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Melissa Sawaya

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Chronic Inflammation and The Risk of Prostate Cancer: Role of Infections, Calculi, COX-2 gene and their GxE Interaction

Inflammation Chronique et Risque de Cancer de la Prostate : Rôle des Infections, des Calculs, du Gène COX-2 et de leurs Interactions GxE

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LIST OF ABBREVIATIONS

Acronyms	Definition
AI	Artificial Intelligence
ASR	Age Standardized Rate
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
CAPI	Computer Assisted Personal Interview
CC	Case Control
CMV	Cytomegalovirus
Cox-2	Cyclooxygenase 2
CPS-II	Cancer Prevention Study II
CRP	C-Reactive Protein
CT	Computed Tomography
CYP2E1	Enzyme Cytochrome P450 2E1
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
EA	Effect Allele
EAF	Effect Allele Frequency
EBV	Epstein-Barr Virus
EPICAP	Epidemiological study of prostate cancer
FDR	False Discovery Rate
G x E	Gene Environment Interaction
GWAS	Genome-wide Association Studies
HBV	Hepatitis B-virus
HCC	Hospital Based Case Control
HCV	Hepatitis C-virus
HDL	High Density Lipoprotein
HHV	Human Herpes Virus
HPFS	Health Professionals Follow-up Study
HPV	Human Papilloma virus
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IARC	The International Agency for Research on Cancer
IBS	Identity by State
IGF-1	Insulin-like Growth Factor-1
IL-6	Interleukin-6
INSEE	National Institute of Statistics and Economics Studies
IPSOS	French Polling Institute
ISUP	The International Society of Urological Pathology
LUTS	Lower Urinary Tract Symptoms
MAF	Minor Allele Frequency
MDSC	Myeloid Derived Suppressor Cells
MetS	Metabolic Syndrome

MRI	Magnetic Resonance Imaging
NCC	Nested Case Control
NCHGR	National Center for Human Genome Research
NF-κB	Factor Kappa B
NHL	Non-Hodgkin Lymphoma
NSAIDS	Non-steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PAHs	Polycyclic Aromatic Hydrocarbons
PC	Prostate Cancer
PCA	Principle Component Analysis
PCC	Population Based Case Control
PET-CT	Positron Emission Tomography Computed Tomography
PIA	Proliferative Inflammatory Atrophy
PIN	Prostatic Intraepithelial Neoplasia
PRS	Polygenic Risk Scores
PSA	Prostate Specific Antigen
PSA	Prostate Specific Antigen
PTGS2	Prostaglandin-endoperoxide Synthase 2
RA	Reference Allele
RCC	Renal Cell Carcinoma
RCS	Retrospective Cohort Study
ROS	Reactive Oxygen Species
RR	Relative Risk
SES	Socioeconomic Status
SHBG	Sex Hormone-binding Globulin
SIR	Standardized Incidence Ratio
SNPs	Single Nucleotide Polymorphism
SRR	Standardized Relative Risk
STAT3	Signal Transducer and Activator of Transcription
STIs	Sexually Transmitted Infections
TLRs	Toll-like Receptors
TNF-α	Tumor Necrosis Factor-alpha
TNM	Primary Tumor, Lymph Nodes, Metastasis
UTUC	Upper Tract Urothelial Carcinoma
VZV	Varicella-Zoster Virus
WC	Waist Circumference
WHR	Waist-Hip Ratio

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Résumé Substantiel

Introduction

Le cancer de la prostate est un enjeu majeur de santé publique à l'échelle mondiale, se classant au deuxième rang des cancers les plus fréquents chez les hommes. Selon les données de GLOBOCAN, environ 1,4 million de nouveaux cas ont été diagnostiqués dans le monde en 2022, représentant 15,3 % de tous les cancers masculins (à l'exclusion des cancers de la peau autres que le mélanome) [19].

Le taux d'incidence standardisé selon l'âge était de 29,4 pour 100 000 individus. Les taux d'incidence varient considérablement selon les régions, avec les taux les plus élevés observés en Europe du Nord (82,8 pour 100 000) et les plus bas en Afrique du Nord (16,1 pour 100 000) et en Asie du Sud-Est (12,7 pour 100 000). En France, spécifiquement, 57 357 nouveaux cas ont été rapportés en 2022, représentant 21,8 % de tous les cas de cancers masculins. Le taux d'incidence standardisé selon l'âge en France était de 82,3 pour 100 000, avec une incidence passant de 6,5 pour 100 000 chez les hommes de moins de 54 ans à 689,5 pour 100 000 chez les hommes de 65 ans et plus [19].

À l'échelle mondiale, le cancer de la prostate a causé 397 430 décès en 2022, avec un taux d'incidence standardisé selon l'âge de 7,3 pour 100 000. Les taux de mortalité montrent une variation régionale significative, avec les taux les plus élevés en Afrique australe (29,7 pour 100 000) et en Afrique centrale (27,2 pour 100 000), tandis que les taux en Asie sont généralement inférieurs à 5 pour 100 000 (sauf en Asie de l'Ouest). En France, 9 264 décès ont été enregistrés en 2022, représentant 4,9 % de tous les décès par cancer chez les hommes, avec un taux d'incidence standardisé de 8,2 pour 100 000 [19–21].

Malgré une forte morbidité et mortalité associées au cancer de la prostate, l'étiologie de ce cancer demeure largement inconnue. Les seuls facteurs de risque bien établis sont l'âge avancé, l'origine ethnique et les antécédents familiaux de cancer de la prostate et sont des facteurs non-modifiables. Cependant, des études menées sur les migrants montrent que les hommes asiatiques vivant aux États-Unis présentent un taux d'incidence de cancer de la prostate bien plus élevé que ceux vivant dans leur pays d'origine, suggérant ainsi le rôle des facteurs de mode de vie et environnementaux [29].

L'inflammation chronique est de plus en plus reconnue pouvant jouer un rôle dans le développement des cancers, y compris le cancer de la prostate. L'inflammation chronique

représenterait environ 20 % de toutes les carcinogenèses humaines et peut durer des semaines, des mois, voire des années, contrairement à l'inflammation aiguë [76, 83–85]. Elle peut perturber le fonctionnement normal du système immunitaire et augmenter la susceptibilité à diverses affections. Le lien entre l'inflammation chronique et le cancer repose sur deux mécanismes : le mécanisme intrinsèque, déclenché par des événements génétiques conduisant à la néoplasie, et le mécanisme extrinsèque, influencé par des conditions inflammatoires ou infectieuses [75, 80–82]. En fait, les infiltrats inflammatoires situés près des zones d'atrophie inflammatoire proliférative (AIP) et des néoplasies intraépithéliales prostatiques (PIN), considérées comme des lésions précancéreuses de la prostate, renforcent l'hypothèse d'un lien possible entre l'inflammation chronique et le cancer de la prostate [76].

Bien que la cause de l'inflammation prostatique demeure incertaine, plusieurs facteurs liés à l'inflammation pourraient être des agents potentiels contribuant à l'apparition du cancer de la prostate. Les causes potentielles d'inflammation prostatique incluent les infections, les fluctuations hormonales, le reflux urinaire, les habitudes alimentaires et la prédisposition génétique [84]. Des agents infectieux, tels que des bactéries et des virus, ont été identifiés comme infectant la prostate et provoquant une réponse inflammatoire, ce qui pourrait contribuer au développement du cancer de la prostate [76]. La recherche a étudié divers agents infectieux en relation avec le risque de cancer de la prostate, y compris les infections sexuellement transmissibles (IST) comme la gonorrhée, la chlamydia et l'herpès, ainsi que les infections non sexuellement transmissibles telles que la prostatite. Cependant, les résultats restent contradictoires, et peu d'études ont pris en compte l'agressivité du cancer.

La lithiase urinaire implique la formation de dépôts minéraux dans les voies urinaires et est une affection courante, souvent récurrente, affectant 7 à 10 % de la population [236]. Bien que des études suggèrent un lien potentiel entre les calculs urinaires et un risque accru de cancers des voies urinaires, le lien avec les cancers systémiques, y compris le cancer de la prostate, reste incertain et peu étudié.

Les calculs biliaires sont des dépôts solidifiés qui peuvent différer en taille et en composition, souvent composés de cholestérol, de bilirubine, de sels de calcium et d'autres matériaux [245, 246]. Environ 10 à 15 % des adultes sont concernés par ces calculs [124]. Une méta-analyse récente a analysé sept études explorant l'association entre les calculs biliaires et le cancer de la prostate, trouvant des associations notables soutenant un lien potentiel avec le cancer de la prostate. Cependant, aucune de ces études n'a étudié l'agressivité du cancer [133].

Les facteurs génétiques inflammatoires liés à l'inflammation sont essentiels dans la régulation de la réponse immunitaire et peuvent influencer le risque de maladies par leur rôle dans l'inflammation [135–137]. Les polymorphismes mononucléotidiques (SNPs) dans les gènes liés à l'inflammation peuvent altérer la fonction des protéines impliquées dans l'inflammation, influençant ainsi la susceptibilité au cancer [136, 138, 139]. Par exemple, des SNPs dans des gènes tels que COX-2, TNF α , et IL1RN ont été associés à un risque accru de cancer de la prostate [142, 143]. COX-2, une enzyme impliquée dans l'inflammation, est souvent surexprimée dans le cancer de la prostate et est associée à la progression de la maladie [145–147]. Des études ont montré que les SNPs de COX-2 peuvent modifier le risque de cancer de la prostate, en particulier lorsqu'ils interagissent avec des facteurs environnementaux tels que l'utilisation d'AINS. Par exemple, le SNP rs2745557 de COX-2 est lié à un risque réduit de cancer de la prostate avec l'utilisation d'AINS, soulignant l'importance des facteurs génétiques et environnementaux dans le risque de maladie [151]. Cependant, les recherches dans ce domaine sont limitées et contradictoires, avec un accent minimal sur l'agressivité des différents types de cancer.

Bien que des progrès aient été réalisés dans la recherche, de nombreux aspects de la relation entre l'inflammation chronique et le cancer de la prostate restent encore mal connus définis. Par conséquent, cette thèse est d'étudier le rôle de l'inflammation chronique et des facteurs associés dans la survenue du cancer de la prostate, en mettant particulièrement l'accent sur ses formes agressives, à partir des données de l'étude cas-témoins EPICAP (Epidémiologie des Cancers de la Prostate) menée en France.

Dans ce contexte, les trois objectifs spécifiques de cette thèse sont les suivants :

1. Analyser le rôle des agents infectieux, qu'ils soient bactériens ou viraux, et qu'ils concernent des infections sexuellement transmissibles ou non, dans la survenue du cancer de la prostate.
2. Examiner l'influence des calculs rénaux et des calculs biliaires sur la survenue du cancer de la prostate.
3. Étudier les polymorphismes mononucléotidiques (SNPs) de COX-2, ainsi que l'interaction (GxE) de ces SNPs avec les variables d'intérêt, telles que les infections et les calculs, dans la survenue du cancer de la prostate.

Matériels et Méthodes

L'étude EPICAP a été conçue pour explorer l'étiologie du cancer de la prostate en étudiant les facteurs environnementaux, les facteurs génétiques et leurs interactions. Les objectifs scientifiques principaux de cette étude étaient d'étudier comment l'inflammation chronique, les facteurs hormonaux et métaboliques, la perturbation circadienne, les expositions professionnelles, et les prédispositions génétiques contribuent à la survenue du cancer de la prostate, avec un intérêt particulier pour les cancers agressifs.

EPICAP est une étude cas-témoins réalisée en population générale et menée dans le département de l'Hérault, dans le sud de la France.

Les cas éligibles étaient des hommes nouvellement diagnostiqués avec un cancer de la prostate entre 2012 et 2013, âgés de moins de 75 ans au moment du diagnostic, et résidant dans le département de l'Hérault. L'identification des cas a été réalisée par des infirmières de recherche clinique, spécialement recrutées et formées pour l'étude, dans tous les centres participants, comprenant trois hôpitaux publics et trois cliniques privées d'urologie. Le registre a été utilisé pour la validation a posteriori des cas inclus dans l'étude EPICAP. De plus, les patients n'ont été inclus dans l'étude qu'après avoir donné leur consentement, et seuls les cas confirmés histologiquement ont été considérés.

Les témoins ont été sélectionnés aléatoirement parmi la population masculine générale sans antécédents de cancer et résidant dans le département de l'Hérault au moment du diagnostic des cas. Afin d'obtenir une correspondance en fréquence et d'assurer une similarité dans la distribution des âges entre les cas et les témoins, des quotas basés sur l'âge ont été établis par tranches de 5 ans. De plus, des quotas basés sur le statut socio-économique (SES) ont été définis a priori pour contrôler le biais de sélection lié aux taux de participation différent selon les catégories SES. Les quotas basés sur le SES ont été déterminés en utilisant les données de recensement spécifiques à chaque zone d'étude fournies par l'Institut National de la Statistique et des Études Économiques (INSEE). L'objectif était d'obtenir une distribution du SES parmi les témoins qui corresponde de près à la distribution du SES parmi les hommes de la population générale tout en tenant compte de l'âge.

Parmi les 1 098 cas de cancer de la prostate éligibles identifiés et les 1 109 témoins éligibles identifiés dans l'étude EPICAP, 819 cas et 879 témoins ont été inclus au total, avec des taux de participation respectifs de 75 % et 79 %.

Les participants ont été interrogés en face à face par une infirmière de recherche clinique dûment formée, avec des procédures identiques appliquées aux deux groupes. Les entretiens se sont déroulés au domicile des participants, et les données recueillies comprenaient des réponses à des questionnaires, des mesures anthropométriques et des échantillons biologiques. Les participants avaient la possibilité de fournir un échantillon de sang, avec un échantillon de salive proposé comme alternative en cas d'impossibilité ou de refus de prélèvement sanguin.

L'interrogatoire des cas et des témoins était réalisé à l'aide d'un questionnaire standardisé sur système CAPI (Computer Assisted Personal Interview), méthode de recueil sur micro-ordinateur qui durait en moyenne deux heures. Ce questionnaire recueillait des informations détaillées sur les caractéristiques sociodémographiques, l'historique professionnel et résidentiel, le mode de vie, les antécédents médicaux personnels et familiaux et l'origine ethnique. Les facteurs environnementaux tels que les détails sur les lieux de résidence, l'utilisation du tabac et de l'alcool, les habitudes de sommeil, les activités de loisirs et l'activité physique ont été enregistrés. Le questionnaire couvrait également les antécédents familiaux de cancer chez les parents au premier et au deuxième degré, y compris l'occurrence, le lieu et l'âge de survenue. De plus, des informations sur les facteurs infectieux et inflammatoires ont été collectées, en se concentrant sur les antécédents d'hospitalisation, les chirurgies, les maladies infectieuses (sexuellement et non sexuellement transmissibles), les conditions inflammatoires (calculs rénaux et biliaires) et les antécédents médicamenteux, y compris les anti-inflammatoires non stéroïdiens.

Les mesures anthropométriques, comprenant le poids, la taille, le périmètre abdominal et le tour de hanche, ont été réalisées par les infirmières pour compléter les données du questionnaire. Des échantillons biologiques, soit de sang soit de salive, ont été prélevés pour établir une banque de l'ADN conservée au Centre de Ressources Biologiques (CRB Epigenetec) à Paris. Au total, 1 626 participants, dont 794 cas et 832 témoins, ont fourni des échantillons biologiques, avec une extraction suffisante d'ADN pour 1 565 sujets.

Les données cliniques des cas ont été obtenues à partir des dossiers médicaux ou du registre des cancers de l'Hérault, comprenant des détails tels que la valeur initiale du PSA, le score de Gleason, les stades TNM et les informations sur les traitements.

Nous avons analysé 12 types distincts d'infections, y compris les infections bactériennes comme la gonorrhée, la syphilis et le trichomonas, ainsi que les infections virales telles que l'herpès, Epstein-Barr et l'hépatite virale. Chaque infection a été classée comme une variable binaire, indiquant si le participant avait un antécédent de l'infection avant la date de référence – la date

de diagnostic pour les cas et la date de l'entretien pour les témoins. En plus des infections individuelles, nous avons créé des variables combinées pour examiner des catégories plus larges, telles que les infections bactériennes sexuellement transmissibles, les infections virales et les infections globales. Ces variables combinées nous ont permis d'explorer l'effet cumulatif potentiel de plusieurs infections sur le risque de cancer de la prostate.

De même, nous avons étudié la présence de calculs rénaux et de calculs biliaires, les considérant comme des variables binaires pour indiquer si un participant avait connu un épisode avant la date de référence. Nous avons également créé des variables combinées pour évaluer l'impact des calculs rénaux en conjonction avec des conditions telles que la prostatite et la pyélonéphrite, connues pour provoquer une inflammation dans le système génito-urinaire et associées au cancer de la prostate. En catégorisant ces conditions en différents niveaux, nous avons pu évaluer l'impact combiné de ces comorbidités sur le risque de cancer de la prostate.

Notre analyse statistique a été réalisée à l'aide du logiciel SAS® version 9.4. Nous avons commencé par une analyse descriptive pour comparer les facteurs sociodémographiques, les facteurs de mode de vie et les antécédents médicaux entre les cas et les témoins. Toutes les variables ont été représentées qualitativement à l'aide de fréquences et de pourcentages. Nous avons utilisé le test du chi-square pour comparer ces caractéristiques et identifier les facteurs potentiellement associés aux infections et aux conditions liées aux calculs.

Nous avons utilisé des modèles de régression logistique non conditionnelle pour étudier l'association entre les infections spécifiques, les calculs et le cancer de la prostate, en calculant des Odds Ratio (OR) et des intervalles de confiance à 95 %. Le groupe de référence pour chaque analyse était composé d'hommes sans antécédents de la condition étudiée. De plus, nous avons utilisé des modèles de régression logistique multinomiale pour explorer la relation entre ces conditions de santé et l'agressivité du cancer de la prostate, telle que déterminée par le score de Gleason au diagnostic.

Dans nos modèles, nous avons systématiquement ajusté sur les facteurs de risque établis du cancer de la prostate – âge, ethnie et antécédents familiaux – et ajusté davantage pour d'autres facteurs de confusion potentiels tels que l'activité physique, la circonférence de taille, l'éducation et l'utilisation d'anti-inflammatoires non stéroïdiens (AINS).

Nous avons réalisé une analyse d'interaction pour explorer si l'hypertriglycéridémie, un facteur de risque connu du syndrome métabolique, modifiait la relation entre les calculs rénaux, les calculs biliaires et le risque de cancer de la prostate. En stratifiant notre analyse en fonction du

statut d'hypertriglycéridémie, nous avons cherché à déterminer si des niveaux élevés de triglycérides influençaient l'association entre ces conditions et le cancer de la prostate.

Pour assurer la fiabilité de nos résultats, nous avons effectué plusieurs analyses de sensibilité.

Tout d'abord, nous avons limité le groupe de témoins aux individus ayant subi un dépistage du cancer de la prostate dans les deux années précédant la date de référence, réduisant ainsi la probabilité d'inclure des cas de cancer de la prostate non diagnostiqués ou latents parmi les témoins. Nous avons affiné cette analyse en incluant uniquement les témoins avec des résultats normaux au dépistage. De plus, nous avons stratifié le groupe de témoins en fonction de la fréquence des tests de PSA, en les divisant en groupes en fonction du nombre de tests de PSA réalisés.

Concernant les facteurs génétiques liés à l'inflammation, nous avons étudié comment les polymorphismes mono nucléotidiques (SNPs) associés à l'inflammation dans le gène COX-2 situé sur le chromosome 1 influencent le risque de cancer de la prostate.

Pour garantir la qualité des données génétiques, plusieurs étapes ont été mises en œuvre. Nous avons d'abord éliminé les échantillons en double et vérifié la concordance des sexes. Nous avons également exclu les individus ayant plus de 5 % de données de génotype manquantes. Ensuite, nous avons utilisé une Analyse en Composantes Principales (PCA) pour confirmer que les participants étaient d'ascendance européenne. En combinant ces différentes étapes, nous avons finalement retenu 1 515 participants (732 cas et 783 témoins) pour l'analyse. Concernant les SNPs, nous avons mis en œuvre plusieurs mesures de contrôle de qualité supplémentaires. Nous avons exclu les SNPs avec un taux de données manquantes supérieur à 5 %, supprimé ceux qui déviaient significativement de l'équilibre de Hardy-Weinberg, ainsi que les SNPs redondants et ceux avec une fréquence allélique mineure (MAF) de zéro. Après ces étapes, nous avons retenu 20 SNPs du gène COX-2 avec une MAF supérieure à 1 % pour l'analyse.

L'analyse statistique a été réalisée à l'aide du logiciel R (version 4.3.3). Nous avons d'abord décrit les caractéristiques sociodémographiques et les modes de vie des cas et des témoins, et comparé ces facteurs en utilisant des tests du chi-square. Pour évaluer l'association entre les SNPs et le risque de cancer de la prostate, nous avons réalisé une analyse de régression logistique, calculant les Odds Ratio (OR) et les intervalles de confiance à 95 %, et en ajustant pour des facteurs tels que les antécédents familiaux de cancer de la prostate, l'âge, l'utilisation d'AINS, la circonférence de taille, l'éducation, l'activité physique et les niveaux de triglycérides. Les modèles ont également pris en compte l'agressivité du cancer.

Pour tenir compte des différences ethniques potentielles, nous avons ajusté pour les sept premiers composants principaux (PC) dérivés d'une Analyse en Composantes Principales (PCA) de 33 426 SNPs. Nous avons appliqué une correction du FDR aux valeurs p pour gérer le risque de faux positifs.

Pour analyser le gène COX-2, nous avons examiné chaque SNP en utilisant différents modèles génétiques : additif, co dominant et récessif. Les modèles additif et co dominant ont évalué comment chaque allèle mutant supplémentaire affectait le risque de cancer de la prostate, tandis que le modèle récessif s'est concentré sur les individus ayant deux copies de l'allèle mineur.

De plus, nous avons exploré les interactions potentielles gène-environnement en utilisant une approche par SNP. Cela a impliqué des modèles linéaires généralisés (GLM) pour tester les interactions entre les SNPs de COX-2 et les facteurs environnementaux, y compris les infections, les calculs rénaux et les calculs biliaires. Les effets d'interaction ont été analysés et corrigés pour les multiples comparaisons en utilisant la méthode FDR.

Résultats

Parmi les cas de cancer de la prostate de l'étude, 22,7 % étaient classifiés comme agressifs ou de haut grade. La majorité de la population de l'étude était caucasienne, avec 97,1 % des cas et 97,7 % des témoins se déclarant comme tels. Aucune différence significative n'a été observée entre les cas et les témoins en termes d'âge, de niveau d'éducation, de facteurs de mode de vie (y compris la consommation de tabac et d'alcool), d'activité physique, d'indice de masse corporelle (IMC) ou de circonférence abdominale. Cependant, l'utilisation d'anti-inflammatoires non stéroïdiens (AINS) était plus fréquente parmi les témoins comparativement aux cas, et les cas étaient plus susceptibles d'avoir des antécédents familiaux de cancer de la prostate chez les proches au premier degré.

Concernant les infections bactériennes sexuellement transmissibles (gonorrhée, trichomonas, syphilis), aucune association significative avec le risque de cancer de la prostate n'a été observée. Pour les infections virales (herpès zoster, dengue, herpès labial, polio, hépatite virale), aucune association significative avec le risque de cancer de la prostate n'a été trouvée. Le groupe global des infections virales avait un rapport de cotes (OR) de 1,11 (IC à 95 % : 0,90–1,35), et les infections virales sexuellement transmissibles avaient un OR de 1,12 (IC à 95 % : 0,91–1,38). Lorsqu'on combine les infections bactériennes et virales, les infections bactériennes et virales sexuellement transmissibles ensemble avaient un OR de 1,05 (IC à 95 % : 0,86–1,29). Pour les individus avec une ou plusieurs infections, l'OR était de 1,07 (IC à 95 % : 0,86–1,34), augmentant à 1,17 (IC à 95 % : 0,88–1,56) avec plusieurs infections. Aucune de ces associations n'était statistiquement significative, même en tenant compte de l'agressivité du cancer.

Concernant les antécédents de calculs rénaux, il y avait une augmentation significative du risque de cancer de la prostate global (OR : 1,46, IC à 95 % : 1,13–1,90) et spécifiquement pour les cancers de bas grade (OR : 1,49, IC à 95 % : 1,13–1,98). Cependant, cette association n'était pas significative pour le cancer de haut grade. Les calculs vésiculaires n'ont pas montré d'association significative avec le risque de cancer de la prostate, que ce soit pour les cancers de bas ou de haut grade. En considérant les facteurs combinés, les calculs rénaux étaient plus fortement associés au cancer de la prostate en présence de pyélonéphrite (OR : 5,43, IC à 95 % : 1,16–25,4), notamment pour le cancer de bas grade (OR : 1,47, IC à 95 % : 1,10–1,95) et le cancer de haut grade (OR : 10,9, IC à 95 % : 1,94–61,3) mais non avec la prostatite. Lorsque les données ont été stratifiées selon le statut des triglycérides, les calculs vésiculaires n'étaient pas significativement

associés au risque de cancer de la prostate chez les individus avec des triglycérides normaux, mais étaient liés à un risque significativement plus élevé de cancer de haut grade chez ceux avec une hypertriglycémie (OR : 3,58, IC à 95 % : 1,05–12,22).

En ce qui concerne les données génétiques liées au gène COX-2, certains SNPs étaient associés à un risque accru de cancer de la prostate. En particulier, le génotype AA de rs10911898 et le génotype AG de rs2206593 étaient liés à un risque plus élevé dans tous les cas et pour le cancer de bas grade, tandis que le génotype AG de rs4648261 était associé au cancer de haut grade. Le génotype AC de rs2745559 a également montré une association significative avec le cancer de la prostate global et le cancer de haut grade. Cependant, après ajustement pour le taux de fausses découvertes (FDR), seul le génotype AG de rs4648261 est resté significativement associé au cancer de haut grade. Dans les interactions gène-environnement, l'allèle G de rs964570 était associé à un risque accru de cancer de la prostate de haut grade, mais cette association n'était pas significative après correction pour le FDR. Aucune interaction significative n'a été trouvée entre les variantes du gène COX-2/PTSG2 et le cancer de la prostate en tenant compte des calculs rénaux ou vésiculaires.

Discussion

Bien que les facteurs liés à l'inflammation, tels que les infections, aient été largement et fréquemment étudiés en relation avec le cancer de la prostate, les résultats restent inconsistants, notamment en ce qui concerne les formes agressives de la maladie. D'autres facteurs, tels que les divers types de calculs et les variations génétiques dans le gène COX-2, ont été moins explorés en relation avec toutes les formes du cancer de la prostate. Par conséquent, cette thèse se concentre sur l'étude de divers facteurs liés à l'inflammation et leur association avec toutes les formes de cancer de la prostate, en utilisant les données de l'étude EPICAP.

Le taux de participation global à cette étude était de 77 %, ce qui est considéré comme un taux généralement bon. L'identification des cas a été effectuée dans tous les hôpitaux privés et publics de cancérologie du département de l'Hérault, avec le registre des cancers de l'Hérault signalant 770 nouveaux cas de cancer de la prostate en 2011. Étant donné que le nombre de cas observés en 2012-2013 était prévu similaire, environ 1 150 nouveaux cas étaient anticipés durant la période d'étude. Le recrutement des cas a été assez exhaustif puisque le nombre de cas éligibles identifiés était de 1 098 durant la période d'étude, limitant ainsi le potentiel de biais de sélection. De plus, bien que le taux de participation des cas ait été de 75 %, la répartition par âge et les scores de Gleason des cas non répondants étaient comparables à ceux des cas répondants, minimisant ainsi le biais de survie potentiel. En outre, les entretiens ont été réalisés peu après l'identification, avec seulement 8 cas éligibles (0,7 %) décédés avant de pouvoir être interviewés. De plus, la disponibilité du score de Gleason nous a permis d'évaluer l'agressivité du cancer, un facteur rarement pris en compte dans les études précédentes.

Les témoins ont été sélectionnés aléatoirement dans la population générale du département de l'Hérault, en utilisant des quotas par âge (± 5 ans) pour refléter la répartition par âge observée parmi les cas, et des quotas pour le statut socio-économique (SES) pour garantir que la distribution du groupe témoin reflète la distribution du SES de l'ensemble du département de l'Hérault, afin d'obtenir un groupe témoin similaire à la population générale masculine. Après le processus de sélection, la distribution par SES entre le groupe témoin et la population masculine générale du département de l'Hérault a été comparée. Aucune différence significative n'a été trouvée, indiquant qu'aucun biais de sélection majeur lié au SES n'a eu lieu au sein de notre population témoin.

Les incohérences dans l'association entre les infections et le risque de cancer de la prostate à travers les études peuvent être dues à plusieurs facteurs. Les différences raciales et ethniques peuvent influencer les taux de déclaration des IST, avec des taux plus élevés dans les populations latinos et africaines pouvant mener à des associations plus fortes avec le risque de cancer de la prostate. La durée des infections non traitées, comme la gonorrhée, peut être prolongée en raison d'un accès médical limité ou de problèmes de traitement, ce qui peut intensifier l'inflammation. Le moment des infections est également crucial, car les infections acquises à un jeune âge pourraient affecter le risque de cancer différemment de celles acquises plus tard. Les facteurs de confusion, les variations dans les méthodes d'évaluation des infections et les différences de taille d'échantillon et de puissance statistique entre les études peuvent également influencer les résultats. Bien que notre étude n'ait trouvé aucune association, nous devons considérer la possibilité d'un biais de détection et les limites qu'il peut poser. Nous ne pouvons pas entièrement exclure le biais de rappel, notamment parce que nos données d'exposition reposent sur des auto-évaluations, ce qui peut entraîner une sous-estimation des infections sexuellement transmissibles (IST) en raison de la stigmatisation ou du manque de sensibilisation. Malgré cela, le recueil des données a été standardisée et en face à face, les taux déclarés de gonorrhée parmi les témoins correspondant étroitement aux estimations de la population générale, suggérant un biais minimal. Cependant, la prévalence de la syphilis dans notre étude était plus basse que prévu, indiquant une possible sous-estimation. Aucune donnée biologique n'était disponible pour confirmer les infections. Le biais de détection pourrait affecter nos résultats, notamment pour les cancers moins agressifs, mais les analyses de sensibilité soutiennent la solidité de nos estimations de risque. Les tailles d'échantillon limitées pour certaines infections ont été abordées en groupant les infections similaires. Nous manquons de données détaillées sur le timing des infections par rapport au diagnostic du cancer. Les analyses de sensibilité excluant les utilisateurs d'AINS et comparant les cas des cliniques publiques et privées ont confirmé que nos résultats n'étaient pas significativement influencés par ces facteurs. Les ajustements statistiques pour les facteurs de confusion, y compris l'éducation et l'activité physique, n'ont pas modifié nos résultats.

En ce qui concerne l'association entre les calculs et le cancer de la prostate, il y avait une association significative entre les calculs rénaux et le cancer de la prostate, en particulier lorsque les calculs rénaux étaient combinés avec une pyélonéphrite, ce qui augmentait de manière notable le risque de cancer de la prostate de haut grade. Cette association peut être expliquée

par le rôle de l'inflammation chronique, qui pourrait favoriser un environnement propice au développement du cancer de la prostate. En revanche, l'association globale entre les calculs de la vésicule biliaire et le cancer de la prostate n'était pas significative, bien qu'une interaction avec l'hypertriglycéridémie ait été observée, suggérant que l'inflammation et les conditions métaboliques pourraient influencer la relation entre les calculs de la vésicule biliaire et le risque de cancer de la prostate.

La dépendance aux données auto-déclarées sur les calculs introduit également un biais potentiel de rappel, car les individus peuvent se souvenir de manière inexacte des épisodes de calculs rénaux ou biliaires, notamment pour les cas asymptomatiques ou non diagnostiqués. Cependant, le recueil des données a été réalisé en face à face par une infirmière formée utilisant un questionnaire standardisé, ce qui a aidé à garantir la cohérence entre les cas et les témoins. De plus, nous manquons d'informations sur les caractéristiques des calculs, telles que le type, la taille, et qui pourraient influencer la gravité des symptômes et la probabilité de détection.

Pour minimiser le biais de classification, nous avons comparé nos résultats avec d'autres études et trouvé des prévalences similaires de calculs de la vésicule biliaire et de calculs rénaux parmi les témoins. Les petites tailles d'échantillon dans certaines analyses stratifiées, en particulier concernant le cancer de haut grade, pourraient avoir limité la puissance statistique. Les analyses de sensibilité qui ont restreint les témoins à ceux ayant subi des tests de PSA récents ou des dépistages PSA normaux dans les deux ans ont soutenu la robustesse des résultats, montrant que les résultats n'étaient pas significativement influencés par le statut de dépistage PSA. De plus, l'analyse de la fréquence des dépistages de PSA a révélé une association significative entre les calculs rénaux et le cancer de la prostate pour ceux ayant été testés 2 à 5 fois, mais pas pour ceux ayant été testés moins fréquemment ou plus fréquemment. Cela suggère que le biais de détection lié à la fréquence de dépistage est peu probable pour expliquer les résultats.

Enfin, la plupart des variables suspectées de confusion n'ont pas eu d'impact significatif sur le résultat, les groupes de cas et de témoins étant hautement comparables. Nous avons identifié plusieurs variables liées aux résultats ou aux variables d'intérêt. Pour limiter le biais de confusion, nous avons appliqué des ajustements statistiques à toutes les variables suspectées. De plus, nous avons pris en compte les facteurs de risque bien établis pour le cancer de la prostate dans tous les modèles analytiques. Malgré ces ajustements, nos résultats sont restés cohérents et inchangés.

En se concentrant sur l'association entre des polymorphismes mono nucléotidiques (SNP) spécifiques du gène COX-2 et le risque de cancer de la prostate, l'allèle A du SNP rs4648261 a été notablement associé à un risque accru de cancer de la prostate de haut grade. Cette association est demeurée significative même après correction pour le taux de fausses découvertes (FDR), soulignant son importance potentielle dans le risque de cancer de la prostate, en particulier pour les formes plus agressives de la maladie.

Les analyses génétiques ont inclus 1 515 sujets, représentant 89 % de la population de l'étude EPICAP, et ces participants avaient des caractéristiques sociodémographiques similaires à celles de l'échantillon global. Nos résultats reposaient sur une liste ciblée de gènes et un nombre restreint de SNP (20 SNP), offrant une analyse approfondie de la variabilité génétique du gène inflammatoire COX-2/PTG2. Nous avons appliqué diverses mesures de contrôle de la qualité des données, y compris des critères stricts de sélection des SNP, des vérifications de doublons et des évaluations de cohérence, afin de minimiser les erreurs de génotypage et d'assurer l'exactitude des données. De plus, l'utilisation de plusieurs modèles génétiques a garanti un test rigoureux des associations entre les SNP et le risque de cancer de la prostate, et l'application de la correction FDR a renforcé la fiabilité de nos résultats.

Cependant, il y a des limitations. L'étude a analysé un nombre relativement restreint de SNP, ce qui peut ne pas capturer l'ensemble du paysage génétique associé au risque de cancer de la prostate. La taille de l'échantillon pourrait également limiter la détection des effets plus faibles ou des interactions. La prédominance de sujets caucasiens restreint la généralisabilité des résultats à des populations plus diverses. De plus, la dépendance aux données auto-déclarées pour les facteurs environnementaux introduit la possibilité de biais de rappel, pouvant affecter l'exactitude des résultats.

En conclusion, ces résultats soulignent la nécessité de recherches supplémentaires sur les facteurs liés à l'inflammation. Il serait important d'examiner la durée de ces facteurs et l'efficacité des traitements pour comprendre comment l'inflammation chronique peut influencer le risque de cancer. Les résultats génétiques basés sur une approche préliminaire par SNP indiquent des associations potentielles qui nécessitent des investigations plus approfondies pour confirmer et élargir ces découvertes. Enfin, étant donné l'importance du cancer de la prostate agressif et son pronostic défavorable, de futures recherches devraient explorer spécifiquement les facteurs génétiques et environnementaux qui l'influencent et comprendre les mécanismes sous-jacents afin de développer de meilleures stratégies de prévention et des traitements plus efficaces.

CHAPTER 1 – GENERAL INTRODUCTION

1. Overview of Prostate Anatomy and Function

1.1. Anatomy

The prostate gland, positioned on the floor of the pelvis, serves as the male's largest sexual accessory gland and plays a crucial role in the male reproductive system. This walnut-sized organ is located just below the bladder and in front of the rectum. It is surrounded by a fibrous covering called the prostatic capsule, which helps maintain its shape and structure, and it consists of several lobes, typically described as anterior, posterior, and lateral lobes. Through the center of the prostate runs the urethra, a tube that carries both the urine and semen from the bladder and the reproductive system, respectively.

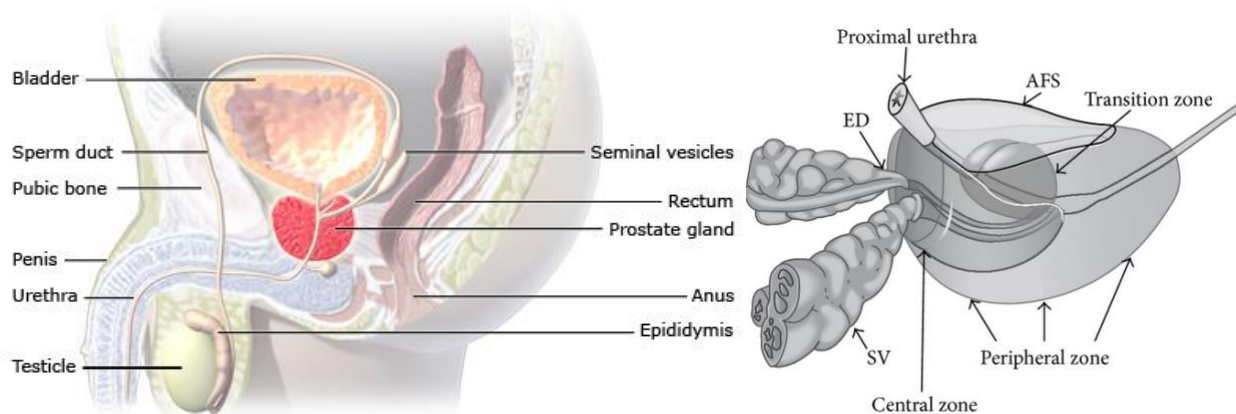


Figure 1 The Male Reproductive System(left) [1] and Zonal anatomy of the Prostate (right) [2]

The prostate gland is divided into three major histological zones based on its anatomical and functional differences (Figure 1):

- **Peripheral Zone:**

Located at the posterior part of the gland, constitutes the largest zone, accounting for approximately 70-80% of the glandular tissue. It encircles most of the central and transition zone. This zone is also where the majority of prostate cancer originates (about 70-75%).

- **Central Zone**

Surrounding the ejaculatory ducts and forming the base, this zone is responsible for the production of prostatic fluid, an essential component of semen. While prostate cancer can develop in this zone, it is less common compared to the peripheral zone,

and if it does occur in this zone, it tends to be quite aggressive, even though it constitutes only 2.5% of prostatic cancer cases.

- **Transition zone**

Constitutes the smallest glandular zone, accounting at approximately 5% of the total glandular tissue, is made of two small lobules that encircle a portion of the urethra near the bladder. With age, this zone tends to enlarge, leading to a condition known as benign prostatic hyperplasia (BPH). Despite its smaller size, 20% of prostatic cancer originates in the transition zone.

- **Anterior Fibromuscular Stroma**

Although not considered a major zone in the prostate, this area consists mainly of fibrous and muscular tissue, and it is located at the front of the prostate gland. It does not contain significant glandular tissues and is not typically associated with conditions like prostate cancer or benign prostatic hyperplasia (BPH). However, it plays an essential role in providing structural support to the gland.

1.2. Function

The prostate is a hormonally-dependent hormone whose growth and activity are regulated by 5-dihydrotestosterone; a hormone derived from testosterone. This exocrine gland plays a crucial role in male reproductive physiology, primarily through its secretion of prostatic fluid, which contributes to sperm viability and motility. During ejaculation, prostatic fluid combines spermatozoa from the testes, transported through the deferent ducts, and seminal plasma from the accessory seminal vesicles, forming seminal fluid. This mixture provides nourishment and protection to spermatozoa and aids in the transportation of the sperm through the reproductive tract, enhancing the chances of fertilization.

While weighing around 30 grams in adults, its volume tends to increase progressively with age, potentially doubling in cases of prostatic pathologies [1–3].

2. Prostate Carcinogenesis

Prostate cancer (PC) is the most common type of cancer in men worldwide, aside from skin cancer, often asymptomatic in its early stages. It is characterized by being either slow-growing and benign or aggressive and potentially fatal, with the capacity to metastasize beyond the prostate gland. While adenocarcinoma, originating from gland cells, comprises the majority of

PC cases, rare subtypes like small cell carcinoma, neuroendocrine, and sarcoma tumors also exist (less than 5%) [4].

2.1. Clinical signs, Diagnosis, and Screening of Prostate Cancer

Prostate cancer often remains asymptomatic and progresses silently in its early stages. When symptoms do arise, usually during advanced stages of the disease, due to compression of the prostatic urethra, they typically include lower urinary tract symptoms (LUTS) such as nocturia, straining to void, and hematuria. Lower back pain, bone pain, pain during ejaculation, or erectile dysfunction are also symptoms that are commonly associated with prostate cancer. However, these symptoms are not specifically associated with prostate cancer and can overlap with benign prostate hyperplasia (BPH), making diagnosis challenging if only based on symptoms.

The diagnostic process for prostate cancer starts with clinical assessment, including a digital rectal exam (DRE) and a blood test for prostate-specific antigen (PSA) levels. A PSA level below 4 (ng/mL) is considered normal, but higher levels may indicate prostate cancer, though they may also rise due to benign conditions such as BPH, inflammation, infection, or recent DRE. Therefore, while high PSA levels raise suspicion, further evaluation is needed to confirm the diagnosis. If suspicion persists, a prostate biopsy is conducted to collect tissue samples for examination and subsequent histological examination of the sampled tissue to confirm the diagnosis and guide treatment decisions. Extension assessment, including imaging tests such as whole-body bone scans, MRI, PET-CT scans, or CT scans, may follow to evaluate lymph node involvement and if the cancer has metastasized beyond the prostate gland.

While screening methods for prostate cancer are available, organized screening is not universally recommended due to uncertainties regarding its impact on mortality and the potential risks of over diagnosis and overtreatment. Instead, individual screening is advised for men aged 50 to 70 years with an estimated survival of over 10 years, with earlier screening recommended for those at higher risk due to factors like ethnicity or family history. Screening intervals, typically every 2 to 4 years, involve a combination of rectal examination and serum PSA testing [4–6].

2.2. Tumor Classification

Tumor classification is essential offering standardized methods to categorize cancers and guide treatment decisions. Systems like TNM classification assess tumor size, lymph node

involvement, and metastasis. Additionally, prognostic classifications such as the Gleason histoprognostic score, the ISUP classification derived from Gleason score grades, and the D'Amico classification estimating post-treatment relapse risk are essential to accurately assess cancer progression, predict patient outcomes, and tailor treatment strategies accordingly.

2.2.1. Gleason Score

The diagnosis of prostate cancer relies on anatomopathological examination of prostate biopsies, which assess tumor differentiation levels. The Gleason grading system serves as the standard and most common grading system for prostate cancer, acting as the most valuable predictor for cancer behavior and aggressiveness. This system evaluates the architectural patterns of tumor cells observed in prostate biopsies. The Gleason score combines two histological grades, depending on the progressive nature of the cancer. Each pattern is scored on a scale of 1 to 5, where 1 resembles normal tissue with good differentiation, and 5 resembles abnormal tissue with poor differentiation. The scores from both patterns are then added together to yield a total Gleason score ranging from 2 to 10 [7, 8].

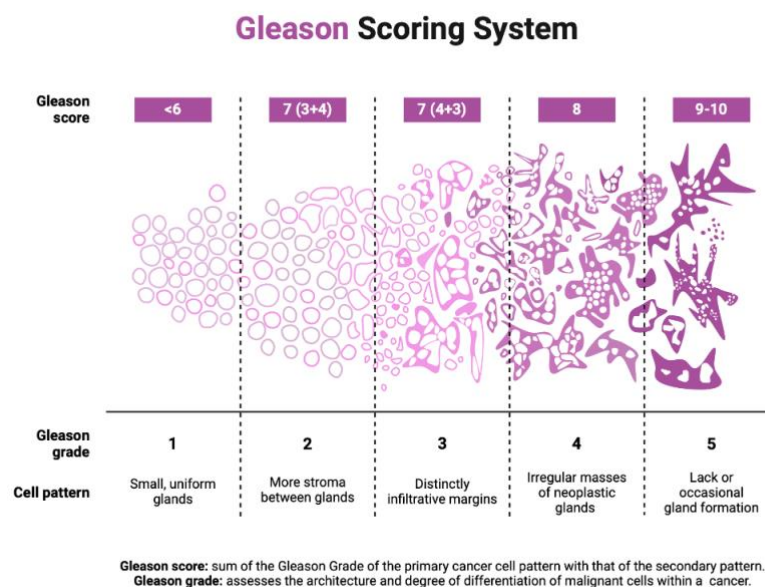


Figure 2 Schematic diagram of Gleason grading system [9]

The different Gleason scores are as follows (figure 2):

- **Gleason 6 or lower:** Cells are well differentiated, indicating a good prognosis.

- **Gleason 7:** Moderately differentiated cells that can be further classified into intermediate (3+4) or high-grade (4+3) cancer, reflecting different levels of aggressiveness.
- **Gleason 8, 9, or 10:** Cells are poorly differentiated, indicating a very poor prognosis.

In 2013, Johns 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 scores [10].

Table 1 New Gleason grading system based on group

<i>Risk Group</i>	<i>Grade Group</i>	<i>Gleason Score</i>
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

2.2.2. ISUP Classification

The International Society of Urological Pathology (ISUP) classification for prostate cancer is a grading system that is used to address some of the limitations of the traditional Gleason scoring system. Also known as the Grade Group system, was introduced to provide a more accurate approach to grading prostate cancer, which grades prostate cancer from 1 (least aggressive) to 5 (most aggressive) based on the Gleason score and the pattern of the tumor cells.

