Master of Public Health

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Role of Infections in the Occurrence of Prostate Cancer: A Case Control Study in France (EPICAP)

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Abstract

Introduction: Infections account to 20% of all human carcinogenesis. Whether prostate cancer - the second most common type of cancer in men worldwide is associated with infections remains questionable. Unfortunately, the etiology of prostate cancer remains obscure where age, ethnicity and family history of prostate cancer are the only well-established risk factors. Therefore, the aim of this case control study is to investigate the role of sexually transmitted infections in the occurrence of prostate cancer with a specific interest on aggressive cancer.

Methods: EPICAP is a population-based case control study carried out in the department of Hérault, France in 2012-2013. A total of 819 males <75 years old newly diagnosed with prostate cancer and 879 controls of the same age living in the same department. Collection of data about potential risk factors, socio-demographic characteristics, lifestyle, personal and family history was done through a face to face interview and biological samples for both cases and controls. Odds ratio (OR) and their 95% confidence intervals were computed using logistic regression.

Results: There was no association observed between gonorrhea (OR:0.83 95%CI:0.57-1.22) or Trichomonas (OR:0.88 95%CI:0.33-2.32) or syphilis (OR: 0.41 95%CI:0.11-1.52) and prostate cancer. In addition, overall STDs were non-significant for all cases (OR:0.82 95%CI: 0.58-1.17) and high-grade cancer (OR:0.71 95%CI:0.38-1.34). Finally, when stratifying to urethritis we observed a positive significant association among low grade cancer when having urethritis (OR:4.92 95% CI:1.08-22.3), and no significant association when stratifying for non-users of NSAIDS in all grades of cancer.

Conclusion: Our results showed that STDs particularly gonorrhea, trichomonas, and syphilis do not seem to be risk factors for prostate cancer in the EPICAP study. Therefore, further investigation is needed to help advance our understanding of the role of STDs in the etiology of prostate cancer with a focus on its most aggressive types.

Key words:

Prostate cancer | Infections | STDs | Gonorrhea | Trichomonas | Syphilis | Infections | Risk Factors | Prostatitis | Urethritis. | NSAIDs | Purulent discharge |

Résumé

Introduction : Les infections représentent 20% de toute la cancérogenèse humaine. Seuls l'âge, l'origine ethnique et les antécédents familiaux de cancer de la prostate sont reconnus comme facteurs de risque de ce cancer. Donc, notre objectif principal est d'étudier le rôle des infections sexuellement transmissibles dans la survenue du cancer de la prostate avec un intérêt particulier pour le cancer agressif.

Méthodes : EPICAP est une étude cas-témoin réalisée dans le département de l'Hérault en France en 2012-2013. Un total de 819 hommes de moins de 75 ans nouvellement diagnostiqués par un cancer de la prostate et 879 hommes de même âge et vivant dans le même département. Recueil de données sur les facteurs de risque potentiels et autres caractéristiques a été effectuée en face à face. Des mesures anthropométriques et des échantillons biologiques ont également été collectés. Les Odds Ratio (OR) d'association et leur intervalle de confiance à 95% ont été obtenus par régression logistique.

Résultats : Aucune association n'a été observée entre la gonorrhée (OR: 0,83 IC95%:0,57-1,22) ou le trichomonas (OR: 0,88 IC95%:0,33-2,32) ou la syphilis (OR: 0,41 IC95%:0,11-1,52) et le cancer de la prostate. De plus, les résultats des tous ces IST étaient également non significatifs pour tous les cas (OR:0,82 IC95%:0,58-1,17). Enfin, la stratification à l'urétrite a montré une association significative positive en cas d'urétrite (OR: 4,92 IC95%:1,08-22,3) et aucune association significative lors de la stratification pour les non-utilisateurs d'AINS dans tous les grades de cancer.

Conclusion : Nos résultats ont montré que les IST, en particulier la gonorrhée, le trichomonas et la syphilis, ne semblent pas être des facteurs de risque de cancer de la prostate. Des recherches supplémentaires sont nécessaires pour comprendre le rôle des IST dans l'étiologie du cancer de la prostate.

Mots-clés :

Cancer de la prostate | Infections | ISTs | Gonorrhée | Trichomonas | Syphilis | Infections | facteurs de risque | Prostatites | Urétrites | Écoulement purulent | AINS |

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List of Acronyms

Acronyms	Definition
PC	Prostate Cancer
EPICAP	Epidemiological study of prostate cancer
LUTS	Lower Urinary Tract Symptoms
DRE	Digital Rectal Examination
PSA	Prostate Specific Antigen
BPH	Benign Prostatic Hyperplasia
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
PET-CT	Positron Emission Tomography Computed Tomography
TNM	Primary Tumor, Lymph Nodes, Metastasis
HIFU	High Intensity Ultra Sound
ASR	Age Standardized Rate
STDs	Sexually Transmitted Diseases
STIs	Sexually Transmitted Infections
CAPI	Computer Assisted Personal Interview
NSAIDS	Non-steroidal Anti-inflammatory Drugs
BMI	Body Mass Index
DAG	Directed Acyclic Graph

1. INTRODUCTION

1.1. Prostate

1.1.1. Anatomy

Prostate is the male's largest sexual accessory gland that plays an important role in the male reproduction system. It is located on the floor of the pelvis and surrounds the urethra at the neck of the urinary bladder (figure 1). The three major histological zones of the prostate are:

a. *Central Zone* (25% of the glandular tissue) which surrounds the ejaculatory ducts and forms the base. Only 2.5% of prostatic cancer develop in this zone but can be quite aggressive.
b. *Peripheral Zone* (70% of the glandular tissue) is the biggest zone and it encircles most of the central and transition zone. Nearly 80% of prostatic cancer develop in this zone.
c. *Transition zone* (5% of the glandular tissue) is a small glandular zone made of two small lobules that encircles a portion of the urethra. This zone accounts to approximately 20% of prostatic cancer [1,2].

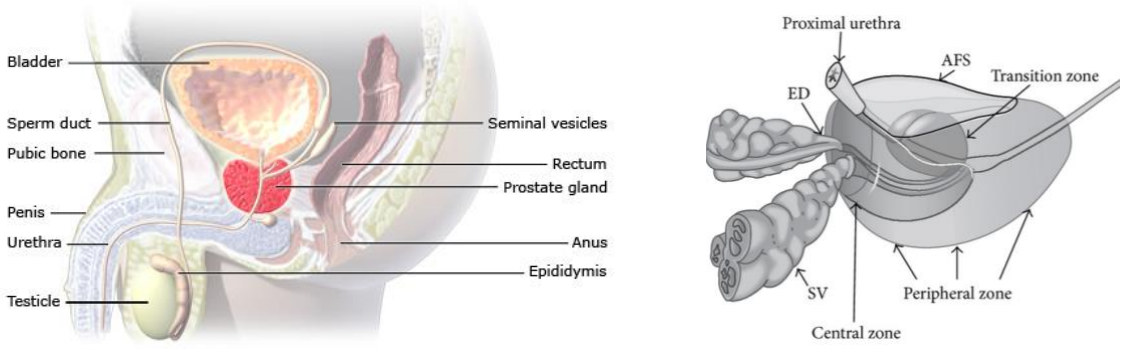


Figure 1 The Male Reproductive System[3] (left) and Zonal anatomy of the Prostate[2] (right)

1.1.2. Function

The prostate secretes thin, slightly basic fluid that gives rise to a portion of the seminal fluid. These secretions are crucial for the proper functioning of the sperms i.e. mobility and viability, which in turn ensures fertility in men. In addition, the prostate stores this seminal fluid and its muscles allow the semen stored to be expelled outwards during ejaculation after being pressed forcefully into the urethra[2,3].

1.2. Prostate Carcinogenesis

Prostate cancer (PC) is characterized by uncontrolled (malignant) cell growth in the prostate gland[4]. In fact, it is the most common type of cancer in men worldwide, apart from skin cancer, and is usually asymptomatic in the beginning[4]. Furthermore, this type of cancer can either be

benign and progress slowly or can be aggressive and fatal where it can metastasize and spread outside the borders of the prostate gland.

The most frequent type of prostate cancer is the adenocarcinomas where they develop in the gland cells. However, other types of cancer can initialize in the prostate but in very rare cases (<5%) such as small cell carcinoma, neuroendocrine tumors, transitional cell carcinomas, and sarcomas[5].

1.2.1. Symptoms and Diagnosis

Symptoms that are widely known to be associated to prostate cancer include lower urinary tract symptoms (LUTS) such as nocturia, straining to void, and hematuria due to its location next to the urethra. Erectile dysfunction is also another symptom that is common and is associated with PC[6,7]. Unfortunately, it is difficult to differentiate between prostate cancer and benign prostate hyperplasia (BPH) based on symptoms only, therefore digital rectal examination (DRE) or/and prostate specific antigen (PSA) facilitate their diagnosis[6].

When prostate cancer is suspected physicians start with clinical diagnosis through a DRE to check for any abnormality[6,7]. Furthermore, they undergo biological diagnosis by determining the total serum level of PSA (<4 ng/ml) in the body. PSA is not by any means specific to prostate cancer, serum levels change if there is BPH, inflammation, or infection in the prostate as well. Therefore, the ratio free PSA / total PSA further identifies with better precision whether it is PC (ratio <10%) or BPH (ratio >20%)[8]. Afterwards, a prostate biopsy can confirm if there was a suspected PC, and to check whether the tumor is spread, certain imaging tests such as whole-body bone scan, Computed Tomography (CT), Magnetic Resonance Image (MRI), or Positron Emission Tomography – Computed Tomography (PET-CT) are used [7, 8].

1.2.2. Tumor Classification

1.2.2.1. Gleason Score

The Gleason grading system is the standard and most common grading system of prostate cancer because it is the most valuable predictor for cancer behavior and aggressiveness. First of all, a prostate tissue is obtained during biopsy procedure and is given a grade that ranges from 1 to 5, where 1 resembles a normal tissue and 5 “high grade” resembles abnormal tissue. The Gleason score is then obtained by adding two of those histological grades depending on how progressive the cancer is[9].

The different Gleason scores are (figure 2):

- Gleason 6 or lower: Cells are well differentiated and they have a good prognosis.
- Gleason 7: Moderately differentiated cells that can be classified into intermediate (3+4) or high-grade (4+3) cancer.
- Gleason 8,9, or 10: Cells are poorly differentiated and have a very poor prognosis.

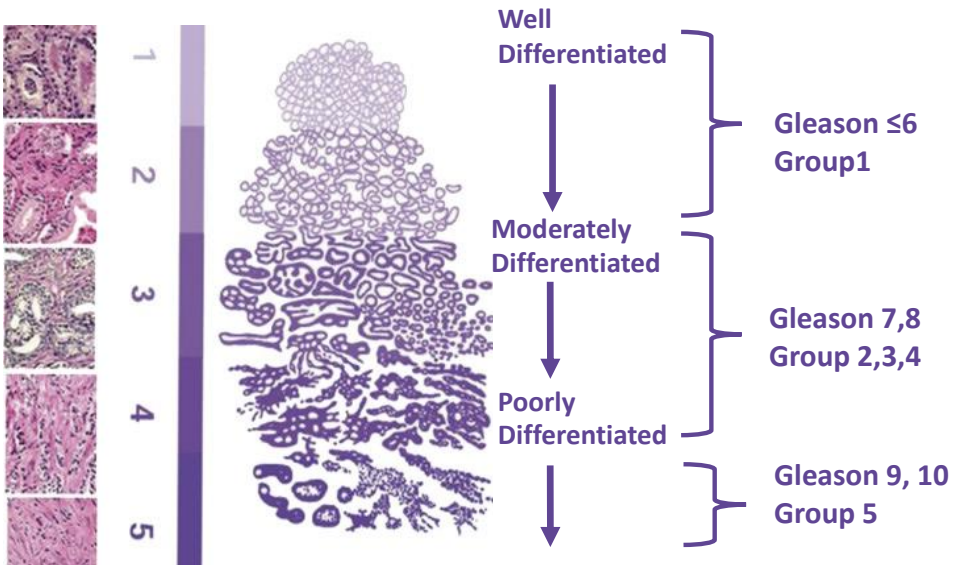


Figure 2 Schematic diagram of Gleason grading system[9]

- In 2013 John Hopkins Hospital proposed a new grading system that is somewhat different from the traditional one with five distinct grade groups (Table 1) based on Gleason scores10.

