirus, termed XMRV, in PCa samples from patients with homozygous germline RNase L mutations [25]. A study conducted by Barykova et al. [26] highlighted the important efforts underway to identify potential infectious agents that could be possibly linked to chronic inflammation as commonly observed in PCa patients, which could be potentially associated with its development. Future work involving establishing a probable causal role for microorganism(s) in prostate carcinogenesis should include efforts to localize the organism(s) of interest in PCa tissues in order to determine if the presence of the organism correlates to its histo-pathological features including patterns of inflammation, or prostatic lesions (atrophy, prostatic intraepithelial neoplasia, cancer). The identification of *H. pylori* in the stomach of cancer patients and the association of *H. pylori* with gastric inflammation and gastric atrophy helped to form the body of evidence that eventually proved that *H. pylori* plays an etiologic role in gastric carcinogenesis. In the present study we have for the first time demonstrated by molecular evidence the presence of *H. pylori* DNA in patients with BPH and prostatitis and 1 patient with PCa. The limitations of this study include the small number of PCa patients to provide statistical difference between BPH and PCa, and the small number of positive samples for *H. pylori*. It would be interesting to look for *H. pylori* DNA in normal prostatic tissue of a control group.

Conclusions

This study provides, for the first time, evidence of the presence of *H. pylori* DNA in prostatic tissue of patients with BPH and PCa. The small number of PCa patients included in this study is the main limitation of the study in order to generate more positive samples as well as additional data related to significant statistical difference between BPH and PCa. This study should be an incentive for further multicenter studies to look for the association of *H. pylori* infection and BPH or PCa, because if this is true then the management of these diseases could be reformed.

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