The five groups based on this system are defined as follows:

- **ISUP Grade Group 1:** Corresponds to a Gleason score of 6 (3+3); cells are well differentiated and closely resemble normal prostate tissue, and cancer is likely to grow very slowly, if at all.
- **ISUP Grade Group 2:** Corresponds to a Gleason score of 7 (3+4); cells are moderately differentiated and mostly resemble prostate cells, and cancer is likely to grow slowly.
- **ISUP Grade Group 3:** Corresponds to Gleason score of 7 (4+3); cells are moderately differentiated and with some resemblance to normal prostate cells, and the cancer is likely to grow at a moderate rate.

- **ISUP Grade Group 4:** Corresponds to a Gleason Score of 8 (4+4); cells are poorly differentiated with more abnormal-looking cells, and the cancer is likely to grow at a moderate rate.
- **ISUP Grade Group 5:** Corresponds to a Gleason score of 9 or 10 (4+5, 5+4, or 5+5); cells are poorly differentiated, and the cancer is likely to grow at a very fast rate [11].

2.2.3. TNM Classification

The TNM classification system is a widely used staging system for solid tumors, including prostate cancer. It categorizes tumors based on three key parameters: Tumor size (T), which describes the size and extent of the primary tumor within the prostate gland; lymph node involvement (N), which indicates whether cancer has spread to nearby lymph nodes, and the presence of metastasis (M) signifies the presence or absence of distant metastasis. This system, which was developed by the American Joint Committee on Cancer (AJCC), provides valuable information about the extent of the disease, aiding in treatment planning and prognosis determination [12].

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

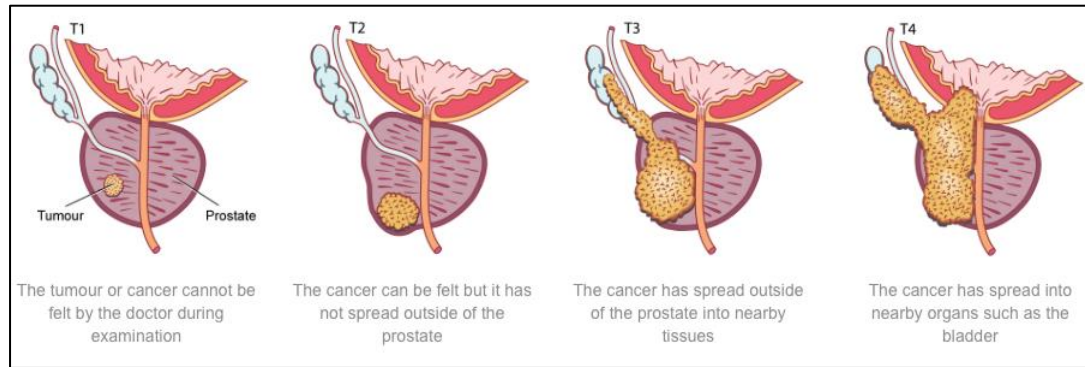


Figure 3 The primary tumor stages in prostate cancer [13]

2.2.4. D'amico Classification

The Amico classification is a risk stratification system used in prostate cancer to assess the likelihood of recurrence post-treatment. This classification divides patients into three categories: low, intermediate, and high risk based on prostate-specific antigen (PSA) levels, Gleason score, and TNM classification

The three risk groups based on the Amico classification are as follows:

- **Low risk:** PSA < 10 ng/mL and Gleason score ≤ 6 and clinical stage T1c (Tumor not palpable nor visible) or T2a (Involves less than half of a prostate lobe).
- **Intermediate risk:** PSA between 10 and 20 ng/mL or Gleason score 7 or clinical stage T2b (Involves more than half of a prostate lobe).
- **High risk:** PSA > 20 ng / mL or Gleason score ≥ 8 or clinical stage T2c (Involves both prostate lobes) [14].

2.3. Treatment

Treatment strategies for prostate cancer are primarily determined by the cancer's stage, grade, and the patient's overall health preferences. Based on the nature of prostate cancer, treatments can be broadly categorized into three main groups: treatments for localized prostate cancer, treatments for locally advanced prostate cancer, and treatments for metastatic prostate cancer.

- Treatment for localized prostate cancer

For patients with localized prostate cancer and a life expectancy of less than 10 years, simple surveillance is recommended, especially in cases of multiple comorbidities. Curative treatment options are considered for patients with a life expectancy exceeding 10 years, including active surveillance-deferred treatment, radical prostatectomy, external radiotherapy, or interstitial brachytherapy. In general, the choice among these options is influenced by various factors,

including the patient's age, the cancer's grade, and the potential side effects of treatment [6, 15, 16].

- **Locally Advanced Prostate Cancer:**

In patients under 75 years old with locally advanced prostate cancer and a life expectancy of over 10 years, treatment approaches differ based on risk stratification. For intermediate-risk tumors, options include total prostatectomy with extended lymph node dissection, external radiotherapy with or without brachytherapy, or multimodal therapy. High-risk tumors may be managed with hormone radiotherapy or total prostatectomy with extended lymph node dissection in younger patients [6, 16, 17].

- **Metastatic Prostate Cancer:**

Metastatic prostate cancer is managed with palliative medical treatment, primarily androgen suppression therapy. Hormone therapy, either pharmacological or surgical castration, is the mainstay of treatment, supplemented by symptomatic management. In cases of castration resistance, treatment options include second-line hormone therapy, chemotherapy, or surveillance, depending on symptoms and disease progression [6, 16, 18].

2.4. Epidemiology

2.4.1. Incidence

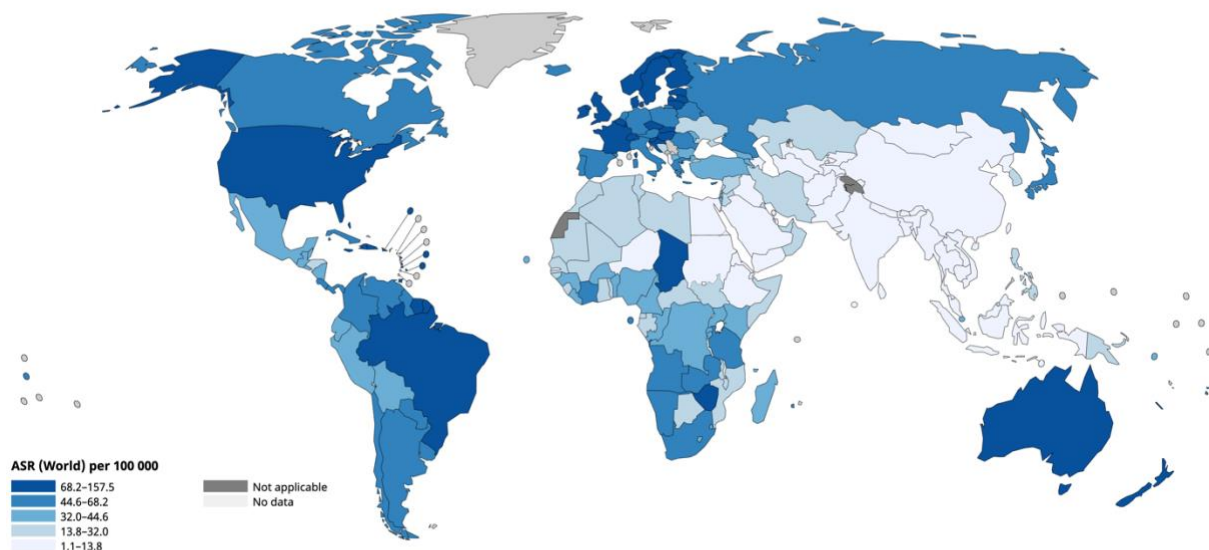
Prostate cancer continues to be a major public health concern worldwide, ranking as the second most common cancer among men worldwide. According to data from GLOBOCAN, 2022, there were approximately 1.4 million new cases of prostate cancer diagnosed globally, with varying regional distributions. In Europe, an estimated 473,011 cases were recorded, followed by 386,424 in Asia, 255,782 in North America, and 103,050 in Africa. Prostate cancer accounted for 15.3% of all cancers diagnosed in men, excluding non-melanoma skin cancers, with an age-standardized incidence rate (ASR) of 29.4 per 100,000 individuals [19].

Incidence rates of prostate cancer vary significantly across the world, where the highest ASR is observed in northern Europe (82.8 per 100,000), followed by Australia-New Zealand (78.1 per 100,000), Caribbean (73.9 per 100,000), North America (73.5 per 100,000) and Western Europe (63.7 per 100,000). Conversely, ASR notably declines to 16.1 per 100,000 in Northern Africa and to 12.7 per 100,000 in South-Eastern Asia. Additionally, the risk of Prostate cancer increases with age. While the rate of diagnosis among men 54 years and younger is 1.6 per

100,000, it rises to 66.1 per 100,000 among men aged between 50 and 64 and significantly higher to 291.4 per 100,000 among men aged 64 years and above [19].

In France, prostate cancer stands as the most frequently diagnosed cancer in males, with 57,357 new cases reported in 2022, accounting for 21.8% of all male cancer cases. This places PC at the forefront of cancer incidence in France, surpassing lung, colorectum, bladder, and non-Hodgkin lymphoma (NHL), where the ASR is 82.3 per 100,000 individuals. While the rate of diagnosis among men 54 years and younger is 6.5 per 100,000, it rises to 255.2 per 100,000 among men aged between 50 and 64 and significantly higher to 689.5 per 100,000 among men aged 65 years and above [19].

Age-Standardized Rate (World) per 100 000, Incidence, Males, in 2022
Prostate



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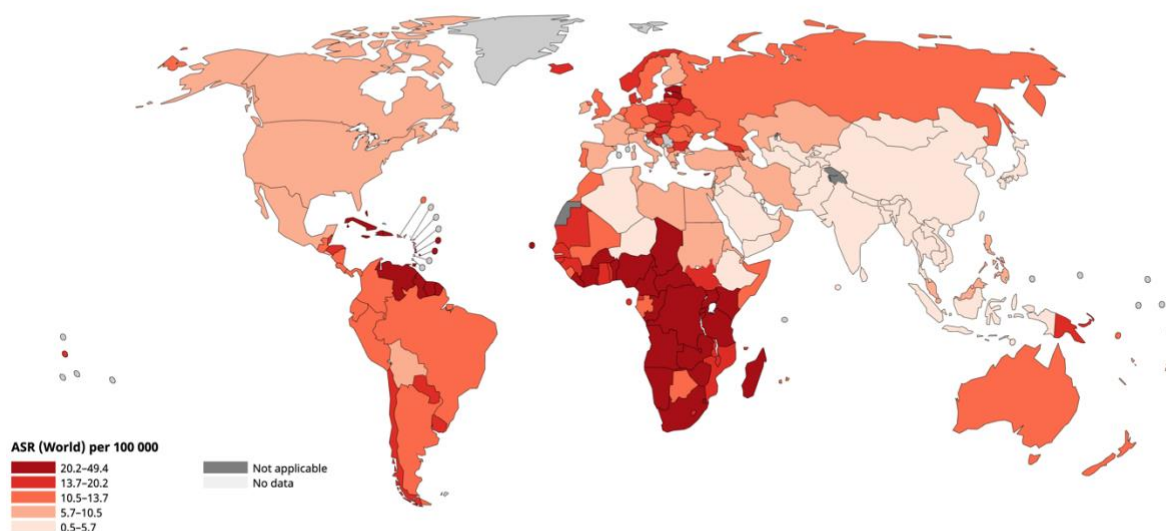
Figure 4 Age-Standardized Rate per 100,000 for Prostate Cancer Incidence [18]

2.4.2. Mortality

According to Globocan, globally, prostate cancer significantly contributes to cancer-related mortality among men, accounting for a total of 397,430 deaths worldwide. This places prostate cancer as a leading cause of cancer death, with an age-standardized mortality rate (ASR) of 7.3 per 100,000. The mortality rate varies across continents, with Asia experiencing the highest number of deaths at 120,485, followed by Europe with 115,182, and North America with 39,605 deaths [19].

When comparing age-standardized mortality rates (ASR) for prostate cancer across different continents, significant disparities are evident. For instance, mortality rates tend to be higher in regions such as Africa and the Caribbean compared to Asia, where rates are comparatively lower. In both Western and Eastern Europe, ASR varies from 10 to 13 per 100,000. North America demonstrates an ASR of 8.3 per 100,000, while Australia - New Zealand show an ASR of 11 per 100,000. Except for Western Asia, the ASR in Asia does not surpass 5 per 100,000. The highest rates of mortality are seen in southern Africa, with an ASR of 29.7 per 100,000, in Middle Africa at 27.2 per 100,000, and in the Caribbean at 26.4 per 100,000. This disparity implies patients in developed countries may benefit from early-stage diagnosis, leading to a more favorable prognosis, whereas those in underdeveloped countries might have been diagnosed at a very late stage with a poor prognosis [19–21].

Age-Standardized Rate (World) per 100 000, Mortality, Males, in 2022
Prostate



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Figure 5 Age-Standardized Rate per 100,000 for Prostate Cancer Mortality [18].

In essence, these variations across continents underscore the different factors influencing prostate cancer mortality, which could be related to healthcare infrastructure, screening practices, and access to treatment. In France, prostate cancer is the second leading cause of mortality in men, excluding non-melanoma skin cancers. In 2022, there were 9,264 deaths attributed to prostate cancer; this accounts for 4.9% of all cancer-related deaths in men,

indicating a relatively better prognosis from prostate cancer compared to other cancers, with an ASR of 8.2 per 100,000 [19–21].

2.4.3. Trends and Patterns

Over the past few decades, the trend for prostate cancer has been characterized by a significant increase in both incidence and mortality rates, with notable geographical and socioeconomic disparities. According to the Global Burden of Disease study and GLOBOCAN, the number of incident cases and deaths of prostate cancer increased substantially from 1990 to 2019. In North America, selected Nordic countries, and Australia, there was a rapid increase in PC incidence rate from the late 1980s to the early 1990s due to the widespread introduction of PSA testing. These increases were followed by a notable decline within a few years, reflecting changes in PSA-based screening guidelines. In contrast, less pronounced trends have been reported in greater Europe, Southern and Central America, and Asia, reflecting a more recent adaptation of PSA testing. Meanwhile, between 1995 and 2018, incidence rates continued to rise in China, countries in the Baltic and Eastern Europe. In sub-Saharan Africa, the increase ranged from 2% to 10%, partly due to heightened awareness and improvement in healthcare systems that facilitated the availability of PSA testing and transurethral resections [22, 23].

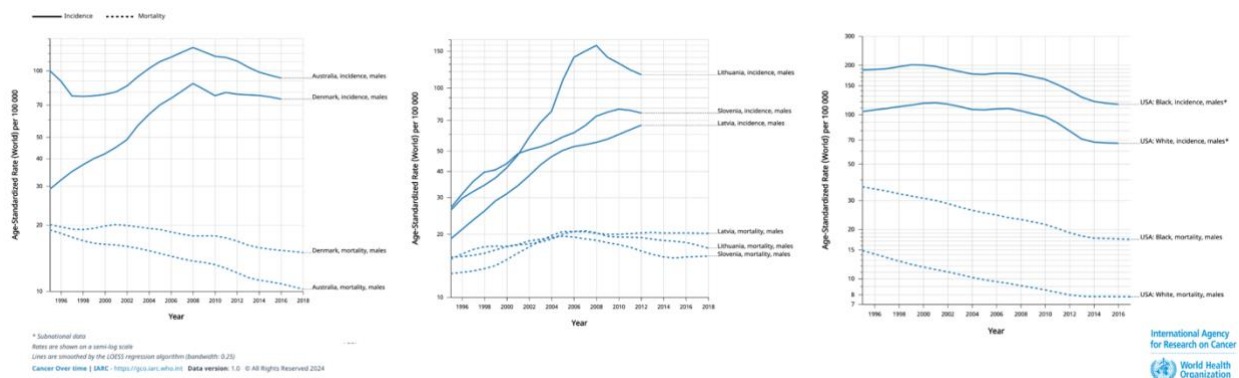


Figure 6 Trends for Prostate Cancer Incidence and Mortality [18]

Mortality trends do not closely follow the patterns of incidence. Most developed countries, including those in Northern America, Oceania, and Northern and Western Europe, have witnessed decreased mortality rates since the mid-1990s, likely due to advancements in effective treatment and earlier detection. Conversely, during the same period, many countries in Central and Eastern Europe, Asia, and Africa, mortality rates have increased, reflecting a simultaneous rise in incidence rate, worsened by limited access to PSA testing and curative treatment options. Recent trends indicate that mortality rates continue to decline in greater

Europe, excluding the Baltic countries and Eastern Europe. In the United States, mortality rates have stabilized after decades of decline, partly due to an increase in advanced-stage disease [6, 22, 23].

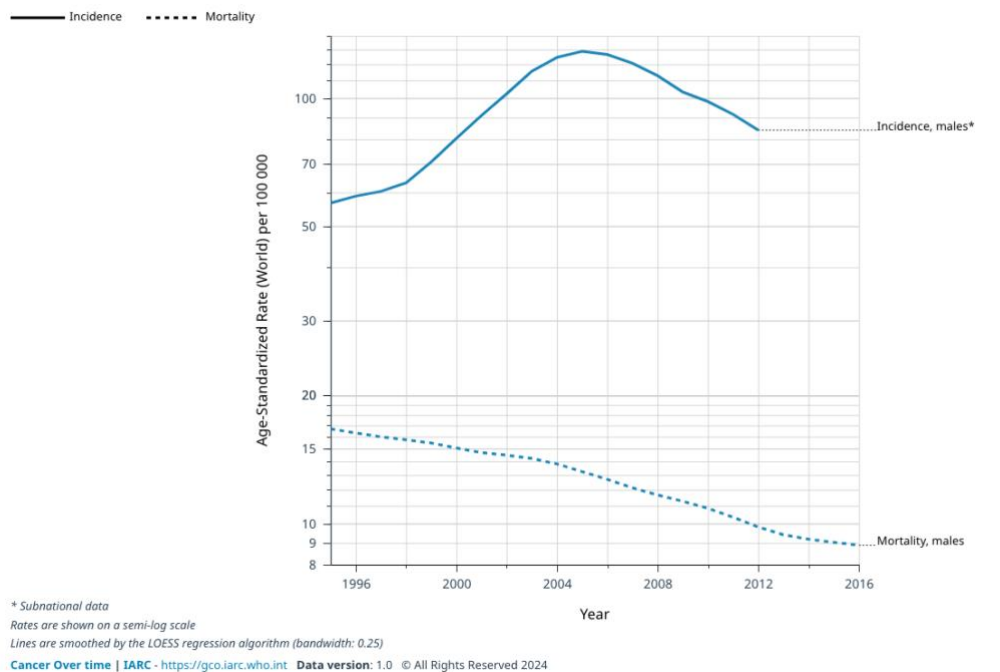


Figure 7 Trends in France for Prostate Cancer [18]

In France, a sharp increase in the incidence of prostate cancer began in the mid-1990s, peaking around the year 2005. As mentioned above, this rise could partly be attributed to the introduction and widespread adoption of PSA testing. Following the peak, a noticeable decline may be due to the adoption of new PSA guidelines [6, 22, 23].

In contrast, the mortality rates for prostate cancer show a different pattern. In fact, the rates have been relatively stable over the years, with a slight downward trend, which could be indicative of improvement in treatment, advancement in medical interventions, and better healthcare access.

2.5. Etiology of Prostate Cancer

2.5.1. Established Risk Factors

Prostate Cancer, has only three well-established non-modifiable risk factors to date: advancing age, ethnicity, and family history of prostate cancer.

2.5.1.1. Advancing Age

The risk of developing prostate cancer increases with age, making it the foremost risk factor for prostate cancer. The incidence of prostate cancer rises significantly with increasing age, particularly after the age of 50, with the average age at the time of diagnosis being 66 years. Statistics underscore this trend, revealing an increased incidence rate from 6.5 per 100,000 among men aged less than 54 years to a striking 689.5 per 100,000 among those aged 65 years and above [19, 24, 25].

2.5.1.2. Ethnicity

Ethnicity significantly influences prostate cancer risk, with certain ethnic groups showing higher incidence and mortality rates. Studies consistently demonstrate that men of African descent, particularly African American, have a higher risk of developing prostate cancer and are more likely to experience aggressive forms of the disease. This elevated risk extends to populations from the Caribbean and sub-Saharan African countries. Conversely, individuals of Asian descent, including Chinese or Japanese and Pacific Islander descent, demonstrate notably lower incidence rates, which is 50% less in comparison to Caucasians [25–27].

2.5.1.3. Family History of Prostate Cancer

A family history of prostate cancer, especially among first-degree relatives like fathers or brothers, significantly increases an individual's risk of developing the disease. For instance, men with a first-degree relative diagnosed with prostate cancer face a two to threefold increase in risk compared to the general population. The risk of developing cancer is also high when the diagnosis in first-degree relatives occurs before the age of 60. Moreover, the risk increases proportionally with the number of affected relatives. In 15 to 25% of prostate cancer cases, there is family aggregation, which means at least two cases among first-degree relatives. Within these familial cases, there are hereditary forms characterized by the presence of at least three cases among first- or second-degree relatives or two cases diagnosed before the age of 55. These hereditary cases represent 5 to 10% of all prostate cancer cases [25–28].

2.5.2. Suspected Risk Factors

Despite the extensive and ongoing research, the etiology of prostate cancer remains largely unknown. Over the years, a multitude of suspected risk factors have been explored, including hormonal factors, environmental and occupational factors, lifestyle and dietary habits, anthropometric and metabolic factors, inflammatory factors, and genetic factors.

2.5.2.1. Environmental and Occupational Factors

Studies on Asian migrants residing in North America suggest higher rates of prostate cancer compared to those living in their countries of origin, suggesting the role of lifestyle and environmental factors [29]. Among environmental exposures, certain chemicals and physical substances have been extensively studied, suggesting their role in the development of prostate cancer.

Endocrine disruptors, such as pesticides, have the ability to bind to hormonal receptors, exerting estrogenic and anti-androgenic actions that disrupt the endocrine system [30]. Pesticide exposure, particularly in agricultural settings, shows a higher risk of prostate cancer, specifically for certain pesticides such as organophosphates and organochlorines [31, 32].

Exposure to Agent Orange, chlordane, bisphenol A, and PAHs from different sources, such as grilled meat and cigarette smoke, also increases the risk of prostate cancer [33]. The International Agency for Research on Cancer (IARC) classified night shift work involving disruption of the circadian rhythm as probably carcinogenic to humans (Group 2A), although evidence specifically for prostate cancer in humans remains limited (IARC Monograph) [34, 35]. However, one study showed an elevated risk of prostate cancer among night shift workers compared to non-night shift workers [36]. Long-term exposure to night shift work was associated with an excess risk for the aggressive type as well [36]. Firefighters and workers in industries are at a high risk of developing prostate cancer due to exposure to different types of toxic substances [37]. Blue-collar workers, such as farmers and pesticide applicators, also have a higher risk due to exposure to organophosphorus and organochlorine insecticides [32, 38].

2.5.2.2. Lifestyle Factors

Prostate cancer is believed to be influenced by a range of lifestyle factors also suggested by migrant studies. From dietary habits such as diverse food intake, alcohol consumption, and cigarette smoking to different physical activity levels.

- Dietary Habits

The relationship between dietary habits and the risk of prostate cancer has been extensively studied, with various findings suggesting that certain foods and dietary patterns may influence the risk of developing prostate cancer. For instance, an increased risk was associated with higher consumption of red meat and processed meat; the association persisted with grilled or

when cooked at high temperatures partly due to the formation of carcinogenic and chemical agents such as heme iron and polycyclic aromatic hydrocarbons [25, 33, 39].

Additionally, a high intake of dairy products such as milk, cheese, and dietary calcium was associated with an increased risk of prostate cancer [25, 33]. The proposed mechanism includes the role of calcium in reducing the levels of circulating 1,25-dihydroxyvitamin D₃, the active form of vitamin D, which may have protective effects against cancer by promoting cellular differentiation and inhibiting proliferation [25, 27, 33]. High intake of fat was also associated with the risk of prostate cancer, partly due to the fact that animal fat intake promotes the development of cancer through androgens [25, 33].

Conversely, a diet rich in fruits, cruciferous vegetables, lycopene, whole grains, and certain nutrients like omega-3 fatty acids and vitamin E has been associated with a decreased risk of prostate cancer, possibly due to their antioxidant activity, hormonal modulation, and anti-inflammatory effect [40–42].

- Alcohol Consumption

The relationship between alcohol consumption and prostate cancer has been studied to an extent in various studies. While some studies suggest that there is a link between alcohol intake, particularly heavy or binge drinking, others found no significant association or even suggest a potential protective effects of moderate alcohol consumption [25, 43]. A meta-analysis has shown a strong link between alcohol consumption and the risk of prostate cancer [44]. Other studies highlighted that liquor, but not wine or beer, was positively associated with the risk of prostate cancer [45]. A dose-response relationship has also been investigated in a large meta-analysis study showing a strong association with prostate cancer among low, medium, high, and high drinkers in comparison to non-drinkers [44, 46]. Additionally, one study showed that excessive drinking may also be associated with aggressive types of prostate cancer [47].

Although the mechanisms behind this are still not fully understood, one possible explanation could be acetaldehyde toxicity, an alcohol metabolite that can bind to DNA and proteins, leading to mutagenesis and contributing to the initiation and growth of prostate cancer cells. Another possible mechanism is that alcohol consumption can induce the oxidation of ethanol by the enzyme cytochrome P450 2E1 (CYP2E1), which in turn generates reactive oxygen species (ROS) that can cause oxidative stress and DNA damage. This DNA damage can lead to mutations that can contribute to prostate carcinogenesis [43].

- Cigarette Consumption

Despite being responsible for over 25% of all deaths globally and being the primary risk factor for lung cancer [19], cigarette consumption has not yet been conclusively associated with prostate cancer despite the extensive research it has undergone. Studies have shown that current smokers have a moderately increased risk of prostate cancer compared to non-smokers, with a dose-response relationship observed, where a higher number of packs-years smoked was associated with a higher risk of prostate cancer. Additionally, smoking appears to be more strongly associated with aggressive or advanced forms of prostate cancer [48–50].

Multiple mechanisms were proposed, one of which is that cigarettes contain carcinogens, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and N-nitrosamines, which can induce DNA damage and mutations, potentially initiating prostate carcinogenesis. Hormonally, smoking may alter levels of androgens and estrogens, favoring prostate cancer growth, with increased bioavailable testosterone and reduced bioavailable estradiol (total and free) observed in smokers. Finally, smoking is associated with epigenetic modifications like DNA methylation and histone alterations, affecting gene expression and contributing to cancer growth [25, 48].

- Physical Activity

Even studies investigating the relationship between physical activity and prostate cancer risk have yielded conflicting results. However, a majority of these studies pointed towards an inverse or protective association. For instance, evidence from a prospective cohort study: The Health Professionals Follow-Up Study (HPFS) cohort, showed that men over 65 years old in the highest quintile of vigorous activity exhibited a remarkable 77% lower risk of advanced prostate cancer [51]. Another study further supports the notion of a lower risk of prostate cancer, irrespective of its aggressiveness, associated with regular physical activity, combining both occupational and leisure-time physical activity [52]. Additionally, a significant inverse dose-response relationship has been observed between vigorous-intensity recreational physical activity during early adulthood and the risk of prostate cancer [53]. Similarly, findings from the Cancer Prevention Study II (CPS-II) cohort revealed that men with the highest level of recreational physical activity had a 31% lower risk of aggressive prostate cancer compared to those who were not physically active [54].

Physical activity influences hormonal regulation, inflammation, and oxidative stress, contributing to its potential protective role against prostate cancer. Physical activity reduces circulating levels of metabolic and sex hormones, such as testosterone, while increasing sex hormone-binding globulin (SHBG), and insulin-like growth factor-1 (IGF-1), thereby contributing to lower risks of prostate cancer. Additionally, regular physical activity has anti-inflammatory effects, reducing inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), mitigating prostate carcinogenesis. Finally, exercising reduces oxidative stress by increasing antioxidant enzyme activity, thereby reducing DNA damage and inhibiting cancer development [25, 26, 55–57].

2.5.2.3. Hormonal Factors

The prostate, a hormonally dependent organ, is regulated by androgens, primarily testosterone and dihydrotestosterone, for its growth and function [25]. While the involvement of androgens in prostate cancer pathogenesis is widely acknowledged, the exact nature of this relationship has not been conclusively established.

In fact, epidemiological studies have not consistently yet linked circulating androgens with an increased risk of prostate cancer. While some studies report a positive association between higher levels of androgen and increased risk of prostate cancer, others suggest an inverse relationship or no significance at all [58–60].

Furthermore, other hormonal pathways, such as insulin-like growth factors and their binding proteins, have been studied. The IGF family consists of insulin receptor (INSR), IGF-1 receptor (IGF-1R), and mannose 6-phosphate receptor (M6P/IGF-2R), along with ligands insulin, IGF-1, and IGF-2, and binding proteins (IGFBP1-6) [25, 59, 61, 62]. Despite the extensive research, conflicting results persist regarding the association between serum IGF-1 level and prostate cancer risk.

2.5.2.4. Anthropometric and Metabolic Factors.

Obesity has been a significant public health concern globally, particularly in the Western world, with its prevalence on the rise. Its association with various types of cancer, including prostate cancer, has been extensively studied. Notably, a meta-analysis found an increase in the risk of prostate cancer with higher BMI [63]. Additionally, another one showed a positive association between increased BMI and aggressive forms of prostate cancer [64]. Waist circumference, a measure of abdominal obesity, may be a relevant risk factor for prostate cancer compared to

overall obesity measured by BMI alone. A meta-analysis done by Genkinger et al. found that men in the highest category of waist circumference ≥ 110 cm had a significantly increased risk of high-grade prostate cancer compared to those in the lowest category < 90 cm [63]. Multiple mechanisms might explain the link between obesity and prostate cancer, involving metabolic, hormonal, and inflammatory pathways.

Obesity is associated with a state of chronic low-grade inflammation, which can facilitate the development of prostate cancer [65–68]. In obese individuals, adipose tissue becomes infiltrated with macrophages, which serves as a significant source of inflammation. Adipose tissue is an active endocrine organ that releases numerous adipocytokines into the bloodstream, significantly secreting pro-inflammatory molecules such as IL-6, TNF-alpha, and leptin while secreting a few anti-inflammatory adipokines such as adiponectin [69]. Adiponectin exhibits anti-inflammatory and insulin-sensitizing properties and may play a role in carcinogenesis by acting against the development of insulin resistance [70, 71].

Additionally, a group of metabolic abnormalities including abdominal obesity, insulin resistance, dyslipidemia, and hypertension, received attention as risk factors of prostate cancer. Individuals with metabolic syndrome often exhibit elevated levels of insulin and insulin-like growth factor (IGF-1) or elevated levels of triglycerides and reduced high-density lipoprotein (HDL) cholesterol, which may be associated with an increased risk of prostate cancer, potentially through mechanisms involving insulin signaling and lipid metabolism [65, 69, 70, 72, 73].

3. Chronic Inflammation

3.1. Inflammation

Chronic inflammation, characterized by a prolonged immune response to tissue injury or harmful stimuli, is a biological process involved in various diseases [67, 74, 75]. Unlike acute inflammation, which is a short-term protective response by upregulating an inflammatory activity aimed at eliminating pathogens and promoting tissue repair – a process that resolves when the threat subsides, chronic inflammation can persist for weeks, months, or even years [67, 74, 75]. Systemic Chronic inflammation can be triggered by a range of factors such as social, physiological, environmental, and biological, leading to a dysregulated response and inhibiting the resolution of acute inflammation, resulting in a persistent low-grade, non-

infective state [74]. Prolonged inflammatory response can disrupt normal immune function and tolerance, leading to widespread alterations in tissues, organs, and cellular function. This may increase the susceptibility to a variety of health conditions, including metabolic syndrome, cardiovascular diseases, depression, and neurodegenerative diseases [74] (figure 8).

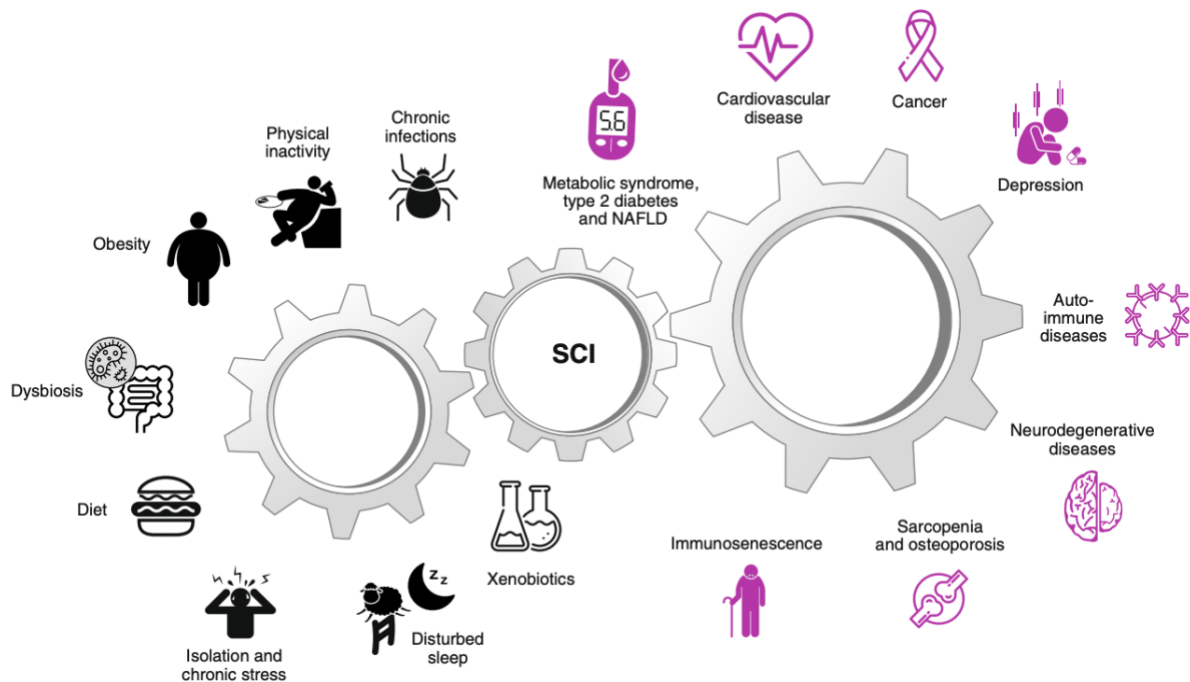


Figure 8 Causes and consequences of low-grade systemic chronic inflammation [74]

The initiation of the inflammatory response occurs when components of microorganisms bind to Toll-like receptors (TLRs). These receptors, known as pattern-recognition receptors, have the capacity to serve either pro- or anti-tumorigenic functions. This highlights the versatility of inflammatory responses, where a given inflammatory mediator may either contribute to present a potential therapeutic avenue or lead to tumor development [75].

3.2. Chronic Inflammation and Cancer Development

The relationship between chronic inflammation and cancer has been a subject of intense research for the past 25 years. In 1863, Virchow proposed that cancers originate from areas of chronic inflammation, noting leukocyte infiltrates in neoplastic tissues. He suggested that exposure to irritants and subsequent tissue damage trigger inflammation, promoting cell proliferation. In the 2000s, research further supported chronic inflammation as a potential cause of cancer, particularly within the tumor microenvironment. This environment, rich in inflammatory cells and cytokines, fosters carcinogenesis, tumor progression, and

immunosuppression. Additionally, genetic alterations in inflammation response genes exacerbate this effect, potentially leading to genetic modifications [66].

Accumulating evidence suggests that chronic inflammation plays a crucial role in the initiation, promotion, and progression of various malignancies [67]. In fact, chronic inflammatory states account for about 20% of all human carcinogenesis [75–77]. Inflammation has been involved in the development of cancer in various organs. For instance, stomach cancer often arises from *Helicobacter Pylori*-induced gastric inflammation, while chronic hepatitis is a known precursor to liver cancer. Additionally, lung cancer may arise due to inflammation triggered by factors like infections, smoking, or lung fibrosis [78, 79].

The connection between cancer and inflammation involves two pathways: the intrinsic pathway, driven by genetic events leading to neoplasia, and the extrinsic pathway, influenced by inflammatory or infectious conditions. In the intrinsic pathway, genetic alterations can activate oncogene or inactivate tumor suppressor genes, leading to the transformation of normal cells into cancerous cells. In turn, these cells can produce inflammatory mediators that contribute to the creation of an inflammatory microenvironment. The extrinsic pathway is driven by inflammatory conditions that predispose to cancer, such as chronic infections, autoimmune diseases, or exposure to inflammatory agents leading to an environment that promotes genetic mutation and supports the growth and survival of malignant cells (figure 9) [75, 80–82].

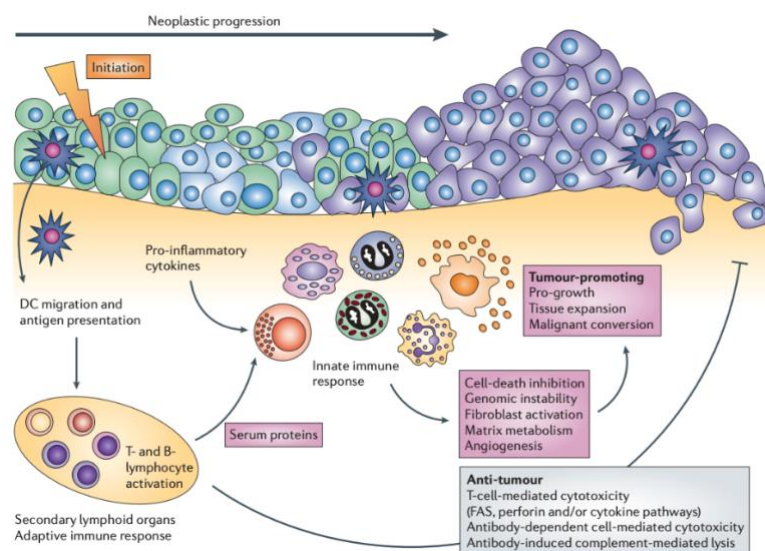


Figure 9 The innate and adaptive immune response in inflammation-related factors [80].

The convergence of both pathways leads to the stimulation of key transcription factors within tumor cells, including factor-kappa B (NF-κB), signal transducer and activator of transcription

3 (STAT3), and hypoxia-inducible factor 1-alpha (HIF1 α). These, in turn, induce the expression of cyclooxygenase 2 (COX-2) that catalyzes the production of prostaglandins and activates various inflammatory mediators such as chemokines and cytokines that attract inflammatory cells to the tumor site, including neutrophils, macrophages, and lymphocytes, which release additional pro-inflammatory cytokines and enzymes [80, 82]. Pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) further amplify the inflammatory response, promoting tumor cell proliferation, survival, and migration [66, 75, 79]. This interplay between growth factors, chemokines, enzymes, and pro-inflammatory cytokines creates an environment for tumor growth.

3.3. Chronic Inflammation and Prostate Cancer

Chronic inflammation in the prostate gland has been increasingly recognized as a potential risk factor and driver of prostate cancer development. Histopathological evidence from prostate tissue samples from prostate cancer patients has consistently found the presence of inflammatory cells infiltrating the tumor environment, while epidemiological studies have shown an association between chronic prostatic inflammation and an increased risk of prostate cancer [76, 83, 83, 84].

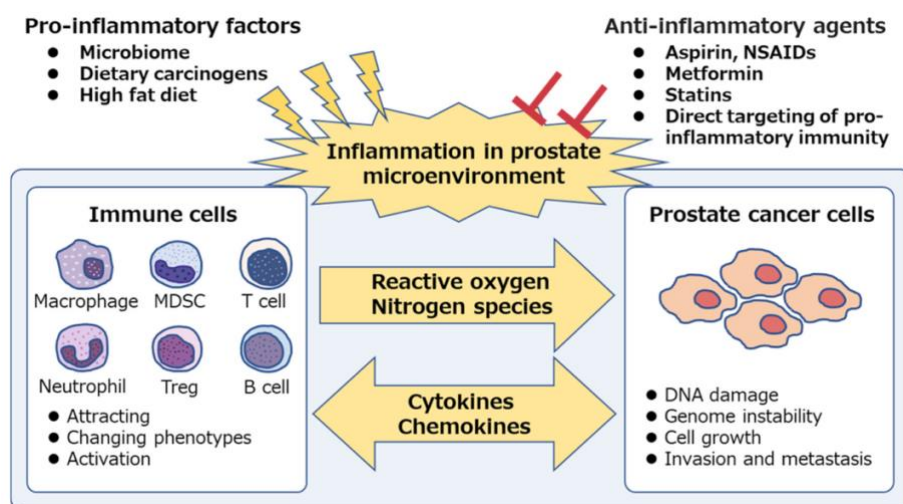


Figure 10 Chronic Inflammation and Prostate Cancer [83]

Figure 10 shows pro-inflammatory factors that are key elements behind prostatic inflammation, including microbiome and dietary carcinogens. Upon the exposure of these factors, various immune cells, macrophages, myeloid-derived suppressor cells (MDSC), T cells, neutrophils, regulatory T cells (Treg), and B cells participate in the inflammatory response. This inflammation leads to the generation of reactive oxygen and nitrogen species, which can

induce DNA damage in prostate epithelial cells and potentially initiate carcinogenesis. Cytokines and chemokines secreted by both immune and prostate cancer cells create an inflammatory microenvironment conducive to cancer progression [80, 82]. However, non-steroidal anti-inflammatory drugs (NSAIDs), metformin, statins, and agents that directly target pro-inflammatory immunity. These agents can disrupt the cycle of inflammation and may inhibit the development and progression of prostate cancer [82, 84]. In fact, a case-control study showed that aspirin had a protective effect against prostate cancer [85].

It is believed that a condition known as prostatic intraepithelial neoplasia (PIN), which involves the presence of abnormal cells within the prostate gland is considered a precursor to prostate cancer, where the apoptotic epithelial cells undergo morphological and genetic alterations. The inflammatory process in the prostate can lead to the formation of proliferative inflammatory atrophy (PIA), which is thought to contribute to the development of PIN and, ultimately, prostate cancer (figure 11) [66, 76, 80].

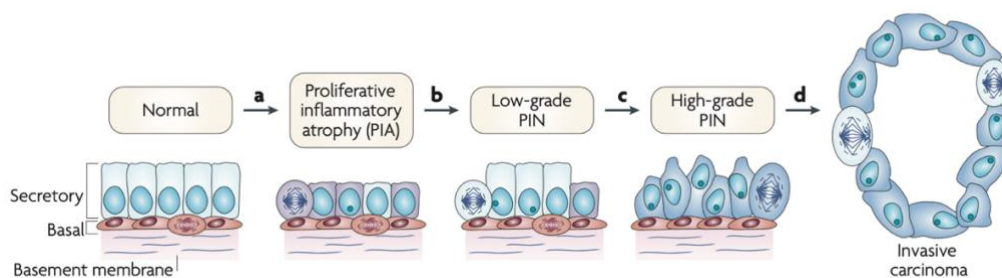


Figure 11 Cellular and molecular model of early prostate neoplasia progression [76]

Chronic inflammation may pose a significant risk for prostate cancer, with various factors contributing to its development. Although the underlying causes behind prostatic inflammation remain unclear. Various factors, including infections, hormonal fluctuations, urine reflux, and dietary patterns, all contribute to perpetuating inflammatory responses within the prostate gland (figure 12).

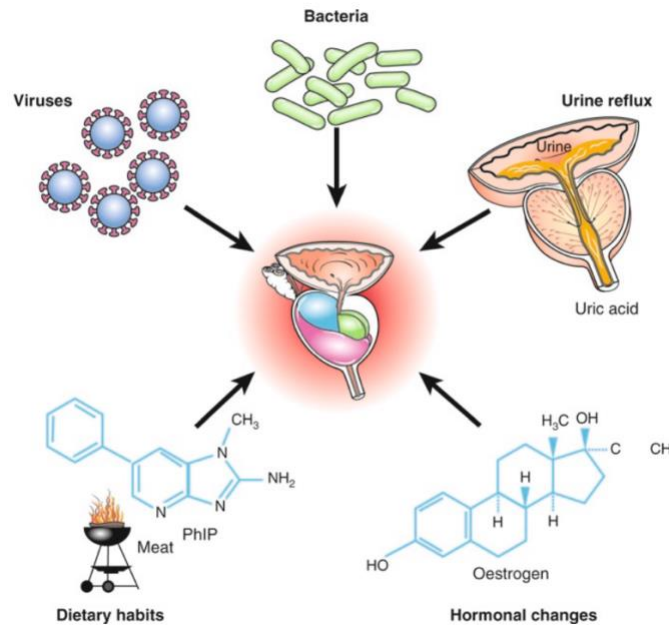


Figure 12 Possible Causes of Prostate Inflammation [86]

Additionally, genetic predisposition further modulates inflammatory responses, with emerging evidence suggesting that allelic variants of genes involved in inflammatory pathways, such as single nucleotide polymorphisms (SNPs) may influence the likelihood of developing prostate cancer [76, 82, 86, 87].

3.3.1. Infectious-related factors

The role of infectious agents, including bacteria and viruses, in the risk of developing prostate cancer has been a topic of extensive investigation for two decades. In fact, infectious agents have been observed to infect the prostate and trigger an inflammatory response, potentially contributing to prostate carcinogenesis. Sexually transmitted infections (STIs) have received extensive research compared to non-sexually transmitted infections. Studies have investigated the role of various pathogens, including *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, syphilis, herpes simplex virus (HSV), herpes papillomavirus (HPV) 16 and 18, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) in the occurrence of prostate cancer, yielding inconsistent results. According to a recent meta-analysis that included 47 studies and examined over 10 different infections, an association was observed between men who reported having any sexually transmitted infection (STI) and prostate cancer [88]. Early investigations of sexually transmitted infections in case-control studies were assessed by self-report, medical records abstraction, or registry query that focused mainly on gonorrhoea,

syphilis, and genital herpes [89–101]. Until recently, some prospective cohort studies investigated the relationship between STIs and PC [102–105]. Blood-borne viral infections such as hepatitis B and C that tend to infect and damage the liver were also studied for multiple types of cancers, including prostate cancer [41, 106–108]. Since STIs tend to be asymptomatic, additional resources for the study of prostate cancer have been developed. For instance, cohort studies with blood collection enable the prospective analyses of sexually transmitted infections and the risk of prostate cancer as well as serological detection of these infections [109]. The role of HSV-1 and HSV-2 viruses, CMV, *Trichomonas vaginalis*, and EBV were also studied through serological essays with varying results [110–117].