Table 1 New Gleason grading system based on groups[10]

Risk Group	***Grade Group***	***Gleason Score***
Low/Very Low	Group 1	Gleason ≤6
Intermediate	Group 2	Gleason 7 (3 + 4)
	Group 3	Gleason 7 (4 + 3)
High/Very high	Group 4	Gleason 8 (4 + 4)
	Group 5	Gleason 9, 10

1.2.2.2. TNM Classification

TNM classification was developed by the American Joint Committee on cancer (AJCC)[8,11] which is used to see whether the tumor has spread beyond the prostate or not.

The three references for tumor staging are:

- The primary tumor (T) has four stages (Figure 3):
  - ⇒ T1: Tumor not visible on imaging.
  - ⇒ T2: Tumor not spread outside the prostate.
  - ⇒ T3: Tumor has spread outside the prostate into nearby tissues.
  - ⇒ T4: Tumor has spread into nearby organs.
- The affected regional lymph nodes (N):
  - ⇒Nx: Not assessed
  - ⇒N0: No Spreading of the cancer
  - ⇒N1: Spreading through nearby lymph nodes
- Metastasis to different parts of the body (M):

⇒Mx: Not assessed

⇒M0: No spread

⇒M1: The cancer is either spread to M1a. Lymph nodes, M1b. Bones, M1c. organs

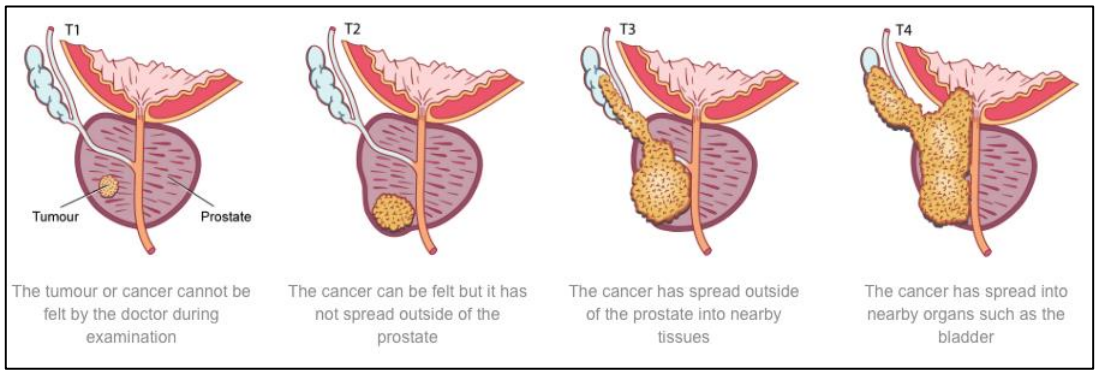


Figure 3 The primary tumor stages in prostate cancer (source rghospital)

1.2.2.3. D'amico Classification

This type categorizes cancer into three groups according to their risk of progression[8]:

- Low risk: PSA<10 ng/mL and Gleason score ≤6 and clinical stage T1c or T2a.
- Intermediate risk: PSA between 10 and 20 ng/mL or Gleason score 7 or stage T2b.
- High risk: PSA> 20 ng / mL or Gleason score ≥ 8 or clinical stage T2c.

1.2.3. Treatment

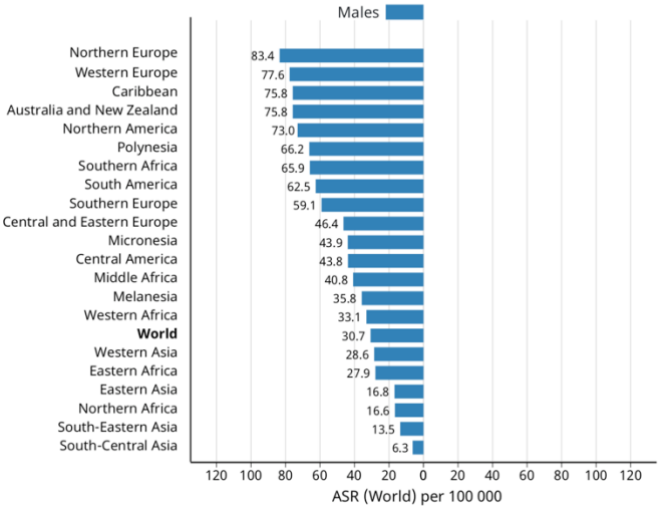
Treatments are based on previous classifications and a multidisciplinary consultation from different departments such as oncologists, radiotherapists, urologists, and pathologists etc... For starters, one of the therapeutic options is active surveillance that requires follow up on PSA and biopsies which is typically used on patients with low risk of progression[8]. Other types of treatments to tackle prostate cancer depend on the clinical conditions and outcomes, such as surgery, radiation therapy, proton beam therapy, chemotherapy, hormonal therapy, and high intensity focused ultrasound (HIFU)[12,13]. In fact, choosing the appropriate treatment depends on whether the cancer is localized or metastasized, and the life expectancy of the individual[14,15].

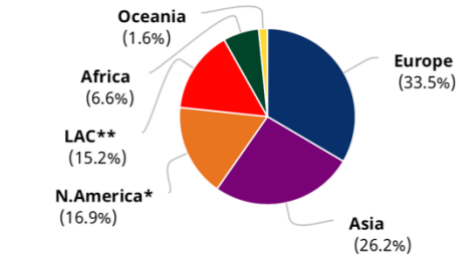
1.3. Epidemiology

1.3.1. Incidence

Prostate cancer is the second most common type of cancer in men worldwide, with 1,414,259 new cases representing 7.3% of all cancers in men, and the most common male cancer in France with more than 65,000 new cases estimated in 2020[16](Figure 4). Incidence rates of prostate cancer varies significantly across the world, where age standardized rate (ASR) is the highest in Northern Europe with an ASR of 83.4 per 100,000, followed by Western Europe, Australia, New Zealand, and North America with an average ASR of 75.5 per 100,000[16].

Moreover, Southern Africa, Southern Europe, and South America have an average ASR of 64 per 100,000[16]. Conversely, Western and Eastern Asia, Northern and Eastern Africa have a significantly lower ASR than the developed countries with an average of 22 per 100,000[16] (Figure 4). Furthermore, the risk of Prostate cancer increases with age where the rate of diagnosis among men 50 years and younger is 3.9 per 100,000, whereas the rate increases to 252.5 per 100,000 among men aged between 50 and 64, and 622.1 per 100,000 among men aged 64 years and above[17].



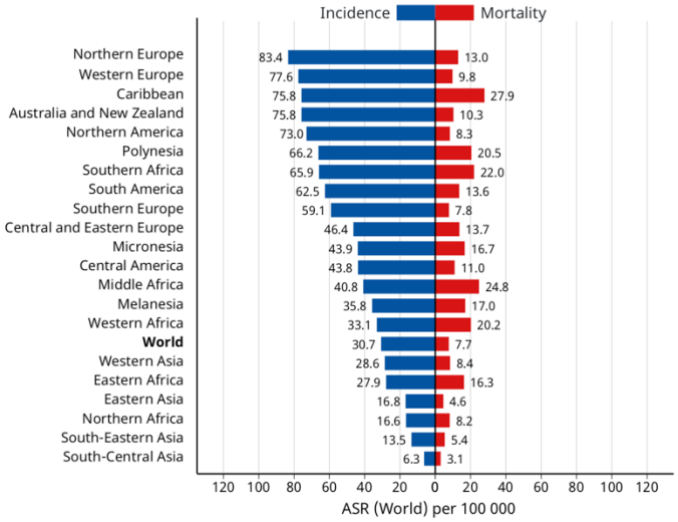


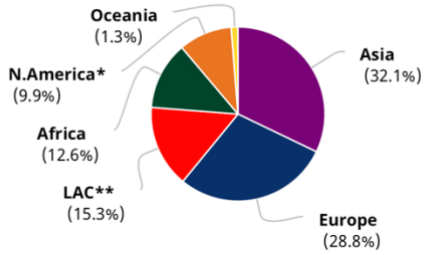
Population	Number
Europe	473 344
Asia	371 225
*Northern America	239 574
**Latin America and the Caribbean	214 522
Africa	93 173
Oceania	22 421
Total	1 414 259

Figure 4 Incidence ASR rates and numbers of PC worldwide[16]

1.3.2. Mortality

The number of prostate cancer related deaths is 375,304 worldwide (3.8% of all deaths caused in men) in 2020[16] (figure 5). However, there is a large disparity in the rate of mortality worldwide, where the rate is the highest in middle Africa and Caribbean with an average of 26 per 100,000. Whereas in the developed continents such as America, Europe and Australia the rate declines to an average of 10 per 100,000[16](Figure 5). This disparity implies that in the





Population	Number
Asia	120 593
Europe	108 088
**Latin America and the Caribbean	57 415
Africa	47 249
*Northern America	37 192
Oceania	4 767
Total	375 304

Figure 5 Mortality ASR rates and Numbers of PC worldwide[16]

developed countries patients might have been diagnosed at an early stage with a better prognosis, whereas underdeveloped countries might have been diagnosed at a very late stage with poor prognosis.

1.3.3. Trends

For the past decades, the incidence of prostate cancer worldwide has gradually increased, most likely due to the increased aging population and presence of diagnosis methods such as PSA testing particularly in western countries. For instance, in the United States, Canada, and Australia there were a significant increase in the incidence rates due to PSA testing in the 80's and 90s. Moreover, for the past 20 years there was a 2% to 10% increase in incidence rates in sub-Saharan Africa which might be because of an increase in health awareness and improvement in the health system. In developing countries, the mortality rates were then decreased since there are better detection techniques as well as better and advanced treatments. However, the exact opposite is currently happening in underdeveloped countries perhaps due to the lack of effective treatments and proper screening[18].

Figure 6 shows trends for incidence and mortality rates for USA, Australia, and France that are age-standardized rates per 100 000. Blue lines denote incidence and red lines mortality[19].

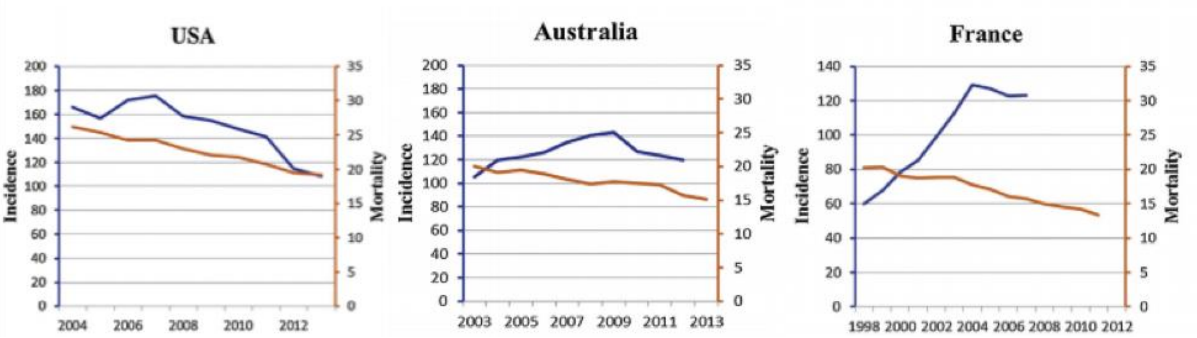


Figure 6 Temporal trends for PC incidence and mortality by country in the past two decades[19].

1.4. Etiology of Prostate Cancer

1.4.1. Established Risk Factors

Unfortunately, unlike other types of cancer, prostate cancer has only three well-established non-modifiable risk factors to date which are advancing age, ethnicity and family history of prostate cancer.

1.4.1.1. Age

The risk of having prostate cancer increases sharply with age. Statistics have shown that the incidence rate increases from 9.2/100,000 for men aged 40-44 years to 984/100,000 for men aged 70-74 years[20].

1.4.1.2. Ethnicity

Depending on the population, ethnic origin has been significantly proven to be a risk factor. For instance, the risk of prostate cancer is 60% higher among African American men then

white American men[21]. On the contrary, the risk of prostate cancer among the Asian population is extremely low[16].

1.4.1.3. History of prostate cancer

Various genetic studies indicate that hereditary factors could be responsible to 5% to 10% of prostate cancer. Relatives of affected men are at a higher risk. For instance, men with a first-degree relative who is diagnosed with prostate cancer have a two to threefold increase in the risk compared to the general population. The more relatives are diagnosed with prostate cancer the higher the risk[22].

1.4.2. Suspected Risk Factors

Even though there are only three non-modifiable risk factors for prostate cancer, a considerable number of suspected risk factors for prostate cancer have been investigated. Of which are environmental and occupational, personal medical history, lifestyle and dietary habits as well as genetics.

1.4.2.1. Environmental and Occupational Factors

Epidemiological studies on migrants showed an increase in the incidence of PC for Asians living in the United states compared to those living in their native countries, suggesting the role of lifestyle and environmental factors[23]. Occupational factors were also suspected to be associated with prostate cancer. Night shift work (doctors, pilots, police) are known to disrupt the circadian rhythm therefore studies on whether there is an association with increased risk of prostate cancer were done. In fact, an IARC monograph depicts that night shift work is classified as a probable carcinogen of group 2A, based on strong and sufficient evidence in experimental animals but limited to human studies[24].

1.4.2.2. Anthropometric and Metabolic Factors.

Obesity has been a major public health problem for the past decade especially in the western world, and it is increasing rapidly. Obesity has been proven to be a risk factor for several types of cancer, and there has been extensive research regarding its association with prostate cancer. However, obesity has been largely associated to aggressive prostate cancer particularly for indicators such as waste circumference and waist-hip ratio. A meta-analysis done by MacInnis showed the association of prostate cancer with obesity through BMI, waist circumference, and waist-hip ratio which showed that the risk increases particularly for advanced types[25].

1.4.2.3. Lifestyle Factors

While smoking has also been a risk factor to more than 30% of all cancers worldwide, it has not yet been associated to elevated risk of prostate cancer. A meta-analysis done by

Huncharek about smoking as a risk factor of prostate cancer and it showed that being a current smoker didn't significantly increase the risk of prostate cancer (RR = 1.04; 95% CI = 0.87-1.24), however it was significant when stratified by the number of cigarettes smoked (RR = 1.22; 95% CI = 1.01-1.46) [26].

1.4.2.4. Hormonal Factors

Prostate gland development is dependent on Androgens (testosterone, dihydrotestosterone and their derivatives), however, the precise role of androgens PC development is not clear[27]. Studies have shown contradictory results as to the role of circulating androgens in the occurrence of prostate cancer as well as other factors such as insulin-related growth factors and their binding proteins (IGFs and IGFBPs) [27,28].

1.4.2.5. Chronic Inflammation

Epidemiological and histopathological studies showed that chronic inflammation and environmental agents enhances the development of different types of cancer[29,30]. In fact, emerging evidence suggest that inflammatory infiltrates localized near areas of proliferative inflammatory atrophy and prostatic intraepithelial neoplasia considered to be prostatic lesions might play a role in the occurrence of prostate cancer[31,32]. An example of a certain infection that causes inflammation is shown through a meta-analysis done on prostatitis which yielded a significant association OR 1.64 [1.36-1.98] with prostate cancer[33].

Despite the significant advances in our understanding of prostate cancer risk factors over the last two decades, it still remains unclear what the risk factors are for this disease and therefore, our current knowledge does not permit conclusive guidelines or recommendations for effective preventive behavioral interventions.

1.5. Hypothesis and Objectives

Chronic infections or chronic inflammatory states accounts to about 20% of all human carcinogenesis[31]. Several epidemiological studies have shown that infections may play a role in prostate cancer carcinogenesis due to the chronic inflammation they cause. Genitourinary infections had quite an increasing attention regarding its association with prostate cancer. Prostatitis, urethritis, orchi-epididymitis, or acute pyelonephritis and their association with prostate cancer were all studied but the results differ[34,35]. In fact, a study done by Doat et. al showed that higher number of infections increases the risk of prostate cancer OR 2.45 [1.04-5.76][35]. On the other hand, sexually transmitted diseases (STDs) pose a major public health problem worldwide, with around 385,000 cases reported in 2013 and more than 3 million between 2004 and 2013 only in Europe[37]. Furthermore, statistics show that chlamydia is the most common sexually transmitted infection with a rate of 182 per 100,000, while gonorrhea and syphilis may not be as common, they still showed an increasing trend in Europe with

52,995 and 22,237 reported cases in 2013 respectively[37]. Some of the pathogenic organisms that are known to infect and induce an inflammatory response in the prostate are neisseria gonorrhea, chlamydia, trichomonas vaginalis, and treponema pallidum. Several epidemiological studies have focused on the role of sexually transmitted infections in the risk of developing prostate cancer.

For instance, Wang et al. conducted a prospective cohort study and found an association between gonorrhea and PC (HR: 5.66 [1.36–23.52])[38]. A case control study done by Vázquez-Salas et. al found a three-fold increase in the risk of PC when having one or more gonorrhea infections (OR 3.04 [1.99–4.64])[39]. However, there were contradictory results from other studies such as the one done by Sutcliffe et al. that had no association between gonorrhea (RR 1.04 [0.79-1.36]) or syphilis (RR 1.06 [0.44-2.59]) and PC[40]. Moreover, a study done by Cheng et al. also showed no association between STIs and the risk of PC (RR 1.02 [0.91–1.15]), but when they focused specifically on Latinos only the association was significant (RR:1.43 [1.07–1.91])[41]. Table 2 shows several studies that focused on certain and specific sexually transmitted infections while others focused on a larger scale on multiple types of sexually transmitted infections to observe a global association.

Table 2 Studies on the role of STDs in the occurrence of prostate cancer in the past 2 decades

Study	*Country*	*Type*	*Year*	*Data Source*	*Cases (N)*	*OR (95%CI)*
Sanderson et al.[42]	SC	CC	2004	TI	416	OR:1.27 (0.77-2.08)
Fernández L et al.[43]	Cuba	CC	2005	CR + PI	273	OR: 1.70 (1.1-2.5)
Sutcliffe S.[40]	U.S.	PC	2006	SRQ	2,263	RR: 1.08 (0.96-1.20)
Sutcliffe S.[44]	U.S.	NCC	2007	SRQ + SM	691	OR: 1.13 (0.65-1.96)
Huang et al.[45]	U.S.	NCC	2008	SRQ + SM	868	OR: 1.3 (1.0-1.6)
Sutcliffe S.[46]	U.S.	CC	2009	SRQ	616	OR: 0.97 (0.70-1.34)
Cheng et al.[41]	U.S.	PC	2010	SRQ	11,658	RR: 1.02 (0.91-1.15)
Hrbacek et al.[47]	Prague	CC	2011	SM	434	OR:1.07 (0.44-2.99)
Vázquez-Salas et al.[39]	Mexico	CC	2015	PI	402	OR: 3.04 (1.99-4.64)
Wang Y.C. et al.[38]	Taiwan	RC	2016	MF	848	HR: 5.66 (1.36-23.5)

Abbreviations: CC: case control, PC: prospective cohort, NCC: nested case control. RC: retrospective cohort, TI: Telephone Interview, CR: City registry, PI: personal interview, SRQ: self-reported questionnaire, AS: Antibody sero-status, MF: Medical File, SC: South Carolina, US: United states.

Despite the fact that Prostate cancer has a great impact on public health and it is increasingly becoming clear that genetic, environmental, lifestyle and cultural factors are intimately tied with the incidence and mortality rate of this disease, we have yet to fully determine the risk factors. In fact, through decades researchers argued on whether prostate cancer is linked to inflammation and/or infection. Epidemiological studies mainly focused on a certain type of a sexually transmitted infection. In addition, very few of the studies done on STDs considered

low, and high-grade cancer. Finally, these findings were still inconsistent and therefore sexually transmitted infections remains an inconclusive etiology for prostate cancer. Consequently, further studies will help advance our understanding of the role of STDs in the etiology of prostate cancer to build adequate strategies to limits its occurrence especially to its most aggressive types.

1.5.1. General Objective

The main objective of this thesis is to investigate the role of sexually transmitted infections in the occurrence of prostate cancer, with a specific interest on aggressive prostate cancer.

1.5.2. Specific objectives of this thesis

- Study the existence of an overall association between sexually transmitted infections and prostate cancer (overall, low-grade, and high-grade).
- Study the existence of a specific association between each type of the sexually transmitted infections (Gonorrhea, Trichomonas, and Syphilis) and prostate cancer (overall, low-grade, and high-grade).

2. MATERIALS AND METHODS

2.1. Study Population

EPICAP study is a population-based case-control study carried out in the department of Herault in France in particular because of the presence of a general cancer registry, and its involvement in the European randomized study of screening for prostate cancer[48].

2.1.1. Cases

Eligible cases newly diagnosed with prostate cancer in 2012-2013 who were under the age of 75 and lived in the department of Hérault at the time of diagnosis. Clinical research nurses recruited and trained specifically for the study perform case identification in all participating centers: three public hospitals and three private urology clinics. After collecting the subject's consents, the only cases who were included in the study were histologically confirmed that they are cancer positive[48].

2.1.2. Controls

Controls were drawn from the general population of men who were cancer-free and living in the study area (Hérault department) at the time of the cases' diagnosis. In order to achieve frequency-matching, quotas by age were established as a preliminary to yield a control group that was similar to the case group in terms of age (5-year age group). To control for selection bias quotas by socio-economic status were also set a priori. The recruitment of controls was

carried out as follows: phone numbers of private homes were drawn at random via a survey institute from a telephone directory. Men were included if they fit the eligibility criteria and the quotas otherwise they are not allowed to participate[48].

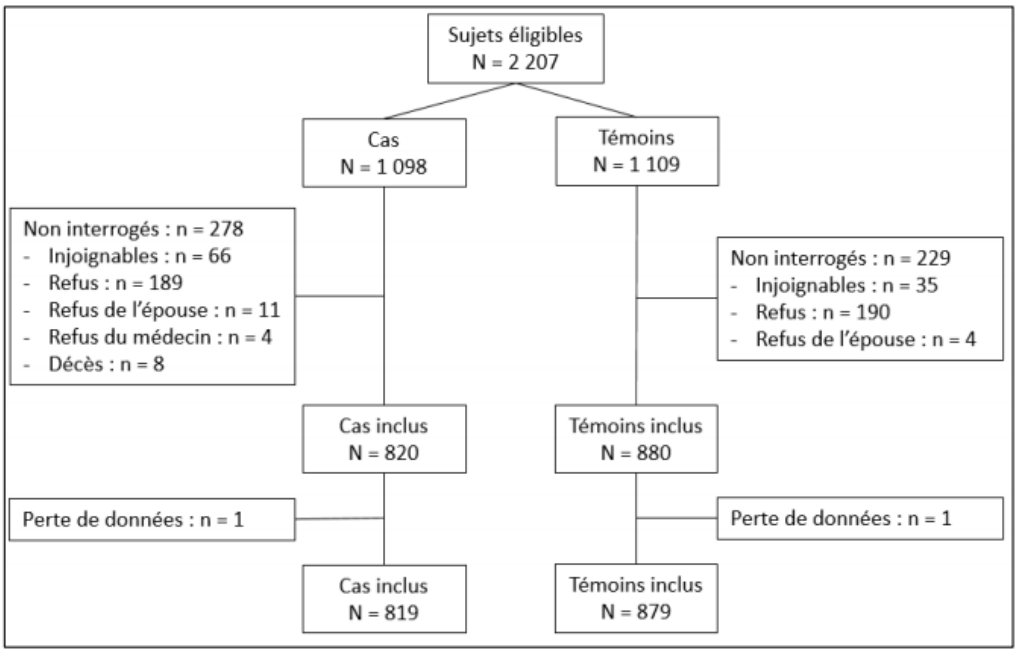


Figure 7 EPICAP cases and controls selection flowchart

⇒ In total EPICAP included 1,098 prostate cancer cases and 1109 population-based controls (Figure 7) with a participation rate of 75% (819) and 79% (879), respectively[48].