Among non-sexually transmitted infections, genitourinary infections such as prostatitis have received particular attention over the years. A meta-analysis that included 20 case-control studies observed an association between a history of prostatitis and prostate cancer [118]. Multiple studies have extended the investigation to study further other genitourinary infections, such as urethritis, orchitis, epididymitis, and pyelonephritis [119, 120]. Herpes Zoster, often known as shingles, is caused by the reactivation of the varicella-zoster virus (VZV) previously latent in the sensory ganglia and dorsal nerve roots after primary infection with VZV earlier in life [121]. Herpes zoster has been suggested to directly affect the development of cancer, including prostate cancer [122].

On the contrary, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to reduce the risk of prostate cancer risk. In fact, NSAIDs, such as aspirin, exert their effects through anti-inflammatory and antithrombotic properties, suppressing inflammation and inhibiting inflammatory metabolic cascade that lead to the synthesis of arachidonic acid, prostaglandins, prostacyclin, and thromboxane by targeting the enzyme cyclooxygenase 1 and 2 (COX) [83, 85].

3.3.2. Urological-related factors

The relationship between different types of stones and prostate cancer has been an interesting area of study that has gained attention in recent years, however; with inconclusive evidence. While a direct link between kidney or gallbladder stones, which are common urological conditions leading to chronic inflammation, and prostate cancer has not been established, some research has suggested that they might be potential risk factors.

Kidney stones, also known as renal calculi, are hard mineral and salt deposits that form in the kidney and can cause severe pain and discomfort when they pass through the urinary tract [123]. They are often composed of substances like calcium oxalate, calcium phosphate, uric acid, and struvite [123]. On the other hand, gallbladder stones are solid particles that vary in size and composition and are primarily made up of cholesterol, bilirubin, calcium salts, and other substances that form in the gallbladder, an organ located beneath the liver [124, 125]. While kidney and gallbladder stones occur in different parts of the body and are composed differently, they share some common risk factors. These include a diet high in oxalates or cholesterol, dehydration, insufficient fluid intake, which can lead to concentrated urine or bile, metabolic disorders, and obesity [126, 127].

The association between renal calculi and different types of cancer has received significant attention [128]. Individuals with a history of kidney stones may face an elevated risk of certain cancers, particularly those affecting the urinary system [127]. For instance, a cohort study revealed a notable increase in the risk of Renal Cell Carcinoma (RCC) among individuals with a history of kidney stones, particularly when stones were diagnosed before the age of 40. Additionally, the study revealed an increased risk of Upper Tract Urothelial Carcinoma (UTUC) among individuals with kidney stones [129], while another study done in Sweden revealed an increased risk for bladder cancer [130].

While research has predominantly focused on the relationship between kidney stones and cancers of the urinary tract, there has been an extended interest in understanding how kidney stones might influence the risk of prostate cancer, given the proximity of the prostate gland to the urinary tract and the potential for shared risk factors and biological pathways between these conditions (chronic inflammation or metabolic abnormalities). A population-based study that focused specifically on prostate cancer revealed that men who reported a history of kidney or bladder calculus had an increased risk of developing prostate cancer compared to those who didn't [131]. One mechanism that could explain why kidney stones contribute to the increased risk of cancer is that they induce chronic irritation and inflammation which typically triggers the recruitment of inflammatory cells, leading to the release of cytokines and chemokines. This process also generates free radical species from oxygen and nitrogen, which promote cancer irritation by enhancing cell proliferation, among other mechanisms [127, 132]. Gallbladder stones, also known as Cholelithiasis, can cause also cause discomfort and complications when they obstruct the bile ducts or gallbladder. Epidemiological studies have

explored the potential association between gallbladder diseases, specifically gallbladder stones, and the risk of prostate cancer. For instance, a meta-analysis, which included 7 studies involving 80,403 individuals, found that gallbladder stones were associated with an increased risk of prostate cancer in both European and Asian populations [133]. Although the exact mechanism underlying this relationship is not fully understood, one potential mechanism considering chronic inflammation has been suggested. Chronic systemic inflammation, often triggered by microbiota dysbiosis in the gut and biliary tract can promote tumorigenesis in the prostate gland. Another potential mechanism revolves around cholesterol metabolism. Cholesterol, essential for cell proliferation and tightly regulated during cell cycle progression, may play a role in prostate cancer development [125, 134].

3.3.3. Inflammatory Genetic Factors

Inflammatory genes play a crucial role in regulating the body's immune response to infection, injury, and other stimuli. They encode proteins involved in various aspects of the inflammatory process, including the production of signaling molecules called cytokines, the activation of immune cells such as macrophages and T-cells, and the regulation of inflammatory pathways. Dysregulation of inflammatory genes can lead to chronic inflammation, which is implicated in the development of various diseases, including cancer [135–137].

Single nucleotide polymorphisms (SNPs) in inflammatory genes can influence the function and regulation of these genes, thereby modulating the inflammatory response which in turn can impact the initiation, progression, and severity of the disease. In other words, SNPs are variations in a single nucleotide within a gene sequence that may affect how the gene is transcribed or translated into a functional protein. In the context of inflammatory genes, SNPs can alter the activity of proteins involved in the immune response. These genetic variations can influence an individual's susceptibility to diseases, their response to treatment, and their risk of developing related conditions [136, 138, 139].

Substantial evidence has shown that SNPs in inflammatory genes have been associated with an increased risk of prostate cancer, including the pattern recognition receptors MSR1, TLR1, and TLR4 [140, 141], the cytokine *TNF α* , and *IL1RN* [142, 143] and the pro-inflammatory gene *COX-2* [137, 144]. Research indicates that SNPs in genes related to the innate immunity and inflammation pathways may contribute to the development and progression of prostate cancer. Cyclooxygenase-2 (COX-2) is an enzyme that plays a crucial role in the

inflammatory process by catalyzing the conversion of arachidonic acid to prostaglandins, which are key mediators of inflammation and pain [137]. The role of Cyclooxygenase-2 (COX-2) in prostate cancer has been extensively studied, revealing its significant involvement in the disease's progression and potential as a therapeutic target. COX-2 is frequently overexpressed in various malignancies, including prostate cancer [145–147]. A recent meta-analysis showed that COX-2 +202 C>T (rs2745557) polymorphism was significantly associated with an increased risk of prostate cancer [148], while another meta-analysis done by Zhang et al. showed an association with prostate cancer in Caucasians but not for other ethnicities [149]. COX-2 is overexpressed in prostate cancer, particularly in the advanced stages of the disease. It has been reported to be consistently elevated in premalignant lesions such as prostatic intraepithelial neoplasia and carcinoma [145]. This overexpression is linked to several key processes in cancer progression, including cell proliferation, inhibition of apoptosis, angiogenesis, and the facilitation of metastasis [79].

3.3.4. Interaction between COX-2 & inflammation related-factors

Variations in inflammation-related genes may serve as modifiers of disease susceptibility rather than acting as sole determinants. Gene-environment interactions (G×E) occur when the impact of environmental exposures on disease risk varies depending on individuals' genetic makeup, or vice versa. Investigating G×E interactions helps predict disease risk based on genotype, identifies the most vulnerable subgroups, and could aid in identifying risk factors by targeting those susceptible subgroups [150].

Currently, there is a lack of research on the interaction between infection or stone-related factors and inflammation genes, particularly COX-2 gene, and prostate cancer. However, the G×E between COX-2 polymorphism and the use of NSAIDs in relation to prostate cancer risk is a significant area of research. One research highlighted that certain SNPs in the COX-2 gene are associated with a modified risk of prostate cancer when interacting with NSAID use. For instance, the SNP rs2745557 in the COX-2 gene was found to be significantly associated with a lower risk of prostate cancer [151]. This interaction effect was particularly noted for the use of ibuprofen, suggesting a protective effect in men carrying the minor allele [151]. Therefore, this interaction indicates that both genetic predisposition and environmental exposure are important in modulating prostate cancer risk.

4. Hypothesis and Objectives

Chronic inflammation emerged as a common denominator in the development of several cancers, spanning the esophagus, stomach, liver, colon, and bladder. In fact, chronic inflammatory states account for about 20% of all human carcinogenesis. De Marzo et al. proposed a biological mechanism for prostate carcinogenesis, suggesting 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 [76].

Understanding the potential link between different infectious agents and prostate cancer is important, given the established role of chronic inflammation in cancer development. Various pathogens, whether transmitted sexually or through other means, can trigger inflammation within the prostate. Despite the existing literature suggesting a potential association, the majority of studies have focused on specific pathogens with inconsistency in the results. Therefore, taking into account the role of multiple pathogens and their combined effect is imperative. Additionally, limited attention has been paid to the role of viral infections especially non-sexually transmitted viral infections, leaving a critical gap in the understanding of infectious agents. Therefore, a comprehensive consideration of all types of infectious agents encompassing both bacterial and viral pathogens, whether transmitted sexually or not is crucial to clarify their potential role in prostate cancer development.

Certainly, both kidney and gallbladder stones are common urological conditions with a very high prevalence in the general population. Given their significant impact on urological health, particularly due to the chronic inflammation they induce, it is also essential to investigate their potential role as risk factors for prostate cancer. However, research in this area is relatively limited, with existing studies offering inconsistent results and leaving significant gaps in our understanding. Therefore, despite their potential relevance, the relationship between calculi and cancer, particularly prostate cancer, remains largely undefined, highlighting the need for further investigation.

Several findings, particularly through genome-wide association studies (GWAS) and fine-mapping efforts, have revealed that over 100 common SNPs are associated with prostate cancer susceptibility [152]. For instance, genetic variation in the COX-2 gene may influence the expression and function of the COX-2 enzyme, thereby, making the individual susceptible to

prostate cancer. Several potentially functional variants that are associated with prostate cancer risk have been acknowledged within the COX-2 gene. However, the existing research in this area is limited, with relatively few studies specifically focusing on COX-2 genetic variations, and the results obtained so far are contradictory. Moreover, the sample sizes of previous studies have often been small, limiting their statistical power to detect any significant associations.

Finally, the majority of research, whether focusing on the association of infectious agents, different types of stones, or genetic susceptibility with prostate cancer, has primarily investigated the overall prostate cancer risk without specifically exploring their impact on the aggressive forms of the disease. Given that aggressive forms of prostate cancer affect approximately 20% of cases, often occurring in younger men, it is crucial to investigate further the different risk factors associated with prostate cancer while taking into account its aggressive forms.

Chronic inflammation represents potential avenues for investigation, and addressing the gaps in our understanding of inflammation-related factors is crucial for advancing preventive and therapeutic strategies. Consequently, it is important to identify modifiable risk factors for prostate cancer to further understand its etiology and mitigate its impact on public health.

In this context, the general objective of this thesis was to investigate the role of chronic inflammation and related factors in the occurrence of prostate cancer, particularly focusing on its aggressive forms, using data from a population-based case-control study conducted in France also known as EPICAP (EPIdémiologie des Cancers de la Prostate).

The three specific objectives of this thesis were to:

- 1) Study the role of infectious agents, both bacterial and viral, whether sexually or non-sexually transmitted infections, in the occurrence of prostate cancer.
- 2) Study the role of kidney and gallbladder stones in the occurrence of prostate cancer.
- 3) Study the role of single nucleotide polymorphisms (SNPs) of COX-2, and the interaction (GxE) of these SNPs with our variables of interest, namely infections and stones, in the occurrence of prostate cancer.

The first part of this work focused on the existing state of knowledge regarding prostate cancer and its etiology. In the second part, we will present the EPICAP study upon which this thesis is based. The third part will explore the impact of infectious agents in the risk of developing prostate cancer. A fourth part will address the role of kidney and gallbladder stones in prostate cancer risk. In the fifth part, we will present the genetics part of EPICAP, focusing on the role of SNPs of COX-2 gene, and its interaction with our factors of interest. The sixth part will be an integrated discussion encompassing all three objectives. Finally, to conclude this work, we will explore potential avenues for further research perspectives to enhance our understanding in this field.

CHAPTER 2 – PRESENTATION OF THE EPICAP STUDY

1. EPICAP Study

The EPICAP study was designed to address multiple research questions related to prostate cancer etiology. Its primary objective was to investigate the role of environmental and genetic factors in the occurrence of prostate cancer, with a specific interest on tumor aggressiveness. This includes examining the impact of chronic inflammation, hormonal and metabolic factors, circadian disruption, professional factors, and genetic predispositions. A secondary objective will be to assess prognostic factors.

EPICAP is a population-based case-control study that was conducted in the department of Hérault in the South of France (figure 13). Hérault was particularly selected due to several factors. Firstly, it hosts a comprehensive cancer registry established 26 years ago, with a specific interest on prostate cancer, due to the collaborative efforts with the Regional Association for Clinical Research. The department's diverse landscape, including both agricultural and urban elements, was particularly interesting for the study of pesticides. Coupled with the size of its population exceeding one million inhabitants, this diversity enabled the identification of a significant number of cases and efficient data collection in a relatively short period of time. [153].

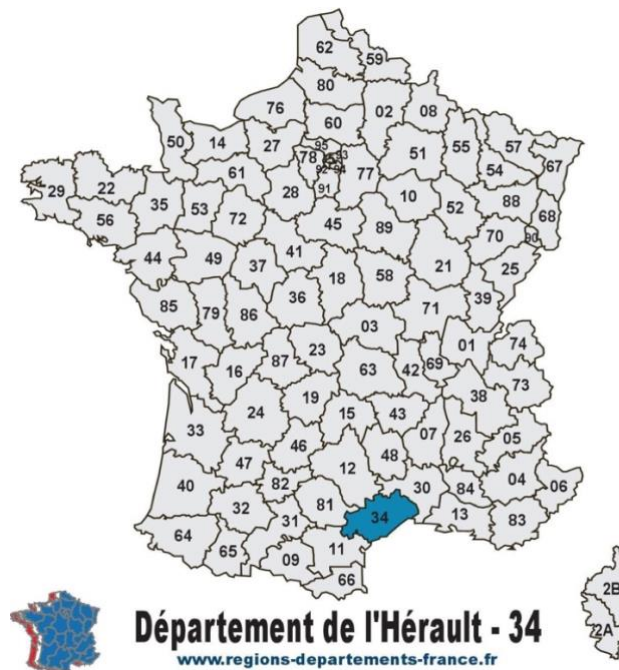


Figure 13 Geographic Location of the department of Hérault [154]

1.1. Study Population

1.1.1. Selection of Cases

Eligible cases for inclusion in the study are individuals who were newly diagnosed with prostate cancer between 2012 and 2013, were under 75 years old at the time of diagnosis, and were residents of the Hérault department. Clinical research nurses, who were specifically recruited and trained for the study, conducted the identification of cases across all participating centers, including three public hospitals and three private urology clinics. The registry was used for the postpriori validation of cases included in the EPICAP study. Furthermore, patients were only included in the study after obtaining their consent, and only those with histologically confirmed cases were considered.

1.1.2. Selection of Controls

Controls were randomly selected from the general male population without a history of cancer and residing in the study area (Hérault department) at the time of cases' diagnosis. In order to achieve frequency matching and ensure similarity in age distribution between cases and controls, quotas based on age were established within 5-year age groups. Additionally, quotas based on socioeconomic status (SES) were set as a priori to control for selection bias stemming from differential participation rates across SES categories. Quotas based on socioeconomic status (SES) were determined using census data specific to each study area provided by the National Institute of Statistics and Economics Studies (INSEE). The goal was to achieve an SES distribution among controls that closely matched the SES distribution among men in the general population while considering age.

The recruitment on controls followed a structured process: random phone numbers from private residences were drawn through a French polling institute (IPSOS) and selected through public procurement. To reach all households in the department, including those listed on the do-not-call registry, a method involving incrementing the selected telephone number by 1 in the directory was done, and each selected phone number was dialed up to 20 times at varying times and days until contact was established with residents.

If a man fitting the age and SES criteria was reached, he was invited to participate in the EPICAP study unless the quotas for his demographic group had already been filled. Participants were excluded when the quota was achieved. The list of participating male controls was provided

to the research team on a monthly basis, and the clinical research nurses contacted them within 2 to 3 days.

⇒ Among the 1,098 identified eligible prostate cancer cases and 1,109 identified eligible population-based controls in the EPICAP Study, 819 cases and 879 controls were included in total, with participation rates of 75% and 79%, respectively (figure 14).

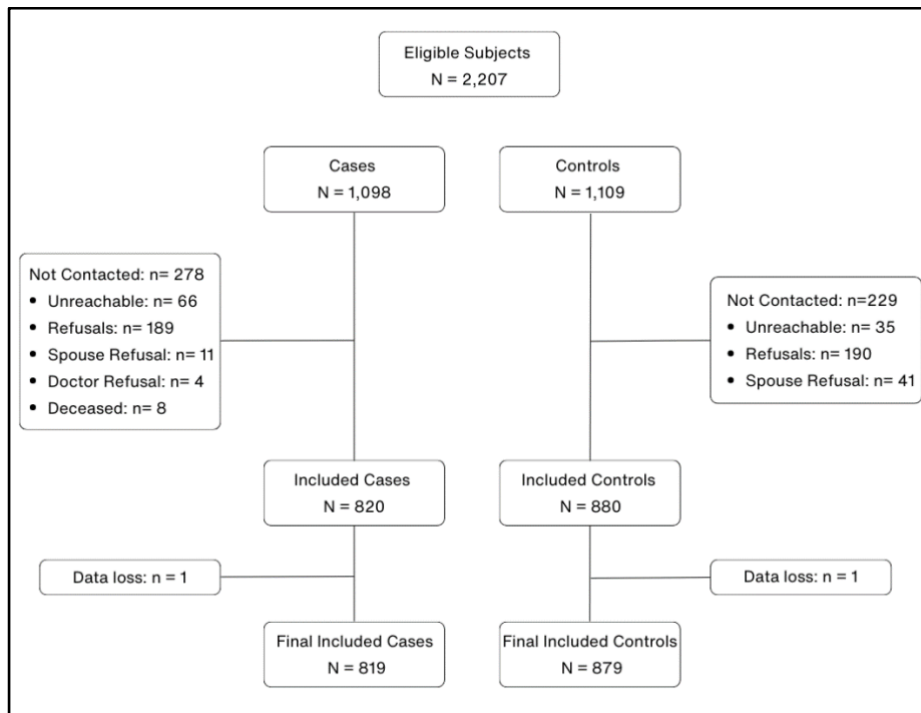


Figure 14 EPICAP cases and controls selection flowchart

1.2. Data Collection

Cases and controls underwent face-to-face interviews conducted by a research clinical nurse well-trained for this study. The data collection process was identical for both cases and controls. Participants were offered the option of providing a blood sample, a saliva sample was proposed as an alternative. However, if both options were not feasible or if the participant declines both options, that does not lead to their exclusion from the study.

For data collection, both cases and controls were interviewed under the same conditions, conducted at the homes of the participants. Data collection involved administering questionnaires, conducting anthropomorphic measurements, taking biological samples, and consulting medical records to gather case-specific medical information.

1.2.1. General Questionnaire

Interviews with both cases and controls in the EPICAP study were conducted using a system-standardized questionnaire administered through a face-to-face method known as CAPI (Computer Assisted Personal Interview). These interviews, lasting 2 to 4 hours, aimed to gather comprehensive information on the various aspects, including sociodemographic characteristics, professional and residential history, lifestyle habits, medical history, and ethnic origin.

Environmental factors, encompassing details on places of residence and lifestyle habits such as tobacco, alcohol consumption, sleep patterns, leisure activities, and physical activity, were collected.

Family history of cancer among first and second-degree relatives was also examined, documenting cancer occurrence, localization, and age of onset for each affected relative.

Infectious and inflammatory factors were collected through detailed questions on hospitalization, surgeries, infectious diseases (sexually and non-sexually transmitted infections), inflammatory conditions, and medication history including non-steroidal anti-inflammatory drugs and antibiotics.

Overall, the questionnaire covers a wide range of factors, providing a comprehensive understanding of participants' health, lifestyle, environment, and familial background.

1.2.2. Anthropomorphic Measurements

Nurses conducted measurements of weight, height, abdominal circumference, and hip circumference for both the cases and controls, supplementing the information obtained from the questionnaire.

1.2.3. Biospecimen Collection

Blood samples were proposed to both cases and controls by nurses. When participants refused blood sampling, saliva collection via an Oragene kit was proposed as an alternative. These samples were used to establish a DNA bank (DNAthèque) stored at the Biological Resources Center (CRB Epigenetec) of Saints-Pères in Paris (INSERM U1147). In total, 1626 subjects; 794 cases and 832 controls, underwent either blood or saliva sampling. Among the available samples, sufficient DNA was extracted from 1,565 subjects, of which 766 were cases, and 799 were controls.

1.2.4. Clinical Data for Cases

Clinical data for cases were collected by clinical research nurses either from medical records at the time of diagnosis or from the cancer registry of Hérault postpriori. This included the initial PSA value at diagnosis, Gleason score derived from histological examination of biopsy and/or prostatectomy specimens, TNM stages, and details of treatments administered.

1.3. Variables of Interest

1.3.1. Established Risk Factors of Prostate Cancer

1.3.1.1. Age

The age considered was the age at the reference date, meaning the date of diagnosis for cases and the date of interview for controls. Subsequently, the reference age was categorized into five ordinal classes in 5-year intervals: <55 years, 55-59 years, 60-64 years, 65-69 years, and ≥ 70 years to describe the distribution by age groups of the participants.

1.3.1.2. Ethnicity

The ethnic group was created by combining the participant's declared ethnic group and country of birth. This allowed us to distinguish three primary ethnic groups: individuals of Caucasian descent, individuals of African heritage (including those from the Caribbean, Reunion Island, and African countries), and others (including individuals from Latin America, Asia, and the Middle East). Due to the limited size of the last two ethnic groups, we combined individuals of African heritage and those from other ethnic group backgrounds into one single category for statistical analysis.

1.3.1.3. Family history of Prostate Cancer

Information on family history of prostate cancer among first-degree relatives (parents, children, siblings) and second-degree relatives (grandchildren, nephews, nieces) were collected. For each affected relative, the site of occurrence and age of cancer onset were recorded. We focused on the diagnosis of prostate cancer in at least one first-degree relative (father, son, brothers). Therefore, the variable "Family History of Prostate Cancer" was categorized into two classes: yes if at least one first-degree relative had been diagnosed with prostate cancer and no if none of the first-degree relatives had been affected by this cancer.

1.3.2. Principle Variables

1.3.2.1. Exposure Variables

In our study, we examined exposure variables categorized into two main groups: infectious agents and calculi.

- Infectious Agents: we have identified approximately 15 distinct infections, including both bacterial and viral pathogens that can be either transmitted through sexual or non-sexual routes. These infections have been categorized separately into two classes for the analysis. Individuals were classified as 0 if they were free from any infection, whereas those classified under class 1 were infected with the identified pathogen.
- Calculi: In the calculi group, we have identified two primary types of calculi, including kidney stones and gallbladder stones. These calculi are also categorized into two classes, distinguishing between individuals who have experienced these conditions separately (coded as 1) and those who have not (coded as 0)

1.3.2.2. Outcome Variable

The Gleason score at diagnosis was obtained from the collected data. The Gleason score was categorized into two different groups while combining the different grades:

- Low-grade or mildly aggressive tumors: This category included Gleason score values <7 or $=7$, including subjects whose tumors predominantly exhibited grades 3+4. Cases with unknown tumor aggressiveness were included in this group based on the assumption that the absence of grade information suggests that prostatic cells are still differentiated and likely represent low grades of prostate cancer.
- High-grade or aggressive tumors: This category included Gleason score values >7 or $=7$, including subjects whose tumors predominantly exhibited grades 4+3. These tumors were considered aggressive due to the presence of higher-grade cells.

In summary, we established two dependent variables. The first variable indicates whether the individual was diagnosed with cancer, coded as 0 in the absence of cancer and 1 if diagnosed with cancer. The second variable indicates the aggressiveness of cancer and is categorized into three classes: 0 for no cancer, 1 for low-grade cancer, and 2 for high-grade cancer.

1.3.3. Potential Confounding Variables

1.3.3.1. Education Level

Education level was determined by the highest diploma achieved. Within the study group, individuals ranged from those without diplomas to those with qualifications equivalent to primary level (including Certificate of Primary Studies (CEP), Vocational Certificate (BEP), Vocational Aptitude Certificate (CAP), or equivalent), secondary (such as baccalaureate, vocational diploma), or university level (including Baccalaureate + 2 years or higher diploma). Finally, the education level variable was categorized into three groups: " \leq Primary," "Secondary," and "Tertiary."

1.3.3.2. Body Mass Index (kg/m²)

The variable "Body Mass Index" (BMI) was calculated by dividing the weight in kilograms, two years prior to the reference date reported by both cases and controls, by the square of height in meters. Subsequently, according to the international classification established by the World Health Organization (WHO), participants' BMI was categorized into three ordinal classes: BMI < 25 kg/m², BMI between 25 and 29 kg/m², and BMI \geq 30 kg/m².

1.3.3.3. Waist Circumference (Cm)

The variable "Waist Circumference" was categorized into two groups using the European standard: those with a WC of 94 cm or less at the reference date, and those with a waist circumference greater than 94 cm.

1.3.3.4. Smoking Status

The variable describing smoking status was categorized into three classes distinguishing between non-smokers, former smokers, and current smokers.

1.3.3.5. Alcohol Consumption

The variable describing alcohol consumption was categorized into two classes: those who had never consumed alcohol in their life, and those who had reported regular consumption, which is defined as consuming alcohol at least once a month for one year.

1.3.3.6. Physical Activity (MET -h/wk/yr)

The EPICAP questionnaire included a question regarding weekly physical activity lasting at least one hour for a year. Those responding "No" were labeled as "Non-active." For "Yes"

responses, details on activity type, duration, and frequency were gathered. Using this data, energy expenditure for each activity was estimated in metabolic equivalent (MET). MET hours/week/year were then calculated by summing activity-specific MET values, divided by age to obtain the average. Quartiles were derived from control population data, categorizing physical activity into five levels: Non-active, Q1 (< 6.25 MET-h/week/year), Q2 (6.25-13.0 MET-h/week/year), Q3 (13.0-24.15 MET-h/week/year), and Q4 (\geq 24.15 MET-h/week/year).

1.3.3.7. Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

The variable "Total NSAIDs" was defined to encompass aspirin and non-aspirin NSAIDs (including COX-2 inhibitors such as Celebrex[®] and Vioxx[®]). These three types of drugs were classified into a binary variable (exposed/non-exposed). Exposure was defined as consuming aspirin or non-aspirin NSAIDs at least once a month, or both. Subjects who had never taken NSAIDs or took them less than once a month were considered non-exposed.

1.3.3.8. Hypertriglyceridemia

Hypertriglyceridemia was assessed by combining information from lipid profile data, if participants had undergone testing, and responses to the question "Has a doctor ever diagnosed you with hypertriglyceridemia?" EPICAP study subjects were considered to have hypertriglyceridemia if their triglyceride levels were equal to or greater than 1.5 g/L or if they had received a diagnosis of hypertriglyceridemia. Treatment for hypertriglyceridemia, was also taken into account and evaluated based on the question "Have you ever been treated for hypertriglyceridemia?"

1.3.3.9. Hypercholesterolemia

Hypercholesterolemia was determined based on lipid profile data, if available, and responses to the question "Has a doctor ever diagnosed you with hypercholesterolemia?" EPICAP male participants were considered to have hypercholesterolemia if their HDL-cholesterol levels were below 0.4 g/L or if they had received a diagnosis of hypercholesterolemia. Treatment for hypercholesterolemia, was also considered and evaluated based on the question "Have you ever been treated for hypercholesterolemia?"

1.4. Description of EPICAP Population Characteristics

1.4.1. Description of Cases

The majority of cases exhibited a low-grade tumor (77.3%) and had a PSA level at diagnosis ranging between 4 and 10 ng/ml (70.4%). The characteristics of prostate cancer cases are outlined in Table 2.

Table 2 Clinical Characteristics of Cases at Diagnosis

	Cases n=819 (%)
Gleason Score	
≤ 7 (3+4)	623 (77.3)
≥7 (4+3)	183 (22.7)
PSA level at Diagnosis (ng/ml)	
<4	33 (4.1)
4-10	562 (70.4)
>10	203 (25.4)

1.4.2. Comparison of Characteristics between Cases and Controls

The distribution of characteristics between cases and controls was similar (Table 3). The distribution of age did not show a statistically significant difference between cases and controls ($p=0.144$), with an average age of 65 years and a standard deviation of 6 years. The ethnic origin was predominantly Caucasian, with 97.1% among cases and 97.7% among controls, which was statistically comparable ($p=0.396$). Anthropomorphic measurements, including BMI distribution ($p=0.534$) and waist circumference (0.086), showed no significant differences between cases and controls. Sociodemographic and lifestyle characteristics such as education level ($p=0.609$), smoking status ($p=0.288$), alcohol consumption ($p=0.591$), and physical activity ($p=0.109$) were quite comparable between the two groups. Notably, the use of non-steroidal anti-inflammatory drugs ($p=0.043$) was more frequent among cases (27%) than in controls (22.5%). Regarding the lipid profile, hypertriglyceridemia differed slightly between cases and controls, with respective percentages of 18.4% and 22.5% ($p=0.037$), while hypercholesterolemia exhibited no significant difference between cases and controls ($p=0.263$). As expected, a family history of prostate cancer was significantly more frequent in cases (22.2%) than in controls (8.8%) yielding a p -value <0.001 .

Table 3 Population Characteristics between Cases and Controls from the EPICAP Study

	Cases n=819 (%)	Controls n=879 (%)	P-value*
Age (Years)			<i>0.144</i>
< 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			<i>0.396</i>
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			<i>0.609</i>
≤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)			<i>0.534</i>
<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)			<i>0.086</i>
≤94	209 (25.9)	254 (29.6)	
>94	599 (74.1)	603 (70.4)	
Smoking Status			<i>0.288</i>
Never	240 (29.3)	246 (28)	
Former	455 (55.6)	476 (54.2)	
Current	123 (15.0)	157 (17.9)	
Alcohol Consumption**			<i>0.591</i>
No	72 (8.8)	84 (9.6)	
Yes	746 (91.2)	795 (90.4)	
Physical Activity (MET -h/wk/yr)***			<i>0.110</i>
No	177 (20.1)	191 (23.3)	
<6.5	174 (19.8)	151 (18.4)	
6.25-13.0	174 (19.8)	138 (16.8)	
13.0-24.15	175 (19.9)	147 (17.9)	
≥24.15	174 (19.8)	187 (22.8)	
Nonsteroidal anti-inflammatory drugs			0.043
No	596 (73.0)	593 (68.6)	
Yes	220 (27.0)	272 (31.5)	
Hypertriglyceridemia			0.037
No	668 (81.6)	681 (77.5)	
Yes	151 (18.4)	198 (22.5)	
Hypercholesterolemia			<i>0.263</i>
No	474 (57.9)	496 (56.4)	
Yes	343 (41.9)	376 (42.8)	

*p-value of Chi-square

** For alcohol consumption: at least once a month for one year

*** No Physical Exercise: Less than one hour per week for at least one year

1.4.3. Previous Results Inferred from the EPICAP Study

Within the EPICAP study, significant insights have been inferred regarding the relationship between chronic inflammation and prostate cancer, including several key analyses that explore various inflammatory-related factors and their effect on prostate carcinogenesis. Specifically, these findings highlight the different associations between genitourinary infections and prostate cancer risk, the impact of NSAID use on this relationship, the role of abdominal obesity as a modifiable risk factor for prostate cancer, and the influence of diabetes and metabolic syndrome (MetS) on prostate cancer risk. Furthermore, significant results have been also obtained regarding the associations between family history of prostate cancer, disruptions in circadian rhythms due to night work, and different professional factors.

1.4.3.1. Family History of Prostate Cancer

As expected, EPICAP confirmed the known association between family history of prostate cancer and increased prostate cancer risk, with an odds ratio of 3.10 (95% CI 2.32-4.15) for men with affected first-degree relatives. Additionally, a family history of early breast cancer (before age 50) in first-degree relatives was associated with an increased risk of prostate cancer, particularly for the aggressive forms, with an odds ratio of 1.79 (95% CI 1.09-2.94). This association was strongest for breast cancer in daughters, with a remarkably high odds ratio of 15.26 (95% CI 1.95-120). This may indicate a shared genetic or environmental basis for breast and prostate cancers, potentially involving altered genes in DNA repair mechanisms [155].

1.4.3.2. Circadian Rhythm

Regarding the relationship between night work and prostate cancer risk, taking into account various patterns and durations of night work, results revealed that men who worked more than ten-night shifts per month for over six years had an increased risk of prostate cancer, with an OR of 1.92 (95% CI 0.81-4.58) compared to those who did not engage in night work. Additionally, men working fewer than ten night shifts per month but for over six years had a slightly elevated risk, with an OR of 1.35 (95% CI 0.49-3.76), suggesting that prolonged exposure to night work may contribute to an elevated risk of prostate cancer [156].

To delve deeper into the topic, associations between circadian gene polymorphisms and prostate cancer risk were examined. Results show that the overall circadian pathway was

significantly associated with prostate cancer risk ($p=0.03$), with an even stronger association for the core circadian gene pathway ($p=0.0006$). At the gene level, NPAS2 and PER1 were significantly associated with overall prostate cancer risk (FDR $p=0.06$ for both), while RORA was significantly associated with aggressive prostate cancer (FDR $p=0.09$). Additionally, ever having worked at night showed a suggestive interaction with the circadian pathway ($p=0.01$). Among night workers, significant associations were found for ARNTL, NPAS2, and RORA. Finally, long duration of night work (≥ 20 years) and night shifts >10 hours were associated with an increased risk of aggressive prostate cancer. These findings provide evidence for a link between circadian rhythm disruption and prostate cancer risk, both at the genetic and environmental levels [157, 158].

1.4.3.3. Professional Factors

In terms of different professions, the association between occupational exposure and the risk of developing prostate cancer has been explored, focusing on various professions to see if long-term employment in certain fields may influence cancer risk. Results revealed that specific professions were associated with increased risks of aggressive prostate cancer: medical, dental, and veterinary workers OR: 5.01 (95% CI 1.27; 19.77), surveyors and draughtsmen OR: 2.11 (95% CI 1.06; 4.21), armed forces members OR: 5.14 (95% CI 0.99; 26.71), and fishermen OR: 5.10 (95% CI 1.20; 21.61). Additionally, increased risks of overall prostate cancer were observed for legislative officials and government administrators OR: 3.30 (95% CI 1.10; 9.84), and managers OR: 1.68 (95% CI 1.18; 2.41). In contrast, decreased risks were noted for service workers OR: 0.78 (95% CI 0.60; 1.01), production and transport workers OR: 0.7 (95% CI 0.60; 0.95), and food and beverage processors OR: 0.58 (95% CI 0.35; 0.96). Night shift work, chronic stress, and sedentary behavior are linked to higher prostate cancer risk in professions like medical workers, armed forces members, and administrative staff. Chemical exposures, such as pesticides, may also contribute to prostate cancer risk in certain occupations. In contrast, physical activity in manual labor jobs and higher screening rates in higher socioeconomic status occupations may influence prostate cancer risk differently [159].

1.4.3.4. Metabolic factors

For the role of abdominal obesity in prostate cancer risk, the results showed that indicators such as waist circumference (WC) and waist-hip ratio (WHR) were associated with an increased

risk of prostate cancer, particularly for the aggressive types of the disease. The findings indicated a slight, but not significant, increased risk of prostate cancer for men with WC > 94 cm (OR 1.20, 95% CI 0.92–1.56) and WHR \geq 0.95 (OR 1.30, 95% CI 1.00–1.70). These associations were more pronounced for aggressive prostate cancer, with OR 1.72 (95% CI 1.07–2.77) for WC 94-102 cm, OR 1.80 (95% CI 1.13–2.88) for WC > 102 cm, and OR 1.56 (95% CI 1.01–2.42) for WHR > 1.00 [160]. Additionally, they identified different BMI trajectory groups and their corresponding risks. Men with a consistent pattern of overweight or obesity had higher odds of developing prostate cancer compared to those with a stable normal weight. For instance, the OR for men with a lifetime trajectory of overweight was 1.44 (95% CI 1.08–1.92) compared to those with stable normal weight. Additionally, the risk was more pronounced for aggressive prostate cancer, with an OR of 1.57 (95% CI 1.12–2.20), indicating that maintaining a healthy weight throughout life could be crucial in reducing prostate cancer risk [160, 161].

Finally, the latest analysis examined the role of diabetes and MetS (Metabolic Syndrome) and the risk of prostate cancer. There was no overall association between diabetes and prostate cancer risk with an OR of 0.90 (95% CI 0.67–1.21). However, an inverse association was observed with increasing duration of treated diabetes, showing a significant trend.

Regarding MetS, there was also no significant association with prostate cancer risk, yielding an OR of 0.84 (95% CI 0.65–1.08). However, NSAID use appeared to modify these associations where non-users showed positive associations between MetS components and aggressive prostate cancer, while users exhibited inverse associations [162].

1.4.3.5. Inflammation related factors

Following these insights, results revealed that the use of non-steroidal anti-inflammatory drugs is associated with a reduced risk of prostate cancer. Overall, NSAID use was inversely related to prostate cancer risk, yielding an OR of 0.77 (95%CI: 0.61–0.98). The protective effect was more pronounced for NSAIDs that inhibit COX-2, yielding an OR of 0.48 (95%CI: 0.28–0.79). For non-aspirin NSAID, there was a significant reduction in risk, particularly among men with the aggressive type and those with a history of prostatitis. Finally, aspirin use had a non-significant but negative association, however a significant protective effects with daily use, use for 5-10 years, and current use [163].

Going deeper into the relationship between genitourinary infections and prostate cancer, the findings revealed a significant association, specifically in men with a history of chronic prostatitis yielding an OR of 2.95 (95% CI: 1.26–6.92), and those with a history of acute pyelonephritis yielding an OR of 2.66 (95% CI: 1.29–5.51), indicating an increased risk of prostate cancer. These results suggest that persistent inflammation, potentially initiated by these infections, may play a role in prostate carcinogenesis by creating a microenvironment conducive to cancer development [120]. Another key finding was on the impact of NSAID use on the relationship between genitourinary infections and the risk of prostate cancer. The results revealed that the association was particularly significant in men who did not use NSAIDs. For instance, men who did not use NSAIDs and had a history of prostatitis had an OR of 2.11 (95%CI: 1.29-3.43), suggesting that NSAIDs may mitigate the inflammation-related risk of prostate cancer and highlighting the potential role of anti-inflammatory medications in prostate cancer prevention [120].

These findings collectively address chronic inflammation through various means within data from the EPICAP study. By expanding the scope of our research, we aim to provide further information about other specific inflammatory-related factors and their contribution to prostate cancer risk. Therefore, building on these findings, this thesis continues the exploration of chronic inflammation factors and their relationship with prostate cancer by further investigating other types of infections, the role of kidney and gallbladder stones, and genetic susceptibility specifically targeting the Cox-2 gene.

CHAPTER 3 – INFECTIOUS AGENTS & PROSTATE CANCER

1. Introduction

1.1. Definition and Prevalence

Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, fungi, and parasites [164]. These pathogens are capable of invading the human body and multiply within the host, disrupting normal functions and leading to various illnesses. Infectious diseases can spread through multiple routes, including direct contact with infected individuals, ingestion of contaminated food or water, inhalation of airborne pathogens, or via vectors such as mosquitoes and ticks [164–166].

These infections are prevalent to varying degrees globally, impacting different populations and regions. For instance, Gonorrhoea, caused by the bacterium *Neisseria gonorrhoeae*, was estimated by the WHO with 82.4 million new cases among adolescents and adults, with a global incidence of 21 per 1000 individuals [167]. Syphilis, caused by *Treponema pallidum*, is responsible for around 7.1 million new cases in 2020 among individuals aged between 15 and 49 years old [168]. *Trichomonas vaginalis* infection, known as trichomoniasis, affects an estimated 156 million people aged between 15-49 years old in 2020 [169]. Urethritis, an inflammation of the urethra often caused by sexually transmitted infections like gonorrhoea and chlamydia, has variable prevalence rates depending on the causative agent but remains a common condition in sexually active populations [170].

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* and often affects the lungs, had an estimated 10.6 million new cases in 2022 and a total of 1.3 million died from it [171]. Herpes zoster, or shingles, caused by the reactivation of the varicella-zoster virus, primarily affects older adults and those with weakened immune systems and affects about 1 in 3 people in the United States during their lifetime [172]. Epstein-Barr virus (EBV), the causative agent of infectious mononucleosis, is nearly ubiquitous, with over 90% of adults globally at some point in their lives is usually asymptomatic [173].

Polio, caused by the poliovirus, mainly affects children under the age of 5 and has seen a dramatic decrease in incidence due to vaccination efforts, with only a limited number of cases reported annually in certain regions. Cases have declined by over 99% since 1988, from an estimated 350,000 cases in more than 125 countries to just two endemic countries in October 2023 [174]. Dengue, a mosquito-borne viral infection, affects an estimated 390 million people

annually, with 96 million cases showing clinical manifestations [175]. Herpes simplex virus (HSV) types 1 and 2 cause genital and non-genital herpes, with HSV-1 affecting about 67% of the global population under 50, which is an estimated 3.7 billion people, and HSV-2 affecting around 13%, which is an estimated 491 billion people [176]. Viral hepatitis, including hepatitis B and C, affects millions worldwide, with hepatitis B affecting about 254 million people with 1.2 million new cases each year and 1.1 million deaths [177], while Hepatitis C affecting around 50 million people with 1 million new cases each year with approximately 242,000 death in 2022 [178].

For almost 25 years, research has explored the potential associations between infectious agents and prostate cancer development. Currently, over 20% of the global cancer burden can be attributed to infectious agents such as viruses, bacteria, and parasites [179, 180]. Therefore, the first objective of this thesis is to investigate the role of various infections whether sexually or non-sexually transmitted and their risk in the development of prostate cancer.

1.2. Infectious Agents and Prostate Cancer

Infectious agents, which are inflammation-related factors, have been the subject of extensive research over the past decades. However, the precise contribution of infectious agents to the etiology of prostate cancer remains a subject of ongoing debate.

Table 4 shows a summary of various meta-analyses that have investigated the relationship between different infectious agents and the risk of developing prostate cancer.

Table 4 Description of different meta-analyses on different infectious agents and the risk of prostate cancer

Author (Year)	Nb of Studies	Sample Size	Type of STIs	Estimated Risk (95% CI)
Dennis (2002)	36 studies (17 studies on STI)	-	Venereal disease	RR: 1.44 (1.24-1.66)
			Syphilis	RR: 2.30 (1.34-3.94)
			Gonorrhea	RR: 1.36 (1.15-1.61)
			Any STIs	OR: 1.48 (1.26-1.73)
Taylor (2005)	29 Studies	6,022 Cases/ 7,320 Controls	Gonorrhea	OR: 1.39 (1.05-1.83)
			Syphilis	OR: 1.42 (0.76-2.64)
			HPV	OR: 1.52 (1.12-2.06)
			Any STI	SRR: 1.49 (1.19-1.92)
			Gonorrhea	SRR: 1.20 (1.05-1.37)
			Syphilis	SRR: 1.27 (0.85-1.89)
Caini (2014)	47 Studies	≈10,000 Cases	C. Trachomatis	SRR: 0.93 (0.74-1.18)
			HSV-2	SRR: 1.07 (0.83-1.38)
			HSV (any)	SRR: 0.87 (0.65-1.17)
			HSV (all)	SRR: 0.95 (0.82-1.11)
			HHV-8	SRR: 1.08 (0.55-2.13)
			America	OR:1.23 (1.00-1.50)
GE (2013)	11 Studies	2996 Cases / 3875 Controls	HSV-2	OR:1.14 (0.76-1.72)
			HHV-8	Europe
				OR: 1.12 (0.70-1.79)
			OR: 0.84 (0.37-1.88)	
Lian (2015)	21 Studies	9965 Cases	Gonorrhea	OR: 1.31 (1.14-1.52)
Najafi (2019)	6 Studies	2677 Cases/ 2913 Controls	Trichomonas Vaginalis	OR: 1.17 (1.01-1.36)
Ma (2021)	12 Studies (7 Studies PC)	-	Hepatitis C (HCV)	RR: 0.75 (0.54-1.03)
Tsydenova (2023)	24 Studies	1607 Cases/ 1515 Controls	Human Papilloma Virus (HPV)	OR: 3.07 (1.80-5.21)

The meta-analysis done by Dennis and Dawson included 36 studies, of which 23 studies focus on sexually transmitted infections (STIs) like venereal diseases, gonorrhea, and syphilis,

excluding studies that focused solely on genital warts and herpes titers. The findings suggest an association between STIs and prostate cancer, particularly evident in 17 studies. When examining the type of case-controls used in these studies, those with population-based case-controls showed a slightly higher risk RR: 1.51 (95%CI: 1.26-1.80) compared to hospital-based case-controls RR: 1.30 (95%CI: 1.01-1.68). The risk of prostate cancer increased notably for syphilis when 6 studies were included, reaching an RR of 2.30 (95%CI: 1.34-3.94) in total. As for gonorrhea, 13 studies reported on its risk for prostate cancer, resulting in a pooled RR of 1.36 (95%CI 1.15-1.61) [181] (figure 15).