2.2. Data Collection

Cases and controls were interviewed face to face by a well-trained research clinical nurse particularly for this study, there was also blood or saliva sampling, as well as anthropomorphic measurements[48].

2.2.1. Questionnaire

The cases and controls interviews were conducted using a system-standardized questionnaire (CAPI - Computer Assisted Personal Interview), a face-to-face method for data collection on a microcomputer in the interviewee's home which took around 2 to 4 hours. The questionnaire constitutes information about sociodemographic characteristic, professional and residency history, lifestyle (tobacco, alcohol, and physical activity), personal and family medical history, weight history, as well as ethnicity. The questionnaire also included very detailed questions in order to identify a personal history of sexually transmitted infections (STIs), as well as general questions about urethritis or purulent urine discharge[48].

For infections, the type and number of infections (Gonorrhea, trichomonas, Mycoplasma, Syphilis…) were asked to men, as well as the age at time of infection and in case of several infections, men were asked about their age for their first and last infection (Annex 1).

2.2.2. Anthropomorphic Measurements

Weight, height, abdominal and hip perimeter for both cases and controls were done by nurses where they complement the data taken from the questionnaire[48].

2.2.3. Biospecimen Collection

Blood Sampling was done for both cases and controls who approved and signed a consent. In case of refusal a saliva sample is taken instead using an Oragene kit. The samples made it possible to set up a DNA bank (DNAthèque) [48].

2.3. Variables

2.3.1. Outcome of Interest

Prostate cancer is the dependent variable. In order to distinguish between cases and controls a binary variable was created where controls are free of the disease and cases are diagnosed with Prostate cancer. Two additional variables were created in order to focus specifically on low-grade cancer and high-grade cancer separately. For starters, to focus on low-grade cancer, a binary variable was created that includes all controls free of the disease and low-grade cases of prostate cancer based on the Gleason score that is ≤ 7 (3+4). In order to focus on high-grade cancer, another binary variable was created that includes all controls free of the disease and high-grade cases of prostate cancer based on the Gleason score that is ≥7 (4+3).

2.3.2. Exposure of Interest

The main exposures of interest included in this study are:

- *Gonorrhea:* Initially this variable was made of three levels for the presence or absence of the infection (1: Yes, one time, 2: Yes, more than once, 3: No infection). However, in this study the variable is merged into a binary variable (0: No infection, 1: at least one time).
- *Trichomonas:* Initially this variable was made of three levels for the presence or absence of the infection (1: Yes, one time, 2: Yes, more than once, 3: No infection). However, in this study the variable is merged into a binary variable (0: No infection, 1: at least one time).
- *Syphilis:* This variable was already binary variable stating the presence or absence of syphilis infection among participants (0: No infection 1: Yes).
- *Urethritis:* This variable included in the study since the urethra is connected to the prostate and urethritis is another type of infection that might play a role in the association of PC. We used urethritis as a binary variable (0: No infection, 1: at least one time).
- *Purulent urine discharge:* Since the presence of a discharge might be associated to having a certain type of infection, it was also included in this study. This variable was already a binary variable where 0 having no discharge and 1 presence of discharge.

- *Sexually Transmitted Infections (STD3):* To create a more general variable for sexually transmitted infections, we combined all three infections (gonorrhea, trichomonas, and syphilis) into one binary variable. The first level is 0 where the patient did not have any type of infection and level 1 is when the patient had at least one of the three infections in their lifetime.
- *Sexually transmitted infections (STD5):* Another binary variable was created that included all Sexually transmitted infections along with both urethritis and purulent urine discharge. The first level which is 0 is included subjects that did not have any STD infection or purulent urine discharge or urethritis and the other level which is 1 included subjects that had at least one STD or purulent urine discharge or Urethritis.
- *Sexually Transmitted Infections Global (STDG):* An additional 3 class variable was created that included all sexually transmitted infections along with both urethritis and purulent urine discharge. The first level 0 included subjects that did not have any STD infection or purulent urine discharge or urethritis, the second level included subjects having only 1 type exposure (STD infection, urethritis, purulent urine discharge) and the third level had at least two types of exposure (STD infection, urethritis, purulent urine discharge).

2.3.3. Explanatory Variables

The three known and nonmodifiable risk factors for prostate cancer are:

- *Age* which is the only variable that was both used when it is continuous or in five ordinal classes corresponding to stratification classes (<55, [55-60], [60-65] [65-70], ≥70 years).
- *Family history of Prostate cancer* is categorized into two classes (yes/no) where yes is only for first degree relatives with a history of prostate cancer.
- *Ethnic Origin* is divided into two classes: subjects with Caucasian origin, and the rest of other origin.

The following explanatory variables that we decided to add to this study are:

- *Education which* is divided into three classes: primary, secondary, and university level.
- *Body Mass Index* is constructed from the individual's height at 18 and the individual's weight two years before the reference date. It was then divided into three categories: <25 kg/m² (normal weight subjects), 25-30 kg/m² (overweight subjects), and over 30 kg/m² (obese subjects).
- *Waist circumference* is also included in the study, it was initially a continuous variable but, in this study, it is used as a binary variable where one level includes subjects with a WC ≤ 94 and the other level is >94.
- *Smoking* is divided into: non-smokers, former smokers, and current smokers.

- *Alcohol consumption, physical activity, prostatitis, and nonsteroidal anti-inflammatory drugs (NSAIDs)* were divided into binary variables (yes/no).

2.4. Analysis

2.4.1. Analysis Strategy

2.4.1.1. Descriptive Statistics

For starters, we described characteristics of our population by a case control comparison on well-established risk factors (age, Family history of prostate cancer, ethnicity) and other potential confounders (BMI, education, NSAIDS, lifestyle…). Moreover, we described our exposures of interest (STDs combined, Gonorrhea, Trichomonas, Syphilis…) and then compared the distribution of the variables among cases and controls, then checked for the distribution of the variables among intermediate cases and aggressive cases separately with the controls. Finally, in order to remove the influence of the disease and to see if the potential confounders are associated with the exposure, we described the variables only with the control subjects and we compared them between sexually transmitted infections and those without it.

2.4.1.2. Analysis

To begin with, a separate analysis was performed for combined STDs, and then gonorrhea, syphilis and trichomonas separately. Afterwards, the analysis basically consisted of studying the association between sexually transmitted infections (variables of interest) and prostate cancer (dependent variable) – univariate analysis. We also performed a multivariate analysis between the exposure and outcome of interest adjusted for the known risk factors of prostate cancer. Furthermore, in order to test for potential confounders, we performed a univariate analysis between the explanatory variables and prostate cancer. Likewise, we looked for factors associated with STDs among the explanatory variables. In addition, we performed an adjusted analysis on each potential confounder and we compared the crude effect to the adjusted effect. Finally, we used Directed Acyclic Graph (DAG) to illustrate the relationship between sexually transmitted infections and prostate cancer (figure 8).

The final multivariate analysis was done to study the association between sexually transmitted infection and prostate cancer adjusted to known risk factors as well as confounding factors. Moreover, we carried out another multivariate analysis with the same previous conditions but this time taking into account the aggressiveness of the cancer defined by the Gleason score. Finally, we performed stratification analysis on subgroups of urethritis and nonsteroidal anti-inflammatory (NSAIDS) also considering the aggressiveness of cancer in STD3, STD5, and STDG.

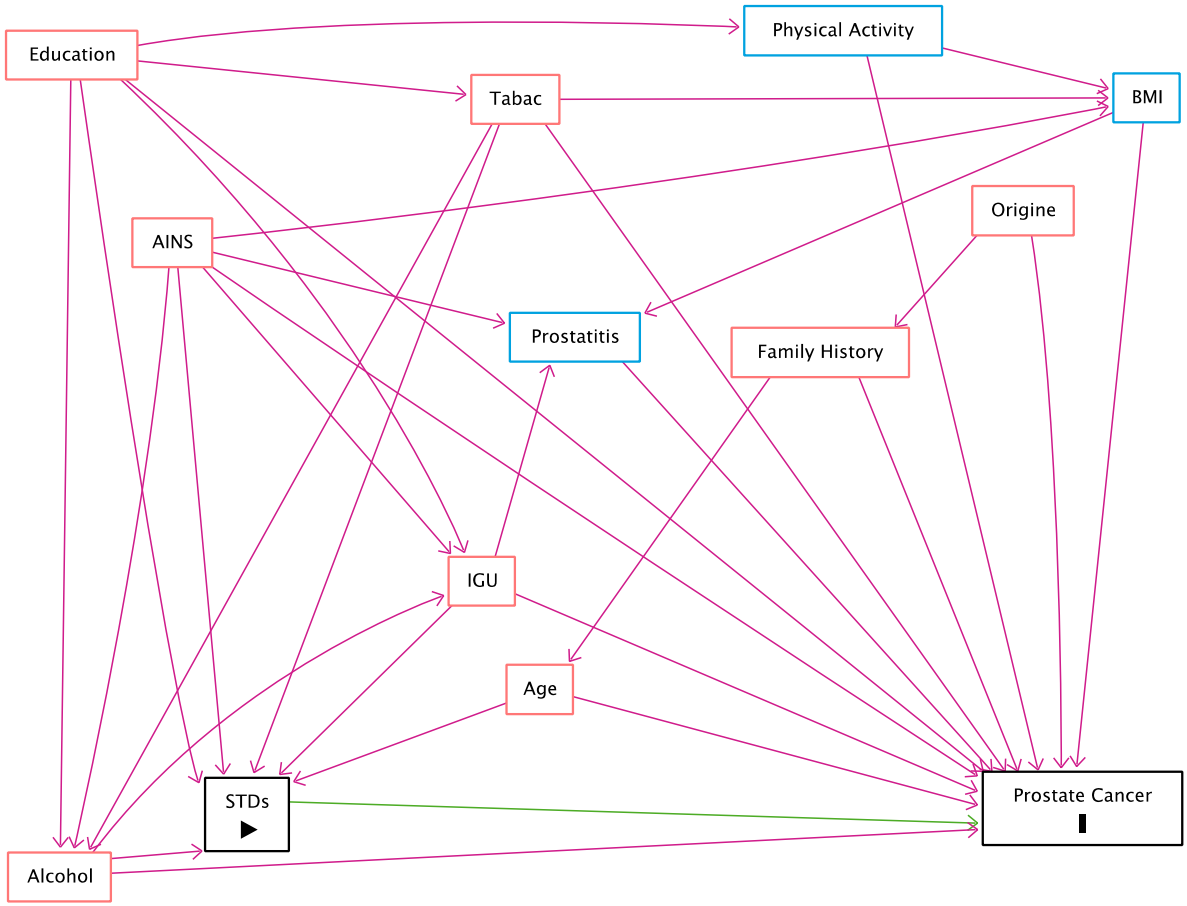


Figure 8 Directed Acyclic Graph (DAG) for the association between STDs and Prostate Cancer

Abbreviations: IGU: genitourinary infections, BMI: body mass index, AINS: non-steroidal anti-inflammatory drugs, STDs: sexually transmitted infections

2.4.2. Statistical Analysis

All statistical analysis was completed using SAS® statistical software version 9.4 (SAS 9.4 TS Level 1M6 X64_10PRO platform).