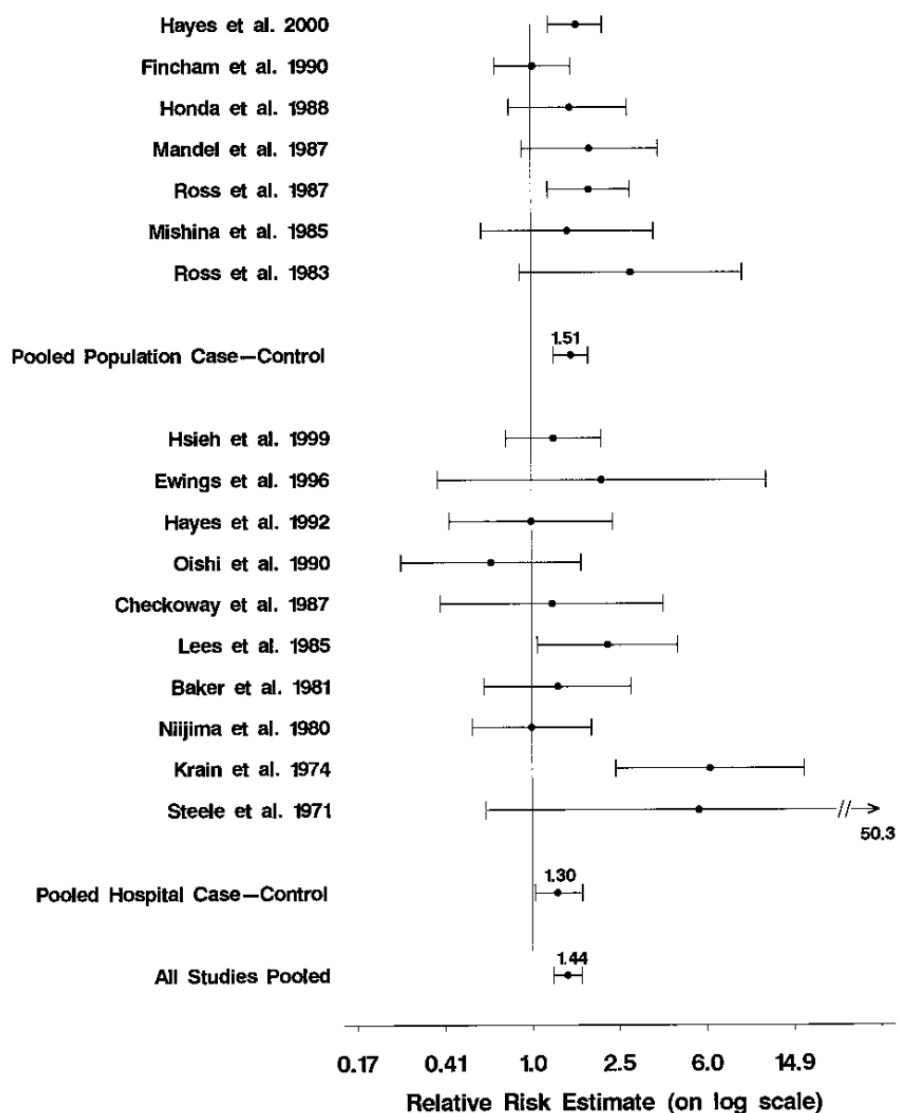


Figure 15 Forest Plot of Estimated RR and 95% CI for History of STIs based on Random-effect Model [181]

Another meta-analysis done by Taylor presents results from 29 case-control studies examining the association between any sexually transmitted infections and prostate cancer. Both fixed

OR: 1.45 (95% CI: 1.30–1.61) and random effects OR: 1.48 (95% CI: 1.26–1.73) models showed elevated overall odds ratios for prostate cancer (figure 16).

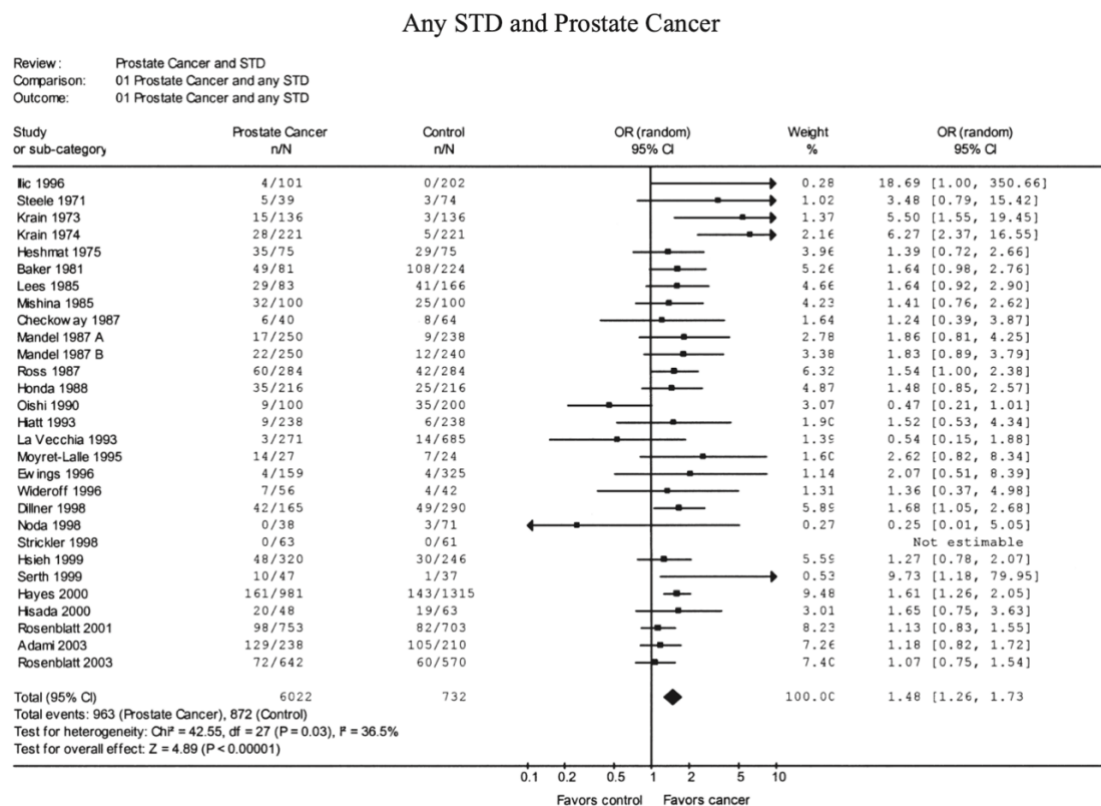


Figure 16 Forest Plot of Estimated OR and 95% CI for History of STIs based on Random-effect Model [182]

The association between gonorrhea and prostate cancer was examined across 11 studies and both fixed OR: 1.35 (95% CI: 1.11–1.64) and random effects OR: 1.39 (95% CI: 1.05–1.83) models showed significantly elevated odds ratios. Regarding syphilis and prostate cancer, seven studies were included, and the fixed effects model revealed an elevated odds ratio OR: 1.61 (95% CI: 1.08–2.39), although the random effects model did not reach significance OR: 1.42 (95% CI: 0.76–2.64). Finally, they investigated the link between human papillomavirus (HPV) and prostate cancer through ten studies, and the fixed effect OR: 1.39 (95% CI: 1.13–1.71) and random effect OR: 1.52 (95% CI: 1.12–2.06) models demonstrated elevated odds ratios for prostate cancer [182].

The meta-analysis conducted by Caini included 47 studies meeting the inclusion criteria. Among these, 34 studies were case-control studies, 10 were nested case-control studies, and 3 were cohort studies. Additionally, 18 were population-based, 20 were hospital-based, and two enrolled cases from both the general population and hospitals. The meta-analysis revealed a significantly increased risk of prostate cancer among patients who reported having a history of gonorrhoea SRR/ 1.20 (95%CI: 1.05-1.37), based on data from more than 10,000 prostate cancer patients. However, the association with prostate cancer was not significant for HSV, HHV-8, and Chlamydia Trachomatis (table 5) [88].

Table 5 Summary Relative Risk (SRR) and 95% Confidence Interval (95%CI) for each STI and Prostate Cancer [88]

Summary relative risk (SRR) and 95% confidence intervals (95% CI) for the association between sexually transmitted infections (STI) and prostate cancer (PCa).

STI	No. of estimates	No. PC cases	SRR	95% CI	I ² (%)
Gonorrhoea	23	10,379	1.20	1.05–1.37	37
Syphilis	17	8693	1.27	0.85–1.89	59
<i>Chlamydia trachomatis</i>	9	5469	0.93	0.74–1.18	46
HSV-2	8	1752	1.07	0.83–1.38	100
HSV (any)	5	3490	0.87	0.65–1.17	8
HSV (all) ^a	14	5571	0.95	0.82–1.11	4
HHV-8	9	2210	1.08	0.55–2.13	77
Any STI	18	6313	1.49	1.19–1.92	68

HSV, Herpes Simplex Virus; HHV, Human Herpes Virus.

I²: proportion of total variation in study estimates that is due to heterogeneity.

^a Includes one estimate for HSV-1, eight estimates for HSV-2, and five estimates for HSV not specified whether -1 or -2.

Finally, men who reported ever having any type of STIs exhibited a significantly increased risk of prostate cancer SRR: 1.49 (95%CI: 1.19-1.92), based on data from 6,313 prostate cancer across 18 studies (figure 17).

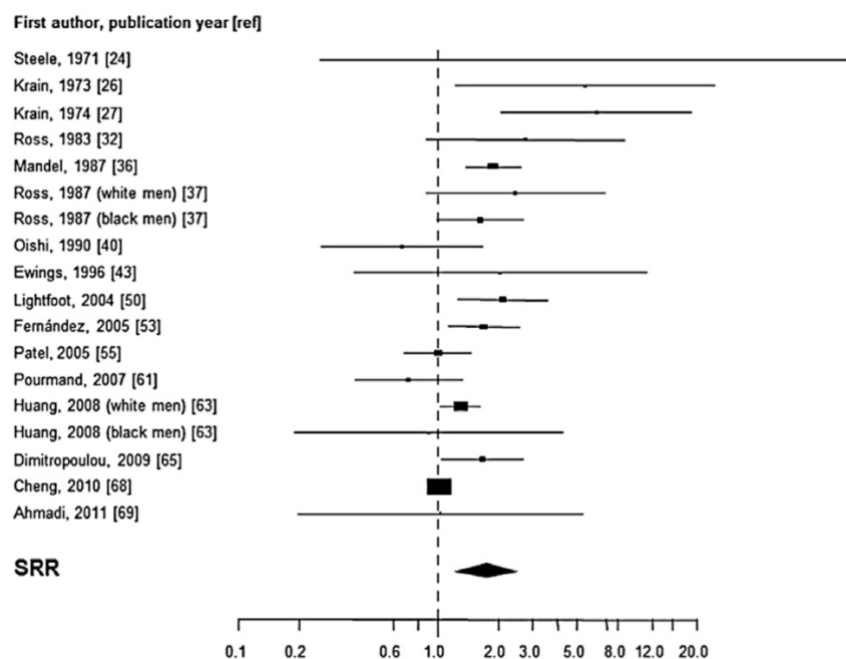


Figure 17 Forest Plot of Relative Risk (SRR) and 95% CI for STIs and the Risk of Prostate Cancer [88]

Several meta-analyses focused solely on specific infections, examining their association with prostate cancer risk. Lian conducted a meta-analysis specifically targeting gonorrhea. Among these 22 studies included in the analysis, 19 were case-control studies, and 2 were cohort studies. The combined results of 21 studies indicated a significant association between gonorrhea and an increased risk of prostate cancer OR: 1.31 (95% CI 1.14–1.52) under the random-effects model (Figure 18). Subgroup analyses based on study design revealed a significantly increased risk of prostate cancer in case-control studies OR: 1.14 (95% CI: 1.24-1.61), particularly in those that were population-based OR: 1.38 (95% CI 1.19–1.61), while cohort studies showed no significant association OR: 1.07 (95% CI 0.95–1.21) [183].

Another meta-analysis conducted by Najafi targeted only *Trichomonas Vaginalis* and included only 6 case-control studies. The results revealed that Trichomoniasis in prostate cancer patients was associated with slightly increased odds ratio of OR 1.17 (95% CI: 1.01-1.36), although this was not statistically significant. Additionally, the meta-analysis showed low heterogeneity in the effect size of prostate cancer [184].

Additionally, a meta-analysis done by Ge examined the association between HSV-2 and HHV-8 infections and prostate cancer. For HSV-2, eight studies were analyzed, showing a marginally positive relationship with prostate cancer OR:1.21 (95% CI,1.00-1.46). For HHV-8, 11 studies were included. The analysis did not find a significant relationship between HHV-8 infection and prostate cancer risk OR=1.11 (95% CI 0.77-1.60) [185].

Another specific meta-analysis focusing only on the role of hepatitis C in the risk of developing prostate cancer was conducted by Ma, which included 7 studies in total. No association was found, with a pooled RR of 0.75 (95%CI: 0.54-1.03) [186].

Finally, a meta-analysis that included 24 studies focused only on human papillomavirus revealed an OR: 3.07 (95%CI: 1.80-5.21) in the random effect model, indicating a significant association between HPV and Prostate cancer [187].

Table 6 shows the details of studies that have evaluated the risk of prostate cancer among individuals with a history of gonorrhoea.

Neisseria gonorrhoeae, known as the bacterium that causes gonorrhoea; an etiologic agent of sexually transmitted diseases, has attracted extensive attention for its possible role in prostate cancer development. This bacteria can adopt both extracellular and intracellular forms, affecting the body's immune response, making it harder for individuals to develop immunity, and leading to repeated infections[188]. Additionally, long-term inflammation of the prostate caused by *N. gonorrhoeae* has been suggested as a potential factor contributing to cancer[189].

Epidemiological research examining the link between *N. Gonorrhoeae* and prostate cancer has been inconclusive. Overall, 26 studies [190–192, 89, 193–196, 102, 91, 197, 92, 93, 198, 54, 97, 98, 103, 117, 99, 104, 112, 100, 101, 105] took into account gonorrhoea in their analysis showing varying results. While 8 studies found a notable association with prostate cancer, 18 studies did not reach a clear conclusion given that the associations were insignificant. These different results may partly be due to the complex nature of sexually transmitted infections, often involving multiple infectious agents [182].

The precise biological mechanism linking gonorrhoea and prostate cancer remains unclear. However, chronic inflammation has been implicated in prostate carcinogenesis [76]. *Neisseria gonorrhoeae*, the causative agent of gonorrhoea, can induce chronic inflammation in the prostate. This inflammatory response recruits inflammatory cells which promote the growth of neoplastic cells, potentially contributing to carcinogenesis within the prostate [199].

Table 6 Studies Evaluating the Risk of Prostate Cancer among those with a History of Gonorrhoea

Author (Year)	Study Design	Cases/Controls	Method of Collection	Estimated Risk (95% CI)
Heshmat (1975)	HCC	75/150	Self-Report	OR: 2.02 (1.05-3.87)
Baker (1981)	HCC	44/134	Self-Report	OR: 4.98 (2.21-11.21)
Lees (1985)	HCC	83/249	Clinical Records	OR: 0.84 (0.41-1.72)
Mishina (1985)	PCC	100/200	Self-Report	OR: 1.32 (0.69-2.55)
Checkoway (1987)	HCC	40 / 104	Self-Report	OR: 1.31 (0.33-5.20)
Honda (1988)	PCC	216 / 432	Self-Report	OR: 1.40 (0.80-2.60)
Oishi (1989)	HCC	83/249	Self-Report	OR: 1.75 (0.20-2.40)
La Vecchia (1993)	HCC	271/956	Self-Report	OR: 1.70 (0.20-2.40)
Hiatt (1996)	PCC	238/476	Medical Record	OR: 1.50 (0.50-4.20)
Ilic (1996)	HCC	101/303	Self-Report	OR: 18.6 (1.00-350.66)
Hsieh (1999)	HCC	320/566	Self-Report	OR: 1.41 (0.91-2.45)
Hayes (2000)	PCC	981/2296	Self-Report	OR: 1.50 (1.10-2.00)
Rosenblatt (2001)	PCC	753/1456	Self-Report	OR: 1.50 (1.02-2.18)
Sanderson (2004)	PCC	416/845	Self-Report	OR: 1.27 (0.77-2.08)
Patel (2005)	PCC	700/1304	Self-Report	OR: 1.00 (0.50-1.50)
Pelucchi (2006)	HCC	280/969	Self-Report	OR: 0.64 (0.20-20.3)
Sarma (2006)	PCC	129/832	Self-Report	OR: 1.78 (1.13-2.79)
Sutcliffe (2006)	Cohort	2263/36033	Self-Report	RR: 1.04 (0.79-1.36)
Haug (2008)	PCC	868/2151	Self-Report	OR: 1.18 (0.83-1.67)
Dimitropoulou (2008)	CC	431/409	Self-Report	OR: 2.24 (0.91-5.55)
Cheng (2010)	Cohort	1658/68675	Self-Report	RR: 1.08 (0.95-1.23)
Hrbacek (2011)	HCC	329/434	Serology	OR: 1.07 (0.42-2.73)
Spence (2015)	PCC	1590/1618	Self-Report	OR: 0.90 (0.69-1.19)
Vazquez-Salas (2015)	PCC	402/805	Self-Report	OR: 3.04 (1.99-4.64)
Wang (2017)	Cohort*	355/1420	Laboratory	HR: 5.66 (1.36-23.52)

HCC – Hospital-Based-Case-Control; PCC- Population-Based-Case-Control

* Population-based retrospective cohort

Table 7 shows the details of studies that have evaluated the risk of prostate cancer among individuals with a history of Syphilis.

Syphilis, recognized as a sexually transmitted infection, is primarily transmitted through sexual contact involving vaginal, anal, or oral routes. However, transmission through non-sexual means, such as direct skin-to-skin contact and exposure to infected blood, is also possible but less common [200]. This infection is caused by the bacterium *Treponema Pallidum* and can lead to chronic inflammatory processes in various organs, including the prostate gland [200]. It has been suggested that this chronic inflammation can play a pivotal role in the pathogenesis of prostate cancer [76].

Epidemiological studies have provided some insights into the potential association between syphilis and prostate cancer. Among the 18 studies [54, 89, 92, 93, 97, 98, 100, 101, 103, 104, 117, 191–195, 198, 201] specifically examining syphilis, only two demonstrated a statistically significant positive association, suggesting a potential correlation between syphilis infection and prostate cancer risk. However, the remaining 16 studies found no significant association between syphilis and prostate cancer.

Biological mechanisms underlying the association between syphilis and prostate cancer involve the chronic inflammatory response triggered by the infection as mentioned above. Upon infection with *Treponema pallidum*, the immune system initiates an inflammatory cascade characterized by the recruitment of immune cells to the site of infection, including the prostate gland. Inflammatory cells, such as macrophages and lymphocytes, release pro-inflammatory cytokines and chemokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8), which can create a microenvironment conducive to tumorigenesis [76, 199].

Table 7 Studies Evaluating the Risk of Prostate Cancer among those with a History of Syphilis

Author (Year)	Study Design	Cases/Controls	Method of Collection	Estimated Risk (95% CI)
Baker (1981)	HCC	44/134	Self-Report	OR: 0.39 (0.05-3.20)
Lees (1985)	HCC	83/249	Clinical Records	OR: 1.39 (0.55-3.50)
Mishina (1985)	PCC	100/200	Self-Report	OR: 1.59 (0.42-5.60)
Checkoway (1987)	HCC	40 / 104	Self-Report	OR: 1.07 (0.17-6.70)
Honda (1988)	PCC	216 / 432	Self-Report	OR: 6.14 (0.73-51.46)
Oishi (1989)	HCC	83/249	Self-Report	OR: 0.49 (0.05-5.20)
Michalek (1993)	HCC	271/956	Self-Report	SIR: 58 (37-86)
Hayes (2000)	PCC	981/2296	Self-Report	OR: 2.83 (1.45-5.52)
Rosenblatt (2001)	PCC	753/1456	Self-Report	OR: 0.52 (0.17-1.55)
Sanderson (2004)	PCC	416/845	Self-Report	OR: 0.60 (0.13-2.82)
Patel (2005)	PCC	700/1304	Self-Report	OR: 1.30 (0.50-3.20)
Pelucchi (2006)	HCC	280/969	Self-Report	OR: 1.75 (0.10-31.4)
Sarma (2006)	PCC	129/832	Self-Report	OR: 1.54 (0.55-4.34)
Sutcliffe (2006)	Cohort	2263/36033	Self-Report	RR: 1.06 (0.44-2.59)
Haung (2008)	PCC	868/2151	Self-Report	OR: 0.40 (0.10-1.90)
Cheng (2010)	Cohort	1658/68675	Self-Report	RR: 1.23 (0.90-1.67)
Spence (2015)	PCC	1590/1618	Self-Report	OR: 0.82 (0.33-2.01)
Vazquez-Salas (2015)	PCC	402/805	Self-Report	OR: 1.59 (0.59-4.32)

HCC – Hospital-Based-Case-Control; PCC- Population-Based-Case-Control; SIR: Standardized Incidence Ratio

Table 8 shows the details of studies that have evaluated the risk of prostate cancer among individuals with a history *Trichomonas Vaginalis*.

Trichomonas vaginalis is a single-celled anaerobic protozoan parasite that commonly infects the urogenital tract and is primarily transmitted through sexual contact [202]. Although infection with *trichomonas* is less common in men than in women, it can still occur and may manifest differently. While many infected men remain asymptomatic, some may experience symptoms such as urethral discharge, urethritis, prostatitis, and epididymitis [203].

Trichomonas vaginalis has been suggested to increase the risk of prostate cancer by inducing chronic inflammation in the prostate tissue [204]. Epidemiological studies have shed light on the potential link between *trichomonas* and prostate cancer. Among the 10 studies [204–207, 100, 208, 114–116, 209] that examined *trichomonas*, only 4 studies demonstrated a statistically significant association. However, the remaining 6 studies found no significant association (Table 8).

Given the nature of it being asymptomatic, it allows the parasite to ascend to the prostate gland and cause chronic inflammation [109, 210]. This chronic inflammation can lead to various mechanisms that contribute to the development of prostate cancer, including the production of pro-inflammatory cytokines, uncontrolled growth factor release, upregulation of anti-apoptotic gene products, and alterations in polyamine metabolism [211, 212]. Although *T. vaginalis* may not directly cause prostate cancer, it can manipulate the intra-prostatic environment by inducing immunosuppressive cytokines, thereby promoting cancer development [210].

Table 8 Studies Evaluating the Risk of Prostate Cancer among those with a History of *Trichomonas vaginalis*

Author (Year)	Study Design	Cases/Controls	Method of Collection	Estimated Risk (95% CI)
Sutcliff (2006)	NCC	691/691	Serology	OR: 1.43 (1.00-2.03)
Sutcliff (2009)	NCC	616/616	Serology	OR: 0.97 (0.70-1.34)
Stark (2009)	NCC	673/673	Serology	OR: 1.23 (0.94-1.61)
Al-Mayah (2013)	CSS	50/40	Serology	OR: 3.90 (1.02-14.93)
Spence (2014)	PCC	1590/1618	Self-Report	OR: 1.15 (0.22-6.05)
Shui (2016)	PCC	146/161	Serology	OR: 0.65 (0.37-1.14)
Fowke (2016)	NCC	296/497	Serology	OR: 1.11 (0.77-1.61)
Marous (2017)	NCC	1786 Caucasian (925/861) 556 African (201/355)	Serology	OR (HPFS): 1.43 (1.00-2.03) OR (PHS): 1.23 (0.94-1.61)
Tsang (2019)	NCC	1485 Cases	Serology	HR (PHS): 0.85 (0.57-1.29) HR (HPFS): 0.87 (0.42-1.80)
Saleh (2021)	CC	126/120	Serology	OR: 2.6 (1.20-5.70)

HCC – Hospital-Based-Case-Control; PCC- Population-Based-Case-Control; CSS – Cross Section Study; CC – Case Control; HPFS - Health Professional Follow-up Study; PHS - Physicians 'Health Study; HR: Hazard Ratio

Table 9 shows the details of studies that have evaluated the risk of prostate cancer among individuals with a history of different types of Herpes Simplex Virus.

Human herpesvirus (HHVs) encompasses a group of viruses known to infect humans, including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV or HHV-4), cytomegalovirus (CMV or HHV-5), human herpesviruses 6 and 7 (HHV-6 and HHV-7), and human herpesvirus 8 (HHV-8). Transmission of HHVs varies depending on the specific virus. HSV-1 and HSV-2 are primarily transmitted through direct contact with infected secretions or lesions, while VZV is transmitted via respiratory droplets or direct contact with skin lesions. EBV is commonly spread through saliva, while CMV can be transmitted through bodily fluids such as saliva and urine [213]. Symptoms can include fever, rash, sore throat, and fatigue [176, 213].

Herpes virus has been suggested to play a role in carcinogenesis, with reported roles in inhibiting cell apoptosis and stimulating DNA synthesis, potentially leading to cancer development [214].

Of the 21 studies examining various types of herpes, 13 specifically addressed herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) [93, 96, 98, 100, 104, 110–112, 117, 191, 215–217]. The majority did not show a significant association with an increased risk of prostate cancer. Six studies [111, 117, 218–221] considered human herpesvirus 8 (HHV-8), and only one study done by Hoffman had a positive significant association with prostate cancer, yielding an OR: 2.24 (1.29-3.90).

Herpes zoster also referred to as shingles, is caused by the reactivation of the varicella-zoster virus (VZV), which remains latent in sensory ganglia and dorsal nerve roots after initial infection with VZV, typically during childhood [121]. Limited research has focused on the association between Herpes Zoster and prostate cancer risk. Among the four studies that examined the varicella-zoster virus (VZV), three reported a significant positive association [222–225].

Epstein-Barr Virus (EBV) is associated with infectious mononucleosis and is well-known for its association with various human malignancies, including Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's lymphoma [226]. While EBV's role in prostate cancer has been explored, a single study considered its association with the disease, yielding non-significant results [110].

Table 9 Studies Evaluating the Risk of Prostate Cancer among those with a History of Herpes Simplex Virus

Author (Year)	Study Design	Cases/Controls	Method of Collection	Type of Herpes	Estimated Risk (95% CI)
Herbert (1978)	CC	28/20	Serology	HSV 1 HSV 2	p-value >0.05
Baker (1981)	HCC	50/159	Serology	HSV2	P-value <0.05
Luleci (1981)	CC	16/26	Serology	HSV 2	p-value >0.05
Rosenblatt (2001)	PCC	753/1456	Self-Report	Genital	OR: 1.65 (0.69-3.99)
Hoffman (2004)	CC	138/140	Serology	HHV 8	OR: 2.24 (1.29-3.90)
Patel (2005)	PCC	700/1304	Self-Report	Genital	OR: 1.1 (0.3-5.2)
Korodi (2004)	CC	165 Cases	Serology	HSV 2 HHV 8	OR: 0.93 (0.44-1.96) OR: 0.74 (0.19-2.88)
Buntinx (2005)	RCS	54 Cases	Medical Records	VZV	HR: 1.90 (0.59-6.14)
Sarma (2006)	PCC	129/832	Self-Report	Herpes HSV 1	OR: 1.12 (0.23-5.47) Not Significant
González (2006)	CC	66 Cases	Serology	HSV2 HHV 6 EBV	Significant Not Significant Not Significant
Sutcliffe (2007)	NCC	691/691	Serology	HHV8	OR: 0.70 (0.52-0.95)
Jenkins (2007)	CC	199/155	Serology	HHV8	OR: 0.63 (0.39-1.04)
Huang (2008)	PCC	868/2151	Self-Report	HSV 2 HHV 8	White OR: 0.9 (0.7-1.3) / 1.3 (0.8-2.0) Black OR: 1.3 (0.9-1.7) / 0.3 (0.1-1.4) 10 months before diagnosis OR:1.17 (0.79-1.73) 94 months before diagnosis OR: 1.60 (1.05-2.44)
Dennis (2009)	NCC	268/268	Serology	HSV2	OR: 1.60 (1.05-2.44)
Cheng (2010)	Cohort	1658/68675	Self-Report	Genital	RR: 0.86 (0.69-1.08)
Hrbacek (2011)	HCC	329/434	Serology	HSV 1 HSV 2	OR: 1.19 (0.42-2.97) OR: 0.95 (0.51-1.88)
McDonald (2011)	Cohort	96/415	Serology	HHV 8	HR: 0.88 (0.46-1.69)
Chiu (2013)	PCC	85 Cases	Medical Records	VZV	HR: 1.90 (1.18-3.09)
Cotton (2013)	PCC	256 Cases	Medical Records	VZV	HR: 2.49 (1.92-3.24)
Spence (2015)	PCC	1590/1618	Self-Report	Genital	OR: 1.15 (0.22-6.05)
Tsao (2020)	PCC	1011 Cases	Medical Records	VZV	HR: 1.15 (1.00-1.32)

HCC – Hospital-Based-Case-Control; PCC- Population-Based-Case-Control; NCC – Nested Case-Control; CC – Case Control; RCS - Retrospective Cohort Study; HSV - Herpes Simplex Virus; HHV-Human Herpes Virus; EBV - Epstein Barr-Virus; VZV - Varicella Zoster Virus; HR - Hazard Ratio

Table 10 shows the details of studies that have evaluated the risk of prostate cancer among individuals with a history of Viral Hepatitis.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-established pathogens primarily affecting the liver, leading to chronic liver disease and hepatocellular carcinoma (HCC) [227, 228]. While their association with liver cancer is extensively documented, their potential link to prostate cancer remains less explored. Limited studies have investigated the relationship between HBV/HCV infections and prostate cancer risk, with inconsistent findings. Among the 9 studies [41, 106–108, 229–233] that focused either on HBV or HCV, 7 studies reported a positive association with either of the two viruses, indicating a potential link with prostate cancer. However, the remaining two studies found no association. The reasons behind the inconsistent findings regarding the association between HCV or HBV infections and prostate cancer remain unclear [186].

Table 10 Studies Evaluating the Risk of Prostate Cancer among those with a History of Viral Hepatitis

Author (Year)	Study Design	Cases/Controls	Method of Collection	Type of Hepatitis	Estimated Risk (95% CI)
Amin (2006)	CS	32 Cases	Serology	HBV HCV	SIR: 0.40 (0.30-0.60) SIR: 0.40 (0.30-0.60)
Omland (2010)	CS	2 Cases	Registry	HCV	SIR: 1.02 (0.12-3.70)
Allison (2015)	CS	293 Cases	Serology	HCV	SIR: 0.62 (0.61-0.63)
Kamiza (2016)	CCS	1820 Cases	Serology	HBV HCV	HR: 0.93 (0.58-1.49) HR 0.84 (0.48-1.46)
Liu (2016)	CCS	93 Cases	Serology	HCV	SIR: 0.73 (0.59-0.90)
Mahale (2017)	CCS	283,367 Cases	Medical Records	HCV	OR: 0.73 (0.66-0.82)
Nyberg (2019)	CS	9751 Cases	Serology	HCV	RR: 1.45 (1.24-1.69)
Mahale (2019)	CS	307,998 Cases	Medical Records	HBV	OR: 0.81 (0.73-0.91)
Hong (2020)	RCS	625 Cases	Medical Records	HBV HCV	HR: 2.51 (1.65-3.82) HR: 1.06 (0.76-1.48)

CC – Case Control; CS - Cohort Study; RCS - Retrospective Cohort Study; HR - Hazard Ratio; SIR: Standardized Incidence Rate

While the etiology of prostatic inflammation remains unclear, various inflammation-related factors are believed to contribute to prostate cancer. However, despite the increasing interest in studying the role of chronic inflammation and infectious agents in the development of prostate cancer, drawing definitive conclusions remains challenging due to inconsistencies among different studies.

Specifically, various case-control and prospective cohort studies have extensively focused on sexually transmitted infections; however, the results have been inconclusive. Research on non-sexually transmitted infections and prostate cancer has primarily centered on genitourinary infections like prostatitis. Beyond prostatitis, there has been limited research on other non-sexually transmitted infections, including herpes zoster, polio, tuberculosis, and dengue, and their potential impact on prostate cancer risk.

Furthermore, most studies have only considered specific types of infections. While some studies have begun to consider the aggressiveness of prostate cancer [100, 101, 103, 104, 115], the broader landscape still lacks a comprehensive exploration of this aspect. Therefore, one of our focuses lies in taking into account different grades of cancer.

Examining specific exposures to different infectious agents allows for more in-depth studies to be conducted to explore this relationship. Therefore, our study aims to explore the association between prostate cancer risk and various types of infectious agents, whether sexually or non-sexually transmitted, using data from EPICAP.

2. Material and Methods

2.1. Study Population

In order to study the relationship between different types of infectious agents and the risk of prostate cancer using data from the EPICAP data, we included a total of 1,698 men, of which 819 are cases of prostate cancer and 879 controls (Details in Chapter 2).

2.2. Data Collection

As mentioned in Chapter 2, information on various aspects, including sociodemographic characteristics, professional and residential history, medical history, and ethnic origin, were collected. Environmental factors, encompassing details on places of residence and lifestyle habits such as tobacco, alcohol consumption, sleep patterns, leisure activities, and physical activity were collected

Detailed questions on infectious diseases (sexually and non-sexually transmitted infections), inflammatory conditions, and medication history, including non-steroidal anti-inflammatory drugs and antibiotics, were collected. Additionally, concerning each infection, the type and number of infections, along with age at the time of infection in instances of multiple infections, as well as the age at which they experienced their first and last infection, were also collected (Appendix 13 and 14).

2.3. Variables of Interest

In total, our analysis included 12 distinct types of infections: gonorrhea, syphilis, trichomonas vaginalis, urethritis, tuberculosis, zoster herpes, mononucleosis, Epstein–Barr, zona, polio, dengue, herpes genital and non-genital, mononucleosis, and viral hepatitis.

Each infection was defined separately based on whether the individual had experienced an infection before the reference date, which was the date of diagnosis for the cases and the date of interview for the controls. Consequently, all infections were represented as binary variables, where 0 indicated no history of infection, and 1 indicated a history of infection.

Similar types of infections were grouped together to have an overall view of the relationship between all types of infections and the risk of prostate cancer.

The different combined variables were as follows:

- **Sexually Transmitted Bacterial Infections:** it was defined by having at least one type of bacterial infection (gonorrhoea, syphilis, trichomonas) before the reference date, making it a binary variable where 0 indicates no history of infection and 1 indicates having at least one of the three infections.
- **Viral Infections:** It was defined by having at least one type of sexually or non-sexually transmitted viral infection or their condition (zoster herpes, polio, dengue, herpes genital and non-genital, Epstein–Barr, viral hepatitis, mononucleosis) before the reference date, making it a binary variable where 0 indicates no history of infection and 1 indicated having at least one of the eight infections.
- **Sexually Transmitted Viral Infections:** it was defined by having at least one type of sexually transmitted viral infection or their condition (mononucleosis, herpes, Epstein–Barr) before the reference date, making it a binary variable where 0 indicates no history of infection and 1 indicated having at least one of the three infections.
- **Sexually Transmitted Bacterial and Viral Infections:** It was defined by having one type of sexually transmitted infection or their conditions before the reference date (gonorrhoea, syphilis, trichomonas, urethritis, mononucleosis, Epstein-Barr, herpes genital and non-genital, and mononucleosis) or having two or more types of infections before the reference date. Overall, two variables were derived from this categorization. The first is a binary variable where 0 indicates having no infection and 1 indicates having at least one type of infection. This second variable is defined with 3 classes where 0 indicates no history of infection, 1 indicates having only one type of infection, and 2 indicates having 2 or more infections.
- **Overall Infections:** It was defined by having one type of infection and their conditions, regardless of whether it was bacterial or viral, or by having two or more types of infections before the reference date. Overall, two variables were derived from this categorization. The first is a binary variable where 0 indicates having no infection, and 1 indicates having at least one type of infection. This second variable is defined with 3

classes where 0 indicates no history of infection, 1 indicates having only one type of infection, and 2 indicates having 2 or more infections.

2.4. Statistical Analysis

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

2.4.1. Descriptive Analysis

To begin with, we examined our population's characteristics including sociodemographic factors, lifestyle factors, medical history, as well as well-established non-modifiable risk factors of prostate cancer (age, ethnicity, and family history of prostate cancer). We compared these factors between both cases and controls within the EPICAP study, as outlined in Chapter 2 (Table 3) using the chi-square test. Additionally, given that all our variables were qualitative, they were represented using frequencies and percentages when comparing them between cases and controls. Subsequently, among the controls, we also used the chi-square test to compare all our population characteristics within each combined group of infections, to determine the possible factors associated with these infections.

2.4.2. Inferential Analysis

For each specific infection, the association with prostate cancer was evaluated using unconditional logistic regression models, allowing for the computation of odds ratios (OR) and their corresponding 95% confidence intervals. Similarly, the same model was used when examining the association of each combined variable. In terms of the reference group, each was defined as individuals having no personal history of the infection or conditions concerned in each group except for overall infections. The reference group for overall infections was defined as individuals who had never experienced any type of infection or condition throughout their lifetime.

Furthermore, multinomial logistic regression models were used to examine the relationship between infections and prostate cancer based on the aggressiveness of cancer using the Gleason score at the time of diagnosis. For non-aggressive or low-grade cancer, the Gleason score is defined as ≤ 7 [including 3+4], which is considered a low or intermediate score, while aggressive or high-grade cancer was characterized by a Gleason score of ≥ 7 [including 4+3], regarded as a high score. Because the Gleason score was unavailable for 13 cases in the EPICAP

study, the analysis on prostate cancer aggressiveness included only 805 cases, with 183 being classified as aggressive.

To start with, we investigated the relationship between every infection and prostate cancer by systematically adjusting the models for established risk factors (age, ethnicity, and family history of prostate cancer). Subsequently, our models were further adjusted for additional potential confounding factors, including variables at the $\alpha=20\%$ threshold such as physical activity, waist circumference, education, and non-steroidal anti-inflammatory drugs (NSAIDs). Using the stepwise approach, we removed the least significant adjustment factors from the model when it did not alter the associations. Therefore, the final model investigating the relationship between infections and prostate cancer was adjusted for age, ethnicity, family history of prostate cancer, physical activity, NSAIDs, waist circumference, and education.

2.4.3. Sensitivity Analysis

Ultimately, sensitivity analysis was performed by limiting the control group to individuals who underwent screening within the two years preceding the reference date. This was done to minimize the likelihood of latent prostate cancer cases among controls, thus limiting the risk of underestimating associations. Following this restriction, the total number of controls was 603.

3. Results

3.1. Comparison of Subjects' Characteristics based on infection status in the control group

Table 11 shows the characteristics of control subjects based on their history of any type of infection, differentiating those without infections from those with either bacterial or viral infections. There were no statistically significant differences in age distribution ($P=0.069$), ethnic origin ($P=0.757$), family history of prostate cancer ($P=0.314$), BMI ($P=0.138$), or alcohol consumption ($P=0.286$) between those with and without a history of infections. However, significant differences were observed in educational levels ($P=0.036$) and smoking status ($P=0.014$). Controls with a history of infections were more likely to have a university education (32.8% vs. 25.1%) and less likely to be current smokers (14.2% vs. 21.9%). Additionally, a higher percentage of those with a history of infections used nonsteroidal anti-inflammatory drugs (34.3% vs. 27.6%, $P=0.039$).

Table 11 Characteristics of Controls based on their history of all types of Infections

<i>Overall Infections</i>	Non n= 383	Yes n=457	P-value* X²
Age (Years)			<i>0.069</i>
< 55	26 (6.8)	28 (6.1)	
[55-60]	53 (13.8)	43 (9.4)	
[60-65]	90 (23.5)	104 (22.8)	
[65-70]	108 (28.2)	167 (36.5)	
≥70	106 (27.7)	115 (25.2)	
Ethnic Origin			<i>0.757</i>
Caucasian	375 (97.9)	446 (97.6)	
Other	8 (2.1)	11 (2.4)	
Family History of Prostate Cancer			<i>0.314</i>
No	351 (92.1)	411 (90.1)	
Yes	30 (7.9)	45 (9.9)	
Education			<i>0.036</i>
Primary	85 (22.3)	101 (22.1)	
Secondary	201 (52.6)	206 (45.1)	
University	96 (25.1)	150 (32.8)	
Body Mass Index (kg/m²)			<i>0.138</i>
<25 - Normal	109 (29.1)	126 (28.6)	
[25-30] - Overweight	162 (43.2)	216 (49.1)	
≥30 - Obese	104 (27.7)	98 522.3)	
Waist Circumference (cm)			<i>0.202</i>
≤94	101 (26.9)	137 (30.9)	
>94	275 (73.1)	306 (69.1)	
Smoking Status			<i>0.014</i>
Never	102 (26.6)	132 (28.9)	
Former	197 (51.4)	260 (56.9)	
Current	84 (21.9)	65 (14.2)	
Alcohol Consumption			<i>0.286</i>
No	41 (10.7)	39 (8.5)	
Yes	342 (89.3)	418 (91.5)	
Physical Activity (MET -h/wk/yr)			<i>0.996</i>
No	77 (20.2)	90 (19.9)	
<6.5	75 (19.9)	91 (20.1)	
6.25-13.0	78 (20.4)	88 (19.4)	
13.0-24.15	77 (20.2)	94 (20.8)	
≥24.15	75 (19.6)	90 (19.9)	
Nonsteroidal anti-inflammatory drugs			<i>0.039</i>
No	275 (72.4)	293 (65.7)	
Yes	105 (27.6)	153 (34.3)	

*p-value of Chi-square

Table 12 compares the characteristics of control subjects based on their history of sexually transmitted bacterial infections, distinguishing those without a bacterial infection (n=792) from those with one type of bacterial infection (n=79). There were no significant differences in age (p=0.167), ethnic origin (p=0.851), family history of prostate cancer (p=0.707), education (p=0.086), BMI (p=0.222), waist circumference (p=0.894), alcohol consumption (p=0.140), physical activity (p=0.678), and use of NSAIDs (p=0.265) between the two groups, indicating similar distributions across these factors. However, there is a borderline significance in smoking status, with a higher percentage of former smokers in the group with bacterial infections (66.7% vs. 52.7%; p=0.049).

Table 12 Characteristics of controls based on their history of sexually transmitted bacterial Infections

<i>Sexually Transmitted Bacterial Infections</i>	No n=792	Yes n=79	P-value χ^2
Age (Years)			<i>0.167</i>
< 55	52 (6.6)	6 (7.4)	
[55-60]	94 (11.9)	4 (4.9)	
[60-65]	177 (22.4)	22 (27.2)	
[65-70]	251 (31.7)	32 (39.5)	
≥ 70	217 (27.4)	17 (21.0)	
Ethnic Origin			<i>0.851</i>
Caucasian	774 (97.9)	79 (97.5)	
Other	17 (2.2)	2 (2.5)	
Family History of Prostate Cancer			<i>0.707</i>
No	720 (91.3)	72 (90.0)	
Yes	69 (8.8)	8 (10.0)	
Education			<i>0.086</i>
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/m²)			<i>0.222</i>
<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)			<i>0.697</i>
≤ 94	231 (29.7)	21 (27.6)	
>94	545 (70.2)	55 (72.4.1)	
Smoking Status			<i>0.049</i>
Never	230 (29.1)	15 (18.5)	
Former	417 (52.7)	54 (66.7)	
Current	144 (18.2)	12 (14.8)	
Alcohol Consumption			<i>0.140</i>
No	79 (10.0)	77 (95.1)	
Yes	712 (90.0)	4 (4.9)	
Physical Activity (MET -h/wk/yr)			<i>0.678</i>
No	158 (20.1)	18 (23.1)	
<6.5	153 (19.4)	19 (24.4)	
6.25-13.0	157 (19.9)	15 (19.2)	
13.0-24.15	158 (20.1)	14 (18.0)	
≥ 24.15	162 (20.6)	12 (15.4)	
Nonsteroidal anti-inflammatory drugs			<i>0.265</i>
No	538 (69.0)	49 (62.8)	
Yes	242 (31.0)	29 (37.2)	

*p-value of Chi-square

Table 13 presents a comparison of control subjects based on their history of viral infections, dividing them into groups with having a history of viral infections vs without. There was a similar distribution in ethnicity ($p=0.644$) and family history of prostate cancer ($p=0.954$). There was also no significant difference in education levels across primary, secondary, and university were comparable ($p=0.299$), and body mass index (BMI) categories ($p=0.219$) or waist circumference measurements ($p=0.209$). Alcohol consumption and physical activity levels also did not differ significantly between the groups, with p -values of 0.953 and 0.876, respectively. The use of nonsteroidal anti-inflammatory drugs was similar across both groups ($p=0.167$). However, smoking status showed a statistically significant difference ($p=0.027$), with a higher proportion of former smokers in the group with infections (56.3% vs. 52.7%).

The determinants of the remaining combined groups are detailed in the appendices 1 through 4, and the results are similar with the findings of the three different groups discussed in this section.