Statistical analysis plan that was followed throughout the study:

- In the descriptive part, all the variables are qualitative and therefore they were described in percentages. To check for comparability between cases and controls, univariate analysis either with Chi2 or fisher test was done depending on the validity conditions.
- The basic model which included the exposure (STD3, STD5, STDG) and outcome of interest was directly adjusted to the known risk factors i.e. age, ethnicity, and family history of prostate and then adjusted to urethritis and purulent urine discharge. In order to compute the odds ratio (OR) and their 95% confidence interval, unconditional logistic regression was used.

- For confounding factors, an association was computed through Chi2 or fisher test. In addition, we followed the step forward approach to look for confounding factors that might affect the association by adding the variables one after the other when we saw a significant change in the crude and adjusted OR.
- We also did multivariate analysis using logistic regression to see whether there was an association between STD3, STD5, STDG and low-grade and high-grade prostate cancer separately, and computed the odds ratio (OR) and 95% confidence intervals.
- Stratification analysis by NSAIDs and urethritis was also done using logistic regression and adjusting to the three known risk factors on all cases and controls, as well as on different grades of prostate cancer (low and high-grade) and STD3, STD5, and STDG.

3. RESULTS

3.1. Population characteristics

In the EPICAP study our population consisted of 819 cases and 879 controls with a participation rate of 75% and 79% respectively. Table 3 shows the study population characteristics. For starters, based on the Gleason score prostate cancer was categorized into two levels, low grade cancer where it accounts for 77.3% of the cases (Gleason <7, [3+4]) and high-grade cancer where it accounts for 22.7% of the cases (Gleason ≥7, [4+3]). The age distribution in five-year groups in controls was similar to the age distribution observed in cases (p=0.144). The study population was predominantly of Caucasian origin with 97.1% among cases and 97.7% among controls which was also comparable (p=0.396). However, as expected family history of prostate cancer was more frequent in cases (22.2%) than in controls (8.8%) with a p-value of <0.001. On the other hand, based on the anthropometric indicators, the BMI (body mass index) distribution was in three levels (normal, overweight, and obese) that were comparable between cases and controls (P=0.534) whereas waist circumference was a bit more frequent in cases than controls (p=0.086). Regarding sociodemographic and lifestyle characteristics, both cases and controls were comparable in terms of education level (p=0.609), smoking status(p=0.288), alcohol consumption(p=0.591), and physical activity (p=0.109). Finally, prostatitis, and use of non-steroidal anti-inflammatory drugs were more frequent among cases than in controls with a p-value of 0.024, 0.003, and 0.043 respectively.

Table 3 Study population characteristics among prostate cancer cases and controls

Variables	*Cases n=819 (%)*	*Controls n=879 (%)*	*P-value* x^2
Gleason Score			
≤ 7 (3+4)	623 (77.3)	-	
≥7 (4+3)	183 (22.7)	-	
Age (Years)			*0.144*
< 55	48 (5.9)	59 (6.7)	
[55-60]	99 (12.1)	99 (11.2)	
[60-65]	217(26.5)	201 (22.9)	
[65-70]	274 (33.5)	285 (32.4)	
≥70	181 (22.1)	235 (26.7)	
Ethnic Origin			*0.396*
Caucasian	795 (97.1)	859 (97.7)	
Other	24 (2.9)	20 (2.3)	
Family History of Prostate Cancer			*<0.001*
No	633 (77.8)	799 (91.2)	
Yes	181 (22.2)	77 (8.8)	
Education			*0.609*
Primary	179 (21.9)	193 (22.0)	
Secondary	380 (46.4)	425 (48.4)	
University	260 (31.8)	260 (29.6)	
Body Mass Index (kg/m²)			*0.534*
<25 - Normal	231 (28.5)	248 (29.1)	
[25-30] - Overweight	399 (49.1)	397 (46.6)	
≥30 - Obese	182 (22.4)	207 (24.3)	
Waist Circumference (cm)			*0.086*
≤94	209 (25.9)	254 (29.6)	
>94	599 (74.1)	603 (70.4)	
Smoking Status			*0.288*
Never	240 (29.3)	246 (28)	
Former	455 (55.6)	476 (54.2)	
Current	123 (15.0)	157 (17.9)	
Alcohol Consumption			*0.591*
No	72 (8.8)	84 (9.6)	
Yes	746 (91.2)	795 (90.4)	
Physical Activity			*0.109*
No	191 (23.4)	177 (20.1)	
Yes	627 (76.7)	702 (79.9)	
Prostatitis			*0.024*
No	735 (89.7)	816 (92.8)	
Yes	84 (10.3)	63 (7.2)	
Nonsteroidal anti-inflammatory drugs			*0.043*
No	596 (73.0)	593 (68.6)	
Yes	220 (27.0)	272 (31.5)	

3.2. Determinants of Sexually Transmitted Infections

In order to remove the influence of the disease and to see if the potential confounders are associated with the exposure, we described the variables only with the control subjects and we compared them between sexually transmitted infections and those without it (Table 4). The majority of the variables were comparable among men who have a history of STDs and those who do not. For instance, age (p=0.167), ethnicity (p=0.850), BMI (p=0.222), and alcohol consumption (p=0.140) were not statistically significant and are comparable whereas education (p=0.086) and smoking status (p=0.049) were significant. No change was observed when adjusting for them in our final models.

Table 4 Descriptive statistics between men with a history of STDs and without a history of STDs

Variables	*STD=0*	*STD=1*	*P-value* X^2
Age (Years)			*0.167*
< 55	52 (6.6)	6 (7.4)	
[55-60]	94 (11.9)	4 (4.9)	
[60-65]	117 (22.4)	22 (27.2)	
[65-70]	251 (31.7)	32 (39.5)	
≥70	217 (27.4)	17 (21.0)	
Ethnic Origin			*0.850*
Caucasian	774 (97.8)	79 (97.5)	
Other	17 (2.2)	2 (2.5)	
Family History of Prostate Cancer			*0.707*
No	720 (91.2)	72 (90.0)	
Yes	69 (8.8)	8 (10.0)	
Education			*0.086*
Primary	175 (22.2)	18 (22.2)	
Secondary	390 (49.4)	31 (38.3)	
University	225 (28.5)	32 (39.5)	
Body Mass Index (kg/m^2)			*0.222*
<25 - Normal	232 (30.1)	16 (20.8)	
[25-30] - Overweight	354 (45.9)	39 (50.7)	
≥30 - Obese	185 (24.0)	22 (28.6)	
Waist Circumference (cm)			*0.785*
≤94	230 (29.7)	22 (28.2)	
>94	545 (70.3)	56 (71.8)	
Smoking Status			*0.049*
Never	230 (29.1)	15 (18.5)	
Former	417 (52.7)	54 (66.7)	
Current	144 (18.2)	12 (14.8)	
Alcohol Consumption			*0.140*
No	79 (10.0)	4 (4.9)	
Yes	712 (90.0)	77 (95.1)	
Physical Activity			*0.631*
No	158 (20.0)	18 (22.2)	
Yes	633 (80.0)	63 (77.8)	
Nonsteroidal anti-inflammatory drugs			*0.265*
No	538 (69.0)	49 (62.8)	
Yes	242 (31.0)	29 (37.2)	

3.3. Sexually Transmitted Infections and Prostate Cancer

Univariate analyses (Chi or Fisher) were carried out to test for associations between potential confounders (BMI, education, smoking…) with the main exposure and outcome of interest in this study. No significant association was found between all potential confounders and main exposure and outcome (Annex 2). Therefore, the models used in this study were controlled only for the main risk factors of prostate cancer (age, ethnicity, and family history of prostate cancer).

3.3.1. Specific sexually transmitted infections

Gonorrhea, Trichomonas, and Syphilis were the three main infections being studied. First of all, there were 7.7% (n=67) controls and 6.8% (n=55) cases who self-declared gonorrhea. In addition, there were 1.2% (n=10) controls and 0.9% (n=7) cases who self-declared Trichomonas. Finally, there were 1.0% (n=9) controls and 0.4% (n=3) cases (Table 5).

Table 5 Association between gonorrhea, trichomonas, syphilis and prostate cancer separately

	Controls	***Cases***					
		All		**Low grade cancer**		**High-grade cancer**	
	n=879 (%)	**n=819 (%)**	**OR* (95% CI)**	**n=623 (%)**	**OR* (95% CI)**	**n=183 (%)**	**OR* (95% CI)**
Gonorrhea							
No	804 (92.3)	759 (93.2)	1.00 *reference*	574 (92.7)	1.00 *reference*	173 (95.1)	1.00 *reference*
Yes	67 (7.7)	55 (6.8)	0.90 (0.61-1.35)	45 (7.3)	0.99 (0.64 – 1.51)	9 (4.9)	0.59 (0.27 – 1.29)
Trichomonas							
No	854 (98.8)	803 (99.1)	1.00 *Reference*	613 (99.5)	1.00 *reference*	177 (97.8)	1.00 *reference*
Yes	10 (1.2)	7 (0.9)	0.90 (0.34 – 2.38)	3 (0.5)	0.51 (0.14-1.86)	4 (2.2)	2.49 (0.75 – 8.31)
Syphilis							
No	867 (99.0)	816 (99.6)	1.00 *Reference*	621 (99.7)	1.00 *reference*	182 (99.5)	1.00 *Reference*
Yes	9 (1.0)	3 (0.4)	0.48 (0.13– 1.83)	2 (0.3)	0.41 (0.09 – 1.98)	1 (0.5)	0.81 (0.10 – 6.70)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer

The multivariate analysis by logistic regression showed that having a history of gonorrhea (OR=0.90, 95% CI: 0.61-1.35) or trichomonas (OR=0.90, 95% CI:0.34 – 2.38) or syphilis (OR:0.48, 95% CI: 0.13–1.83) was not associated with prostate cancer. In addition, there was no significance when testing for any association between gonorrhea and low grade (OR=0.99, CI 95%: 0.64-1.51) or high-grade (OR:0.59, 95% CI: 0.27-1.29) cancer. Similarly, for trichomonas there was no association with low grade (OR=0.51, 95% CI: 0.14-1.86) but positive non-significant association with high-grade cancer (OR=2.49, 95% CI: 0.75-8.31). For Syphilis, there was also no association among low grade (OR=0.41, 95% CI: 0.09-1.98) and high-grade cancer (OR=0.81, 95% CI: 0.10-6.70).

3.3.2. Overall sexually transmitted infections (STDs)

The overall result of STDs gives us a more general assumption about the association between infections and prostate cancer. There were 9.3% (n=81) controls, 7.9% (n=64) cases, 8.3% (n=51) low grade cancer and 6.6% (n=12) high-grade cancer that reported STDs. In addition, STD5 which includes at least one of the STD infections, urethritis, and purulent liquid discharge had 13.7% (n=119) controls, 13% (n=106) cases. Regarding STDG those that have at least one infection among the controls are 11.3% (n=98), and 10.3% (n=84) among cases. However, among men having two or more of the exposure, controls were 2.4% (n=21), and cases 2.7% (n=22) (Table 6).

Table 6 Association between STD3, STD5, and STDG separately with prostate cancer

	Controls	***Cases***					
		All		**Low grade cancer**		**High-grade cancer**	
	n=879 (%)	**n=819 (%)**	**OR* (95% CI)**	**n=623 (%)**	**OR* (95% CI)**	**n=183 (%)**	**OR* (95% CI)**
STD3*							
No	791 (90.7)	747 (92.1)	1.00 *reference*	565 (91.7)	1.00 *reference*	170 (93.4)	1.00 *reference*
Yes	81 (9.3)	64 (7.9)	0.82 (0.58-1.17)	51 (8.3)	0.85 (0.58-1.24)	12 (6.6)	0.71 (0.38-1.34)
STD5*							
No	749 (86.3)	706 (87.0)	1.00 *reference*	539 (86.9)	1.00 *reference*	156 (87.2)	1.00 *reference*
Yes	119 (13.7)	106 (13.0)	0.91 (0.68– 1.23)	81 (13.1)	0.89 (0.65 – 1.22)	23 (12.9)	0.93 (0.58 – 1.51)
STDG*							
No	749 (86.3)	706 (87.0)	1.00 *reference*	539 (86.9)	1.00 *reference*	156 (87.2)	1.00 *reference*
Yes, 1	98 (11.3)	84 (10.3)	0.87 (0.64– 1.20)	64 (10.3)	0.85 (0.60-1.20)	18 (10.1)	0.87 (0.51-1.49)
Yes, ≥ *2*	21 (2.4)	22 (2.7)	1.12 (0.60-2.09)	17 (2.8)	1.09 (0.55-2.13)	5 (2.8)	1.23 (0.45-3.37)

* OR Adjusted on Age, Ethnicity, and Family History of Prostate Cancer.

*STD3 (Gonorrhea, Trichomonas, Syphilis), STD5 & STDG (gonorrhea, trichomonas, syphilis, urethritis, and purulent liquid discharge).

The multivariate analysis by logistic regression showed that having a history of at least one type of STD was not associated with prostate cancer (OR=0.82, 95% CI: 0.58-1.17), low grade cancer (OR=0.85, 95% CI: 0.58-1.24), or high-grade cancer (OR=0.71, 95% CI: 0.38-1.34). Similar results were yielded for STD5 when tested for all prostate cancer cases (OR=0.91, 95% CI: 0.68-1.23), low grade (OR=0.89, 95% CI: 0.65-1.22), and high-grade (OR=0.93, 95% CI:0.58-1.51). On the other hand, STDG had a positive non-significant association among all cases (OR:1.12 95%CI: 0.60-2.09), low grade cancer (1.09 95%CI: 0.55-2.13), and high-grade cancer (OR: 1.23 95%CI: 0.45-3.37).

3.4. Final Model

Sexually transmitted infections with liquid discharge and urethritis

We wanted to investigate the association of sexually transmitted infections and prostate cancer in the presence of liquid discharge and urethritis when adjusted to the three main risk factors of prostate cancer.

Table 7 shows the results from a multivariate logistic regression analysis for STD3, liquid purulent discharge and urethritis. The end result showed that the odds of having prostate cancer increases to 1.05 when having at least one type of STD with urethritis and liquid discharge, however the association was non-significant (95% CI: 0.21-5.38). In addition, the odds of having low grade cancer increases to 1.48 (95% CI: 0.27-8.03). The association was also not significant for both liquid discharge and urethritis in all grades of cancer.

Table 7 Association between STDs and Prostate cancer including liquid discharge and urethritis

	Controls	***Cases***					
		All		**Low & Intermediate**		**Aggressive**	
	n=879 (%)	**n=819 (%)**	**OR* (95% CI)**	**n=623 (%)**	**OR* (95% CI)**	**n=183 (%)**	**OR* (95% CI)**
STD3*							
No	791 (90.7)	747 (92.1)	1.00 *reference*	565 (91.7)	1.00 *reference*	170 (93.4)	1.00 *reference*
Yes	81 (9.3)	64 (7.9)	1.05 (0.21– 5.38)	51 (8.3)	1.48 (0.27-8.03)	12 (6.6)	<0.001 (<0.001 - >999)
Liquid Discharge							
No	772 (96.4)	722 (95.1)	1.00 *reference*	547 (95.0)	1.00 *reference*	163 (95.3)	1.00 *reference*
Yes	29 (3.6)	37 (4.9)	1.26 (0.69-2.28)	29 (5.0)	1.22 (0.64 – 2.35)	8 (4.7)	1.69 (0.71-4.02)
Urethritis							
No	836(97.0)	786 (96.8)	1.00 *reference*	601 (96.9)	1.00 *reference*	173 (96.6)	1.00 *Reference*
Yes	26 (3.0)	26 (3.2)	0.73 (0.32– 1.70)	19(3.1)	0.47 (0.17-1.31)	6 (3.4)	1.11 (0.34 – 3.68)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer.
*STD3 (gonorrhea, trichomonas, Syphilis).

3.5. Stratification

3.5.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

A study done by Doat et al. from the EPICAP study showed that there was an association between infections and prostate cancer among men who did not use non-steroidal anti-inflammatory drugs[49]. In other words, there was a negative association with NSAIDS and prostate cancer and taking anti-inflammatory drugs decreases chronic inflammation and with its presence we cannot see the real association if there had been inflammation with the infection. Therefore, we decided to stratify on NSAIDs in order to see whether there is an association between sexually transmitted infections and prostate cancer among those who did not take anti-inflammatory drugs. Overall, 29% (n=492) reported NSAIDs, of which 10.7% (n=29) had at least one type of STD, and 13.8% (n=37) for STD5, and 9.7% (n=26) had one

of the exposures, and 4.1% (n=11) had at least two or more of the exposures. There was no statistically significant association observed in the groups of subjects (table 8).

Table 8 Association between STD3, STD5, STDG and prostate cancer stratified on NSAIDS

		Controls	***Cases***					
			ALL		**Low grade**		**High-grade**	
		N=593	**N=596**	**OR (95% CI)**	**N=446**	**OR (95% CI)**	**N=140**	**OR (95% CI)**
NSAINS=0, N=1189	**STD3***							
	No	538 (91.7)	552 (93.6)	1.00 *reference*	408 (92.5)	1.00 *reference*	135 (97.1)	1.00 *reference*
	Yes	49 (8.4)	38 (6.4)	0.73 (0.47-1.15)	33 (7.5)	0.86 (0.53-1.37)	4 (2.9)	0.33 (0.12-0.95)
	STD5*							
	No	507 (86.5)	519 (87.8)	1.00 *Reference*	388 (87.4)	1.00 *reference*	123 (89.8)	1.00 *Reference*
	Yes	79 (13.5)	72 (12.2)	0.88 (0.62-1.25)	56 (12.6)	0.91 (0.62-1.32)	14 (10.2)	0.76 (0.41-1.39)
	STDG*							
	No	507 (86.5)	519 (87.8)	1.00 *reference*	388 (87.4)	1.00 *Reference*	123 (89.8)	1.00 *Reference*
	Yes, 1	69 (11.8)	61 (10.3)	0.85 (0.59-1.24)	47 (10.6)	0.86 (0.58 – 1.29)	12 (8.8)	0.74 (0.38-1.42)
	Yes, ≥ 2	10 (1.7)	11 (1.9)	1.09 (0.45-2.64)	9 (2.0)	1.20 (0.47-3.03)	2 (1.5)	0.89 (0.19-4.25)
		N=272	**N=220**	**OR (95% CI)**	**N=175**	**OR (95% CI)**	**N=42**	**OR (95% CI)**
NSAINS=1, N=492	**STD3***							
	No	242 (89.3)	193 (85.5)	1.00 *reference*	156 (90.2)	1.00 *reference*	34 (81.0)	1.00 *reference*
	Yes	29 (10.7)	25 (11.5)	1.08 (0.60-1.93)	17 (9.8)	0.87 (0.45-1.68)	8 (19.1)	2.04 (0.85 -4.86)
	STD5*							
	No	231 (86.2)	185 (84.9)	1.00 *Reference*	150 (86.2)	1.00 *reference*	32 (78.1)	1.00 *Reference*
	Yes	37 (13.8)	33 (15.1)	1.04 (0.62 -1.77)	24 (13.8)	0.87 (0.48-1.56)	9 (22.0)	1.94 (0.85 – 4.46)
	STDG*							
	No	231 (86.2)	185 (84.9)	1.00 *reference*	150 (86.2)	1.00 *Reference*	32 (78.1)	1.00 *Reference*
	Yes, 1	26 (9.7)	22 (10.1)	0.97 (0.52-1.80)	16 (9.2)	0.80 (0.40 – 1.60)	6 (14.6)	1.85 (0.70-4.92)
	Yes, ≥ 2	11 (4.1)	11 (5.1)	1.23 (0.51-3.02)	8 (4.6)	1.03 (0.39-2.76)	3 (7.3)	2.16 (0.56-8.32)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer
*STD3 (Gonorrhea, Trichomonas, Syphilis), STD5 & STDG (gonorrhea, trichomonas, syphilis, urethritis, and purulent liquid discharge).

Among non-users of anti-steroidal anti-inflammatory drugs there was no statistical association between having sexually transmitted infections 0.73 (95% CI: 0.47-1.15), and between STD5 0.88 (95% CI:0.62-1.25), and between STDG for having one type of exposure 0.85 (95% CI:0.59-1.24) and between STDG for having at least two types of exposure 1.09 (95% CI: 0.45-2.64) and prostate cancer. We observed no association as well among low and high-grade of prostate cancer. In addition, among users of anti-steroidal anti-inflammatory drugs there were also no statistical association between having sexually transmitted infections 1.08 (95% CI: 0.60-1.93), and between STD5 1.04 (95% CI:0.62-1.77), and between STDG for

having one type of exposure 0.97 (95% CI:0.52-1.80) and between STDG for having at least two types of exposure 1.23 (95% CI: 0.51-3.02) and prostate cancer.

3.5.2. Urethritis

In the final model we observed that the risk of prostate cancer increases in the presence of urethritis. Therefore, we wanted to study the association between sexually transmitted infections and prostate cancer stratified on urethritis. Overall, 3% (n=52) men reported having urethritis, and among these subjects 42.3% (n=11) had at least one type of STD, and 34.6% (n=9) had only gonorrhea in controls, and among cases 54.23% (n=13) had at least one type of STD and 12 (50%) had only gonorrhea. (table 9).

Table 9 Association between STD3, gonorrhea and prostate cancer stratified on urethritis

		Controls	***Cases***					
			ALL		**Low grade**		**High-grade**	
			N	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
Urethritis=0, N=1622	**STD3***							
	No	768 (92.5)	731 (93.6)	1.00 *reference*	557 (93.3)	1.00 *reference*	163 (94.5)	1.00 *reference*
	Yes	62 (7.5))	50 (6.4)	0.84 (0.57-1.25)	40 (6.7)	0.87 (0.57-1.33)	9 (5.2)	0.72 (0.35-1.48)
	Gonorrhea							
	No	779 (94.0)	742 (94.6)	1.00 *Reference*	565 (94.2)	1.00 *reference*	166 (96.5)	1.00 *reference*
	Yes	50 (6.0)	42 (5.4)	0.85 (0.55–1.31)	35 (5.8)	0.93 (0.59-1.47)	6 (3.5)	0.58 (0.24-1.39)
Urethritis=1, N=52	**STD3***							
	No	15 (57.7)	11 (45.8)	1.00 *reference*	6 (35.3)	1.00 *reference*	4 (66.7)	1.00 *reference*
	Yes	11 (42.3)	13 (54.2)	2.44 (0.72-8.24)	11 (64.7)	4.92 (1.08-22.3)	2 (33.3)	0.67 (0.09-4.99)
	Gonorrhea							
	No	17 (65.4)	12 (50.0)	1.00 *Reference*	7 (41.2)	1.00 *Reference*	4 (66.7)	1.00 *reference*
	Yes	9 (34.6)	12 (50.0)	3.12 (0.86–11.28)	10 (58.8)	4.74 (1.08-20.73)	2 (33.3)	1.28 (0.17-9.70)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer
*STD3 (Gonorrhea, Trichomonas, Syphilis)

When comparing subjects among all types of cancer, there was no significant difference between the presence 2.44 (95% CI:0.72 – 8.24) and absence 0.84 (95% CI:0.57-1.25) of having urethritis. Though, it is interesting to note that we observed that the association in the presence of urethritis did increase to 2.44. Moreover, when comparing subjects based on low grade cancer, the risk of having prostate cancer significantly increases to 4.92 (95% CI:1.08-22.3) in the presence of urethritis from 0.87 (95% CI:0.57-1.33). The association remained high when observing the association on gonorrhea alone which yielded OR 4.74 (95% CI:1.08-20.73). On the contrary, there was no statistically significant association when comparing subjects among high-grade cancer in presence 0.67 (95% CI:0.09-4.99) and absence 0.72 (95% CI:0.35-1.48) of urethritis.