Table 13 Characteristics of Controls based on their history of Viral Infections

<i>Viral Infections</i>	No n=443	Yes n=398	P-value* χ^2
Age (Years)			<i>0.215</i>
< 55	31 (6.9)	23 (5.8)	
[55-60]	57 (12.7)	40 (10.1)	
[60-65]	106 (23.7)	88 (22.2)	
[65-70]	130 (29.0)	145 (36.6)	
≥ 70	124 (27.7)	100 (25.3)	
Ethnic Origin			<i>0.644</i>
Caucasian	437 (97.5)	387 (97.7)	
Other	11 (2.5)	9 (2.3)	
Family History of Prostate Cancer			<i>0.954</i>
No	408 (91.5)	359 (90.9)	
Yes	38 (8.5)	36 (9.1)	
Education			<i>0.299</i>
Primary	97 (21.7)	91 (23.0)	
Secondary	228 (51.0)	181 (45.7)	
University	122 (27.3)	124 (31.3)	
Body Mass Index (kg/m²)			<i>0.219</i>
<25 - Normal	123 (28.5)	111 (28.8)	
[25-30] - Overweight	192 (44.4)	190 (49.4)	
≥ 30 - Obese	117 (27.1)	84 (21.8)	
Waist Circumference (cm)			<i>0.209</i>
≤ 94	119 (27.4)	119 (30.7)	
>94 - ≤ 102	145 (33.4)	130 (33.5)	
> 102	170 (39.2)	139 (35.8)	
Smoking Status			<i>0.021</i>
Never	114 (25.5)	120 (30.3)	
Former	236 (52.7)	223 (56.3)	
Current	98 (21.9)	53 (13.4)	
Alcohol Consumption			<i>0.953</i>
No	44 (9.8)	37 (9.3)	
Yes	401 (90.2)	359 (90.7)	
Physical Activity (MET -h/wk/yr)			<i>0.876</i>
No	91 (20.6)	79 (20.0)	
<6.5	85 (19.3)	80 (20.2)	
6.25-13.0	92 (20.9)	72 (18.2)	
13.0-24.15	88 (20.0)	84 (21.2)	
≥ 24.15	85 (19.3)	81 (20.5)	
Nonsteroidal anti-inflammatory drugs			<i>0.167</i>
No	317 (71.4)	252 (65.3)	
Yes	127 (28.6)	134 (34.7)	

*p-value of Chi-square

3.2. Association Between Each Infection and Prostate Cancer

Table 14 shows the association between different types of bacterial infections and prostate cancer risk, stratifying cases into low-grade and high-grade based on Gleason scores, with controls as a reference. There is no significant association observed between sexually transmitted bacterial infections for both low-grade (OR 0.85, 95% CI: 0.57-1.25) and high-grade prostate cancer (OR 0.83, 95% CI: 0.44-1.58). Specifically, Gonorrhea shows no significant risk across all groups (OR: 0.90, 95% CI: 0.61-1.33), and similar trends are shown for Urethritis (OR 1.04, 95% CI: 0.58-1.88) and Tuberculosis (OR 1.11, 95% CI: 0.70-1.74). Trichomonas has an increased risk for high-grade cancer (OR: 2.53, 95% CI: 0.76-8.39); however, it was not statistically significant. Similarly, Syphilis had no significant association among both low-grade (OR: 0.37, 95% CI: 0.08-1.73) and high-grade prostate cancer (OR: 0.51, 95% CI: 0.06-4.15).

Table 14 Association between Bacterial Infections and Prostate Cancer

	Controls		Cases				
	n=879 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections^a</i>							
No	792 (90.9)	750 (92.4)	1.00 Reference	568 (92.1)	1.00 Reference	170 (93.4)	1.00 Reference
Yes	79 (9.1)	62 (7.6)	0.85 (0.59-1.22)	49 (7.9)	0.85 (0.57-1.25)	12 (6.6)	0.83 (0.44-1.58)
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 (0.61-1.33)	45 (7.3)	0.93 (0.62-1.41)	9 (4.9)	0.73 (0.35-1.52)
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)	0.74 (0.27-2.07)	3 (0.5)	0.31 (0.07-1.53)	4 (2.2)	2.53 (0.76-8.39)
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)	0.39 (0.11-1.46)	2 (0.3)	0.37 (0.08-1.73)	1 (0.5)	0.51 (0.06-4.15)
Urethritis							
No	836 (97.0)	786 (96.8)	1.00 Reference	601 (96.9)	1.00 Reference	173 (96.7)	1.00 Reference
Yes	26 (3.0)	26 (3.2)	1.04 (0.58-1.88)	19 (3.1)	0.88 (0.46-1.69)	6 (3.4)	1.25 (0.49-3.19)
Tuberculosis							
No	835 (95.2)	774 (94.6)	1.00 Reference	589 (94.5)	1.00 Reference	172 (94.5)	1.00 Reference
Yes	42 (4.8)	44 (5.4)	1.11 (0.70-1.74)	34 (5.5)	1.14 (0.70-1.86)	10 (5.5)	1.07 (0.51-2.23)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason \leq 7 (3+4) *** Gleason \geq 7 (4+3)

^aSexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

Table 15 presents the association between various viral infections and the risk of prostate cancer, with cases also categorized into low-grade and high-grade based on the Gleason scores. The presence of any viral infection shows no significant association with either low-grade (OR 1.16, 95% CI: 0.93-1.44) or high-grade prostate cancer (OR 1.02, 95% CI: 0.73-1.42). There is no significant association between Zoster Herpes and prostate cancer across any groups (OR for low-grade: 1.11, 95% CI: 0.80-1.53; OR for high-grade: 0.96, 95% CI: 0.58-1.58). Similarly, there is no significant association with prostate cancer for Dengue among either low-grade (OR:1.03, 95% CI: 0.45-2.34) or high-grade (OR:0.62, 95% CI: 0.13-2.88). Polio shows a non-significant high risk among high-grade prostate cancer (OR: 2.51, 95% CI: 0.21-30.44). Finally, hepatitis, was also not significant among all grades of prostate cancer.

Table 15 Association Between Viral Infections and Prostate Cancer

	Controls		Cases				
	n=879 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
Viral Infections^a							
No	443 (52.7)	408 (50.9)	1.00 Reference	305 (50.1)	1.00 Reference	95 (53.1)	1.00 Reference
Yes	398 (47.3)	393 (49.1)	1.11 (0.90-1.35)	304 (49.9)	1.16 (0.93-1.44)	84 (46.9)	1.02 (0.73-1.42)
Zoster Herpes							
No	761 (87.6)	713 (87.5)	1.00 Reference	542 (87.0)	1.00 Reference	158 (87.6)	1.00 Reference
Yes	108 (12.4)	102 (12.5)	1.04 (0.77-1.41)	80 (13.0)	1.11 (0.80-1.53)	22 (12.2)	0.96 (0.58-1.58)
Polio							
No	872 (99.5)	816 (99.8)	1.00 Reference	622 (99.8)	1.00 Reference	181 (99.5)	1.00 Reference
Yes	4 (0.5)	2 (0.2)	1.46 (0.20-10.58)	1 (0.2)	1.18 (0.11-13.21)	1 (0.6)	2.51 (0.21-30.44)
Dengue							
No	858 (98.3)	803 (98.4)	1.00 Reference	610 (98.2)	1.00 Reference	181 (98.9)	1.00 Reference
Yes	15 (1.7)	13 (1.6)	0.92 (0.42-2.03)	11 (1.8)	1.03 (0.45-2.34)	2 (1.1)	0.62 (0.13-2.88)
Viral Hepatitis							
No	780 (90.7)	725 (89.2)	1.00 Reference	554 (89.6)	1.00 Reference	159 (87.4)	1.00 Reference
Yes	80 (9.3)	88 (10.8)	1.18 (0.85-1.65)	64 (10.4)	1.13 (0.70-1.62)	23 (12.6)	1.56 (0.93-2.62)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

Table 16 show the association between sexually transmitted viral infections and prostate cancer among all its grades. Regarding overall sexually transmitted viral infections, there is a non-significant positive risk across all prostate cancer cases (OR: 1.12, 95% CI: 0.91-1.38) and low-grade (OR: 1.17, 95% CI: 0.93-1.47) but not for high-grade (OR: 0.98, 95% CI: 0.69-1.40). For Genital herpes, the analysis indicates no significant association across all grades of cancer (OR for all cases: 0.69, 95% CI: 0.38-1.27; OR for high-grade: 0.62, 95% CI: 0.21-1.83). Epstein-Barr virus shows no significant correlation with all prostate cancer cases (OR: 0.92, 95% CI: 0.46-1.86) or for high-grade (OR:1.08, 95% CI: 0.34-3.41). Similarly, Herpes labialis is associated with a slightly increased, but not significant, risk of prostate cancer (OR for all cases: 1.21, 95% CI: 0.97-1.50; OR for high-grade: 1.05, 95% CI: 0.73-1.52).

Table 16 Association between Sexually Transmitted Viral Infections and Prostate Cancer

	Controls		Cases				
	n=879 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Viral Infections^a</i>							
No	575 (66.9)	524 (64.9)	1.00 Reference	392 (63.7)	1.00 Reference	123 (68.3)	1.00 Reference
Yes	284 (33.1)	284 (35.2)	1.12 (0.91-1.38)	223 (36.3)	1.17 (0.93-1.47)	57 (31.7)	0.98 (0.69-1.40)
Genital Herpes							
No	847 (96.8)	793 (97.3)	1.00 Reference	602 (97.0)	1.00 Reference	178 (97.8)	1.00 Reference
Yes	28 (3.2)	22 (2.7)	0.69 (0.38 -1.27)	18 (3.0)	0.73 (0.38-1.39)	4 (2.2)	0.62 (0.21-1.83)
Epstein-Barr							
No	849 (98.0)	786 (97.9)	1.00 Reference	599 (97.9)	1.00 Reference	174 (97.8)	1.00 Reference
Yes	17 (2.0)	17 (2.1)	0.92 (0.46-1.86)	13 (2.1)	0.89 (0.42-1.90)	4 (2.3)	1.08 (0.34-3.41)
Herpes labialis							
No	615 (70.9)	555 (68.1)	1.00 Reference	416 (67.2)	1.00 Reference	130 (71.0)	1.00 Reference
Yes	253 (29.1)	260 (31.9)	1.21 (0.97-1.50)	203 (32.8)	1.26 (0.99-1.59)	53 (29.0)	1.05 (0.73-1.52)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason \leq 7 (3+4) *** Gleason \geq 7 (4+3)

^a Sexually Transmitted Viral Infections: Herpes labial & genital, mononucleosis, Epstein-Barr

Table 17 shows the association between the overall infections and prostate cancer risk. The overall odds ratio (OR) for having any sexually transmitted bacterial and viral infection was 1.05 (95% CI: 0.86-1.29) across all cases which was not statistically significant. For specific cancer grades, low-grade cancer cases had an OR of 1.06 (95% CI: 0.85-1.32), while high-grade cases showed an OR of 0.97 (95% CI: 0.69-1.38), indicating no significant risk with prostate cancer. Furthermore, Individuals with just one type of sexually transmitted infection showed an odds ratio of 1.05 (95% CI: 0.85-1.30) across all prostate cancer cases. Similarly, for those reporting two or more infections, the odds ratio was 1.04 (95% CI: 0.67-1.59).

When assessing all types of infections combined whether bacterial/viral or sexually/non-sexually transmitted, the pattern remained similar, with an OR of 1.10 (95% CI: 0.90-1.35) for all prostate cancer cases, and slightly increased risks for individuals with multiple infections two or more infections (OR: 1.17, 95% CI: 0.88-1.56), though these findings were not statistically significant. The results remained non-significant for both low-grade and high-grade. A higher number of infections (two or more) had an OR slightly of 1.17 (95% CI: 0.88-1.56) for all cases that was statistically not significant. It was also not significant among low-grade and high-grade cancer.

Table 17 Association Between All Types of Infections and Prostate Cancer

	Controls		Cases				
	n=879 (%)	n=819 (%)	All OR* (95% CI)	Low grade cancer** n=623 (%)	OR* (95% CI)	High-grade cancer*** n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial & Viral Infections^a</i>							
No	511 (60.1)	476 (59.3)	1.00 Reference	358 (58.5)	1.00 Reference	111 (62.4)	1.00 Reference
Yes	340 (40.0)	327 (40.7)	1.05 (0.86-1.29)	254 (40.5)	1.06 (0.85-1.32)	67 (37.6)	0.97 (0.69-1.38)
1	287 (33.7)	277 (34.5)	1.05 (0.85-1.30)	216 (35.2)	1.07 (0.85-1.35)	55 (30.9)	0.93 (0.65-1.35)
≥ 2	53 (6.2)	50 (6.2)	1.04 (0.67-1.59)	38 (6.2)	0.97 (0.61-1.56)	12 (6.7)	1.23 (0.62-2.43)
<i>Overall Infections^b</i>							
No	383 (45.6)	351 (43.9)	1.00 Reference	264 (43.4)	1.00 Reference	81 (45.5)	1.00 Reference
Yes	457 (54.4)	448 (56.1)	1.10 (0.90-1.35)	344 (56.6)	1.11 (0.89-1.38)	97 (54.5)	1.07 (0.77-1.50)
1	317 (37.7)	305 (38.2)	1.07 (0.86-1.34)	232 (37.7)	1.07 (0.84-1.35)	66 (37.1)	1.03 (0.71-1.49)
≥ 2	140 (16.7)	143 (17.9)	1.17 (0.88-1.56)	112 (18.4)	1.21 (0.89-1.64)	31 (17.4)	1.18 (0.73-1.89)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Sexually Transmitted Bacterial & Viral Infections: Herpes labial & genital, Mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Urethritis

^b Overall Infections: Herpes labial & genital, mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Polio, Viral Hepatitis, Dengue, Zona, Urethritis, tuberculosis

3.3. Sensitivity Analysis

In this study, we performed additional sensitivity analyses by limiting the control group to participants who had undergone screening within two years before being included in the EPICAP study. This analysis was done to reduce the potential inclusion of latent cases among the controls, which could otherwise lead to an underestimation of the associations observed. Out of the 875 control participants, 602 had been screened for prostate cancer within two years prior to their interview. When we restricted the controls to those who were screened within the two years leading up to the reference date, the patterns of associations remained consistent. We did not observe any significant changes in the risk estimates across all studied groups of infections, including combined ones. Sensitivity analyses was also performed for each specific infection, and there were no major changes observed; detailed results are provided in the appendices 5 through 7.

For instance, the overall odds for sexually transmitted bacterial infections showed no significant association with either low-grade or high-grade prostate cancer (OR for low-grade: 0.80, 95% CI: 0.52-1.2) OR for high-grade: 0.78, 95% CI: 0.40-1.51). Viral infections also did not show significant associations, with overall viral infections yielding an OR of 1.03 (95% CI: 0.82-1.28) across all prostate cancer cases. Additionally, the results for overall infections, including both bacterial and viral types, also displayed non-significant associations in the sensitivity analysis, similar to the pre-analysis findings table 18.

Table 18 Association Between All Types of Infections and Prostate Cancer while restricting the control group to those screened in the last 2 years

	Controls		Cases				
	n=603 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections</i> ^a							
No	540 (90.3)	750 (92.4)	1.00 Reference	568 (92.1)	1.00 Reference	170 (93.4)	1.00 Reference
Yes	57 (9.6)	62 (7.6)	0.79 (0.53-1.18)	49 (7.9)	0.80 (0.52-1.22)	12 (6.6)	0.78 (0.40-1.51)
<i>Viral Infections</i> ^b							
No	297 (51.1)	408 (50.9)	1.00 Reference	305 (50.1)	1.00 Reference	95 (53.1)	1.00 Reference
Yes	284 (48.9)	393 (49.1)	1.03 (0.82-1.28)	304 (49.9)	1.08 (0.85-1.37)	84 (46.9)	0.94 (0.66-1.32)
<i>Sexually Transmitted Bacterial & Viral Infections</i> ^c							
No	344 (58.9)	476 (59.3)	1.00 Reference	358 (58.5)	1.00 Reference	111 (62.4)	1.00 Reference
Yes	240 (41.1)	327 (40.7)	0.96 (0.77-1.20)	254 (40.5)	0.98 (0.77-1.25)	67 (37.6)	0.89 (0.62-1.27)
1	202 (34.6)	277 (34.5)	0.96 (0.76-1.22)	216 (35.2)	0.99 (0.77-1.28)	55 (30.9)	0.85 (0.58-1.24)
≥ 2	38 (6.5)	50 (6.2)	0.95 (0.60-1.22)	38 (6.2)	0.90 (0.54-1.49)	12 (6.7)	1.15 (0.56-2.36)
<i>Overall Infections</i> ^d							
No	255 (44.1)	351 (43.9)	1.00 Reference	264 (43.4)	1.00 Reference	81 (45.5)	1.00 Reference
Yes	323 (55.9)	448 (56.1)	1.01 (0.81-1.27)	344 (56.6)	1.04 (0.82-1.32)	97 (54.5)	0.99 (0.70-1.41)
1	224 (38.8)	305 (38.2)	0.98 (0.77-1.25)	232 (37.7)	1.00 (0.77-1.30)	66 (37.1)	0.96 (0.65-1.41)
≥ 2	99 (17.1)	143 (17.9)	1.09 (0.77-1.25)	112 (18.4)	1.13 (0.81-1.58)	31 (17.4)	1.07 (0.65-1.75)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Sexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

^b Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

^c Sexually Transmitted Bacterial & Viral Infections: Herpes labial & genital, Mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Urethritis

^d Overall Infections: Herpes labial & genital, mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Polio, Viral Hepatitis, Dengue, Zona, Urethritis, tuberculosis

4. Discussion

4.1. Synthesis of Main Results

The main findings of our first objective on the relationship between various infections and prostate cancer indicate a generally non-significant association across both bacterial and viral infections with prostate cancer risk, regardless of cancer grade. Specifically, for sexually transmitted bacterial infections, there was no significant risk increase for either low-grade or high-grade prostate cancer, with an Odds Ratio (OR) of 0.85 (95% CI: 0.57-1.25) for low-grade and 0.83 (95% CI: 0.44-1.58) for high-grade cancers. Individual infections such as gonorrhea, urethritis, and tuberculosis showed no significant associations across any group, highlighting a lack of substantial link between these bacterial infections and the risk of developing prostate cancer.

Regarding viral infections, the overall presence of any viral infection similarly showed no significant effect on prostate cancer risk with an OR of 1.16 (95% CI: 0.93-1.44) for low-grade and 1.02 (95% CI: 0.73-1.42) for high-grade cancer. Specific viral infections such as Zoster Herpes, Polio, Viral Hepatitis, and Dengue did not demonstrate significant associations with prostate cancer. Even more notably, sexually transmitted viral infections such as genital herpes and Epstein-Barr virus also did not exhibit significant associations with prostate cancer across different grades.

Overall, the synthesis of these findings does not support a strong or consistent link between the infections studied and the risk of developing either low-grade or high-grade prostate cancer.

4.2. Comparison of Results to the Literature

Over the past decades, numerous studies have explored potential risk factors for prostate cancer, yet definitive associations remain uncertain. Among these, infectious agents have been extensively investigated. Our findings align with ten previous studies suggesting no significant association between STIs and prostate cancer risk, as reviewed by Caini et al. However, these results contrast with six other studies that suggest a possible link [88].

Further supporting the potential role of STIs, data from various meta-analyses suggest a significant association with prostate cancer. A pooled analysis of 17 studies indicated a slightly increased risk of prostate cancer associated with STIs, with a summary relative risk (SRR) of

1.49 (95%CI:1.19-1.92) [88]. Another meta-analysis reported similar elevated odds ratio (OR) of 1.30 (95%CI: 1.30-1.61) [182]. When considering other studies that relied on self-reported STIs, the evidence was mixed. Two studies reported a potential link with prostate cancer yielding an OR of 1.70 (95%CI: 1.1-2.5) and an OR 1.68 (95%CI: 1.05-2.70), respectively [95, 99]. Conversely, two other studies found no significant association with the risk of prostate cancer, with an OR of 1.00 ((95% CI: 0.7–1.5) and 1.02 (95% CI: 0.91–1.15), aligning closely with our own findings [96, 104].

Several studies investigating the relationship between sexually transmitted infections (STIs) and prostate cancer have particularly focused extensively on gonorrhea. Our null findings align with nine studies reviewed by Taylor et al.[182], conducted between 1975 and 2001, and 18 studies by Caini et al. [88], spanning from 1971 to 2011. Despite our null results, the standardized relative risks (SRRs) reported in these meta-analyses were significant for gonorrhea, with Taylor et al. reporting an SRR of 1.39 (95% CI: 1.05-1.83) and Caini et al. an SRR of 1.20 (95% CI: 1.05-1.37) [88, 182]. Additionally, Lian et al. conducted a meta-analysis specifically focusing on gonorrhea, yielding an odds ratio OR of 1.31 (95% CI: 1.14-1.52), which also contrasts with our findings [183]. Additionally, when comparing our results with studies that specifically focused on individual types of infections, our null findings remain consistent with four case-control studies [97, 99, 100, 198] and two cohort studies [103, 104] that also found no significant links between gonorrhea and prostate cancer. However, three other studies reported findings that are different from ours [91, 93, 98].

To our knowledge, only a limited number of studies have investigated the association between *Trichomonas* infection and prostate cancer. Among these, a meta-analysis by Najafi, which included studies evaluating serologically confirmed *Trichomonas* infections, reported an odds ratio OR of 1.17 (95% CI: 1.01-1.36) [184]. This finding suggests a potential association between *Trichomonas* infection and an increased risk of prostate cancer, which contrasts with our null results. Findings from studies that focused specifically on *trichomonas* largely align with our results. For instance, Tsang et al. reported no link between *Trichomonas* and prostate cancer, with hazard ratios (HRs) from the Physicians' Health Study (PHS) and the Health Professionals Follow-up Study (HPFS) being 0.85 (95% CI: 0.57-1.29) and 0.87 (95% CI: 0.42-1.80), respectively [116]. Similarly, Marous et al. found no association across all grades of prostate cancer, with an overall odds ratio OR of 0.97 (95% CI: 0.73-1.27), and specific ORs of 1.02 (95% CI: 0.73-1.42) for low-grade and 0.88 (95% CI: 0.59-1.30) for high-grade cancer [115].

Additionally, a study by Sutcliffe et al. observed that even high seropositivity for *Trichomonas* did not significantly affect prostate cancer risk, yielding an OR of 0.97 (95% CI: 0.70-1.34) [204]. However, one case-control study reported an OR of 2.6 (95% CI: 1.20-5.70) that didn't align with our study findings [209].

Syphilis and its potential association with prostate cancer has been extensively studied over the past decades. Meta-analyses, such as the ones done by Taylor et al. and Caini et al., have largely supported our findings, indicating no significant association between syphilis and prostate cancer [88, 182]. Taylor et al.'s meta-analysis aligns with our results, except for a study by Hayes in 2000 [92], which contrasts with our null finding. Similarly, out of the seventeen studies reviewed in Caini et al.'s meta-analysis, fourteen were aligned with our findings of no significant link, while only three did not [88]. The summarized relative risks (SRR) from these meta-analyses, 1.42 (95% CI: 0.67-2.64) and 1.27 (95% CI: 0.85-1.89), were not statistically significant. Considering studies that specifically focused on syphilis, five case-control studies [93, 96-98, 100] and two cohort [103, 104] were consistent with our findings, whereas two showed different results from our findings [92, 201].

In the literature, studies assessing the risk of prostate cancer associated with herpes simplex virus have consistently shown no significant correlation, aligning with our findings. For genital herpes, four case-control studies yielded odds ratios that were non-significant: OR: 1.65 (95% CI: 0.69-3.99), OR: 1.1 (95% CI: 0.3-5.2), OR: 1.12 (95% CI: 0.23-5.47), and OR: 1.15 (95% CI: 0.22-6.05) [93, 96, 98, 100]. A cohort study also supported these findings with a relative risk of RR: 0.86 (95% CI: 0.69-1.08) [104]. Additionally, studies considering both HSV-1 and HSV-2, whether case-control or cohort, were consistent with our results [110-112, 117, 216]. Only the study by Dennis et al., which analyzed HSV-2 up to 94 months before diagnosis, showed a slightly elevated risk that was statistically significant, OR: 1.60 (95% CI: 1.05-2.44). Concerning varicella-zoster virus, only one retrospective cohort study suggested an increased risk, HR: 1.90 (95% CI: 0.59-6.14) [222], while three other population-based case-control studies did not find consistent evidence of an association [223-225]. Finally, a study examining Epstein-Barr virus was also consistent with our findings, showing no significant association [110].

Meta-analyses of hepatitis C related to prostate cancer included seven studies that generally aligned with our results, showing a relative risk RR of 0.75 (95% CI: 0.54-1.03). Notably, all included studies used serology or medical records for data collection. Of these, three studies specifically focusing on Hepatitis C Virus (HCV) found no significant association with prostate

cancer, reporting a standardized incidence ratio (SIR) of 1.02 (95% CI: 0.12-3.70), and hazard ratios (HR) of 0.84 (95% CI: 0.48-1.46) and 1.06 (95% CI: 0.76-1.48) [108, 230, 232]. Conversely, the remaining five studies presented either an inverse or positive association [41, 106, 229, 231, 233]. As for Hepatitis B Virus (HBV), one study showed no significant association HR: 0.93 (95% CI: 0.58-1.49) [232], while three others did find significant associations [61, 107, 229]. However, our findings are limited by the inability to specify which type of hepatitis was considered, thus making it difficult to compare specific types of hepatitis with our results. Finally, the study conducted by Rosenblatt considered the association between urethritis and prostate cancer, yielding results consistent with our own findings, with an odds ratio of OR 0.80 (95% CI: 0.38-1.68), indicating no significant association. To our knowledge, there are no studies that have specifically examined the relationship between tuberculosis, polio, or dengue and the risk of prostate cancer.

Very few studies have considered the aggressiveness of prostate cancer in their analyses. The California Men's Health Study, a cohort study, found no significant associations when analyzing the aggressiveness of cancer; non-aggressive cases had a relative risk (RR) of 1.00 (95% CI: 0.86–1.15), and aggressive cases had an RR of 1.06 (95% CI: 0.87–1.29), consistent with our findings [104]. The study also included gonorrhea, syphilis, and genital herpes, which were also not statistically significant [104]. Similarly, the Health Professionals Study, another cohort study, explored the association with gonorrhea and found no significant links [103]. Additionally, a case-control study by Spence et al. in Canada, which also accounted for the aggressiveness of prostate cancer, showed no significant associations for gonorrhea, syphilis, genital herpes, and trichomonas, further supporting our results that infection status might not significantly impact the aggressiveness of prostate cancer [100].

The inconsistencies observed in the association between infections and prostate cancer risk across various studies can be explained due to several factors. Firstly, racial and ethnic differences impact STD reporting rates, with higher rates often noted among Latino and African populations compared to Caucasians [104]. This could indicate a higher prevalence of repeated infections or coinfections in these groups, potentially having a stronger association with prostate cancer risk. Additionally, the duration of untreated infections, such as gonorrhea among other infections, might extend due to challenges in accessing medical care, ineffective treatments, or non-compliance, leading to prolonged inflammatory responses [92].

Secondly, the timing of exposure to infections plays a critical role; infections contracted at a younger age may influence prostate cancer risk differently than those acquired later. Confounding factors might also contribute to inconsistencies, as inadequate adjustment for variables can influence the results. Moreover, the methodologies used to assess infection, ranging from self-reports to medical records or biological markers, can also influence the results of study findings. Furthermore, sample size and statistical power vary across studies. Some may lack the necessary size to detect any effect, particularly for rarer infections, leading to non-significant findings. Although our study did not find any association, unlike other studies, we cannot rule out detection bias and must acknowledge this limitation.

4.3. Strengths and Limitations

In this part of my research, I explored the association between various infections and the risk of prostate cancer using data from the EPICAP study, which has several strengths. EPICAP was conducted in the department of Hérault, covering a well-defined geographical area. The overall participation rate for this study was 77%, which is considered a generally good rate.

Case identification was done in all private and public cancer hospitals in the Department of Hérault, with the Hérault cancer registry reporting 770 new prostate cancer cases in 2011. Given that the number of cases observed in 2012-2013 was expected to be similar, approximately 1,150 new cases were anticipated during the study period. The recruitment of cases was quite exhaustive as the number of identified eligible cases was 1,098 during the study period, thus limiting the potential of selection bias. Moreover, even though the participation rate in cases was 75%, the age distribution and Gleason scores of non-responding cases were comparable to those of responding cases, thereby minimizing potential survival bias. Furthermore, interviews were conducted shortly after identification, with only 8 (0.7%) eligible cases dying before they could be interviewed. Additionally, the availability of the Gleason score allowed us to assess the aggressiveness of cancer, a factor that is rarely taken into account in previous studies.

Controls were randomly selected from the general population of the Hérault department, using quotas by age (± 5 years) to reflect the age distribution observed among the cases, and quotas for Socioeconomic status (SES) to ensure the distribution of the control group reflects the SES distribution of the entire department of Hérault to yield a control group similar to the general population of men. After the selection process, the distribution by SES between the

control group and the general male population of the department of Hérault was compared. No significant difference was found, indicating that no major selection bias by SES had occurred within our control population.

We cannot rule out the potential for recall bias, therefore, recognizing it is crucial, particularly as our method of collection relies on self-reporting of our exposure. This could lead to differential classification bias, especially when dealing with sexually transmitted infections (STIs), which are often asymptomatic and stigmatized. This may result in the underestimation of their prevalence due to reluctance to report, lack of awareness, or inadequate knowledge about the nature of the infection. However, data collection was conducted face-to-face by a trained clinical nurse using standardized questionnaire, ensuring consistency between cases and controls. Furthermore, the prevalence of gonorrhea reported among our controls was 7.7%, closely aligning with the 6% reported among the general French population over age 45 [234]. This similarity supports a minimal classification bias in our findings. However, the prevalence of syphilis observed in our study (1%) is considerably lower than the general population estimate in France (around 4%), suggesting a possible underestimation of our results [234]. No medical or biological data were available to verify the presence of reported infections.

Furthermore, while a detection bias potentially affecting the robustness of our findings cannot be entirely ruled out, particularly concerning associations with less aggressive cancers, the results of our sensitivity analyses allowed us to be confident with our observed risk estimates. During the analysis of all infections, some specific infections may have had limited statistical power due to small sample sizes, especially when considering the aggressiveness of cancer. To address this, we grouped similar infections, enhancing the power of our analyses.

Moreover, our study faced limitations in conducting more nuanced analyses, such as assessing the timing of infection relative to the diagnosis of prostate cancer. This was primarily due to insufficient data regarding the exact timing of infection, restricting our ability to explore how short vs long-standing infections might impact cancer risk.

We also conducted additional sensitivity analyses to further validate our findings. First, we included only men with no history of NSAID use to account for the potential impact of NSAIDs on inflammatory responses, however, there was no significant changes in our results, indicating that NSAID use did have a substantial effect on the association between infections and prostate cancer (Appendix 8). Second, we compared cases from public and private clinics

to address potential differences in healthcare utilization and prevention behaviors. The results also remained consistent across both groups, suggesting that our findings are not influenced by the type of healthcare setting (Appendix 9 and 10).

Finally, in our study, most suspected confounding variables did not impact the outcomes, with case and control groups showing high comparability. Several variables related to the outcomes or the variables of interest were identified. Statistical adjustments were applied to all suspected variables to limit confounding bias. Well-established risk factors for prostate cancer were also considered in all analytical models. Despite these adjustments for non-modifiable risk factors and major potential confounders such as level of education, physical activity, waist circumference, and non-steroidal anti-inflammatory drugs, our results remained unchanged.

We observed no significant association between both sexually transmitted and non-sexually transmitted infections and the incidence of prostate cancer, suggesting that infections may not play a central role in the etiology of prostate cancer in our study population. Given the variability in findings from prior research, further investigations are needed to clarify the potential role of infectious and inflammatory agents in the development of prostate cancer. Such studies could help refine preventive strategies aimed at reducing the risk of prostate cancer. In the next chapter, we will shift our focus to examine the role of calculi, including kidney and gallbladder stones, in the risk of prostate cancer, expanding our understanding to other inflammation-related risk factors.

CHAPTER 4 – CALCULI AND PROSTATE CANCER

1. Introduction

1.1. Calculi Definitions & Prevalence

Calculi, commonly known as stones, are hard, solid masses that can form within various organs of the body. These calculi are typically composed of mineral salts and other substances that crystallize and aggregate over time [235]. There are several different types of calculi that can form in various parts of the body while having distinct characteristics such as kidney stones, gallstones, bladder stones, salivary stones, and pancreatic duct stones.

Gallstones affect approximately 10-15% of adults, particularly in Western populations [124]. Kidney stones have a lifetime prevalence of about 10% for men and 7% for women, with rising incidence globally [236]. Bladder stones are less common, but they predominantly affect older men and those with bladder outlet obstruction, with an estimated prevalence of about 1-5% in at-risk populations [237]. Pancreatic stones, though rare, occur in individuals with chronic pancreatitis, affecting 50% of patients with this condition [238]. Among these, gallstones and kidney stones are the most prevalent and well-studied.

Kidney stones, also known as nephrolithiasis, are a common urological condition with increasing prevalence worldwide [239, 240]. They are hard deposits made of minerals and salts that form inside the kidneys. The most common types of kidney stones are calcium oxalate (60-80%), followed by calcium phosphate (5-10%), uric acid (5-10%), struvite (7-8%), and cystine (1-2%) [241]. They can cause severe pain and urinary complications as they pass through the urinary tract. In the United States, the prevalence of kidney stones has doubled since the 1960s, with the most recent data showing a prevalence of 8.8% overall, 10.6% in men, and 7.1% in women [236, 239]. Similar increasing trends have been observed in other countries, such as Germany, Spain, and Italy [239]. In France, the prevalence of kidney stones is estimated to be around 10% of the general population, with an increasing trend, especially among adults aged above 45 years [241]. Factors contributing to the rising prevalence may be changes in dietary patterns (e.g., high animal protein, high sodium, and high oxalate intake), obesity, diabetes, and metabolic disorders [236, 239, 241]. If left untreated, the presence of kidney stones can potentially block the flow of urine, resulting in swelling and damage to the kidney tissues [241–243]. This obstruction can trigger an inflammatory response that may lead to chronic kidney damage and other related conditions [242, 243].

Gallstones, also known as Cholelithiasis, are a common gastrointestinal disorder with a global prevalence of approximately 10-15% in the Western population [124, 244]. They are hardened deposits made from cholesterol, bilirubin, and bile that form in the gallbladder, a small organ located beneath the liver [245, 246]. The most common types of gallstones are cholesterol stones, pigment (bilirubin) stones, and mixed stones, with cholesterol stones accounting for over 85% of cases in developed countries. Prevalence rates vary geographically, with the highest rates observed in USA, Europe, and among certain ethnic groups like Native Americans [124, 246–249]. Recent trends indicate an increasing prevalence of gallstones in younger populations, potentially due to rising obesity rates and changes in dietary habits [124]. The prevalence of gallstones increases with age and is higher in women than in men [124]. Factors contributing to gallstone formation include obesity, high-fat diets, rapid weight loss, and certain genetic predisposition [124, 245, 246, 250]. Chronic inflammation of the gallbladder, known as cholecystitis, can occur when gallstones obstruct the bile ducts, leading to severe pain, infection, and potential complications such as gallbladder rupture [245, 246]. This chronic inflammation is characterized by gallbladder wall thickening, fibrosis, and impaired motility, leading to symptoms like abdominal pain, nausea, and vomiting, which can later contribute to further complications, including an increased risk of gallbladder cancer and other related conditions [245, 246, 251].

Kidney stones and gallbladder stones are common health concerns worldwide, impacting millions of individuals and contributing to significant morbidity. While the potential associations between these types of calculi and cancer development have not been extensively studied, emerging research suggests possible links. Therefore, this thesis investigates the role of kidney stones and gallbladder stones and the risk of prostate cancer.

1.2. Calculi and Prostate Cancer

The potential associations between different types of calculi, such as gallstones and kidney stones, and the risk of developing prostate cancer have been an area of interest for the past few years. While kidney stones and gallstones are common health issues that affect millions of people worldwide, their role in the pathogenesis of prostate cancer has not been extensively studied, and the body of research remains limited.

To address the relationship between gallstones and prostate cancer, a meta-analysis done by Li et al, included seven studies. Among these studies, there were 3 cohort studies and three case-control studies. Geographically, three were conducted in Europe and three were conducted in Asia. The findings suggest an association between cholelithiasis and prostate cancer, yielding a pooled RR: 1.35 (95%CI: 1.17-1.56) figure 18 but not with gallstones RR: 1.16 (95%CI: 0.55-2.46). Specifically, among the seven studies included only two did not have a significant association between gallstones and the risk of prostate cancer (Figure 18) [133].

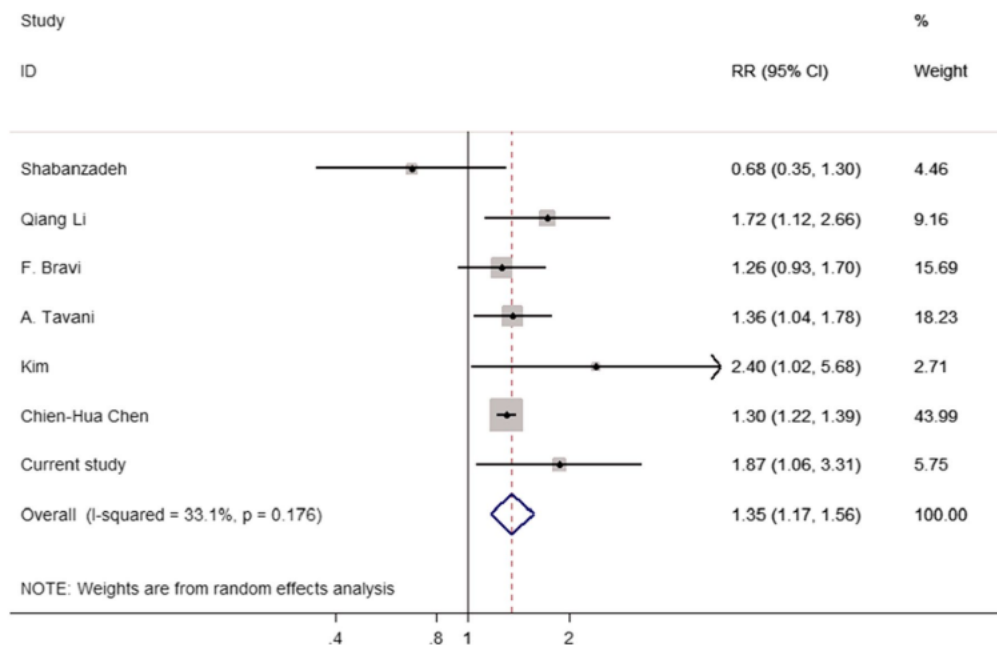


Figure 18 Forest Plot of the Meta-analysis done Li (2022) Pooling Relative Risk for Prostate Cancer

For a detailed examination of the relationship between gallstones and the risk of prostate cancer, table 19 shows the different types of studies that have been conducted. A recent case-control study involving 221 cases and 219 controls showed a significant association between cholelithiasis and prostate cancer with an estimated risk of RR: 1.98 (95%CI: 1.13-3.36) [133]. The association was even stronger between gallstones and prostate cancer with an estimated risk of RR: 2.77 (95%CI: 1.20-6.40) [133]. Another case-control included 1,582 cases and 2,231 controls also found a significant association between gallstones and prostate cancer, with an OR of 1.35 (95%CI: 1.04-1.78) [252]. Additionally, two cohort studies also showed a positive significant association between gallstones and prostate cancer, yielding an HR of 1.30 (95%CI: 1.22-1.39)[253] and an HR of 1.79 (95%CI:0.81-3.94) for localized cancer and an HR of 2.29 (95%CI: 1.21-4.35) for advanced prostate cancer [254]. Finally, one case control study and another cohort study had no significant association yielding an OR of 1.26 (95% CI: 0.93-1.70)[255] and HR of 0.67 (95% CI: 0.35-1.30)[256], respectively. In summary, the results of these studies suggest a mixed but generally positive association between gallstones or cholelithiasis and the risk of prostate cancer.

Table 19 Studies Evaluating the Risk of Prostate Cancer among those with a History of Gallstones or Cholelithiasis.

Author (Year)	Study Design	Cases/Controls	Method of Collection	Estimated Risk (95% CI)
Li (2022)	Meta-analysis	80,403 Total	-	Cholelithiasis OR: 1.35 (1.17-1.56) Gallstones OR: 1.16 (0.55-2.46)
Li (2022)	Case-control	221 Cases/ 219 Controls	Medical Records	Cholelithiasis OR: 1.98 (1.13-3.36) Gallstones OR: 2.77 (1.20-6.40)
Shabanzadeh (2017)	Cohort	3017 Total	Ultrasound	Gallstones HR: 0.67 (0.35-1.30)
Chen (2016)	Cohort	47,478 Total	Diagnosis	Gallstones HR: 1.30 (1.22-1.39)
Tavani (2011)	Case-control	1582 Case/ 2231 Controls	Self-Report	Gallstones OR: 1.36 (1.04-1.78)
Quang Li (2011)	Cohort	1,096 Cases/ 23,362 Control	Self-Report	Gallstones Localized HR: 1.79(0.81-3.94) Advanced HR: 2.29 (1.21-4.35)
Bravi (2006)	Case-control	1294 Cases/ 1451 Control	Self-Report	Gallstones OR: 1.26 (0.93-1.70)
Kim (2004)	Case-control	184 Cases/ 267 Control	Self-Report	Gallstones OR: 2.40 (1.02-5.68)

SIR: Standardized Incidence Rate; HR: Hazard Ratio; OR: Odds Ratio

Table 20 summarizes the findings from several studies on the association between different types of urinary calculi and the risk of prostate cancer. The study by Pelucchi (2006) included 280 cases and 689 controls and found a non-significant association between urinary calculi and prostate cancer with an odds ratio (OR) of 1.53 (95% CI: 0.84-2.78) [97]. A cohort study with a large sample size of 2,900 cases and 14,500 controls, showed for overall urinary an OR of 1.63 (95% CI: 1.47-1.80), and significant associations for kidney stones (OR: 1.71, 95% CI: 1.42-2.05) and bladder stones (OR: 2.06, 95% CI: 1.32-2.23), but not for ureter stones (OR: 1.11, 95% CI: 0.82-1.51) [131]. Shih (2014) examined a smaller cohort of 141 cases of prostate, finding a strong association between urinary calculi and prostate cancer with an SIR of 4.02 (95% CI: 3.39-4.75). Lastly, a recent cohort showed SIRs of kidney stones (1.01, 95% CI: 0.97-1.05), ureter stones (1.04, 95% CI: 1.01-1.08), and bladder stones (1.10, 95% CI: 0.97-1.24), indicating a slight but not statistically significant increased risk for prostate cancer associated with ureter stones, while kidney and bladder stones did not show significant associations [240].

Table 20 Studies Evaluating the Risk of Prostate Cancer among those with Urinary Calculi

Author (Year)	Study Design	Cases/Controls	Method of Collection	Estimated Risk (95% CI)
Pelucchi (2006)	Case-control	280 Cases/ 689 Controls	Self-Report	Urinary OR: 1.53 (0.84-2.78) Urinary OR: 1.63 (1.47-1.80)
Chung (2013)	Cohort	2,900 Cases/ 14,500 Controls	Diagnosis	Kidney OR: 1.71 (1.42-2.05) Ureter OR: 1.11 (0.82-1.51) Bladder OR: 2.06 (1.32-2.23)
Shih (2014)	Cohort	141 Cases	Diagnosis	Urinary SIR: 4.02 (3.39-4.75)
Hemminki (2018)	Cohort	7164 Cases	Registry	Kidney SIR: 1.01 (0.97-1.05) Ureter SIR 1.04 (1.01-1.08) Bladder SIR 1.10 (0.97-1.24)

SIR: Standardized Incidence Rate; OR: Odds Ratio, SIR: Standardized Incidence Risk

2. Material & Methods

2.1. Population Study

In order to study the relationship between different types of calculi and the risk of prostate cancer using data from the EPICAP study, we included a total of 1,698 men, of which 819 are cases of prostate cancer and 879 controls.

2.2. Data Collection

As mentioned in Chapter 2, information on various aspects, including sociodemographic characteristics, professional and residential history, medical history, and ethnic origin, were collected. Environmental factors, encompassing details on places of residence and lifestyle habits such as tobacco, alcohol consumption, sleep patterns, leisure activities, and physical activity were collected.

Detailed questions on different types of calculi (Kidney stones and gallbladder stones), inflammatory conditions, dyslipidemia (hypercholesterolemia, hypertriglyceridemia), and medication history, including non-steroidal anti-inflammatory drugs and antibiotics, were collected. Additionally, concerning each type of stone, the number of episodes, along with age at the time of infection in instances of multiple episodes, as well as the age at which they experienced their first and last episode, were also collected (Appendix 15).

2.3. Variables of Interest

Our analysis included 2 distinct types of stones: kidney stones and gallbladder stones.

Each type of stone was defined separately based on whether the individual had experienced an episode before the reference date, which was the date of diagnosis for the cases and the date of interview for the controls. Consequently, both variables were represented as binary variables, where 0 indicated no history of stones, and 1 indicated having a history of stones.

The two types of calculi were grouped together to have an overall view of the relationship with the risk of prostate cancer. Prostatitis and Pyelonephritis were also represented as binary variables, where 0 indicated no history of the condition, and 1 indicated having a history of the condition.

Regarding the combined variables, they were as follows:

Calculi: it was defined as having at least one type of stone (Kidney or gallbladder) before the reference date, making it a binary variable where 0 indicated no history of stones and 1 indicated having at least one type of stones.

To better understand the relationship between kidney stones and prostate cancer, we created combined variables that include a history of prostatitis or pyelonephritis, as these conditions have been previously associated with prostate cancer as mentioned in chapter 2, and because both conditions cause inflammation that affect the genitourinary system.

Kidney stones + Prostatitis: it was defined in four classes, where level 0 indicated having neither Kidney stones nor prostatitis, level 1 indicated the absence of kidney stones, but the presence of prostatitis, level 2 indicated the presence of kidney stones but the absence of prostatitis, and level 3 indicated the presence of both conditions.

Kidney stones + Pyelonephritis: it was defined in four classes, where level 0 indicated having neither Kidney stones nor pyelonephritis, level 1 indicated absence of kidney stones but presence of pyelonephritis, level 2 indicated presence of kidney stones but absence of pyelonephritis, and level 3 indicated presence of both conditions.

2.4. Statistical Analysis

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

2.4.1. Descriptive Analysis

Given that we are using the same study data from EPICAP, we examined the same factors as in our first objective, including sociodemographic characteristics, lifestyle factors, medical history, and well-established non-modifiable risk factors for prostate cancer (age, ethnicity, and family history). We compared these factors between cases and controls using the chi-square test (results outlined in Chapter 2 – Table 3).

Additionally, given that all our variables were qualitative, they were represented using frequencies and percentages when comparing them between cases and controls. Subsequently, among the controls, we also used the chi-square test to compare all our population characteristics within each type of stone, including the combined one.

2.4.2. Inferential Analysis

For each specific stone, the association with prostate cancer was evaluated using unconditional logistic regression models, allowing for the computation of odds ratios (OR) and their corresponding 95% confidence intervals. Similarly, the same model was used when examining the association of the combined calculi variable.

Furthermore, multinomial logistic regression models were used to examine the relationship between calculi and prostate cancer based on the aggressiveness of cancer using the Gleason score at the time of diagnosis. For non-aggressive or low-grade cancer, the Gleason score is defined as ≤ 7 [including 3+4], which is considered a low or intermediate score, while aggressive or high-grade cancer was characterized by a Gleason score of ≥ 7 [including 4+3], regarded as a high score. Because the Gleason score was unavailable for 13 cases in the EPICAP study, the analysis on prostate cancer aggressiveness included only 805 cases, with 183 being classified as aggressive.

To start with, we investigated the relationship between stones and prostate cancer by systematically adjusting the models for established risk factors (age, ethnicity, and family history of prostate cancer). Subsequently, our models were further adjusted for additional potential confounding factors, including variables at the $\alpha=20\%$ threshold such as physical activity, waist circumference, education, and non-steroidal anti-inflammatory drugs (NSAIDs). Using the stepwise approach, we removed the least significant adjustment factors from the model when it did not alter the associations. Therefore, the final model investigating the relationship between infections and prostate cancer was adjusted for age, ethnicity, family history of prostate cancer, physical activity, NSAIDs, waist circumference, education, and hypertriglyceridemia.

In order to understand the combined impact of kidney stones with either pyelonephritis or prostatitis, a differential risk assessment is conducted to identify whether prostate-specific inflammation (prostatitis) or kidney-related infections (pyelonephritis) have stronger associations with prostate cancer. Kidney stones, prostatitis, and pyelonephritis often occur as comorbidities, with kidney stones potentially causing urinary tract blockages and infections that lead to pyelonephritis, while prostatitis can be linked to or exacerbated by these infections.

Hypertriglyceridemia is a known risk factor for metabolic syndrome and can influence the development of various types of calculi differently. Stratifying the analysis based on hypertriglyceridemia status was done to determine whether elevated triglyceride levels influence the association between kidney stones and gallbladder stones and the risk of prostate cancer. This stratification helps to uncover whether hypertriglyceridemia modifies the risk profile if both elevated triglycerides and gallstones might have a higher risk of prostate

cancer. Following stratification, an interaction analysis with Hypertriglyceridemia was conducted to further explore whether or not there is a modifying effect.

2.4.3. Sensitivity Analysis

Ultimately, sensitivity analysis was performed by limiting the control group to individuals who underwent screening within the two years preceding the reference date. This was done to minimize the likelihood of latent prostate cancer cases among controls, thus limiting the risk of underestimating associations. Following this restriction, the total number of controls was 603.

To further reduce the risk of misclassification bias, another sensitivity analysis was conducted by further limiting the control group to individuals who underwent screening within the two years preceding the reference date and had normal screening results. This method more effectively excludes individuals with undiagnosed or latent prostate cancer among the controls, thereby reducing potential bias and improving the reliability of the association being studied.

Finally, given that the incidence of prostate cancer in France may be related to mass screening through PSA testing, another sensitivity analysis was conducted by stratifying the control group based on the frequency of PSA testing. The control group was divided into three groups: individuals who had undergone PSA testing only once (n=63), those who had undergone PSA testing two to five times (2-5 times), and those who had undergone more than five PSA tests (n=291). Restricting the control group to individuals with varying frequencies of PSA tests allowed for consideration of potential detection bias associated with different levels of screening intensity.

3. Results

3.1. Comparison of Subjects' Characteristics based on Calculi Status in the control group

Table 21 shows the characteristics of control subjects based on their history of having either kidney or gallstones, differentiating those with from those without. There is no significant differences in age ($p=0.092$), ethnic origin ($p=0.250$), family history of prostate cancer ($p=0.255$), education levels ($p=0.720$), Body Mass Index (BMI) ($p=0.090$), waist circumference ($p=0.078$), smoking status ($p=0.801$), alcohol consumption ($p=0.678$), physical activity levels ($p=0.949$), use of nonsteroidal anti-inflammatory drugs (NSAIDs) ($p=0.321$), hypertriglyceridemia ($p=0.425$), hypercholesterolemia ($p=0.232$), and pyelonephritis ($p=0.745$) between the two groups. However, there is a significant difference in the prevalence of prostatitis ($p=0.012$), with 11.4% of individuals with calculi having prostatitis compared to 6.1% without calculi.

Table 21 Characteristics of Controls based on their history of Calculi (Kidney stones & Gallstones)

Calculi	Yes n=193	No n=673	P-value*
Age (Years)			0.092
< 55	9 (4.7)	49 (7.3)	
[55-60]	20 (10.4)	77 (11.4)	
[60-65]	34 (17.6)	164 (24.4)	
[65-70]	68 (35.2)	214 (31.8)	
≥70	62 (32.1)	169 (25.1)	
Ethnic Origin			0.250
Caucasian	191 (99.0)	657 (97.6)	
Other	2 (1.0)	16 (2.4)	
Family History of Prostate Cancer			0.255
No	170 (89.0)	616 (91.7)	
Yes	21 (11.0)	56 (8.3)	
Education			0.720
≤Primary	39 (20.3)	153 (22.7)	
Secondary	93 (48.4)	325 (48.3)	
University	60 (31.3)	195 (29.0)	
Body Mass Index (kg/m²)			0.090
<25 - Normal	43 (23.2)	199 (30.4)	
[25-30] - Overweight	88 (47.6)	304 (46.5)	
≥30 - Obese	54 (29.2)	151 (23.1)	
Waist Circumference (cm)			0.078
≤94	45 (24.2)	203 (30.9)	
>94	141 (75.8)	455 (69.2)	
Smoking Status			0.801
Never	51 (26.4)	193 (28.7)	
Former	108 (56.0)	360 (53.5)	
Current	34 (17.6)	120 (17.8)	
Alcohol Consumption**			0.678
No	17 (8.8)	66 (9.8)	
Yes	176 (91.2)	607 (90.2)	
Physical Activity (MET -h/wk/yr)***			0.949
No	41 (21.2)	133 (19.9)	
<6.5	35 (18.1)	133 (19.9)	
6.25-13.0	39 (20.2)	132 (19.8)	
13.0-24.15	37 (19.2)	138 (20.7)	
≥24.15	41 (21.2)	132 (19.8)	
Nonsteroidal anti-inflammatory drugs			0.321
No	126 (66.0)	461 (69.7)	
Yes	65 (34.0)	200 (30.3)	
Hypertriglyceridemia			0.425
No	145 (75.1)	524 (77.9)	
Yes	48 (25.0)	149 (22.1)	
Hypercholesterolemia			0.232
No	103 (53.4)	381 (56.6)	
Yes	90 (46.6)	285 (42.4)	
Prostatitis			0.012
No	171 (88.6)	632 (93.9)	
Yes	22 (11.4)	41 (6.1)	
Pyelonephritis			0.745
No	189 (98.9)	659 (98.7)	
Yes	2 (1.1)	9 (1.4)	

*p-value of Chi-square

Table 22 shows the characteristics of control subjects based on their history of having gallstones, differentiating those with from those without. There are no significant differences in age ($p= 0.147$), ethnic origin ($p= 0.686$), family history of prostate cancer ($p= 0.669$), education levels ($p= 0.871$), smoking status ($p= 0.822$), alcohol consumption ($p= 0.466$), physical activity levels ($p= 0.922$), use of nonsteroidal anti-inflammatory drugs (NSAIDs) ($p = 0.749$), hypertriglyceridemia ($p = 0.211$), hypercholesterolemia ($p= 0.096$), prostatitis ($p= 0.914$), and pyelonephritis ($p= 0.337$) between the two groups. However, a notable difference is observed in Body Mass Index (BMI) ($p= 0.011$), with 30.1% of individuals without gallstones being of normal weight compared to 16.4% with gallstones, and 23.2% of individuals without gallstones being obese compared to 37.3% with gallstones. Waist circumference shows a borderline significance ($p= 0.059$), with more individuals with gallstones having a waist circumference over 94 cm compared to those without.

Table 22 Characteristics of Controls based on their history of Gallstones

Gallstones	Yes n=67	No n=802	P-value χ^2
Age (Years)			<i>0.147</i>
< 55	2 (3.0)	55 (6.9)	
[55-60]	8 (11.9)	88 (11.0)	
[60-65]	9 (13.4)	191 (23.8)	
[65-70]	24 (35.8)	259 (32.3)	
≥70	24 (35.8)	209 (26.1)	
Ethnic Origin			<i>0.686</i>
Caucasian	66 (98.5)	784 (97.8)	
Other	1 (1.5)	18 (2.2)	
Family History of Prostate Cancer			<i>0.669</i>
No	62 (92.5)	727 (91.0)	
Yes	5 (7.5)	72 (9.0)	
Education			<i>0.871</i>
≤Primary	16 (24.2)	176 (22.0)	
Secondary	30 (45.5)	389 (48.0)	
University	20 (30.3)	237 (30.0)	
Body Mass Index (kg/m²)			<i>0.011</i>
<25 - Normal	11 (16.4)	234 (30.1)	
[25-30] - Overweight	31 (46.3)	361 (46.6)	
≥30 - Obese	25 (37.3)	180 (23.2)	
Waist Circumference (cm)			<i>0.059</i>
≤94	13 (19.4)	237 (30.4)	
>94	54 (80.6)	543 (69.6)	
Smoking Status			<i>0.822</i>
Never	21 (31.3)	223 (27.8)	
Former	35 (52.2)	437 (54.5)	
Current	11 (16.4)	142 (17.7)	
Alcohol Consumption			<i>0.466</i>
No	8 (11.9)	74 (9.2)	
Yes	59 (88.1)	728 (90.8)	
Physical Activity (MET -h/wk/yr)			<i>0.922</i>
No	15 (22.4)	160 (20.0)	
<6.5	12 (17.9)	158 (19.8)	
6.25-13.0	14 (20.9)	158 (19.8)	
13.0-24.15	15 (22.4)	160 (20.1)	
≥24.15	11 (16.4)	161 (20.2)	
Nonsteroidal anti-inflammatory drugs			<i>0.749</i>
No	46 (70.8)	544 (68.9)	
Yes	19 (29.2)	246 (31.1)	
Hypertriglyceridemia			<i>0.211</i>
No	56 (83.6)	617 (76.9)	
Yes	11 (16.4)	185 (23.1)	
Hypercholesterolemia			<i>0.096</i>
No	30 (44.8)	457 (57.0)	
Yes	37 (55.2)	338 (42.1)	
Prostatitis			<i>0.914</i>
No	62 (92.5)	745 (92.9)	
Yes	5 (7.5)	57 (7.1)	
Pyelonephritis			<i>0.337</i>
No	66 (100.0)	785 (98.6)	
Yes	0 (0.0)	11 (1.4)	

*p-value of Chi-square

Table 23 shows the characteristics of control subjects based on their history of having kidney stones, differentiating those with from those without. There are no significant differences in age ($p= 0.333$), ethnic origin ($p= 0.201$), education levels ($p= 0.831$), Body Mass Index (BMI) ($p= 0.489$), waist circumference ($p= 0.177$), smoking status ($p= 0.465$), alcohol consumption ($p= 0.677$), physical activity levels ($p= 0.728$), use of nonsteroidal anti-inflammatory drugs (NSAIDs) ($p= 0.067$), hypertriglyceridemia ($p= 0.093$), hypercholesterolemia ($p= 0.505$), and pyelonephritis ($p = 0.833$) between the two groups. However, there is a borderline significant difference in family history of prostate cancer ($p= 0.052$), with 13.2% of controls with kidney stones having a family history of prostate cancer compared to 8.1% of those without kidney stones. There is also a significant difference in the prevalence of prostatitis ($p= 0.004$), with 6.2% of individuals without kidney stones having prostatitis compared to 13.0% with kidney stones.

Table 23 Characteristics of Controls based on their history of Kidney Stones

Kidney Stones	Yes n=138	No n=732	P-value*
Age (Years)			0.333
< 55	8 (5.8)	50 (6.8)	
[55-60]	13 (9.4)	85 (11.6)	
[60-65]	26 (18.8)	173 (23.6)	
[65-70]	45 (32.6)	238 (32.5)	
≥70	46 (33.3)	186 (25.4)	
Ethnic Origin			0.201
Caucasian	137 (99.3)	714 (97.5)	
Other	1 (0.7)	18 (2.5)	
Family History of Prostate Cancer			0.052
No	118 (86.8)	672 (91.9)	
Yes	18 (13.2)	59 (8.1)	
Education			0.831
≤Primary	28 (20.3)	165 (22.6)	
Secondary	69 (50.0)	351 (48.0)	
University	41 (29.7)	215 (29.4)	
Body Mass Index (kg/m²)			0.489
<25 - Normal	32 (24.6)	211 (29.6)	
[25-30] - Overweight	63 (48.5)	331 (46.4)	
≥30 - Obese	35 (26.9)	171 (24.0)	
Waist Circumference (cm)			0.177
≤94	32 (24.4)	217 (30.3)	
>94	99 (75.6)	500 (69.7)	
Smoking Status			0.465
Never	33 (23.9)	212 (29.0)	
Former	80 (58.0)	390 (53.3)	
Current	25 (18.1)	130 (17.8)	
Alcohol Consumption			0.677
No	12 (8.7)	72 (9.8)	
Yes	126 (91.3)	660 (90.2)	
Physical Activity (MET -h/wk/yr)			0.728
No	29 (21.0)	145 (19.9)	
<6.5	26 (18.8)	144 (19.8)	
6.25-13.0	26 (18.4)	146 (20.1)	
13.0-24.15	24 (17.4)	151 (20.8)	
≥24.15	33 (23.9)	141 (19.4)	
Nonsteroidal anti-inflammatory drugs			0.067
No	85 (62.0)	503 (70.0)	
Yes	52 (38.0)	216 (30.0)	
Hypertriglyceridemia			0.093
No	99 (71.7)	573 (78.3)	
Yes	39 (28.3)	159 (21.7)	
Hypercholesterolemia			0.505
No	77 (55.8)	411 (56.2)	
Yes	61 (44.2)	314 (42.9)	
Prostatitis			0.004
No	120 (87.0)	687 (93.9)	
Yes	18 (13.0)	45 (6.2)	
Pyelonephritis			0.833
No	135 (98.5)	717 (98.8)	
Yes	2 (1.5)	9 (1.2)	

*p-value of Chi-square

3.2. Association between Calculi and Prostate Cancer

Table 24 shows the association between each type of stone and the risk of prostate cancer. The findings indicate that 21.5% of prostate cancer cases had kidney stones, with an odds ratio OR of 1.46 (95% CI: 1.13-1.90), suggesting a significant association. Specifically, for low-grade prostate cancer, the OR is 1.48 (95% CI: 1.12-1.96), while for high-grade prostate cancer, the association is not significant OR: 1.15 (95% CI: 0.74-1.79). For gallbladder stones, 8.7% of prostate cancer cases had a history of these stones, but the association is not significant OR: 1.17 (95% CI: 0.82-1.69). When combining kidney stones and gallbladder stones as calculi, 28.1% of prostate cancer cases had a history of these stones, with an OR of 1.38 (95% CI: 1.10-1.74), showing a significant association, particularly for low-grade prostate cancer OR: 1.41 (95% CI: 1.09-1.81). However, the association with high-grade prostate cancer remains non-significant OR: 1.16 (95% CI: 0.79-1.70).

Table 24 Association between Kidney stones, Gallbladder stones, Calculi and the Risk of Prostate Cancer

	Controls		Cases				
	n=879 (%)	n=819 (%)	All OR* (95% CI)	Low grade cancer** n=623 (%)	OR* (95% CI)	High-grade cancer*** n=183 (%)	OR* (95% CI)
Kidney Stones							
No	732 (84.1)	639 (78.5)	1.00 reference	487 (78.6)	1.00 reference	146 (80.2)	1.00 reference
Yes	138 (15.9)	175 (21.5)	1.46 (1.13-1.90)	133 (21.5)	1.48 (1.12-1.96)	36 (19.8)	1.15 (0.74-1.79)
Gallbladder stones							
No	802 (92.3)	743 (91.3)	1.00 reference	569 (91.9)	1.00 reference	161 (88.5)	1.00 reference
Yes	67 (7.7)	71 (8.7)	1.17 (0.82-1.69)	50 (8.1)	1.12 (0.76-1.67)	21 (11.5)	1.41 (0.82-2.42)
Calculi ^a							
No	673 (77.7)	583 (71.9)	1.00 reference	44 (72.0)	1.00 reference	133 (73.1)	1.00 reference
Yes	193 (22.3)	228 (28.1)	1.38 (1.10-1.74)	173 (28.0)	1.41 (1.09-1.81)	49 (26.9)	1.16 (0.79-1.70)

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education, Hypertriglyceridemia

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Calculi: Kidney Stones, Gallbladder Stones

3.3. Stratification Analysis

Table 25 shows the association between kidney stones and gallstones and the risk of prostate cancer when stratifying on triglyceride status. In individuals with normal triglyceride levels, kidney stones are significantly associated with an increased risk of prostate cancer overall OR: 1.69 (95% CI: 1.26-2.20) and particularly with low-grade prostate cancer OR: 1.75 (95% CI: 1.27-2.40), but not with high-grade prostate cancer OR: 1.21 (95% CI: 0.74-1.99). Gallbladder stones do not show a significant association with prostate cancer in this group OR: 0.99 (95% CI: 0.66-1.48). Among those with hypertriglyceridemia, the association between gallbladder stones and prostate cancer is higher, particularly for high-grade prostate cancer OR: 3.58 (95% CI: 1.05-12.22), but this association is borderline significant for overall prostate cancer risk OR: 2.27 (95% CI: 0.99-5.28), and not significant for low-grade prostate cancer OR: 2.07 (95% CI: 0.83-5.17). The presence of kidney stones in individuals with hypertriglyceridemia does not show a significant association with prostate cancer overall OR: 0.84 (95% CI: 0.47-1.50), low-grade prostate cancer OR: 0.78 (95% CI: 0.41-1.49), or high-grade prostate cancer OR: 1.19 (95% CI: 0.46-3.08). Additionally, interaction analysis between gallstones and hypertriglyceridemia and the risk of prostate cancer was borderline significant yielding a p-value of 0.05.

Table 25 Association between Kidney and Gallbladder stones and the Risk of Prostate Cancer when Stratifying on triglyceride Status

		Controls		Cases				
			ALL		Low grade**		High-grade***	
		N=673	N=666	OR* (95% CI)	N=507	OR* (95% CI)	N=147	OR* (95% CI)
Normal Triglyceride Status, N=1338	Gallbladder stones							
	No	617 (91.7)	612 (92.0)	1.00 Reference	468 (92.5)	1.00 Reference	132 (89.8)	1.00 Reference
	Yes	56 (8.3)	53 (8.0)	0.99 (0.66-1.48)	38 (7.5)	0.95 (0.62-1.51)	15 (10.2)	1.21 (0.66-2.25)
	Kidney Stones							
	No	573 (85.3)	517 (77.6)	1.00 Reference	392 (77.3)	1.00 Reference	119 (81.0)	1.00 Reference
Yes	99 (14.7)	149 (22.4)	1.69 (1.26-2.20)	115 (22.7)	1.75 (1.27-2.40)	28 (19.0)	1.21 (0.74-1.99)	
Hypertriglyceridemia Status, N=346		N=198	N=149	OR* (95% CI)	N=113	OR* (95% CI)	N=35	OR* (95% CI)
	Gallbladder stones							
	No	185 (94.4)	131 (87.9)	1.00 Reference	101 (89.4)	1.00 Reference	29 (82.3)	1.00 Reference
	Yes	11 (5.6)	18 (12.1)	2.27 (0.99-5.28)	12 (10.6)	2.07 (0.83-5.17)	6 (17.1)	3.58 (1.05-12.22)
	Kidney Stones							
No	159 (80.3)	122 (82.4)	1.00 Reference	95 (84.1)	1.00 Reference	27 (77.1)	1.00 Reference	
Yes	39 (19.7)	26 (17.6)	0.84 (0.47-1.50)	18 (15.9)	0.78 (0.41-1.49)	8 (22.9)	1.19 (0.46-3.08)	

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

Table 26 examines the combined effects of kidney stones with either prostatitis or pyelonephritis on the risk of prostate cancer. For kidney stones and prostatitis, individuals with only prostatitis had an increased risk of prostate cancer overall OR: 1.74 (95% CI: 1.16-2.61) and specifically high-grade prostate cancer OR: 2.08 (95% CI: 1.13-3.81). Those with only kidney stones also showed a significant association with prostate cancer overall OR: 1.59 (95% CI: 1.21-2.10) and low-grade OR: 1.59 (95%CI: 1.18-2.15).

For kidney stones and pyelonephritis, individuals with both conditions had a significantly higher risk of prostate cancer overall (OR: 5.43, 95% CI: 1.16-25.4) and particularly high-grade prostate cancer (OR: 10.90, 95% CI: 1.94-61.3). Those with only kidney stones also showed a significant association with prostate cancer overall (OR: 1.41, 95% CI: 1.08-1.83). This reveals that while kidney stones and prostatitis individually increase the risk of prostate cancer, their combined effect is not significant. In contrast, the combination of kidney stones and pyelonephritis significantly increases the risk of prostate cancer, highlighting the potential impact of these conditions on prostate cancer risk.

Table 26 Association Between Combined Variables and the Risk of Prostate Cancer

	Controls		Cases				
	n=603 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
Kidney Stones (KS) and Prostatitis							
No	687 (79.0)	572 (70.3)	1.00 reference	437 (70.5)	1.00 reference	129 (70.9)	1.00 reference
KS - Prostatitis +	45 (5.2)	67 (8.2)	1.74 (1.16-2.61)	50 (8.1)	1.66 (1.07-2.57)	17 (9.3)	2.08 (1.13-3.81)
KS + Prostatitis -	120 (13.8)	158 (19.4)	1.59 (1.21-2.10)	118 (19.0)	1.59 (1.18-2.15)	34 (18.7)	1.33 (0.84-2.10)
KS + Prostatitis +	18 (2.1)	17 (2.1)	1.14 (0.57-2.29)	15 (2.4)	1.33 (0.64-2.75)	2 (1.1)	0.57 (0.13-2.54)
Kidney Stones (KS) and Pyelonephritis							
No	717 (83.1)	623 (76.7)	1.00 reference	474 (76.7)	1.00 reference	143 (78.6)	1.00 reference
KS - Pyelonephritis +	9 (1.04)	15 (1.9)	1.86 (0.79-4.38)	12 (1.9)	2.00 (0.81-4.91)	3 (1.7)	1.53 (0.40-5.86)
KS + Pyelonephritis -	135 (15.6)	164 (20.2)	1.41 (1.08-1.83)	127 (20.6)	1.47 (1.10-1.95)	31 (17.0)	1.00 (0.63-1.58)
KS + Pyelonephritis +	2 (0.2)	10 (1.2)	5.43 (1.16-25.4)	5 (0.8)	3.69 (0.67-20.2)	5 (2.8)	10.90 (1.94-61.3)

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Education, waist circumference

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

3.4. Sensitivity Analysis

The sensitivity analysis shown in Tables 27 and 28 considered only controls with PSA screening performed within the last two years before the interview, revealing that the results remained largely unchanged for the associations between kidney stones, gallbladder stones, calculi, and prostate cancer risk. Specifically, the odds ratios (ORs) for kidney stones and calculi showed no significant changes from the original analysis. However, there was a notable change in the stratified analysis for high-grade prostate cancer associated with gallbladder stones. Under normal triglyceride status, the OR for high-grade prostate cancer and gallbladder stones adjusted to 0.94 (95% CI: 0.60-1.47), and under hypertriglyceridemia status, the OR adjusted to 2.74 (95% CI: 0.77-9.78).

The sensitivity analysis shown in Tables 29 and 30 considered only controls with Normal PSA screening performed within the last two years before the interview, revealing that the results remained largely unchanged for the associations between kidney stones, calculi, and prostate cancer risk. There was a notable change for gallbladder stones in all the grades of prostate. Additionally, there were notable changes in the association for high-grade prostate cancer under stratified conditions. Specifically, for gallbladder stones under normal triglyceride status, the OR for high-grade prostate cancer with an adjusted OR of 1.00 (95% CI: 0.52-1.90), and under hypertriglyceridemia status, the OR adjusted to 2.71 (95% CI: 0.73-10.05).

The sensitivity analysis shown in Table 31 considered controls based on the frequency of PSA screening, revealing that the associations between calculi and prostate cancer were not highly influenced by the dosage. For gallbladder stones, no significant association was observed across different frequencies of PSA screening. Among those who underwent PSA screening once, the OR was 1.24 (95% CI: 0.42-3.66). For those screened 2-5 times, the OR was 0.89 (95% CI: 0.50-1.58), and for those screened more than 5 times, the OR was 1.17 (95% CI: 0.70-1.95). In contrast, kidney stones showed a significant association with prostate cancer in individuals screened 2-5 times, with an OR of 1.94 (95% CI: 1.17-3.19). However, this association was not significant in those screened only once (OR: 1.62, 95% CI: 0.73-3.61) or more than 5 times (OR: 1.41, 95% CI: 0.98-2.04). When considering all types of calculi, the association was also not significant across different screening frequencies. Importantly, the odds ratios did not consistently increase with increasing frequency of PSA testing in all three variables.

3.4.1. Sensitivity Analysis Considering Controls with PSA Screening < 2 years from Reference Date

Table 27 Association between Kidney stones, Gallbladder stones, Calculi and the Risk of Prostate Cancer (Sensitivity Analysis)

	Controls		Cases				
	n=603 (%)	n=819 (%)	All OR* (95% CI)	Low grade cancer** n=623 (%)	OR* (95% CI)	High-grade cancer*** n=183 (%)	OR* (95% CI)
Kidney Stones							
No	505 (84.7)	639 (78.5)	1.00 reference	487 (78.6)	1.00 reference	146 (80.2)	1.00 reference
Yes	91 (15.3)	175 (21.5)	1.51 (1.13-2.04)	133 (21.5)	1.55 (1.13-2.12)	36 (19.8)	1.26 (0.80-1.99)
Gallbladder stones							
No	546 (91.6)	743 (91.3)	1.00 reference	569 (91.9)	1.00 reference	161 (88.5)	1.00 reference
Yes	50 (8.4)	71 (8.7)	1.14 (0.77-1.69)	50 (8.1)	1.10 (0.72-1.69)	21 (11.5)	1.31 (0.75-2.31)
Calculi ^a							
No	459 (77.4)	583 (71.9)	1.00 reference	44 (72.0)	1.00 reference	133 (73.1)	1.00 reference
Yes	134 (22.6)	228 (28.1)	1.38 (1.06-1.78)	173 (28.0)	1.41 (1.07-1.86)	49 (26.9)	1.19 (0.80-1.78)

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education, Hypertriglyceridemia

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Calculi: Kidney Stones, Gallbladder Stones

Table 28 Association between Kidney and Gallbladder stones and the Risk of Prostate Cancer when Stratifying on triglyceride Status (Sensitivity Analysis)

	<i>Controls</i>		<i>Cases</i>					
			ALL	Low grade**		High-grade***		
	N=439	N=666	OR* (95% CI)	N=507	OR* (95% CI)	N=147	OR* (95% CI)	
Normal Triglyceride Status	Gallbladder stones							
	No	398 (90.7)	612 (92.0)	1.00 Reference	468 (92.5)	1.00 Reference	132 (89.8)	1.00 Reference
	Yes	41 (9.3)	53 (8.0)	1.10 (0.58-2.10)	38 (7.5)	0.93 (0.57-1.51)	15 (10.2)	0.94 (0.60-1.47)
	Kidney Stones							
	Yes	63 (14.4)	149 (22.4)	1.74 (1.24-2.45)	115 (22.7)	1.81 (1.27-2.61)	28 (19.0)	1.28 (0.76-2.17)
Hypertiglyceridemia Status		N=159	N=149	OR* (95% CI)	N=113	OR* (95% CI)	N=35	OR* (95% CI)
	Gallbladder stones							
	No	148 (94.3)	131 (87.9)	1.00 Reference	101 (89.4)	1.00 Reference	29 (82.3)	1.00 Reference
	Yes	9 (5.7)	18 (12.1)	2.21 (0.90-5.40)	12 (10.6)	2.13 (0.80-5.72)	6 (17.1)	2.74 (0.77-9.78)
	Kidney Stones							
Yes	28 (17.6)	26 (17.6)	0.92 (0.50-1.72)	18 (15.9)	0.88 (0.45-1.77)	8 (22.9)	1.24 (0.47-3.31)	

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason \leq 7 (3+4) *** Gleason \geq 7 (4+3)

3.4.2. Sensitivity Analysis Considering Controls with Normal PSA Screening < 2 years from Reference Date

Table 29 Association between Kidney stones, Gallbladder stones, Calculi and the Risk of Prostate Cancer (Sensitivity Analysis)

	Controls		Cases				
	n=537 (%)	n=819 (%)	All OR* (95% CI)	Low grade cancer** n=623 (%)	OR* (95% CI)	High-grade cancer*** n=183 (%)	OR* (95% CI)
Kidney Stones							
No	449 (84.7)	639 (78.5)	1.00 reference	487 (78.6)	1.00 reference	146 (80.2)	1.00 reference
Yes	81 (15.3)	175 (21.5)	1.54 (1.13-2.08)	133 (21.5)	1.57 (1.14-2.17)	36 (19.8)	1.29 (0.81-2.05)
Gallbladder stones							
No	484 (91.2)	743 (91.3)	1.00 reference	569 (91.9)	1.00 reference	161 (88.5)	1.00 reference
Yes	47 (8.9)	71 (8.7)	1.05 (0.70-1.58)	50 (8.1)	1.01 (0.66-1.57)	21 (11.5)	1.22 (0.69-2.15)
Calculi ^a							
No	406 (76.9)	583 (71.9)	1.00 reference	44 (72.0)	1.00 reference	133 (73.1)	1.00 reference
Yes	122 (23.1)	228 (28.1)	1.35 (1.03-1.76)	173 (28.0)	1.38 (1.04-1.84)	49 (26.9)	1.17 (0.78-1.76)

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education, Hypertriglyceridemia

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Calculi: Kidney Stones, Gallbladder Stones

Table 30 Association between Kidney and Gallbladder stones and the Risk of Prostate Cancer when Stratifying on triglyceride Status (Sensitivity Analysis)

	<i>Controls</i>			<i>Cases</i>				
		N=391	N=666	ALL OR* (95% CI)	Low grade** N=507	OR* (95% CI)	High-grade*** N=147	OR* (95% CI)
Normal Triglyceride Status	Gallbladder stones							
	No	351 (89.8)	612 (92.0)	1.00 Reference	468 (92.5)	1.00 Reference	132 (89.8)	1.00 Reference
	Yes	40 (10.2)	53 (8.0)	0.85 (0.54-1.33)	38 (7.5)	0.83 (0.51-1.36)	15 (10.2)	1.00 (0.52-1.90)
	Kidney Stones							
	No	331 (85.3)	517 (77.6)	1.00 Reference	392 (77.3)	1.00 Reference	119 (81.0)	1.00 Reference
Yes	57 (14.7)	149 (22.4)	1.73 (1.22-2.46)	115 (22.7)	1.81 (1.25-2.65)	28 (19.0)	1.29 (0.76-2.20)	
Hypertiglyceridemia Status		N=142	N=149	OR* (95% CI)	N=113	OR* (95% CI)	N=35	OR* (95% CI)
	Gallbladder stones							
	No	133 (95.0)	131 (87.9)	1.00 Reference	101 (89.4)	1.00 Reference	29 (82.3)	1.00 Reference
	Yes	7 (5.0)	18 (12.1)	2.28 (0.88-5.91)	12 (10.6)	2.17 (0.77-6.11)	6 (17.1)	2.71 (0.73-10.05)
	Kidney Stones							
No	118 (83.1)	122 (82.4)	1.00 Reference	95 (84.1)	1.00 Reference	27 (77.1)	1.00 Reference	
Yes	24 (16.9)	26 (17.6)	1.01 (0.53-1.92)	18 (15.9)	0.99 (0.49-2.02)	8 (22.9)	1.34 (0.50-3.64)	

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

3.4.3. Sensitivity Analysis Considering Controls based on the Frequency of Screening

Table 31 Association between Calculi and the Risk of Prostate Cancer while Considering Frequency of Screening among Controls (Sensitivity Analysis)

	All Cases			Controls				
	N=819	PSA one time		N=180	PSA 2-5 times		PSA > 5 times	
		N=63	OR* (95% CI)		OR* (95% CI)	N=289	OR* (95% CI)	
Gallbladder Stones								
No	743 (91.3)	58 (93.6)	1.00 reference	162 (90.0)	1.00 reference	264 (91.4)	1.00 reference	
Yes	71 (8.7)	4 (6.5)	1.24 (0.42-3.66)	18 (10.0)	0.89 (0.50-1.58)	25 (8.7)	1.17 (0.70-1.95)	
Kidney Stones								
No	639 (78.5)	53 (87.9)	1.00 reference	159 (88.3)	1.00 reference	237 (82.0)	1.00 reference	
Yes	175 (21.5)	8 (13.1)	1.62 (0.73-3.61)	21 (11.7)	1.94 (1.17-3.19)	52 (18.0)	1.41 (0.98-2.04)	
Calculi ^a								
No	583 (71.9)	49 (80.3)	1.00 reference	142 (79.3)	1.00 reference	215 (74.7)	1.00 reference	
Yes	228 (28.1)	12 (19.7)	1.43 (0.72-2.85)	37 (20.7)	1.47 (0.97-2.22)	73 (25.4)	1.30 (0.94-1.81)	

*Adjusted on Age, Ethnicity, and family history of prostate cancer, Physical Activity, NSAIDs, Waist circumference, Education, Hypertriglyceridemia

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Calculi: Kidney Stones, Gallbladder Stones

4. Discussion

4.1. Synthesis of Main Results

In summary, several key associations between different types of calculi and the risk of prostate cancer were identified. To begin with, 21.5% of prostate cancer cases had kidney stones, with an odds ratio (OR) of 1.46 (95% CI: 1.13-1.90), suggesting a significant association. This association was particularly notable for low-grade prostate cancer (OR: 1.48, 95% CI: 1.12-1.96), while for high-grade prostate cancer, the association was not significant (OR: 1.15, 95% CI: 0.74-1.79). For gallbladder stones, the overall association with prostate cancer was not significant (OR: 1.17, 95% CI: 0.82-1.69), although stratification by triglyceride status revealed a higher risk for high-grade prostate cancer in individuals with hypertriglyceridemia (OR: 3.58, 95% CI: 1.05-12.22). Additionally, the interaction analysis between gallbladder stones and hypertriglyceridemia was borderline significant (p-value=0.05).

When combining kidney stones and gallbladder stones as calculi, 28.1% of prostate cancer cases had a history of these stones, with a significant OR of 1.38 (95% CI: 1.10-1.74), particularly for low-grade prostate cancer (OR: 1.41, 95% CI: 1.09-1.81). The analysis of combined effects revealed that kidney stones and prostatitis individually increased the risk of prostate cancer (prostatitis: OR: 1.74, 95% CI: 1.16-2.61; kidney stones: OR: 1.59, 95% CI: 1.21-2.10), but their combined effect was not significant. In contrast, the combination of kidney stones and pyelonephritis significantly increased the risk of prostate cancer overall (OR: 5.43, 95% CI: 1.16-25.4) and particularly for high-grade prostate cancer (OR: 10.90, 95% CI: 1.94-61.3).

4.2. Comparison of Results to the Literature

Our results align with two previous studies that indicated a potential link between kidney stones and prostate cancer risk. One study, a case-control study conducted in Taiwan, reported an odds ratio (OR) of 1.71 (95% CI: 1.42-2.05) [131]. Another nationwide population-based cohort study, also using Taiwan's National Health Insurance database, found a standardized incidence ratio (SIR) of 4.02 (95% CI: 3.39-4.75) [257]. These findings are consistent our results regarding the association between a history of kidney stones and an increased risk of prostate cancer.

However, not all studies have yielded similar results. For instance, a hospital-based case-control study in Italy found no significant association between urinary tract stones and prostate cancer risk, with an OR of 1.53 (95% CI: 0.84-2.78) [97]. Similarly, a cohort study conducted in Sweden indicated that a history of kidney stones was not significantly linked to prostate cancer risk, with an SIR of 0.99 (95% CI: 0.96-1.02) [240].

The association between kidney stones and prostate cancer can be explained through different mechanisms. Metabolic syndrome is characterized by conditions like dyslipidemia, hyperglycemia, hypertension, obesity, and insulin resistance, creating an environment conducive to chronic inflammation. These conditions foster an environment that promotes kidney stone formation and prostate cancer development [258–260]. Dietary factors like increased fat intake can alter urinary composition and promote stone formation, which may also drive hormonal changes, accelerating prostate cancer development [261]. Additionally, kidney stones are commonly composed of calcium salts, and high calcium intake has been linked to an increased risk of prostate cancer [127, 240]. Therefore, elevated calcium levels might influence hormonal pathways that promote prostate cancer development [262]. Chronic inflammation is another significant mechanism linking kidney stones and prostate cancer. Urinary stones can obstruct the urinary tract, leading to urine retention and stasis, which can create a favorable environment for inflammation [263]. Inflammatory mediators produced in response to these conditions may stimulate cell proliferation and DNA damage, potentially leading to the development of cancerous cells [127]. Chronic inflammation induced by urinary calculi can elevate levels of mediators and cytokines, such as tumor necrosis factor- α (TNF- α) and interleukins (IL-1 and IL-6), which may stimulate cell proliferation and DNA damage, leading to the development of cancerous cells [264, 265].

Our findings regarding the association between gallbladder stones and prostate cancer, which showed no significant association (OR: 1.17, 95% CI: 0.82-1.69), align with several studies but differ from others. A meta-analysis from 2022, which included seven studies, found a slightly lower odds ratio for gallstones (OR: 1.16, 95% CI: 0.55-2.46), which was not significant [133]. However, when considering the condition cholelithiasis, the results differed from ours, suggesting a positive association (OR: 1.35, 95%CI: 1.17-1.56) [133]. Additionally, another study that aligns with our results includes a cohort study from Denmark, which used ultrasound for diagnosis and reported a hazard ratio (HR) of 0.67 (95% CI: 0.35-1.30), indicating no significant association [256].

Conversely, several studies reported significant associations that contrast with our findings. A case-control study using medical records found a significant association (OR: 2.77, 95% CI: 1.20-6.40) [133]. A nationwide population cohort study from Taiwan (Chen, 2016) with diagnosis records reported a significant HR of 1.30 (95% CI: 1.22-1.39) [253]. Another case-control study, using self-report data, found a significant association (OR: 1.36, 95% CI: 1.04-1.78) [252]. Additionally, the Ohsaki cohort study from Japan reported significant hazard ratios for advanced prostate cancer (HR: 2.29, 95% CI: 1.21-4.35) [254]. Lastly, a case-control study from South Korea reported a significant OR of 2.40 (95% CI: 1.02-5.68), further supporting a link between gallbladder stones and prostate cancer [266]. Chronic inflammation, a hallmark of many metabolic disorders, also plays an important role in the development of gallbladder stones and prostate cancer [255, 267–269]. In fact, gallbladder stones, among other disorders, often lead to persistent inflammatory states within the biliary tract, which can result in the production of pro-inflammatory cytokines and reactive oxygen species (ROS), creating a microenvironment conducive to DNA damage and subsequent oncogenesis in distant organs such as the prostate [269–271]. Additionally, inflammation-induced changes in lipid metabolism can exacerbate hypertriglyceridemia, leading to cholesterol crystal deposition and gallstone formation [272]. Hypertriglyceridemia contributes to the systemic inflammatory state by promoting the release of adipokines and cytokines, which can further induce cellular proliferation and inhibit apoptosis in prostate cells [270, 271, 273]. It has been suggested that hypertriglyceridemia may increase the risk of both gallbladder stones and prostate cancer [274, 275]. This is also supported by a case-control study done in China, which identifies hypertriglyceridemia as a potential prognostic indicator for prostate cancer, suggesting a shared pathophysiological pathway with gallstones [261].

4.3. Strengths and Limitations

In the previous chapter of this thesis, the strengths of the EPICAP study were thoroughly discussed in section 4.3 of the discussion. To recap, the EPICAP study, conducted in the Hérault department, had an overall participation rate of 77%. The exhaustive case identification process, covering both private and public cancer hospitals, ensured comprehensive inclusion, thereby mitigating potential selection bias. Moreover, even though the participation rate in cases was 75%, the age distribution and Gleason scores of non-responding cases were comparable to those of responding cases, thereby minimizing potential survival bias.

Additionally, the availability of the Gleason score allowed us to assess the aggressiveness of cancer, a factor that is rarely taken into account in previous studies. Controls were randomly selected from the general population of the Hérault department, using quotas by age (± 5 years) and Socioeconomic Status (SES), ensuring a control group representative of the department's male population and thus minimizing major selection bias.

Addressing the potential for recall bias is crucial, especially given that our method of collection relies on self-reporting of our exposure, which introduces the risk of differential classification bias. Individuals may not accurately recall or report episodes of kidney stones or gallbladder stones, particularly if they were asymptomatic, had minor symptoms, or attributed symptoms to other conditions, especially for past episodes that were minor or occurred some time ago. However, data collection was conducted face-to-face by a trained clinical nurse using a standardized questionnaire, ensuring consistency between cases and controls.

Given the unavailability of precise data on gallbladder stone prevalence in France, we compared our findings with those from other relevant studies. In a previous study conducted with a similar demographic, the prevalence of gallbladder stones among controls was 6.2%, indicating a relatively similar prevalence [255]. In addition, the prevalence of kidney stones among controls observed in our study was around 15.9%, which was also similar to the prevalence of gallstones 13.6% in the population of France [276]. This helps minimize the potential impact of classification bias in our findings.

Our study faced limitations regarding diagnostic confirmation, as reliance on self-reported history may have led to inaccuracies, particularly for asymptomatic or undiagnosed cases. Additionally, we lacked information on stone characteristics, such as type, size, and which could influence symptom severity and detection likelihood. We also considered treatment history; however, the available data were limited, preventing a comprehensive assessment of its impact on symptom reporting and disease progression.

Even though our sample size in our stratified analyses was relatively small especially when considering high-grade cancer, we still observed significant associations for gallbladder stones. However, it is important to address that the small sample size may limit the statistical power and the ability to detect consistent associations.

The sensitivity analyses conducted, which restricted controls to those with PSA testing within the last two years or to those with normal PSA screenings within the last two years, provide robust support for our primary findings regarding the association between urinary calculi and

prostate cancer risk. The purpose of these analyses was to mitigate potential classification bias, which could arise from undiagnosed prostate cancer cases being misclassified as controls.

The results remained largely unchanged compared to the original analysis, underscoring the robustness of our findings. This consistency suggests that the observed associations are not significantly influenced by the recency or status of PSA screening, allowing us to be confident with our observed estimates. Additionally, the variation in the results of the stratification by triglyceride status highlights the potential modifying effect of triglyceride levels on the association between gallbladder stones and prostate cancer. Despite these strengths, potential limitations remain. The presence of residual detection bias cannot be completely excluded. Furthermore, smaller sample sizes in the sensitivity analyses, especially when stratified by triglyceride status, may reduce statistical power.

Another sensitivity analysis, which considered controls based on the frequency of PSA screening to eliminate any potential detection bias, also indicates that our findings are robust and not significantly influenced by varying screening practices. For gallbladder stones, no significant association was observed across different screening frequencies, suggesting that the frequency of screening does not affect this relationship. In contrast, kidney stones showed a significant association with prostate cancer in those screened 2-5 times, but not in those screened only once or more than five times. Importantly, the odds ratios did not consistently increase with increasing frequency of PSA testing, indicating that detection bias related to screening frequency is unlikely to explain our results.

In our study, most suspected confounding variables did not impact the outcomes, with case and control groups showing high comparability. Several variables related to the outcomes or the variables of interest were identified. Statistical adjustments were applied to all suspected variables to limit confounding bias. Well-established risk factors for prostate cancer were also considered in all analytical models. Despite these adjustments for non-modifiable risk factors and major potential confounders such as level of education, physical activity, waist circumference, hypertriglyceridemia, and non-steroidal anti-inflammatory drugs, our results remained unchanged.

In this chapter, our analysis revealed several key findings. There was an association between a personal history of kidney stones and an increased risk of Prostate cancer, particularly when combined with a history of pyelonephritis, but not with prostatitis. Our analysis also uncovered a relationship between gallbladder stones and prostate cancer risk, especially in individuals with hypertriglyceridemia. These findings provide valuable insights into the potential role of urolithiasis in prostate cancer etiology and highlight the importance of considering both kidney and gallbladder stones as potential risk factors. Further research is needed to understand the underlying mechanisms driving these associations. In the next chapter, we will shift our focus to examine the role of single nucleotide polymorphisms (SNPs) of COX-2 gene and the interaction (GxE) of these SNPs with our variables of interest, including both infections and stones, in the occurrence of prostate cancer.

CHAPTER 5 – SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) OF COX-2 GENE AND PROSTATE CANCER

1. Introduction

1.1. Genetic Factors and Prostate Cancer

Genetic factors play a significant role in determining an individual's risk of developing prostate cancer, which is known to be the most common type of cancer among men. A study done by Haiman identified multiple susceptibility loci for prostate cancer, indicating that genetic factors play a critical role in the disease's development [277]. Another research done on twins from different European countries has estimated the heritability of prostate cancer to be as high as 42% [278]. This risk can be influenced by a combination of inherited (germline) and acquired (somatic) genetic mutations [279]. Notable mutations in high-risk genes, including BRCA1, BRCA2, and HOXB13, significantly elevate the likelihood of developing prostate cancer. Notably, BRCA2 mutations are associated with a higher risk and more aggressive forms of the disease, while the rare HOXB13 (rs138213197) mutation is particularly prevalent in men with early-onset, familial prostate cancer [280, 281]. Moreover, somatic mutations in genes such as PTEN and TP53, as well as gene fusions like TMPRSS2-ERG, are commonly observed in prostate cancer and are linked to the disease's progression and aggressiveness [282, 283]. Inflammatory genes have been extensively studied, such as IL-1 β , IL-6, and TNF- α have SNPs that modulate the inflammatory response and are implicated in prostate cancer risk. For example, the pattern recognition receptors MSR1, TLR1, and TLR4 [140, 141], the cytokine *TNF α* and *IL1RN* [142, 143], and the pro-inflammatory gene *COX-2* [137, 144] have been associated with an increased risk of prostate cancer.