4. DISCUSSION

4.1. Summary of main results

The main objective of this study was to investigate the role of infections particularly sexually transmitted infections and the occurrence of prostate cancer, with a specific interest on the aggressive types using data from a case control study done in France. For starters, there was no significant association between having a history of gonorrhea (OR=0.83, 95% CI: 0.57-1.22) or trichomonas (OR=0.88, 95% CI:0.33 – 2.32) or syphilis 0.41(0.11–1.52) and prostate cancer. There was also no significance of having a history of gonorrhea, trichomonas, and syphilis with both low-grade (OR=0.88, OR=0.51, OR=0.37) and high-grade tumor (OR:0.64 OR=2.17, OR=0.37) respectively. In addition, we also didn't observe any association when having a history of at least one type of STD and risk of prostate cancer (OR=0.82, 95% CI: 0.58-1.17), low grade cancer (OR=0.85, 95% CI: 0.58-1.24), or high-grade cancer (OR=0.71, 95% CI: 0.38-1.34). However, we did observe a positive non-significant association between STDs and prostate cancer when adjusting to urethritis and purulent liquid discharge and the risk increased as well when testing with low-grade prostate cancer. Since there was negative association between NSAIDS and prostate cancer and it is known to decrease inflammation, we stratified on it in order to observe the real association between infections and prostate cancer. However, the association between sexually transmitted infections and prostate cancer among non-users and NSAIDS was insignificant. In addition, after adjusting to urethritis the association between sexually transmitted infections and prostate cancer was insignificantly increased 1.05 (95% CI: 0.21-5.38) and for low grade cancer as well 1.48 (95% CI: 0.27-8.03). Therefore, we decided to stratify on urethritis where we observed a positive significant association between sexually transmitted infections and low-grade cancer 4.92 (95% CI: 1.08-22.3) as well as with gonorrhea alone 4.74 (95% CI:1.08-20.73) among those who had a history of urethritis.

4.2. Comparison with the literature

For the past decades risk factors for prostate cancer have been extensively studied and yet very few definite associations have been identified. In fact, there was wide variety of studies done on sexually transmitted infections. Based on a meta-analysis done by Caini et al. our null findings for sexually transmitted infections and its association with prostate cancer was consistent with results of ten previous studies but differs from other six previous studies (figure 9). In addition, the SRR from this pooled analysis showed that any STI had a significantly increased prostate cancer risk (SRR 1.49, 95% CI 1.19-1.92)[50].

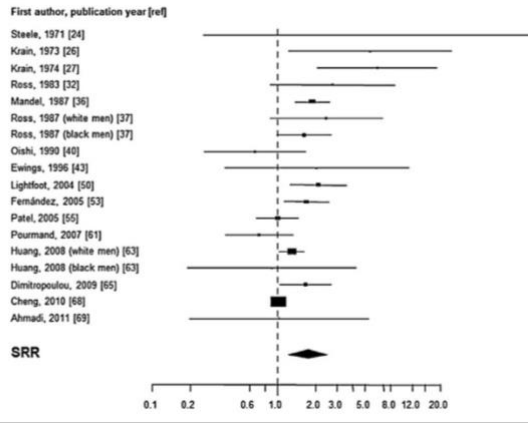


Figure 9 Forest plot of sexually transmitted infections amd prostate cancer risk[50]

4.2.1. Gonorrhea and prostate cancer

Quite a few studies that were done on prostate cancer and STDs focused particularly on gonorrhea infection. In fact, there are two meta-analysis that focused mainly on gonorrhea and our null findings were consistent with nine studies from Taylor et al. done between 1975 and 2001, and 18 studies from Caini et al. done between 1971 and 2011. However, the SRR for both meta-analyses were significant for gonorrhea (SRR 1.39 95% CI 1.05-1.83) and (SRR 1.20, 95% CI 1.05-1.37) respectively (figure 10) [50,51].

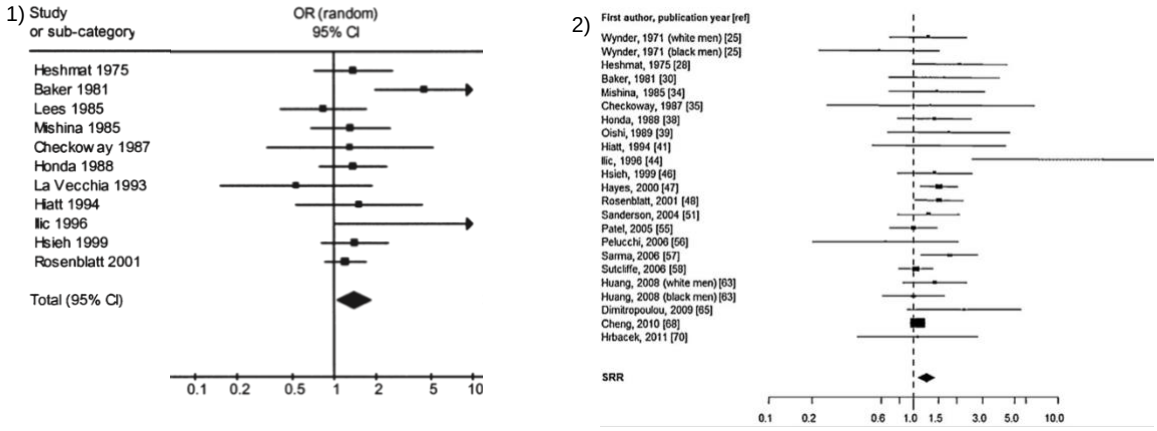


Figure 10 Forest plot of Gonorrhea and prostate cancer from Taylor et al. (1) and Caini et al. (2)[50,51].

4.2.2. Trichomonas and prostate cancer

To our knowledge very few studies were done on this type of infection. The findings of a study done by Tsang et al. showed no association between Trichomonas and prostate cancer[52]. Another study done by Marous et al. also showed no association between trichomonas infection and prostate cancer OR :0.97 95% CI (0.73-1.27), or for low grade cancer OR:1.02 95% CI (0.73-1.42), or for high-grade cancer 0.88 95% CI (0.59-1.30)[53]. In addition, a study done by Sutcliffe et al. showed that even if subjects had high seropositive for trichomonas the odds ratio of prostate cancer was non-significant OR 0.97 95% CI (0.70-1.34)[46]. All these

studies were quite in line with our null findings for trichomonas and its association with prostate cancer.

4.2.3. Syphilis and prostate cancer

Syphilis and its association with prostate cancer has been the focus of many studies for the past decades. The meta-analysis done by Taylor et al. shows that our results of syphilis are consistent with all the studies except the one done by Hayes 2000 where they all show no association with prostate cancer. As for the meta-analysis done by Caini et al fourteen studies were consistent with our results of syphilis whereas only three were not. On the other hand, both SRR 1.42 (0.67 – 2.64) and 1.27 (0.85-1.89) were not statistically significant suggesting that syphilis is not associated with an increased risk of prostate cancer (Figure 11)[50,51].

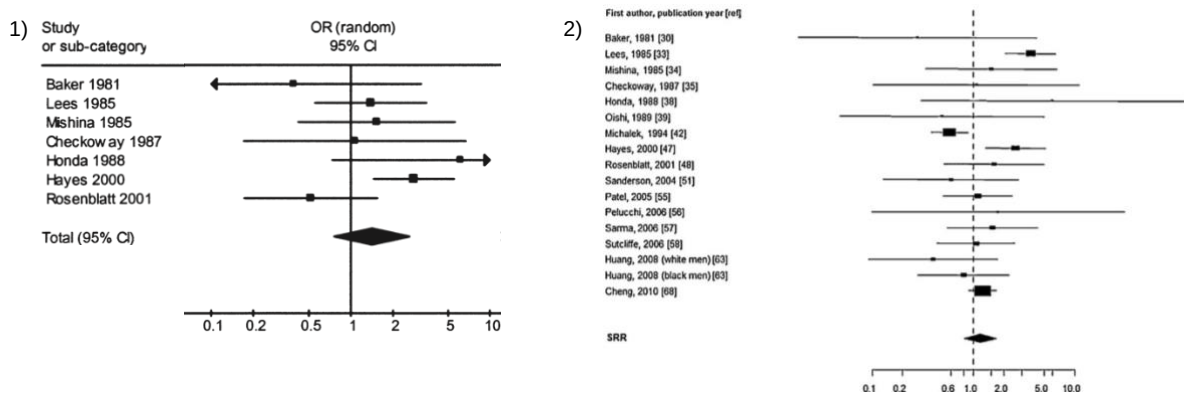


Figure 11 Forest Plot of Syphilis and prostate cancer from Taylor et al. (1) and Caini et al. (2) [50,51]

4.3. Biases

4.3.1. Selection Bias

EPICAP study is a large population-based case-control study that was carried out in the department of Hérault in a well-defined geographical area designed to assess the role of environmental and genetic factors of prostate cancer. The overall participation rate in the EPICAP study was 77% which is generally a good rate.

4.3.1.1. Cases

Case identification was done in all private and public cancer hospitals in the department of Hérault. In 2012, the cancer registry observed around 1,300 cases of prostate cancer. Considering the number of cases observed were similar during the study period, around 1,150 new cases were expected in men aged less than 75 years. The recruitment of cases was quite exhaustive since the identified eligible cases were 1,098 over the study period, thus limiting the potential of having selection bias. Even though participation rate in cases was 75%, the age distribution and the Gleason score were comparable to those of the Hérault Cancer

Registry, which means cases were representative of all eligible cases. Finally, in order to limit bias regarding survival the interviews were carried out right after identification where only 8 (0.7%) eligible cases died.

4.3.1.2. Controls

Controls were selected from the general population in the department of Hérault using quotas defined by age and socioeconomic status (SES). In fact, the age distribution of the controls reflects the age distribution of the cases. In order to avoid selection bias, the SES distribution of the control group reflects the SES distribution of the entire département of Hérault to yield a control group similar to the general population of men of the same age in terms of SES.

4.3.2. Classification Bias

It is very difficult to rule entirely recall bias when the collection method of the study is based on self-declaration of the exposure which might lead to differential classification bias. However, in the EPICAP study data collection was standardized and carried out identically in both cases and controls, and several questions regarding the variables of interest were also formulated differently multiple times allowing cross-referencing and thus limiting classification bias. An argument that may minimize classification bias is the prevalence of controls in gonorrhea which is 7.7% in the EPICAP and in the population of France it was quite comparable because among men aged greater than 45 the prevalence is around 6%[54,55].There were no accurate comparisons with the data from the literature regarding trichomonas and syphilis. Finally, there were no medical or biological data to confirm the presence of the bacterial infections present.

4.3.3. Confounding Bias

In our study most of the suspected confounding variables were not related to the outcome and subjects were very comparable among both cases and controls. There are several variables that were related to the outcomes or to the variables of interest. Therefore, in order to limit confounding bias, statistical adjustment was done to all the suspected variables, and well-established risk factors for prostate cancer were also taken into account in all the models. However, even after adjusting to these variables the results did not change and remained the same.