1.2. Single Nucleotide Polymorphisms (SNPs)

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among individuals, representing a difference in a single nucleotide — the building blocks of DNA, which include adenine (A), cytosine (C), guanine (G), and thymine (T). For instance, a SNP might change the DNA sequence from AAGCCTA to AAGCTTA. These variations can be found in various regions of the genome and can be categorized based on their location and potential impact on gene function (figure 19) [284].

Single nucleotide polymorphisms (SNPs) can occur in both coding and non-coding regions of genes, impacting gene function, protein structure, disease susceptibility, and drug response. In coding regions, SNPs may be synonymous, not altering the amino acid sequence, or non-

synonymous, altering the sequence through missense variants (substituting one amino acid for another) or nonsense variants (introducing premature stop codons, leading to truncated proteins) [285, 286].

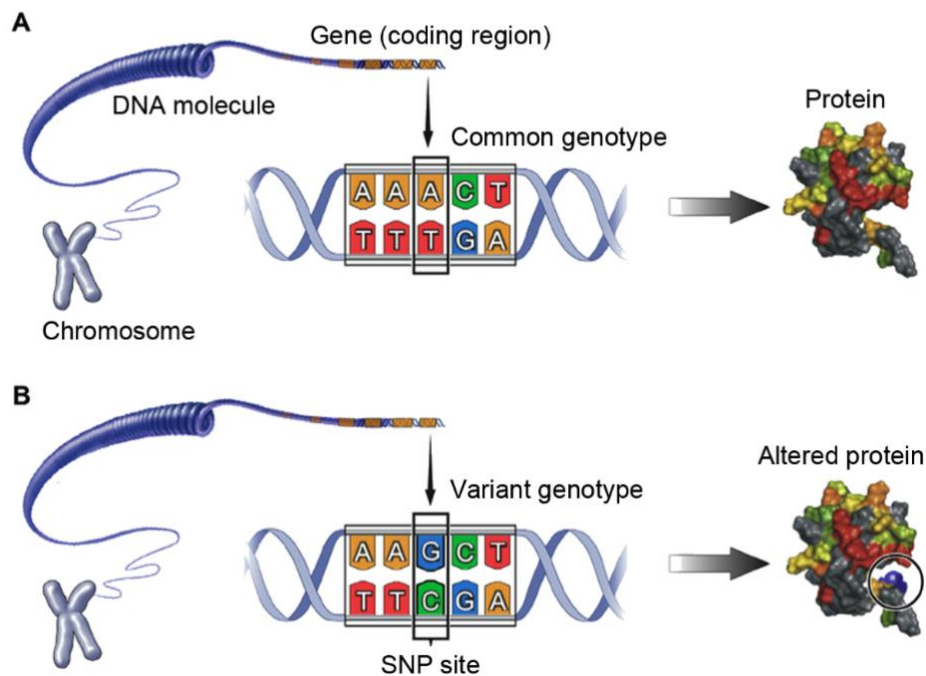


Figure 19 Single Nucleotide Polymorphism (SNPs)[284]

In non-coding regions, SNPs can influence gene regulation by affecting transcription factor binding, gene expression, splicing, and mRNA stability. These variations can significantly impact protein function and increase cancer susceptibility [285, 286].

1.3. Inflammatory Genetic Factors and Prostate Cancer

Inflammatory genes play a crucial role in regulating the body's immune response to infection, injury, and other stimuli. They encode proteins involved in various aspects of the inflammatory process, including the production of signaling molecules called cytokines, the activation of immune cells such as macrophages and T-cells, and the regulation of inflammatory pathways. Dysregulation of inflammatory genes can lead to chronic inflammation, which is implicated in the development of various diseases, including cancer [135–137].

Central to this process is the regulation of inflammatory genes such as *PTGS2*, also known as COX-2 (Cyclooxygenase-2) located on chromosome 1. Cyclooxygenase-2 (COX-2) is an

enzyme pivotal in the inflammatory process by catalyzing the conversion of arachidonic acid to prostaglandins, which are key mediators of inflammation and pain [137].

At the molecular level, COX-2 expression is regulated by several transcription factors in response to extracellular signals, including NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), AP-1 (activator protein 1), and CREB (cAMP response element-binding protein) [287]. NF- κ B is activated by pro-inflammatory cytokines such as IL-1 β and TNF- α , leading to its translocation to the nucleus, where it binds to the COX-2 promoter to initiate transcription [288, 289]. AP-1, composed of c-Jun and c-Fos subunits, is activated by MAPK (mitogen-activated protein kinase) signaling pathways and enhances COX-2 expression [290]. Chronic inflammation can lead to sustained COX-2 expression, causing an increased production of prostaglandin E2 (PGE2), which creates a pro-inflammatory microenvironment conducive to disease progression. Epigenetic changes, such as DNA methylation and histone modifications, may also occur during chronic inflammation, further affecting the regulation of COX-2 and other inflammatory genes [291, 292]

Prolonged activation of inflammatory pathways can alter normal cellular functions, lead to persistent tissue damage, and create a pro-tumorigenic environment [293, 294]. Genetic variations in the COX-2 gene may affect the regulation and expression levels of the enzyme, influencing the inflammatory response and contributing to carcinogenesis [294, 295].

The role of Cyclooxygenase-2 (COX-2) in prostate cancer has been extensively studied, revealing its significant involvement in the disease's progression and potential as a therapeutic target. COX-2 is frequently overexpressed in various malignancies, including prostate cancer [145–147]. A recent meta-analysis showed that COX-2 +202 C>T (rs2745557) polymorphism was significantly associated with an increased risk of prostate cancer [148], while another meta-analysis done by Zhang et al. showed an association with prostate cancer in Caucasians but no other ethnicities [149].

COX-2 is overexpressed in prostate cancer, particularly in the advanced stages of the disease. It has been reported to be consistently elevated in premalignant lesions such as prostatic intraepithelial neoplasia and carcinoma [145]. This overexpression is linked to several key processes in cancer progression, including cell proliferation, inhibition of apoptosis, angiogenesis, and the facilitation of metastasis [79].

Table 32 presents a summary of the different meta-analyses on genetic associations particularly for SNPs of the COX-2 gene.

The meta-analysis conducted by Zhu et al. [296] aimed to evaluate the influence of two COX-2 polymorphisms, rs20417 and rs5275, on the risk of various cancers, including prostate cancer. The findings revealed that neither rs20417 nor rs5275 showed a significant association with prostate cancer across all statistical models.

The meta-analysis done by Shao et al. [297] investigating the relationship between COX-2 polymorphisms and the risk of prostate cancer also revealed no significant association between rs689470 (OR:1.39, 95% CI: 0.86–2.23), rs5277 (OR: 0.91, 95%CI: 0.71–1.15), rs2745557 (OR:1.16, 95%CI:1.00–1.33), rs5275 (OR: 1.00, 95%CI: 0.96–1.05) and prostate cancer. In contrast, high expression of COX-2 was associated with advanced stages of prostate cancer in comparison to early stages ($P < 0.0001$).

In the meta-analysis done by Zhang et al. [149] the association between COX-2 rs2745557 polymorphism and prostate cancer was examined. Overall, there was no significant association between the rs2745557 polymorphism and prostate cancer risk under co-dominant, recessive, over-dominant, and allelic models. However, under the dominant model, rs2745557 was associated with a lower risk of prostate cancer in the overall population (OR: 0.85, 95% CI: 0.74-0.97, $P = 0.02$). When stratified by race, the polymorphism showed a significant protective effect against prostate cancer in Caucasians (OR for Caucasians under the dominant model: OR: 0.86, 95% CI/ 0.75-0.99, $P = 0.04$).

This meta-analysis done by Yang et al. [298] assessed the impact of rs5275 and prostate cancer risk. Overall, there was no significant association between the SNP and prostate cancer risk under any genetic model. However, in a subgroup analysis by ethnicity, a significant association was detected in non-Caucasian populations (Africans and Indians) under the recessive model OR: 1.60 (95%CI: 1.08-2.37), but not in Caucasians OR: 1.01 (95%CI: 0.94-1.09). Another meta-analysis done by Li et al. [299] assessing the same SNP showed no significant association under all five genetic models.

The meta-analysis conducted by Asadian et al. [148] explored the relationship between several COX-2 polymorphisms and the risk of prostate cancer. They found that the COX-2 -765G>C (rs20417), -1195G>A (rs689466), and +8473T>C (rs5275) polymorphisms did not show

significant associations with prostate cancer risk across various genetic models. However, subgroup analysis by ethnicity showed a significant association among Caucasians under the recessive model for rs20417 (OR: 1.52, 95% CI: 1.17-1.97, $p = 0.002$), and among Asians under the heterozygote and dominant model for rs689466. In contrast, the COX-2 +202C>T (rs2745557) polymorphism was found to be significantly associated with an increased risk of prostate cancer under the allele model (T vs. C) (OR: 1.30, 95% CI: 1.84-9.49, $p = 0.001$) and the dominant model (TT+TC vs. CC) (OR: 0.78, 95% CI: 0.66-0.91, $p = 0.002$) Subgroup analyses by ethnicity revealed significant associations among Caucasians under the allele and dominant models, and among Africans under the recessive and dominant models.

Table 32 Summary of Meta-Analyses on Genetic Associations and Estimated Risks of the COX-2 Gene SNPs

Author (Year)	Study Design	Publications	Cases/Controls	SNPs considered (Estimated Risk)
Zhu (2010)	Meta-analysis	33 Studies (2 Studies on PC)	8,090/11,010 14,283/15,489	rs20417 (Not significant in all models) rs5275 (Not significant in all models)
Shao (2012)	Meta-analysis	11 Studies	8,333/7,884	rs689470 (OR:1.39, 95% CI: 0.86–2.23) rs5277 (OR: 0.91, 95%CI: 0.71–1.15) rs2745557 (OR:1.16, 95%CI:1.00–1.33) rs5275 (OR: 1.00, 95%CI: 0.96–1.05)
Zhang (2012)	Meta-analysis	8 Studies	11,356/11,641	rs2745557 (Overall not significant in all models but significant for lower PC risk under dominant model (OR: 0.85 95%CI: 0.74-0.97)
Yang (2013)	Meta-analysis	5 Studies	12,220/12,496	rs5275 (Not significant in all models)
Feng (2015)	Meta-analysis	9 Studies	5,952/5078	rs 20417 (OR: 1.01, 95%CI: 0.93-1.10)
Li (2018)	Meta-analysis	79 Studies (3 Studies on PC)	38,683/55,206	rs5275 (Not Significant in all models)
Asadian (2021)	Meta-analysis	34 Studies	13,248/14,768	rs20417 (Not significant in all models) rs689466 (Not significant in all models) rs2745557 (Significant in Allele and dominant model) rs5275 (Not Significant in all models)

Table 33 presents a comprehensive bibliography of different studies investigating the relationship between variants of the COX-2 gene and the risk of prostate cancer, encompassing in total 17 studies [300, 144, 151, 95, 301, 302, 294, 303–311]. Several SNPs have received particular and consistent attention over the years. Specifically, rs2745557 and rs689470 have been recurrently investigated in different studies. For rs2745557, significant findings were reported in studies by Cheng (2007), Fradet (2009), Amirian (2011), Kopp (2013), and Fawzy (2016), although not all studies confirmed its significance uniformly. Similarly, rs689470 has been examined in studies by Shahedi (2006), Cheng (2007), and Fradet (2009), reflecting its persistent relevance in research on COX-2 gene variants and prostate cancer risk. In contrast, other SNPs such as rs2206593 (Cheng 2007, Fradet 2009), rs20417 (Siemes 2008, Wu 2011), rs5275 (Danforth 2009, Mandal 2011, Kopp 2013), rs689466 (Cui 2015, Kopp 2013), rs20432 (Shahedi 2006), rs3918304, rs20415 (Fernandez 2008), rs4648310 (Fradet 2009), and rs12042763 (Salinas 2010) have also been studied, with varying degrees of significance in their associations with prostate cancer risk.

Table 33 Studies Evaluating the Relationship between Variants of COX-2 Gene and the Risk of Prostate Cancer

Author (Year)	Study Design	Cases/Controls	Method	Significant SNPs
Panguluri (2004)	CC	370/366	SNP Approach	ss5112605 (African Americans) ss5112606 (African American) ss5112607 (All subjects + African Americans)
Shahedi (2006)	CC	1378/782	SNP Approach	rs20432 rs689470
Cheng (2007)	CC	506/506	SNP Approach	rs2745557 rs2206593 rs689470
Fernandez (2008)	CC	151/134	SNP Approach	rs3918304 rs20415
Siemes (2008)	Cohort	216 Cases	SNP Approach	rs20417 (Not significant)
Dossus (2009)	Cohort	8008/8604	SNP Approach	12 SNPs (Not Significant)
Danforth (2009)	CC	1162/1399	SNP Approach	rs5275
Fradet (2009)	CC	466/478	SNP Approach	rs2745557 rs5277 rs2206593 rs689470 rs4648310 (Long chain Omega-3) *
Salinas (2010)	CC	1,001/942	SNP Approach	rs12042763 (NSAIDs)
Wu (2011)	CC	218/436	SNP Approach	rs20417
Amirian (2011)	CC	535/533	SNP Approach	rs2745557 (Not significant)
Mandal (2011)	HBCC	195/250	SNP Approach	rs20417 rs5275
Kopp (2013)	CC	370/370	SNP Approach	rs689466 (not significant) rs5275 (not significant) rs2066826 (not significant) rs5277 (not significant) rs2745557 (not significant)
Sugie (2014)	CC	134/86	SNP Approach	rs689465
Cui (2015)	CC	543/753	SNP Approach	rs689466
Fawzy (2016)	CC	112/120	SNP Approach	rs2745557

*Long-chain omega-3 polyunsaturated fatty acids (LC n-3), CC: Case-Control, HBCC: Hospital-based Case-control

1.4. GxE: Interaction between COX-2 & inflammation related-factors

Currently, there is a lack of research on the interaction between infection or stone-related factors and inflammation genes, particularly COX-2 gene, and prostate cancer. However, the G×E between COX-2 polymorphism and the use of NSAIDs in relation to prostate cancer risk is a significant area of research. One research highlighted that certain SNPs in the COX-2 gene are associated with a modified risk of prostate cancer when interacting with NSAID use. For instance, the SNP rs2745557 in the COX-2 gene was found to be significantly associated with a lower risk of prostate cancer[151]. Therefore, this interaction indicates that both genetic predisposition and environmental exposure can be important in modulating prostate cancer risk.

2. Material and Methods

In this objective, we used genetic data to study the variations in single nucleotide polymorphisms (SNPs) associated with inflammatory responses. This section details the methodology for collecting genetic data from biological samples, covering the process from sample collection to DNA genotyping and the constitution of the analyzed sample.

2.1. Collection and Processing of Blood and/or Saliva Samples

Blood samples were proposed to both cases and controls, dependent upon their informed and signed consent. A saliva collection using an Oragene kit was offered if a blood sample was refused.

In total, 1626 subjects (794 cases and 832 controls) provided either a blood or saliva sample.

Genotyping was performed by the National Center for Human Genome Research (CNRGH) using the Infinium® Oncoarray-500K BeadChip from Illumina. This chip, detailed previously [312] contains about 250,000 Single Nucleotide Polymorphisms (SNPs), ensuring genomic coverage, supplemented by approximately 250,000 SNPs selected for their relevance to common cancers, including prostate cancer.

We selected polymorphisms from the COX-2 gene, located on chromosome 1.

2.2. Quality Control of Genotyping Data

The quality control of all genotyping data at both the individual and SNP levels was conducted based on the guidelines of the OncoArray consortium and, more specifically, the PRACTICAL consortium (<http://practical.icr.ac.uk/blog/>).

2.2.1. Quality Control at the Individual Level

To ensure the accuracy and reliability of the data, several quality control measures were implemented at the individual level:

2.2.1.1. Identification of Related Individuals and Duplicates

We identified related individuals and duplicates using the Identity by State (IBS) calculation, which helps determine if two individuals are related from a descent perspective. IBS measures the genetic similarity between two individuals by comparing the number of shared alleles for a given SNP.

Two individuals can either:

- a. Not share any alleles
- b. Share one allele
- c. Share both alleles.

This method is most effective when applied to a group of independent SNPs. Approximately 30,000 independent SNPs (with a genotypic correlation ≤ 0.01) were selected for our analysis.

The criteria for identifying related individuals and duplicates were as follows:

- a. If IBS > 0.185 , the individuals were considered related.
- b. If IBS > 0.98 , the individuals were considered duplicates.

Based on these criteria, we excluded seven subjects with duplicate data. No related individuals were found in the dataset.

2.2.1.2. Call Rate

A missing genotype call rate higher than 5% is generally due to poor DNA quality and/or issues in the genotyping procedure, which can introduce biases in the results. Therefore, we excluded individuals with a call rate below 95%. Consequently, four individuals were excluded from the study.

2.2.1.3. Sex Concordance Verification

To verify that there are no discrepancies between the reported sex and the genetic sex of the individual, the sex chromosomes (X and Y) were examined to see if they conform to the expected patterns for males (typically XY) and females (typically XX). Typically, the average homozygosity rate along the X chromosome is higher than 0.8 for a male and lower than 0.2 for a female. Individuals with a mismatch between reported and genetically determined sex should be excluded. In our study, no sex discordance was found.

2.2.1.4. Population Stratification

In order to ensure a homogenous study population, individuals are selected based on their ancestry. This helps reduce population stratification, which can confound genetic associations studies. The Minor Allele Frequency (MAF) for a SNP can vary significantly according to the ethnic origin of subjects. Selecting individuals based on their ethnic origin is crucial, as ethnic

descent can influence results, leading to the discovery of associations specific to a subgroup of the population.

To identify and confirm individuals of European descent, we used Principal Component Analysis (PCA). A PCA was performed on a set of 2318 SNPs identified as strongly linked to ethnicity by the PRACTICAL consortium, using the first two components. Data from the Haplotype Map (HapMap) project was used as a reference, which provides genetic mapping of individuals based on their ethnic origin.

The Phase 1 data of the HapMap project, consisting of Yoruba (African), CHB_JPT (Asian), and CEU (Caucasian) subjects, were used.

The two PCA components were then used to calculate probabilities of European, African, and Asian ancestry. Ancestry was calculated using the Fastpop program, which provided PCA scores from the 2318 informative markers and a subset of about 47,000 individuals from the GAME-ON consortium.

Individuals were defined as being of European ancestry if they had an estimated European ancestry proportion greater than 0.8. Consequently, based on this criterion, 39 subjects identified as genetically non-Caucasian were excluded.

In total, 50 subjects were excluded, including 39 identified as non-Caucasian, 7 with duplicate data, and 4 with a genotyping rate below 95%, resulting in a final analysis sample of 1515 subjects, consisting of 732 cases and 783 controls (Figure 20).

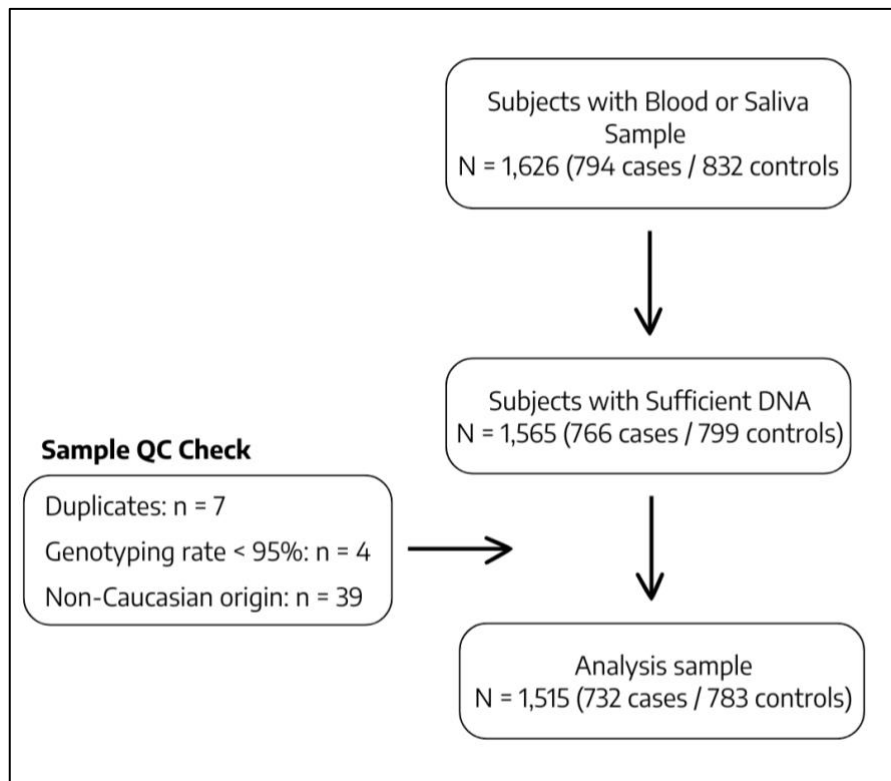


Figure 20 Flow Chart of the Selection of the Genotyped Subjects from the EPICAP Study Sample QC Check

2.2.2. Quality Control at the SNP Level

After controlling for quality at the individual level, the next step involved implementing several stringent quality control measures at the SNP level (Figure 21) to ensure data accuracy and reliability:

2.2.2.1. Call Rate

A missing genotype rate higher than 5% for a given SNP indicates potential problems, such as genotyping errors or issues with the probe design on the DNA chip. Therefore, SNPs with a genotyping rate below the 95% inclusion threshold were excluded to ensure data reliability. Consequently, 13,054 SNPs were excluded from the study.

2.2.2.2. Check for Hardy-Weinberg Equilibrium

The Hardy-Weinberg theorem states that in an ideal population, allele and genotype frequencies remain constant from generation to generation in the absence of other

evolutionary influences. This equilibrium implies that the genetic variation in the population is stable over time unless affected by factors such as mutation, selection, or genetic drift. SNPs deviating from Hardy-Weinberg equilibrium are often indicative of genotyping errors, population stratification, or other underlying issues.

To ensure data integrity, we excluded SNPs that significantly deviated from Hardy-Weinberg equilibrium. Specifically, SNPs with a p-value less than 10^{-7} in controls and less than 10^{-12} in cases were removed from the analysis, as these deviations suggest potential problems that could bias the results.

2.2.2.3. Removal of Duplicated SNPs

When SNPs were found to be redundant based on their chromosomal location, position, and the identity of their minor and major alleles, only one copy of each redundant SNP was retained. The duplicate copies were removed to ensure the accuracy and uniqueness of the SNP data.

2.2.2.4. Removal of Monomorphic SNPs (MAF = 0)

We excluded monomorphic SNPs, which are SNPs that have a zero minor allele frequency (MAF). This means these SNPs do not exhibit any variation in the population and therefore do not provide any useful genetic information for the analysis.

2.2.2.5. Selection of SNPs with MAF >1%

After all exclusions, 447,896 SNPs were available for analysis. From this dataset, we focused on polymorphisms of the COX-2 gene, which is involved in the inflammatory response. Specifically, COX-2 plays a crucial role in catalyzing the conversion of arachidonic acid to prostaglandins, which are key mediators of inflammation. This data was extracted from the list of 26 SNPs in concept form 135 located within $\pm 50 \text{ kb}^1$ of the COX-2 gene.

¹A kilobase is a molecular biology measurement unit representing a length of 1,000 base pairs of double-stranded DNA or 1,000 bases of RNA.

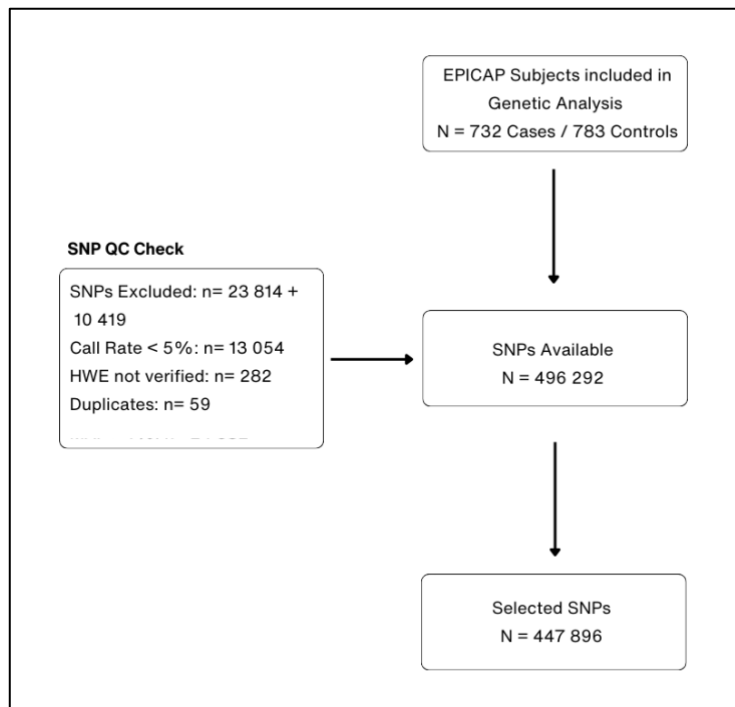


Figure 21 Flow Chart for the Selection of SNPs after Quality Control Check at the SNP Level

Therefore, initially 23 SNPs of the COX-2 gene were identified for potential inclusion. However, three SNPs were excluded due to a Minor Allele Frequency (MAF) of less than 1%. Consequently, our final analysis focused on 20 variants of the COX-2 gene, all of which had a MAF greater than 1%.

2.3. Statistical Analysis

All analyses were conducted using the software R (version 4.3.3).

2.3.1. Descriptive Analysis

The potential risk factors that were included in our two previous epidemiological analyses were also incorporated into our genetic analysis. Therefore, we described the sociodemographic and lifestyle characteristics of the cases and controls included in the genetic analyses, including 732 cases and 783 controls. The distributions of these factors between cases and controls were compared, and p-values were computed using Chi-square tests.

2.3.2. Inferential Analysis

Association analysis was conducted to evaluate the risk of prostate cancer in relation to infections (a combined variable of all types of infections (Overall Infections) studied in objective 1, refer to Materials and Methods for Objective 1), kidney stones, and gallbladder stones. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression among the cases and controls with genetic data, adjusting for family history of prostate cancer, age, NSAID use, waist circumference, education, physical activity, and triglyceride levels. The analysis took into account the aggressiveness of cancer. These variables were also included in the genetic analysis to investigate potential Gene-Environment (GxE) interactions to explore how genetic variations may influence the relationship between these environmental factors and prostate cancer risk.

2.3.3. Analysis of the Gene COX-2 at the SNP level

The associations between SNPs from the inflammatory gene COX-2 and the risk of prostate cancer were studied at the SNP level. The odds ratios (ORs) measuring the association between each SNP and the risk of prostate cancer, along with their 95% confidence intervals (CI), were estimated using unconditional logistic regression, assuming different genetic models. These models included an additive model, a codominant model, and a recessive model, the latter applied only to SNPs that demonstrated higher power in the codominant model.

In the additive and codominant models, the 'SNP' variable was introduced as an independent variable, taking values 0, 1, or 2 corresponding to the number of mutated alleles. This variable was included continuously in the models, so the OR represents the change in prostate cancer risk associated with each mutated allele.

In the recessive model, the SNP variable was introduced as a binary variable, taking values 0 or 1. Here, 0 indicates individuals with 0 or 1 copy of the minor allele, and 1 indicates individuals with 2 copies of the minor allele.

Although the genotyped population was genetically of European ancestry, the results could be influenced by potential residual ethnic effects, especially if some of the variants studied are characteristic of ethnic origin. To account for potential ethnic stratification within our study population, we performed a PCA using data from 33,426 uncorrelated SNPs (including 2,318 ancestry-informative SNPs) with a minor allele frequency (MAF) ≥ 0.05 and a maximum correlation of 0.1 between SNPs. The PCA was carried out using specially designed software (<http://ccge.medschl.cam.ac.uk/software/pccalc>).

Consequently, the analyses were adjusted for age, and the first seven principal components (PCs) derived from the Principal Component Analysis (PCA) to account for potential population stratification. Additionally, the analyses were also adjusted to NSAID use, waist circumference, education, and physical activity.

The p-value for each SNP studied was corrected using a False Discovery Rate (FDR) method. To control for the expected proportion of false positives among the significant findings, balancing the identification of true genetic associations with minimizing false discoveries.

2.3.4. Interaction Analysis: GxE SNP-by-SNP Approach

To investigate potential interactions between genetic variants (SNPs) in the COX-2 gene and environmental factors (E) implicated in inflammation-related conditions (specifically infections, kidney stones, and gallbladder stones), a SNP-by-SNP approach was taken into account.

For each COX-2 SNP, we used generalized linear models (GLMs) to examine interactions with environmental factors (E). The models included the main effects of COX-2 SNPs (X_i), the main effects of environmental factors (Z), and their interaction terms ($X_i * Z$).

The statistical model can be represented as:

$$\log(\text{OR}) = \beta_0 + \beta_{X_i} X_i + \beta_Z Z + \beta_{X_i Z} (X_i * Z) + \epsilon$$

Odds ratios (OR) and their 95% confidence intervals, along with the p-values of the interaction, were computed. To control for multiple comparisons and mitigate false positives, we applied corrections for False Discovery Rate (FDR).

2.4. Description of SNPS from the COX-2 Gene

Table 34 presents a detailed overview of the 20 single nucleotide polymorphisms (SNPs) within the COX-2 gene, highlighting various attributes for each SNP. The columns include the SNP name, the effect allele (EA), the reference allele (RA), the genomic position, the gene name, the exon location, the type of mutation, and the effect allele frequencies (EAF) in both cases and controls.

Table 34 Characteristics of Single Nucleotide Polymorphisms (SNPs) in the COX-2 Gene

SNP	EA	RA	Position	Gene	Exon	Mutation	EAF_Cases	EAF_Controls
rs6658482	G	A	186598526				0.1605	0.1641
rs2383513	G	A	186599524				0.1291	0.1303
rs10911898	A	C	186612593				0.3005	0.2784
rs10911902	A	G	186632317				0.1441	0.1469
rs689470	A	G	186641058	PTGS2	EXON	Silent	0.0328	0.0307
rs2206593	A	G	186642429	PTGS2	EXON	Silent	0.0670	0.0485
rs4648292	G	C	186642856	PTGS2	EXON	Silent	0.0573	0.0723
rs5275	G	A	186643058	PTGS2	EXON	Silent	0.3518	0.3296
rs4648268	A	G	186647138	PTGS2		Silent	0.0929	0.0913
rs5277	G	C	186648197	PTGS2	EXON	Synonymous_V102V	0.1724	0.1822
rs4648261	A	G	186649004	PTGS2		Silent	0.0225	0.0179
rs2745557	A	G	186649221	PTGS2		Silent	0.1990	0.1705
rs20424	C	G	186649618				0.0129	0.0166
rs689466	G	A	186650751				0.1598	0.1858
rs2745559	A	C	186652002				0.1960	0.1692
rs12064238	A	G	186659125				0.2090	0.1839
rs964570	A	G	186684977				0.0635	0.0593
chr1_186685095_C_T	C	T	186685095				0.0155	0.0181
rs6685280	C	A	186685818				0.2398	0.2133
rs4650701	G	A	186704555				0.0669	0.0587

- EA: Effect Allele, RA: Reference Allele, EAF: Minor Allele Frequency

3. Results

3.1. Population Characteristics of EPICAP with Genotyping Data

Table 35 presents the distribution of various potential risk factors between cases (n=732) and controls (n=783) using genotypic data. Significant differences between cases and controls were observed for family history of prostate cancer ($p < 0.0001$), body mass index (BMI) ($p = 0.010$), and use of non-steroidal anti-inflammatory drugs ($P = 0.038$). Specifically, a greater proportion of cases (21.9%) had a family history of prostate cancer compared to controls (9.3%). In terms of BMI, more cases were overweight (50.0%) compared to controls (45.6%), and fewer cases were obese (21.3%) compared to controls (23.6%). Among those who use Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), 27.4% are cases while 32.3% are controls, indicating a higher proportion of NSAID use among the control group compared to the cases. Other factors did not show significant differences between cases and controls: age ($p = 0.150$), ethnic origin ($p = 0.258$), education ($p = 0.797$), waist circumference ($p = 0.082$), smoking status ($p = 0.290$), alcohol consumption ($p = 0.343$), physical activity ($p = 0.119$), and Hypertriglyceridemia ($p = 0.063$), indicating that the distribution of these potential risk factors is relatively similar between the cases and controls in this study.

Table 35 Distribution of Potential Risk factors between Cases and Controls using the Genotypic Data

	Cases n=732 (%)	Controls n=783 (%)	P-value* X²
Gleason Score			
≤ 7 (3+4)	566 (78.5)	-	
≥7 (4+3)	155 (21.5)	-	
Age (Years)			<i>0.150</i>
< 55	42 (5.7)	50 (6.4)	
[55-60]	94 (12.8)	83 (10.6)	
[60-65]	193 (26.4)	183 (23.4)	
[65-70]	244 (33.3)	260 (33.2)	
≥70	159 (21.7)	207 (26.4)	
Ethnic Origin			<i>0.258</i>
Caucasian	724 (98.9)	769 (98.2)	
Other	8 (1.1)	14 (1.8)	
Family History of Prostate Cancer			<0.0001
No	572 (78.1)	710 (90.7)	
Yes	160 (21.9)	73 (9.3)	
Education			<i>0.797</i>
Primary	155 (21.2)	167 (21.4)	
Secondary	339 (46.3)	374 (47.7)	
University	238 (32.5)	242 (31.0)	
Body Mass Index (kg/m²)			0.010
<25 - Normal	206 (28.1)	222 (28.4)	
[25-30] - Overweight	366 (50.0)	357 (45.6)	
≥30 - Obese	156 (21.3)	185 (23.6)	
Waist Circumference (cm)			<i>0.082</i>
≤94	186 (25.4)	232 (29.6)	
>94	546 (73.5)	551 (68.6)	
Smoking Status			<i>0.290</i>
Never	214 (29.2)	223 (28.5)	
Former	409 (55.9)	420 (53.6)	
Current	109 (14.9)	140 (17.9)	
Alcohol Consumption			<i>0.343</i>
No	53 (7.2)	67 (8.6)	
Yes	679 (92.8)	716 (91.4)	
Physical Activity			<i>0.119</i>
No	167 (22.8)	153 (19.5)	
Yes	565 (77.2)	630 (80.5)	
Nonsteroidal anti-inflammatory drugs			0.038
No	530 (72.7)	521 (67.7)	
Yes	199 (27.4)	249 (32.3)	
Hypertriglyceridemia			<i>0.063</i>
No	592 (76.9)	601 (80.9)	
Yes	139 (23.0)	180 (19.1)	

*P-value: chi-square

3.2. Direct Effect of Environmental Variables

The associations between our environmental variables in the genotyped population, including infections, kidney stones, and gallbladder stones, and the risk of prostate cancer are shown in Table 36 while taking into account the aggressiveness of cancer. There was no significant association between infections and prostate cancer risk overall (OR = 1.10, 95% CI: 0.89-1.37). When stratified by cancer grade, infections did not show a significant association with low-grade cancer (OR = 1.14, 95% CI: 0.90-1.43) or high-grade cancer (OR = 1.05, 95% CI: 0.73-1.55). Additionally, there was no significant association between gallbladder stones and prostate cancer risk overall (OR = 1.15, 95% CI: 0.78-1.69). When stratified by cancer grade, gallbladder stones were not significantly associated with low-grade cancer (OR = 1.07, 95% CI: 0.70-1.63) or high-grade cancer (OR = 1.46, 95% CI: 0.81-2.54). However, Kidney stones were significantly associated with an increased risk of prostate cancer overall (OR = 1.59, 95% CI: 1.21-2.09). This association remained significant for low-grade cancer (OR = 1.58, 95% CI: 1.18-2.11) but was not significant for high-grade cancer (OR = 1.36, 95% CI: 0.86-2.12)

Table 36 Association between the Exposure Variables and Prostate Cancer using the Genotypic Data of EPICAP

	Controls		Cases				
	n=783 (%)	n=732 (%)	All	Low grade cancer*		High-grade cancer**	
			OR (95% CI)	n=566 (%)	OR (95% CI)	n=155 (%)	OR (95% CI)
Overall Infections^a							
No	336 (52.0)	310 (43.4)	1.00 Reference	235 (42.7)	1.00 Reference	70 (46.7)	1.00 Reference
Yes	410 (48.0)	404 (56.6)	1.10 (0.89-1.37)	316 (57.4)	1.14 (0.90-1.43)	82 (53.3)	1.05 (0.73-1.55)
Kidney Stones^a							
No	654 (84.4)	559 (76.9)	1.00 Reference	436 (77.4)	1.00 Reference	119 (77.3)	1.00 Reference
Yes	121 (15.6)	168 (23.1)	1.59 (1.21-2.09)	127 (22.6)	1.58 (1.18-2.11)	35 (22.7)	1.36 (0.86-2.12)
Gallbladder Stones^b							
No	714 (92.2)	665 (91.5)	1.00 Reference	519 (92.3)	1.00 Reference	135 (87.7)	1.00 Reference
Yes	60 (7.8)	62 (8.5)	1.15 (0.78-1.69)	43 (7.7)	1.07 (0.70-1.63)	19 (12.3)	1.46 (0.81-2.54)

^a OR adjusted to Family history of Prostate Cancer, Age, NSAIDs, Waist Circumference, Education, Physical Activity

^b OR adjusted to Family history of Prostate Cancer, Age, NSAIDs, Waist Circumference, Education, Physical Activity, Triglyceride

* Gleason ≤ 7 (3+4) ** Gleason ≥ 7 (4+3)

3.3. SNP-by-SNP Analysis of the COX-2 Gene

Table 37 presents significant results for genotypes from each SNP (single nucleotide polymorphism) of the COX-2 gene using the co-dominant model. The AA genotype of rs10911898 showed a higher risk for all cases (OR: 1.44, 95% CI: 1.00-2.09, $p = 0.052$) and for low-grade cancer (OR: 1.51, 95% CI: 1.02-2.23, $p = 0.040$). Similarly, the AG genotype of rs2206593 was associated with an increased risk in all cases (OR: 1.63, 95% CI: 1.16-2.30, $p = 0.005$) and in low-grade cancer (OR: 1.64, 95% CI: 1.14-2.35, $p = 0.008$). The AG genotype of rs4648261 was associated with an increased risk of high-grade prostate cancer (OR: 3.22, 95%CI: 1.59-6.31). The AG genotype of rs2745557 was significant across all cases (OR: 1.38, 95% CI: 1.10-1.73, $p = 0.005$), borderline significant for low-grade cancer (OR: 1.27, 95% CI: 1.00-1.62, $p = 0.058$), and significant for high-grade cancer (OR: 1.70, 95% CI: 1.17-2.46, $p = 0.005$). The AC genotype of rs2745559 was significant in all cases (OR: 1.36, 95% CI: 1.08-1.71, $p = 0.008$) and high-grade cancer (OR: 1.72, 95% CI: 1.18-2.49, $p = 0.004$), but not in low-grade cancer. Additionally, the AA genotype of rs12064238 and the CC genotype of rs6685280 showed significant associations in both all cases and low-grade cancer.

The genotype of SNPs that were not associated with prostate cancer are detailed in appendix 11 and 12.

Table 37 Significant Results for genotypes from each SNP of the COX-2 gene using the Co-dominant Model

	Controls				Cases					
	n=783 (%)	n=732 (%)	All		n=566 (%)	Low grade cancer**		High-grade cancer***		
			OR* (95% CI)	P-value		OR* (95% CI)	P-value	n=155 (%)	OR* (95% CI)	P-value
rs10911898										
CC	407 (52.0)	369 (50.4)	1.00 reference		285 (50.3)	1.00 reference		81 (52.3)	1.00 reference	
AC	316 (40.4)	286 (39.1)	1.03 (0.83-1.28)		219 (38.7)	1.02 (0.81-1.29)		60 (38.7)	0.98 (0.67-1.42)	
AA	60 (7.7)	77 (10.5)	1.44 (1.00-2.09)	0.052	62 (11.0)	1.51 (1.02-2.23)	0.040	14 (9.0)	1.12 (0.56-2.12)	
rs2206593										
GG	712 (91.0)	636 (87.0)	1.00 reference		492 (86.9)	1.00 reference		135 (87.1)	1.00 reference	
AG	64 (8.2)	92 (12.6)	1.63 (1.16-2.30)	0.005	71 (12.6)	1.64 (1.14-2.35)	0.008	19 (12.3)	1.48 (0.83-2.55)	
AA	6 (0.8)	3 (0.4)	0.59 (0.12-2.29)		3 (0.5)	0.79 (0.16-3.08)		0	-	
rs4648261										
GG	754 (96.4)	700 (95.6)	1.00 reference		549 (97.0)	1.00 reference		140 (90.3)	1.00 reference	
AG	28 (3.5)	31 (4.4)	1.21 (0.71-2.05)		16 (2.8)	0.78 (0.40-1.44)		15 (9.7)	3.22 (1.59-6.31)	0.001
AA	1 (0.1)	0	-		1 (0.2)	-		0	-	
rs2745557										
GG	546 (69.7)	464 (63.5)	1.00 reference		368 (65.0)	1.00 reference		92 (59.4)	1.00 reference	
AG	207 (26.4)	243 (33.2)	1.38 (1.10-1.73)	0.005	177 (31.3)	1.27 (1.00-1.62)	0.058	60 (38.7)	1.70 (1.17-2.46)	0.005
AA	30 (3.8)	24 (3.3)	0.98 (0.55-1.71)		20 (3.5)	1.09 (0.59-1.96)		3 (1.9)	0.53 (0.12-1.56)	
rs2745559										
CC	548 (70.0)	469 (64.1)	1.00 reference		373 (65.8)	1.00 reference		92 (59.4)	1.00 reference	
AC	205 (26.2)	239 (32.7)	1.36 (1.08-1.71)	0.008	173 (30.6)	1.23 (0.96-1.57)	0.095	60 (38.7)	1.72 (1.18-2.49)	0.004
AA	30 (3.8)	24 (3.3)	0.97 (0.55-1.70)		20 (3.5)	1.08 (0.59-1.94)		3 (1.9)	0.53 (0.12-1.56)	
rs12064238										
GG	516 (65.9)	466 (63.7)	1.00 reference		358 (63.4)	1.00 reference		104 (67.1)	1.00 reference	
AG	246 (31.4)	226 (30.9)	1.03 (0.82-1.28)		176 (31.0)	1.04 (0.82-1.32)		43 (27.7)	0.87 (0.58-1.28)	
AA	21 (2.7)	40 (5.5)	2.17 (1.27-3.82)	0.006	32 (5.6)	2.29 (1.30-4.12)	0.005	8 (5.2)	1.70 (0.65-4.03)	
rs6685280										
AA	484 (61.8)	430 (61.8)	1.00 reference		326 (57.7)	1.00 reference		99 (63.9)	1.00 reference	
CA	264 (33.7)	253 (35.6)	1.08 (0.87-1.34)		197 (34.7)	1.11 (0.88-1.40)		50 (32.3)	0.91 (0.62-1.32)	
CC	35 (4.5)	49 (6.7)	1.61 (1.02-2.56)	0.040	43 (7.6)	1.85 (1.16-2.98)	0.011	6 (3.9)	0.73 (0.24-1.79)	

*OR: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, Physical Activity, ** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

Table 38 presents result for variants of the COX-2 gene association with prostate cancer using an additive model. The A allele of rs10911898 was significantly associated with an increased risk in all cases (OR: 1.44, 95% CI: 1.00-2.05, $p = 0.047$) and in low-grade cancer (OR: 1.51, 95% CI: 1.04-2.21, $p = 0.032$). The G allele of rs2206593 showed a significant association with all cases (OR: 1.40, 95% CI: 1.03-1.90, $p = 0.030$) and low-grade cancer (OR: 1.43, 95% CI: 1.04-1.98, $p = 0.028$). The A allele of rs2745557 was associated with an increased risk in all cases (OR: 1.21, 95% CI: 1.01-1.46, $p = 0.039$). The A allele of rs12064238 was significantly associated with an increased risk in all cases (OR: 2.15, 95% CI: 1.25-3.70, $p = 0.006$) and in low-grade cancer (OR: 2.26, 95% CI: 1.29-4.02, $p = 0.005$). The C allele of rs6685280 showed a significant association among low-grade cancer (OR: 1.77, 95% CI: 1.12-2.77, $p = 0.019$). Lastly, the A allele of rs4648261 cancer (OR: 2.26, 95% CI: 1.29-4.02, $p = 0.005$) was only significantly associated with high-grade cancer (OR: 3.00, 95% CI: 1.52-5.75, $p = 0.001$). However, after correcting for false discovery rate (FDR), only the association with rs4648261 in high-grade cancer remained significant ($p = 0.007$).