4.3.4. Power of the Study

Our study population has 819 cases and 879 controls. The size of the study will enable the detection of minimum odds ratios of 1.5 and 1.7 for exposure whose prevalence in controls are 5 and 10%, respectively, with a power of 80%, and a type-I error of 5%. Based on literature, prevalence of Gonorrhea is around 8% and close to 10% for STD and the

association observed of OR ranging from 1.2 to 2.0, thus the EPICAP study has enough power regarding overall cancer. However, we probably lacked power for analysis involving exposures with lower prevalence or during subgroup analysis when taking into account aggressiveness of cancer and stratification.

5. CONCLUSION & PERSPECTIVES

In this population-based case-control study that is done particularly in France (EPICAP), no association was observed between any sexually transmitted infections (gonorrhea, trichomonas, and syphilis) and prostate cancer in all its grades. None of the observed associations were altered by adjustments to well-established risk factors, other infections, and potential confounders. No association between sexually transmitted infections and all grades of prostate cancer was observed when stratifying on non-steroidal anti-inflammatory drugs. On the other hand, when stratifying on urethritis we did observe a positive significant association among low grade cancer men in the presence of urethritis.

Prostate cancer remains the second most common type of cancer among men worldwide with a rising trend. Despite the extensive research that has been done over the past decades regarding potential risk factors for prostate cancer, age, ethnicity, and history of prostate cancer remain the only non-modifiable risk factors to this day. We are yet to unravel recognized causal factors for prostate cancer. Therefore, additional studies and further investigations are warranted to help establish the role of STIs in the etiology of prostate cancer with a particular focus on the most aggressive types. On the other hand, it is interesting to focus further on whether multiple episodes of a certain infection, as well as time and duration as to when the infection happened on the risk of prostate cancer.

Beyond this subject from the EPICAP study, further research on the role of other types of infections both sexually and non-sexually transmittable whether viral or bacterial and the development of prostate cancer are yet to be performed in order to fully understand the relationship of infections with prostate cancer. Another avenue of research would also be studying the role of renal diseases in the occurrence of prostate cancer.

An interesting future approach would also be the study of polymorphisms in genes involved in the immune response to infections and inflammation.

In summary, it is extremely necessary to keep on investigating into possible risk factors to help advance our understanding of the etiology of prostate cancer to build adequate strategies to limit its occurrence.

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Annexes

Annex 1

Questionnaire on Sexually Transmitted Infections

BLOC I - INFECTION SEXUELLEMENT TRANSMISSIBLE

A tous
I1. Un médecin vous a-t-il déjà diagnostiqué une ou plusieurs infections à Gonorrhée ?
Oui, une1
Oui, plusieurs2
Non3
NSP4

Si I1=1
I3a. En quelle année où à quel âge, avez-vous eu cette infection à Gonorrhée ?
1. Saisie âge : I3a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I3a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I3a = NSP
I3Ab. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

Si I1=2
I3B. En quelle année où à quel âge, avez-vous eu votre <u>première</u> infection à Gonorrhée ?
1. Saisie âge : I3b.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I3b.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I3B = NSP
I3Bb. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE
ENQ : CITER

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

Si I1=2
I3C. En quelle année où à quel âge, avez-vous eu votre <u>dernière</u> infection à Gonorrhée ?
1. Saisie âge : I3c.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I3c.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I3C = NSP
I3Cb. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

A tous
I4. Un médecin vous a-t-il déjà diagnostiqué une ou plusieurs infections à Trichomonas ?
Oui, une1
Oui, plusieurs2
Non3
NSP4

Si I4=1
I5a. En quelle année où à quel âge, avez-vous eu cette infection à Trichomonas ?
1. Saisie âge : I5a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I5a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I5 = NSP
I5ab. Vous diriez que vous aviez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

Si I4=2
I6a. En quelle année où à quel âge, avez-vous eu votre <u>première</u> infection à Trichomonas ?
1. Saisie âge : I6a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I6a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I6a = NSP
I6ab. Vous diriez que vous aviez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

Si I4=2
I6b. En quelle année où à quel âge, avez-vous eu votre <u>dernière</u> infection à Trichomonas ?
1. Saisie âge : I6b.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I6b.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I6C = NSP
I6bb. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2

Entre 40 et 49 ans 3
Entre 50 et 59 ans 4
Entre 60 et 69 ans 5
70 ans ou plus 6

A tous
I7. Avez-vous déjà eu la Syphilis ?
Oui1
Non2
NSP3

Si I7=1
I8. A-t-elle été diagnostiquée par un médecin ?
Oui1
Non2
NSP3

Si I7=1
I9a. En quelle année où à quel âge, avez-vous eu la Syphilis ?
1. Saisie âge : I9a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I9a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I9 = NSP
I9b. Vous diriez que vous avez …?
UNE SEULE REPONSE POSSIBLE
Moins de 30 ans 1
Entre 30 et 39 ans 2
Entre 40 et 49 ans 3
Entre 50 et 59 ans 4
Entre 60 et 69 ans 5
70 ans ou plus 6

Si (I1=3 ou NSP) et (I4=3 ou NSP) et (I7=NON ou NSP)
I10. Avez-vous déjà consulté un médecin pour un écoulement par l'orifice urinaire d'un liquide épais ?
Oui1
Non2
NSP3

Si I10=1
I11. Quel était son diagnostic ?
ENQ : SI NSP, CITER
ENQ : PLUSIEURS REPONSES POSSIBLES
PLUSIEURS REPONSES POSSIBLES
1. infection à gonorrhée
2. infection à chlamydiae
3. infection à trichomonas
4. infection à mycoplasme
5. infection urinaire
6. NSP
7. Autre 1 (préciser)
8. Autre 2 (préciser)

Pour chaque item de réponses donnés en I11, poser I12, I12C
I12a. En quelle année où à quel âge avez-vous été consulté pour *afficher I11*
1. Saisie âge : I12a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I12a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp

4. Refus

Si I12a = NSP
I12b. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6

Si (I1=3 ou NSP) ou (I4=3 ou NSP) ou (I7=2ou NSP)
I13. Avez-vous déjà fait une urétrite ?
ENQ : Citer
Oui une1
Oui plusieurs2
Non3
NSP4

Si I13=1o2
I14. A-t-elle été diagnostiquée par un médecin ?
Enq : Citer
Oui1
Non2
NSP3

Si I14=1
I15. Quelle était la cause si I13=1, de votre urétrite ? / Si I13=2 « de votre <u>première</u> urétrite)?
Infection sexuellement transmissible1
Urétrite à gonocoque2
Urétrite à chlamydiae trachomatis3
Urétrite à ureaplasma urealyticum4
Autres5
NSP6

Si I14=1~~o2~~
I16. En quelle année où à quel âge vous a-t-on diagnostiqué (si I13=1) « cette urétrite » si (I13=2) « votre première urétrite »?
1. Saisie âge : I16a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I16a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I16 = NSP
I16B. Vous diriez que vous aviez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6
NSP	
Refus	

Si I14=1 and I13=2
I16C. En quelle année où à quel âge vous a-t-on diagnostiqué votre <u>dernière</u> urétrite?

1. Saisie âge : I16c.1 : Age:____\ AN Refus : 97 et NSP : 99

2. Saisie année : I16c.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I16C = NSP
I16D. Vous diriez que vous aviez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6
NSP	
Refus	

Si (I1=3 ou NSP) et (I4=3 ou NSP) et (I7=3 ou NSP)
I17. Un médecin vous a-t-il déjà diagnostiqué une infection ou une maladie de type « sexuellement transmissible »?
Oui1
Non2
NSP3

Si I17=1
I18a. En quelle année où à quel âge vous a-t-on diagnostiqué cette infection?
1. Saisie âge : I18a.1 : Age:____\ AN Refus : 97 et NSP : 99
2. Saisie année : I18a.2: Année ________\ Refus : 9997 et NSp : 9999
3. Nsp
4. Refus

Si I18 = NSP
I18b. Vous diriez que vous avez … ?
UNE SEULE REPONSE POSSIBLE

Moins de 30 ans	1
Entre 30 et 39 ans	2
Entre 40 et 49 ans	3
Entre 50 et 59 ans	4
Entre 60 et 69 ans	5
70 ans ou plus	6
NSP	
Refus	

Annex 2

Adjusting to all potential confounders and risk factors

Table 1: STD3, STD5, STDG adjusted on risk factors and all confounding variables

	Controls	*Cases*					
		All		**Low & Intermediate**		**Aggressive**	
Variables	**n=879 (%)**	**n=819 (%)**	**OR* (95% CI)**	**n=624 (%)**	**OR* (95% CI)**	**n=183 (%)**	**OR* (95% CI)**
STD3*							
No	791 (90.7)	747 (92.1)	1.00 *reference*	565 (91.7)	1.00 *reference*	170 (93.4)	1.00 *reference*
Yes	81 (9.3)	64 (7.9)	0.85 (0.59– 1.21)	51 (8.3)	0.84 (0.57-1.24)	12 (6.6)	0.81 (0.43-1.55)
STD5*							
No	749 (86.3)	706 (87.0)	1.00 *reference*	539 (86.9)	1.00 *reference*	156 (87.2)	1.00 *reference*
Yes	119 (13.7)	106 (13.0)	0.93 (0.69– 1.25)	81 (13.1)	0.88 (0.64-1.22)	23 (12.9)	1.04 (0.63-1.71)
STDG*							
No	749 (86.3)	706 (87.0)	1.00 *reference*	539 (86.9)	1.00 *reference*	156 (87.2)	1.00 *reference*
Yes, 1	98 (11.3)	84 (10.3)	0.89 (0.64– 1.23)	64 (10.3)	0.85 (0.60-1.21)	18 (10.1)	0.99 (0.57-1.71)
Yes, ≥ *2*	21 (2.4)	22 (2.7)	1.10 (0.58-2.07)	17 (2.8)	1.04 (0.53-2.05)	5 (2.8)	1.29 (0.46-3.62)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer, diploma, waist circumference, alcohol, smoking, physical activity, NSAIDs, prostatitis

*STD3 (gonorrhea, trichomonas, and syphilis), STD & STDG (gonorrhea, trichomonas, syphilis, urethritis, and purulent discharge).

Table 2: Model (STD3, Purulent discharge, urethritis) was adjusted on risk factors and all confounding variables

	Controls	*Cases*					
		All		**Low & Intermediate**		**Aggressive**	
STD3							
No	791 (90.7)	747 (92.1)	1.00 *reference*	565 (91.7)	1.00 *reference*	170 (93.4)	1.00 *reference*
Yes	81 (9.3)	64 (7.9)	1.05 (0.21– 5.38)	51 (8.3)	1.48 (0.27-8.03)	12 (6.6)	<0.001 (<0.001->999)
Purulent discharge							
No	772 (96.4)	722 (95.1)	1.00 *reference*	547 (95.0)	1.00 *reference*	163 (95.3)	1.00 *reference*
Yes	29 (3.6)	37 (4.9)	1.26 (0.69-2.28)	29 (5.0)	1.22 (0.64 – 2.35)	8 (4.7)	1.69 (0.71-4.02)
Urethritis							
No	836(97.0)	786 (96.8)	1.00 *reference*	601 (96.9)	1.00 *reference*	173 (96.6)	1.00 *Reference*
Yes	26 (3.0)	26 (3.2)	0.73 (0.32– 1.70)	19(3.1)	0.47 (0.17-1.31)	6 (3.4)	1.11 (0.34 – 3.68)

*Adjusted on Age, Ethnicity, and Family History of Prostate Cancer, diploma, waist circumference, alcohol, smoking, physical activity, NSAIDs, prostatitis