Table 38 Variants of COX-2 Gene Association with Prostate Cancer (SNP-by-SNP Approach using the Additive Model)

SNP	All Cases			Low-Grade Cancer*			High-Grade Cancer**		
	OR (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**
rs6658482	0.96 (0.79-1.17)	0.715	0.904	0.89 (0.71-1.10)	0.296	0.552	1.28 (0.93-1.74)	0.123	0.429
rs2383513	0.98 (0.79-1.21)	0.868	0.902	0.95 (0.75-1.20)	0.680	0.915	1.09 (0.76-1.54)	0.613	0.893
rs10911898	1.44 (1.00-2.05)	0.047	0.413	1.51 (1.04-2.21)	0.032	0.250	1.15 (0.62-2.13)	0.659	0.948
rs10911902	0.97 (0.79-1.19)	0.766	0.902	0.91 (0.72-1.14)	0.415	0.692	1.28 (0.92-1.75)	0.137	0.474
rs689470	1.05 (0.70-1.57)	0.827	0.921	0.93 (0.59-1.45)	0.762	0.872	1.53 (0.81-2.75)	0.168	0.569
rs2206593	1.40 (1.03-1.90)	0.030	0.308	1.43 (1.04-1.98)	0.028	0.280	1.21 (0.71-1.95)	0.459	0.929
rs4648292	0.91 (0.73-1.12)	0.371	0.819	0.88 (0.69-1.12)	0.295	0.523	0.98 (0.68-1.36)	0.898	0.987
rs5275	1.10 (0.94-1.28)	0.244	0.885	1.06 (0.90-1.26)	0.453	0.755	1.24 (0.95-1.60)	0.113	0.376
rs4648268	1.01 (0.79-1.30)	0.898	0.926	1.03 (0.78-1.34)	0.850	0.898	0.98 (0.63-1.48)	0.917	0.943
rs5277	0.92 (0.76-1.12)	0.415	0.815	0.95 (0.78-1.17)	0.637	0.904	0.85 (0.60-1.17)	0.330	0.926
rs4648261	1.28 (0.77-2.13)	0.348	0.806	0.89 (0.48-1.60)	0.698	0.891	3.00 (1.52-5.75)	0.001	0.007
rs2745557	1.21 (1.01-1.46)	0.039	0.386	1.17 (0.96-1.42)	0.120	0.444	1.30 (0.96-1.75)	0.084	0.241
rs20424	0.78 (0.42-1.41)	0.411	0.824	0.90 (0.48-1.68)	0.753	0.914	0.39 (0.06-1.32)	0.202	0.666
rs689466	0.84 (0.69-1.01)	0.061	0.609	0.83 (0.68-1.02)	0.076	0.380	0.87 (0.62-1.19)	0.392	0.896
rs2745559	1.20 (1.00-1.44)	0.052	0.516	1.15 (0.94-1.40)	0.168	0.421	1.31 (0.97-1.76)	0.076	0.222
rs12064238	2.15 (1.25-3.70)	0.006	0.090	2.26 (1.29-4.02)	0.005	0.060	1.99 (0.85-4.45)	0.110	0.360
rs964570	1.06 (0.79-1.42)	0.704	0.916	1.12 (0.81-1.52)	0.491	0.818	0.94 (0.53-1.55)	0.807	0.927
chr1_186685095_C_T	0.84 (0.46-1.51)	0.560	0.946	0.82 (0.43-1.54)	0.546	0.910	0.96 (0.32-2.38)	0.938	0.938
rs6685280	1.54 (0.99-2.43)	0.060	0.413	1.77 (1.12-2.77)	0.019	0.188	0.88 (0.33-2.15)	0.772	0.947
rs4650701	1.13 (0.85-1.52)	0.400	0.881	1.17 (0.86-1.60)	0.308	0.616	1.06 (0.62-1.72)	0.819	0.953

*P-value: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, Physical Activity, **P-value: FDR

*** Gleason ≤ 7 (3+4) **** Gleason ≥ 7 (4+3)

3.4. Interaction Analysis: GxE SNP-by-SNP Approach

Table 39 presents the interaction analysis of gene-environment interactions (GxE) using a SNP-by-SNP approach with infections (E) and prostate cancer in all its grades. Significant findings include the G allele of rs964570, which showed a significant association with all cases (OR: 1.10, 95% CI: 1.15-4.16, $p = 0.031$) and with high-grade cancer (OR: 2.36, 95% CI: 1.16-4.88, $p = 0.019$).

Table 40 and Table 41 present the interaction analysis of gene-environment interactions (GxE) using a SNP-by-SNP approach with kidney stones and gallbladder stones (E) and prostate cancer in all its grades. In Table 47, no significant associations were found between COX-2 gene variants and prostate cancer when considering interactions with kidney stones. Similarly, Table 48 shows no significant associations between COX-2 gene variants and prostate cancer when considering interactions with gallbladder stones.

Table 39 Interaction Analysis: GxE in SNP-by-SNP approach with Overall Infections (E) and Prostate Cancer in all its grades

SNP	All Cases			Low-Grade Cancer ^{***}			High-Grade Cancer ^{****}		
	OR (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**
rs6658482	0.74 (0.47-1.18)	0.205	0.436	0.68 (0.41-1.13)	0.134	0.400	1.07 (0.50-2.32)	0.868	0.987
rs2383513	1.49 (0.27-8.48)	0.643	0.833	0.92 (0.13-6.67)	0.931	0.931	2.70 (0.24-66.66)	0.454	0.957
rs10911898	1.17 (0.55-2.49)	0.682	0.819	1.25 (0.56-2.79)	0.585	0.764	0.67 (0.18-2.59)	0.560	0.884
rs10911902	1.17 (0.28-5.05)	0.827	0.827	2.47 (0.41-20.76)	0.348	0.561	0.46 (0.07-2.93)	0.409	0.772
rs689470	1.42 (0.61-3.33)	0.419	0.803	1.95 (0.77-5.13)	0.167	0.569	0.54 (0.14-1.95)	0.355	0.745
rs2206593	1.48 (0.74-2.98)	0.269	0.653	1.74 (0.83-3.73)	0.147	0.539	0.86 (0.27-2.73)	0.798	0.998
rs4648292	0.89 (0.37-2.19)	0.806	0.875	0.90 (0.34-2.43)	0.834	0.840	1.06 (0.26-4.81)	0.934	0.985
rs5275	0.94 (0.60-1.46)	0.770	0.931	0.99 (0.61-1.60)	0.985	0.985	0.69 (0.31-1.44)	0.307	0.580
rs4648268	1.85 (0.15-24.40)	0.623	0.808	1.06 (0.07-15.16)	0.964	0.964	-	-	-
rs5277	0.99 (0.63-1.56)	0.987	0.987	0.90 (0.55-1.46)	0.664	0.820	1.69 (0.76-3.80)	0.198	0.558
rs4648261	1.18 (0.40-3.49)	0.767	0.841	2.50 (0.09-10.70)	0.174	0.523	0.45 (0.10-1.87)	0.279	0.668
rs2745557	1.02 (0.65-1.60)	0.920	0.920	1.08 (0.67-1.77)	0.735	0.735	0.85 (0.40-1.81)	0.679	0.905
rs20424	0.59 (0.16-2.08)	0.409	0.773	0.52 (0.14-1.97)	0.340	0.579	0.88 (0.31-24.72)	0.929	0.996
rs689466	0.84 (0.57-1.25)	0.398	0.753	0.77 (0.51-1.18)	0.234	0.568	1.04 (0.53-2.09)	0.909	0.996
rs2745559	1.03 (0.66-1.63)	0.872	0.887	1.10 (0.68-1.80)	0.690	0.760	1.09 (1.15-2.37)	0.740	0.921
rs12064238	0.77 (0.23-2.47)	0.667	0.813	0.95 (0.27-3.23)	0.939	0.939	0.88 (0.42-1.87)	0.253	0.597
rs964570	1.10 (1.15-4.16)	0.031	0.249	2.36 (1.16-4.88)	0.019	0.110	1.09 (0.32-3/74)	0.894	0.951
chr1_186685095_C_T	1.49 (0.43-3.33)	0.530	0.751	1.64 (0.43-5.33)	0.476	0.673	1.14 (0.15-10.61)	0.899	0.899
rs6685280	2.13 (0.84-5.69)	0.124	0.303	2.25 (0.84-5.69)	0.111	0.393	1.39 (0.19-12.33)	0.744	0.992
rs4650701	1.69 (0.88-3.30)	0.118	0.268	1.82 (0.91-3.71)	0.094	0.401	1.05 (0.32-3.40)	0.938	0.983

*P-value: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, and Physical Activity **P-value: FDR

*** Gleason ≤ 7 (3+4) **** Gleason ≥ 7 (4+3)

Table 40 Interaction Analysis: GxE in SNP-by-SNP approach with Kidney Stones (E) and Prostate Cancer in all its grades

SNP	All Cases			Low-Grade Cancer ^{***}			High-Grade Cancer ^{****}		
	OR (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**
rs6658482	0.93 (0.56-1.55)	0.789	0.902	0.85 (0.49-1.49)	0.577	0.762	1.33 (0.61-2.87)	0.466	0.818
rs2383513	1.03 (0.60-1.76)	0.922	0.972	1.01 (0.56-1.83)	0.966	0.966	1.00 (0.40-2.33)	0.991	0.997
rs10911898	1.27 (0.51-3.33)	0.612	0.825	1.30 (0.50-3.53)	0.595	0.773	1.26 (0.22-5.83)	0.778	0.987
rs10911902	0.83 (0.50-1.39)	0.474	0.853	0.83 (0.47-1.46)	0.529	0.754	0.99 (0.44-2.16)	0.972	0.997
rs689470	2.06 (0.77-6.06)	0.164	0.368	2.72 (0.96-8.38)	0.067	0.244	0.84 (0.11-4.60)	0.853	0.998
rs2206593	0.93 (0.43-2.10)	0.867	0.867	0.71 (0.30-1.69)	0.440	0.659	2.26 (0.66-7.58)	0.188	0.529
rs4648292	1.25 (0.74-2.16)	0.409	0.669	1.08 (0.59-1.97)	0.792	0.838	1.92 (0.89-4.12)	0.092	0.401
rs5275	1.19 (0.79-1.79)	0.414	0.637	1.23 (0.79-1.90)	0.363	0.569	1.11 (0.55-2.18)	0.769	0.895
rs4648268	0.81 (0.43-1.54)	0.524	0.787	0.69 (0.34-1.38)	0.297	0.544	1.35 (0.45-3.70)	0.574	0.986
rs5277	0.73 (0.44-1.22)	0.235	0.486	0.78 (0.45-1.34)	0.366	0.604	0.68 (0.27-1.62)	0.391	0.781
rs4648261	0.52 (0.17-1.61)	0.248	0.459	0.76 (0.21-2.72)	0.674	0.794	0.30 (0.05-1.46)	0.149	0.384
rs2745557	0.81 (0.50-1.31)	0.378	0.649	0.72 (0.43-1.20)	0.204	0.447	0.97 (0.44-2.07)	0.935	0.999
rs20424	2.93 (0.32-64.8)	0.383	0.627	3.22 (0.34-71.9)	0.347	0.625	-	-	0.993
rs689466	1.12 (0.69-1.83)	0.634	0.823	1.08 (0.64-1.81)	0.773	0.819	1.29 (0.57-2.83)	0.528	0.908
rs2745559	0.82 (0.51-1.34)	0.430	0.704	0.74 (0.44-1.22)	0.236	0.471	1.00 (0.46-2.13)	0.994	0.996
rs12064238	1.14 (0.32-4.73)	0.850	0.901	1.44 (0.39-6.16)	0.600	0.738	0.36 (0.01-3.41)	0.418	0.752
rs964570	1.35 (0.63-2.98)	0.442	0.795	1.46 (0.66-3.32)	0.356	0.640	1.57 (0.37-5.91)	0.515	0.843
chr1_186685095_C_T	1.01 (0.20-5.03)	0.994	0.994	1.43 (0.28-7.44)	0.663	0.918	-	-	0.977
rs6685280	0.95 (0.33-2.94)	0.926	0.925	1.01 (0.34-3.19)	0.986	0.986	0.72 (0.03-6.58)	0.789	0.999
rs4650701	1.24 (0.58-2.73)	0.582	0.849	1.34 (0.61-3.05)	0.471	0.747	1.31 (0.31-4.81)	0.694	0.984

*P-value: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, Physical Activity, and triglyceride **P-value: FDR

*** Gleason ≤ 7 (3+4) **** Gleason ≥ 7 (4+3)

Table 41 Interaction Analysis: GxE in SNP-by-SNP approach with Gallbladder Stones (E) and Prostate Cancer in all its grades

SNP	All Cases			Low-Grade Cancer ^{***}			High-Grade Cancer ^{****}		
	OR (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**	OR* (95%CI)	P-value*	P-value**
rs6658482	0.97 (0.52-1.85)	0.938	0.992	0.86 (0.40-1.81)	0.701	0.834	1.11 (0.44-2.78)	0.819	0.977
rs2383513	0.99 (0.46-2.14)	0.984	0.993	0.67 (0.24-1.71)	0.422	0.668	1.89 (0.67-5.26)	0.220	0.705
rs10911898	0.44 (0.16-1.57)	0.209	0.495	0.34 (0.07-1.41)	0.155	0.386	1.09 (0.47-2.47)	0.971	0.992
rs10911902	0.91 (0.47-1.76)	0.780	0.948	0.87 (0.39-1.88)	0.729	0.830	0.89 50.33-2.30)	0.816	0.988
rs689470	1.51 (0.40-6.47)	0.555	0.913	1.38 (0.28-6.73)	0.682	0.915	1.80 (0.28-11.0)	0.524	0.904
rs2206593	1.28 (0.41-4.51)	0.676	0.841	1.53 (0.47-5.49)	0.490	0.716	0.60 (0.03-4.84)	0.667	0.945
rs4648292	0.64 (0.28-1.30)	0.236	0.499	0.42 (0.09-1.08)	0.125	0.416	0.79 (0.28-1.90)	0.622	0.977
rs5275	0.69 (0.39-1.21)	0.195	0.430	0.67 (0.36-1.22)	0.192	0.411	0.82 (0.34-1.98)	0.662	0.845
rs4648268	0.81 (0.30-2.13)	0.669	0.876	0.43 (0.09-1.48)	0.217	0.459	1.88 (0.51-6.69)	0.324	0.644
rs5277	1.77 (0.80-4.04)	0.167	0.450	2.12 (0.90-5.14)	0.088	0.414	1.06 (0.25-3.83)	0.934	0.983
rs4648261	2.34 (0.40-44.4)	0.428	0.756	2.06 (0.28-34.3)	0.481	0.762	1.75 (0.14-42.77)	0.674	0.945
rs2745557	0.68 (0.35-1.31)	0.252	0.499	0.69 (0.33-1.39)	0.306	0.529	0.62 (0.21-1.62)	0.348	0.602
rs20424	-	-	-	-	-	-	-	-	-
rs689466	0.94 (0.45-1.92)	0.874	0.962	0.73 (0.29-1.65)	0.466	0.681	1.47 (0.51-4.02)	0.457	0.868
rs2745559	0.65 (0.33-1.25)	0.196	0.433	0.66 (0.32-1.34)	0.256	0.487	0.56 (0.19-1.48)	0.263	0.555
rs12064238	0.28 (0.03-1.94)	0.197	0.468	0.39 (0.04-2.72)	0.340	0.587	-	-	-
rs964570	1.96 (0.73-5.54)	0.190	0.454	2.20 (0.76-6.66)	0.151	0.410	2.04 (0.43-8.95)	0.351	0.667
chr1_186685095_C_T	0.59 (0.07-4.18)	0.600	0.752	0.83 (0.09-6.04)	0.857	0.875	-	-	-
rs6685280	0.60 (0.13-2.91)	0.519	0.758	0.80 (0.16-3.91)	0.780	0.917	-	-	-
rs4650701	1.61 (0.60-4.59)	0.355	0.705	1.75 (0.59-5.34)	0.313	0.595	1.71 (0.36-7.36)	0.479	0.910

*P-value: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, Physical Activity, and triglyceride **P-value: FDR

*** Gleason ≤ 7 (3+4) **** Gleason ≥ 7 (4+3)

4. Discussion

4.1. Synthesis of Main Results

Several genotypes showed significant associations in our SNP-by-SNP analysis of the COX-2 gene. The AA genotype of rs10911898 and rs12064238, the CC genotype of rs6685280, and the AG genotype of rs2206593 were linked to a higher risk for all cases and low-grade cancer. The AG genotype of rs2745557 was significant across all cases, borderline significant for low-grade cancer, and significant for high-grade cancer. The AG genotype of rs4648261 was significant in high-grade cancer. Furthermore, the AC genotype of rs2745559 showed significance in all cases (OR = 1.36, 95% CI: 1.08-1.71, $p = 0.008$) and high-grade cancer (OR = 1.72, 95% CI: 1.18-2.49, $p = 0.004$).

When using the additive model, significant associations included the A allele of rs10911898, A allele of rs12064238, and G allele of rs2206593 among all cases and low-grade cancer. The A allele of rs2745557 was associated with increased risk in all cases (OR = 1.21, 95% CI: 1.01-1.46, $p = 0.039$). The C allele of rs6685280 was significantly associated with low-grade cancer. Notably, the A allele of rs4648261 was significantly associated with high-grade cancer (OR = 3.00, 95% CI: 1.52-5.75, $p = 0.001$), and even after FDR correction, this association remained significant ($p = 0.007$).

In our gene-environment interaction analysis, significant findings included the G allele of rs964570 for all cases and low-grade cancer. However, these associations were no longer significant after FDR correction. Additionally, no significant associations were found between COX-2 gene variants and prostate cancer when considering interactions with kidney stones or gallbladder stones.

4.2. Comparison of Results to the Literature

The meta-analyses on the association between COX-2 gene SNPs and prostate cancer risk show inconsistency in the results across different studies. Rs5275 was consistently found to be non-significant across multiple studies, including Zhu (2010), Shao (2012), Yang (2013), Li (2018), and Asadian (2021) [148, 296–298, 313]. The results for rs2745557 varied, with Zhang (2012) finding it significant under a dominant model and Asadian (2021) reporting significance in allele and dominant models, while other studies did not find it significant overall [148, 149]. Lastly, rs5277 did not show a significant association with prostate cancer risk in the study by

Shao (2012) and rs689466 in the study by Asdian (2021) [148, 297]. The majority of COX-2 gene variants studied do not consistently show prostate cancer susceptibility across different populations

The study by Shahedi et al. (2006) was conducted in Sweden, involving 1,378 prostate cancer cases and 782 controls. Five SNPs were included rs2745557, rs20432, rs4648276, rs5275, and rs689470. The variant G allele of rs20432 was associated with a decreased risk of prostate cancer, particularly for localized cancer but not advanced cancer, and the T allele of rs689470 was also associated with a decreased risk and a more pronounced effect observed for localized prostate cancer [144]. Overall, the null results align with our analysis, except for rs689470 where it is inversely associated with prostate cancer.

A case-control study by Cheng et al. (2007) was conducted at the University Hospitals of Cleveland in the USA, involving 506 advanced prostate cancer cases and 506 controls, matched by age, ethnicity, and medical institution [151]. The analysis focused on nine single-nucleotide polymorphisms (SNPs) within the COX-2 gene. Three SNPs demonstrated significant associations with prostate cancer risk: rs2745557 (GA genotype associated with lower risk among all groups of ethnicity and specifically to Caucasians), rs2206593 (CT genotype associated with reduced risk among all groups of ethnicity and specifically to Caucasians), and rs689470 (AA genotype associated with higher risk, especially among African Americans). The other SNPs, including rs689466, rs20417, rs5277, rs2066826, rs5275, and rs4648310, did not show significant associations. Overall, the null results align with our analysis, and for rs2745557 and rs2206593, although they showed inverse associations in study, they align with our results before correcting for multiple tests.

The study by Danforth et al. (2007) was conducted in the US involving 2,321 prostate cancer cases and 2,560 controls in two large nested case-control studies: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the Cancer Prevention Study II (CPS-II) Nutrition Cohort Danforth [294]. No significant association was found for rs5277, rs20432, rs4648276, and rs689470 in either the PLCO or Nutrition Cohort individually or combined. In the PLCO cohort, the rs5275 (Ex10 +837T>C) marker initially showed a suggestive association with prostate cancer risk, but this did not persist after adjustment for multiple comparisons. Overall, the null results align with our results, except for rs5275.

In a study conducted by Dossus et al. (2009) in 8 European countries including 630 cases and 873 controls. The results indicated no significant association between any of these COX-2

polymorphisms, including rs10911902, rs4648298, rs2206593, rs5275, rs5277, rs4648261, rs2745557, rs20417, rs689466, rs12042763, rs7550380, and rs2383529, and prostate cancer risk [302]. Additionally, there was no association when taking into account the aggressiveness of the cancer. Overall, the null results align with the null results of the study, except for rs4648261, rs2206593, and rs2745557 that were significant before FDR correction.

The study by Mandal and Mittal (2011) was conducted in the north of India, involving 195 prostate cancer patients and 250 healthy controls [307]. The results indicated that the -765G>C (rs20417) polymorphism was significantly associated with an increased risk of prostate cancer. Similarly, the +8473T>C (rs5275) polymorphism was significantly associated with an increased risk, particularly for individuals with the CC genotype. No significant associations were observed when taking into account the aggressiveness of cancer. The results align with our null analysis except for rs5275.

The study by Amirian (2011) was conducted in the US, involving 585 non-Hispanic white prostate cancer patients and 585 healthy controls. The results indicated that the rs2745557 polymorphism was significantly associated with an increased risk of prostate cancer. This aligns with our results before the FDR correction [306].

The study by Wu et al. (2011) was conducted in Taiwan, involving 218 prostate cancer patients and 436 healthy controls. The six SNPs studied were G-1195A (rs689466), G-765C (rs20417), T+8473C (rs5275), Intron 1 (rs2745557), Intron 5 (rs16825748), and Intron 6 (rs2066826). However, only rs20417 polymorphism showed a significant association with prostate cancer risk. The results align with our null analysis except for rs2745557 that was significant before the FDR correction [305].

The study by Kopp et al. (2013) was conducted in Denmark, involving 370 prostate cancer cases and 370 matched controls within the Danish "Diet, Cancer, and Health" cohort. No significant association was observed for the COX-2 +8473T/C (rs5275), -1195A/G (rs689466), +3496T/C (rs2066826), +202G/A (rs2745557), and +306C/G (rs5277) polymorphisms. The study also examined interactions with NSAID use, but no significant interactions were found. The results align with our null analysis except for rs2745557 that was significant before the FDR correction [308].

The study by Sugie et al. (2013) was conducted in Japan and included 134 prostate cancer patients and 86 healthy controls matched for age and smoking status. The results indicated

that the COX-2 G1195A rs689465 polymorphism was significantly associated with an increased risk of prostate cancer [309].

The study by Cui et al. (2015) was conducted in Beijing, China involving 543 prostate cancer patients and 753 controls [310]. The results indicated that the COX-2 -1195G>A (rs689470) polymorphism was significantly associated with an increased risk of prostate cancer. The GA genotype showed a higher risk compared to the GG genotype, and the AA genotype showed an even higher risk. Other polymorphisms such as rs2066826, rs20417, and rs5275, did not show a significant association with prostate cancer risk. Contrary to the significant results for rs689470, we found no significance. However, for the other SNPs, our results align with the null findings.

The study by Fawzy et al. (2016) was conducted in Egypt and included 112 prostate cancer patients and 120 controls [311]. The study focused on the COX-2 (rs2745557) polymorphism and its association with prostate cancer. A significant association was found for the GG genotype, which was associated with a 17-fold increased risk for prostate cancer compared to the AA genotype. Additionally, carriers of the G allele were more likely to develop metastatic cancer and exhibit disease aggressiveness. In contrast, in our study, the AG genotype of rs2745557 was found to be significant across all grades of prostate cancer, while the significance for the AA genotype was lost.

Cyclooxygenase-2 (COX-2) is an important enzyme involved in the production of prostaglandins that plays a crucial role in inflammation and has been implicated in various cancers, including prostate cancer [314, 315]. Elevated COX-2 expression can promote tumor growth through several mechanisms, including the stimulation of angiogenesis, enhancement of cell proliferation, and inhibition of apoptosis [137, 146, 314–316]. Genetic variations in COX-2 could potentially alter the expression levels or enzymatic activity of COX-2. The SNP rs2745557, an intronic variant of the COX-2 gene, may affect COX-2 activity and the production of inflammatory prostaglandins [151]. While its exact function is not fully understood, it might have a biological effect on COX-2 activity, influencing prostate cancer susceptibility by promoting inflammation and tumor growth. Similarly, the functional impact of SNP rs2206593 and rs464826, though less well understood, they might influence COX-2 expression levels or activity. Possible mechanisms due to this alteration can maybe cause overexpression of COX-2 that can lead to increased production of pro-inflammatory cytokines like IL-6 and TNF- α , which are known to promote tumorigenesis [317]. Additionally, COX-2-induced

prostaglandins can stimulate the production of vascular endothelial growth factor (VEGF), enhancing angiogenesis and supporting tumor growth and metastasis [318].

To our knowledge, no existing research specifically addresses the interaction analysis between environmental factors and genetic variants in the COX-2 gene in relation to prostate cancer risk. Most studies have primarily focused on the interactions between COX-2 variants and NSAID use, which are believed to decrease the risk of prostate cancer by inhibiting the COX-2 enzyme and subsequently reducing inflammation.

4.3. Strengths and Limitations

The genetic analyses included 1,515 subjects, representing 89% of the EPICAP study population, and these participants had sociodemographic characteristics similar to the overall sample. Our results were based on a targeted list of genes and a focused number of SNPs (20 SNPs), providing an in-depth examination of the genetic variability of the inflammatory gene COX-2. Various data quality control measures, including stringent criteria for SNP selection, duplicate sample checks, and consistency assessments, were employed to minimize genotyping classification errors and ensure the accuracy and reliability of the data used in our analyses. Additionally, the study provides a thorough analysis of both genetic and environmental factors and their potential interactions in relation to prostate cancer risk. Stratification by cancer grade allows for a more detailed understanding of how risk factors may differentially affect cancer severity. The use of multiple genetic types of genetic models ensures robustness in testing the associations between SNPs and prostate cancer risk. Finally, the application of FDR correction to control for potential false positive results enhanced the reliability of our findings.

Despite its strengths, the study has several limitations. One of the limitations is the relatively small number of SNPs (20) analyzed, which may not capture the full genetic landscape associated with prostate cancer risk. This limited SNP selection restricts the ability to identify other potentially relevant genetic variants, thus limiting the comprehensiveness of our genetic analysis. Additionally, the sample size may not be large enough to detect smaller effect sizes or provide sufficient statistical power when considering interaction analysis. The predominance of Caucasian subjects in our study sample limits the generalizability of the findings to broader populations with diverse ethnic backgrounds. Moreover, the environmental variables such as

infections, kidney stones, and gallbladder stones were self-reported, which could introduce recall bias.

In this final objective of my thesis, our analysis showed some preliminary results. The AA genotype of rs10911898 and rs12064238, the CC genotype of rs6685280, the AG genotype of rs2206593 and rs2745557, and the AC genotype of rs2745559 showed significance with prostate cancer, while only the A allele of rs4648261 was significantly associated with high-grade cancer. In our gene-environment interaction analysis, the genetic variations in COX-2 do not significantly interact with these environmental factors in influencing prostate cancer risk. These results suggest a potential role of specific genetic markers within the COX-2 in prostate cancer susceptibility. To build on these results future research is warranted to confirm these associations, explore other genetic variations, and consider additional environmental factors.

CHAPTER 6 – CONCLUSION & PERSPECTIVES

Conclusion

This thesis explored the relationship between chronic inflammation and the risk of prostate cancer, focusing on three different factors, using data from the EPICAP study, a population-based case-control study carried out in the Department of Hérault in France. The hypothesis, therefore, based on this study, took into account the role of inflammation-related factors, whether triggered by infections, calculi, or genetic predisposition, and the risk of prostate cancer in its different aggressive forms.

The first objective of this thesis studied the relationship between various types of infectious agents and prostate cancer. This study contributes to the extensive body of research on infections, especially sexually transmitted infections (STIs), and their potential link to prostate cancer. Previous studies have yielded contradictory results, with some suggesting an increased risk of prostate cancer associated with STIs such as gonorrhoea, trichomonas, and syphilis, while others found no significant associations. Our findings align with the latter, as no significant associations were observed between these STIs and prostate cancer across different grades.

However, this thesis also took into account non-sexually transmitted infections, an area that has been relatively understudied in the context of prostate cancer. By including these infections, we aimed to provide a more comprehensive understanding of the role of infectious agents, whether transmitted sexually or non-sexually, in prostate carcinogenesis. The consistency of our findings with the majority of the studies that reported no significant associations strengthens the argument that such infections might not play a major role in the development of prostate cancer.

The second objective focused on examining whether kidney and gallbladder stones are associated with an increased risk of prostate cancer. The analysis revealed that men with a history of kidney stones significantly increase the risk of having prostate cancer, particularly when combined with a history of pyelonephritis but not with prostatitis. Additionally, gallbladder stones were associated with an increased risk of prostate cancer, especially in individuals with hypertriglyceridemia, emphasizing the role of metabolic conditions and chronic inflammation in prostate cancer etiology. For gallbladder stones, the observed association appears to be more metabolic in nature, potentially tied to lipid metabolism rather than directly driven by inflammation. However, for kidney stones, a stronger association with prostate cancer was observed, particularly when accompanied by pyelonephritis. This

highlights the possibility that localized or chronic inflammation related to kidney stones could play a role in prostate carcinogenesis.

The third objective investigated the genetic susceptibility to prostate cancer, focusing on single nucleotide polymorphisms (SNPs) in the COX-2 gene. While using the co-dominant model, the AA genotype of rs10911898 and rs12064238, the CC genotype of rs6685280, the AG genotype of rs2206593, rs2745557, and rs4648261, and the AC genotype of rs2745559 showed significance with prostate cancer. When using the additive model, significant associations included SNPs rs10911898, rs12064238, rs2206593, and rs2745557. However, only the A allele of rs4648261 was significantly associated with high-grade cancer, and even after False Discovery Rate (FDR) correction, this association remained significant. In our gene-environment interaction analysis, considering infections, kidney stones, and gallbladder stones, and after FDR correction suggests that genetic variations in COX-2 do not significantly interact with these environmental factors in influencing prostate cancer risk. Given the COX-2 gene's established role in inflammatory pathways, this finding suggests that while general inflammation may not broadly drive prostate cancer risk, specific inflammatory genetic variants may influence the risk of more aggressive forms of the disease.

In summary, our findings do not fully support the hypothesis that chronic inflammation broadly drives prostate cancer risk. Instead, they suggest a more complex relationship where metabolic factors, specific inflammatory conditions, and genetic predispositions each contribute to prostate cancer risk in distinct ways. These insights underscore the need for further research to unravel these mechanisms and their interplay, particularly focusing on high-grade and aggressive forms of prostate cancer.

Future Perspectives

Within the EPICAP study, we can delve even deeper into the role of chronic inflammation in prostate cancer due to the availability of comprehensive data on various inflammation-related factors and explore chronic inflammation from different angles. This includes information on the dietary inflammatory index (DII), which measures the inflammatory potential of an individual's diet, and statin use, which involves medications known for their cholesterol-lowering and anti-inflammatory properties.

Beyond the EPICAP, our results obtained from this thesis should be confirmed in future studies that address the methodological weaknesses in our study and current literature. Given the

limitations of case-control studies, which are susceptible to recall bias and temporal ambiguity, future studies should involve large, multi-center longitudinal cohort studies that can establish a temporal relationship between infections and prostate cancer development and provide better evidence for causality. Furthermore, it would be interesting to integrate different and innovative screening techniques into studies to improve the accuracy of infection data collection and enhance the validity of the findings, such as serological assays and PCR testing. To go deeper into the analysis of inflammation, taking into account inflammatory biomarkers in cohort studies would provide valuable insights into the mechanisms linking infections to prostate cancer. Future studies could include regular measurements of different cytokines (e.g., IL-6, TNF- α) and C-reactive protein (CRP), among other markers, through blood sample collection at different intervals to analyze changes over time while correlating levels with infection history. Another important factor to consider is the duration of the infection and the type of treatment received. The length of time an infection persists, and the effectiveness of the treatment could influence the degree of chronic inflammation and subsequent cancer risk. Therefore, it would be interesting to provide insights into how long-term infections and inadequate treatments and whether they might contribute to chronic inflammation and its effect on cancer development.

The relationship between kidney and gallbladder stones and prostate cancer remains largely understudied. More focused research is needed to fill this gap and understand the potential mechanisms linking these conditions to prostate cancer. Therefore, to go beyond this thesis and to further elucidate the relationship between calculi and prostate cancer, it would be interesting to consider taking into account different types of kidney and gallbladder stones, such as calcium oxalate, uric acid, struvite, and cystine stones, which may have distinct biological impacts and inflammatory responses. Future studies should differentiate between stone types and investigate how each type contributes to chronic inflammation in order to understand their specific roles in prostate carcinogenesis. It would also be interesting to look into mechanistic studies to investigate the activation of inflammatory pathways by the presence of these conditions and their impact on prostate tissue. Understanding the biological and cellular processes would, in turn, provide insights into potential therapeutic targets. Future research should also examine the duration and recurrence of kidney and gallbladder stones. Chronic and recurrent stones may lead to prolonged inflammation, increasing the risk of

prostate cancer. Detailed data on the frequency, duration, and management of stone episodes could provide valuable insights.

The genetic findings from our third objective serve as a preliminary result of a SNP-by-SNP approach. Therefore, further research is needed to confirm and expand upon these associations. There are several avenues for advancing this research, both within the EPICAP study and beyond. It would be interesting to delve deeper into the EPICAP study and focus on advanced genetic analysis methods to provide comprehensive insights into the genetic associations with prostate cancer while particularly considering chronic inflammation. One such method is the Adaptive Rank Truncated Product (ARTP) method, which allows for a combined analysis of multiple SNPs. Additionally, investigating epigenetic modifications, such as DNA methylation and histone modifications, alongside genetic variations could allow for additional exploration into regulatory layers contributing to prostate cancer risk.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known for their anti-inflammatory properties, and significant research, including findings from the EPICAP study, have highlighted their potential role in reducing the risk of prostate cancer. This effect is mediated through the inhibition of cyclooxygenase (COX) enzymes involved in inflammation. It is worthwhile to delve deeper into the gene-environment (GxE) interaction between genetic data and NSAID use by studying the effects of specific SNPs on the efficacy and impact of NSAID use in prostate cancer prevention and treatment, with a specific focus on COX-2, as this enzyme plays a key role in the inflammatory process.

Furthermore, gene-based analysis evaluating the effect of multiple variants within a gene can provide further insights into the overall contribution of specific genes to prostate cancer risk. It would be interesting to consider other genes involved in inflammation to make the study more comprehensive. Additionally, calculating Polygenic Risk Scores (PRS) by summing the effects of multiple genetic variants across the genome can help identify high-risk individuals who might benefit from targeted screening and prevention strategies. Additionally, considering imputation methods to predict genotypes at untyped loci will expand genomic coverage and enable a more detailed analysis of genetic variation and its association with prostate cancer risk, potentially uncovering additional significant SNPs related to chronic inflammation within the COX-2 or other related inflammatory genes.

In addition to these approaches, pathway analysis can provide a clear understanding of how genetic variants interact within biological pathways to influence disease risk by examining the

combined effect of genes, rather than analyzing individual SNPs in isolation. This can help identify key pathways involved in inflammation and prostate cancer development, offering an overall view of the underlying biological mechanisms.

Beyond the EPICAP study, several possible research directions can be pursued to further investigate in genetics and prostate cancer. Looking into cross-cohort studies with other large datasets would help enhance the validity and generalizability of findings in different populations and contexts. Another interesting approach would be investigating the role of epigenetic modifications, such as DNA methylation and histone modification analysis, in prostate cancer to dive deeper into how gene expression is regulated and influenced by genetic variations. Finally, Artificial intelligence (AI) and machine learning are driving significant innovation in health research. To advance further, implementing AI and machine learning algorithms to analyze large-scale genetic and clinical data can help identify complex patterns and better predict prostate cancer risk, opening new avenues for research.

The findings of this thesis offer valuable insights for public health strategies despite not confirming an increase in prostate cancer risk from infections and only suggesting a possible role for kidney/gallbladder stones and genetic predispositions. Chronic inflammation remains a significant area of concern, underscoring the need for public health initiatives focused on monitoring and managing this condition.

Aggressive prostate cancer, often associated with poor prognosis and requires more intensive treatments. Until recently taking into account the aggressiveness of cancer in observational studies remains under-explored despite its importance. Identifying genetic and environmental factors particularly for the aggressive types and understanding the underlying mechanisms is crucial for better preventions strategies and more effective treatments.

Public health programs should prioritize regular screening for chronic inflammatory conditions, given their potential role in prostate carcinogenesis. Therefore, managing infections effectively and educating the public about the importance of promptly treating infections and monitoring inflammatory conditions to help reduce overall health risks is important. Public health programs should advocate for regular screening and monitoring of men, particularly those with a history of metabolic conditions or genetic susceptibilities, while also promoting healthy lifestyle choices, such as a balanced diet and regular exercise, to help reduce the incidence of inflammatory conditions.

Finally, it would be valuable if public health initiatives promote genetic screening and counseling research to enable personalized preventive measures and early interventions tailored for individuals with higher genetic risk.

In conclusion, further research into modifiable risk factors for prostate cancer is essential. Large-scale longitudinal studies would help establish causal relationships and better understand the temporal dynamics between these risk factors and prostate cancer development. Investigating mechanistic pathways will provide deeper insights into the biological processes involved in chronic inflammation and prostate carcinogenesis. Finally, addressing the global role of inflammation in the prognosis and progression of prostate cancer is crucial for enhancing patient outcomes, as it is essential to consider both etiological factors and the broader impact of chronic inflammation to allow for the development of targeted strategies to mitigate inflammation and improve prognostic outcomes.

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APPENDICES

Appendix 1 Characteristics of Controls based on their history of Sexually Transmitted Viral Infections

<i>Sexually Transmitted Viral Infections</i>	No n=575	Yes n=284	P-value* X ²
Age (Years)			<i>0.215</i>
< 55	43 (7.5)	15 (5.3)	
[55-60]	65 (11.3)	33 (11.6)	
[60-65]	132 (23.0)	66 (23.4)	
[65-70]	175 (30.4)	101 (35.6)	
≥70	160 (27.8)	69 (24.3)	
Ethnic Origin			<i>0.644</i>
Caucasian	561 (97.6)	278 (97.9)	
Other	14 (2.4)	6 (2.1)	
Family History of Prostate Cancer			<i>0.954</i>
No	526 (91.8)	254 (89.8)	
Yes	47 (8.2)	29 (10.3)	
Education			<i>0.299</i>
Primary	123 (21.4)	66 (23.2)	
Secondary	278 (48.4)	139 (48.9)	
University	173 (30.1)	79 (27.8)	
Body Mass Index (kg/m²)			<i>0.219</i>
<25 - Normal	159 (28.7)	83 (29.9)	
[25-30] - Overweight	259 (45.0)	139 (50.0)	
≥30 - Obese	146 (26.4)	56 (20.1)	
Waist Circumference (cm)			<i>0.069</i>
≤94	154 (27.6)	94 (33.7)	
>94	404 (72.4)	185 (66.3)	
Smoking Status			<i>0.021</i>
Never	153 (26.6)	89 (31.3)	
Former	301 (52.4)	163 (57.4)	
Current	121 (21.0)	32 (11.3)	
Alcohol Consumption			<i>0.953</i>
No	57 (9.9)	27 (9.5)	
Yes	518 (90.1)	257 (90.5)	
Physical Activity (MET -h/wk/yr)			<i>0.239</i>
No	113 (19.8)	61 (21.6)	
<6.5	122 (21.3)	46 (16.3)	
6.25-13.0	119 (20.8)	50 (17.7)	
13.0-24.15	109 (19.1)	64 (22.7)	
≥24.15	109 (19.1)	61 (21.6)	
Nonsteroidal anti-inflammatory drugs			<i>0.167</i>
No	402 (70.5)	177 (64.4)	
Yes	168 (29.5)	98 (35.6)	

*p-value of Chi-square

Appendix 2 Characteristics of Controls based on their history of Sexually Transmitted Bacterial & Viral Infections

<i>Sexually Transmitted Bacterial & Viral Infections</i>	No n=511	Yes n=340	P-value* χ^2
Age (Years)			<i>0.165</i>
< 55	38 (7.4)	19 (5.6)	
[55-60]	59 (11.6)	38 (11.2)	
[60-65]	119 (23.3)	77 (22.7)	
[65-70]	149 (29.2)	125 (36.8)	
≥ 70	146 (28.6)	81 (23.8)	
Ethnic Origin			<i>0.846</i>
Caucasian	500 (97.9)	332 (97.7)	
Other	11 (2.2)	8 (2.4)	
Family History of Prostate Cancer			<i>0.168</i>
No	469 (92.1)	303 (89.4)	
Yes	40 (7.9)	36 (10.6)	
Education			<i>0.914</i>
Primary	113 (22.2)	76 (22.4)	
Secondary	250 (49.0)	162 (47.7)	
University	147 (28.8)	102 (30.0)	
Body Mass Index (kg/m²)			<i>0.095</i>
<25 - Normal	146 (29.4)	95 (28.9)	
[25-30] - Overweight	217 (43.7)	165 (50.1)	
≥ 30 - Obese	134 (29.9)	69 (21.0)	
Waist Circumference (cm)			<i>0.087</i>
≤ 94	137 (27.4)	109 (32.9)	
>94	363 (72.6)	222 (67.1)	
Smoking Status			<i>0.000</i>
Never	139 (27.2)	101 (29.7)	
Former	261 (51.1)	199 (58.3)	
Current	111 (21.7)	40 (11.8)	
Alcohol Consumption			<i>0.326</i>
No	54 (10.6)	29 (8.5)	
Yes	457 (89.4)	311 (91.5)	
Physical Activity (MET -h/wk/yr)			<i>0.386</i>
No	102 (20.0)	69 (20.5)	
<6.5	108 (21.2)	58 (17.3)	
6.25-13.0	107 (21.0)	62 (18.5)	
13.0-24.15	96 (18.8)	76 (22.6)	
≥ 24.15	97 (19.0)	71 (21.1)	
Nonsteroidal anti-inflammatory drugs			<i>0.128</i>
No	357 (70.6)	217 (65.6)	
Yes	149 (29.5)	114 (34.4)	

*p-value of Chi-square

Appendix 3 Characteristics of Controls based on their history of Sexually Transmitted Bacterial & Viral Infections (2 levels)

<i>Sexually Transmitted Bacterial & Viral Infections</i>	Non n=511	Yes (1) n=287	Yes (≥2) n=53	P-value* χ^2
Age (Years)				<i>0.342</i>
0328 < 55	38 (7.4)	17 (5.9)	2 (3.8)	
[55-60]	59 (11.6)	33 (11.5)	5 (9.4)	
[60-65]	119 (23.4)	65 (22.7)	12 (22.6)	
[65-70]	149 (29.2)	108 (37.6)	17 (32.1)	
≥70	146 (28.6)	64 (22.3)	17 (32.1)	
Ethnic Origin				<i>0.951</i>
Caucasian	500 (97.9)	280 (97.6)	52 (98.1)	
Other	11 (2.2)	7 (2.4)	1 (1.9)	
Family History of Prostate Cancer				<i>0.285</i>
No	469 (92.1)	258 (89.9)	45 (86.5)	
Yes	40 (7.9)	29 (10.1)	7 (13.5)	
Education				<i>0.546</i>
Primary	113 (22.2)	65 (22.7)	11 (20.8)	
Secondary	250 (49.0)	141 (49.1)	21 (36.6)	
University	147 (28.8)	81 (28.2)	21 (39.6)	
Body Mass Index (kg/m²)				<i>0.026</i>
<25 - Normal	146 (29.4)	86 (30.9)	9 (17.7)	
[25-30] - Overweight	217 (43.7)	140 (50.4)	25 (49.0)	
≥30 - Obese	134 (26.1)	52 (18.7)	17 (33.3)	
Waist Circumference (cm)				<i>0.194</i>
≤94	137 (27.4)	94 (33.6)	15 (29.4)	
>94	363 (72.6)	186 (66.4)	36 (70.6)	
Smoking Status				<i>0.004</i>
Never	139 (27.2)	89 (31.0)	12 (22.6)	
Former	261 (51.1)	166 (57.8)	33 (62.3)	
Current	111 (21.7)	32 (11.5)	8 (15.1)	
Alcohol Consumption				<i>0.600</i>
No	54 (10.6)	24 (8.4)	5 (9.4)	
Yes	457 (89.4)	263 (91.6)	48 (90.6)	
Physical Activity (MET -h/wk/yr)				<i>0.074</i>
No	102 (20.0)	53 (18.7)	16 (30.8)	
<6.5	108 (21.2)	46 (16.2)	12 (23.1)	
6.25-13.0	107 (21.0)	51 (17.9)	11 (21.2)	
13.0-24.15	96 (18.8)	68 (23.9)	8 (15.4)	
≥24.15	97 (19.0)	66 (23.2)	5 (9.6)	
Nonsteroidal anti-inflammatory drugs				<i>0.090</i>
No	357 (70.6)	189 (67.3)	28 (56.0)	
Yes	149 (29.5)	92 (32.7)	22 (44.0)	

*p-value of Chi-square

Appendix 4 Characteristics of Controls based on their history of All Types of Infections (2 levels)

<i>Overall Infections</i>	Non n=383	Yes (1) n=317	Yes (≥2) n=140	P-value* χ²
Age (Years)				<i>0.296</i>
0328 < 55	26 (6.8)	19 (6.0)	9 (6.4)	
[55-60]	53 (13.8)	29 (9.1)	14 (10.0)	
[60-65]	90 (23.5)	76 (24.0)	28 (20.0)	
[65-70]	108 (28.2)	114 (36.0)	53 (37.9)	
≥70	106 (27.7)	79 (24.9)	36 (25.7)	
Ethnic Origin				<i>0.924</i>
Caucasian	375 (97.9)	309 (97.5)	137 (97.9)	
Other	8 (2.1)	8 (2.5)	3 (2.1)	
Family History of Prostate Cancer				<i>0.600</i>
No	351 (92.1)	286 (90.2)	125 (89.9)	
Yes	30 (7.9)	31 (9.8)	14 (10.1)	
Education				<i>0.152</i>
Primary	85 (22.3)	70 (22.1)	31 (22.1)	
Secondary	201 (52.6)	144 (45.4)	62 (44.3)	
University	96 (25.1)	103 (32.5)	47 (33.6)	
Body Mass Index (kg/m²)				<i>0.410</i>
<25 - Normal	109 (29.1)	87 (28.6)	39 (28.7)	
[25-30] - Overweight	162 (43.2)	149 (49.0)	67 (49.3)	
≥30 - Obese	104 (27.7)	68 (22.4)	30 (22.1)	
Waist Circumference (cm)				<i>0.371</i>
≤94	101 (26.9)	92 (30.1)	45 (32.9)	
>94 - ≤102	275 (73.1)	214 (69.9)	92 (67.2)	
Smoking Status				<i>0.047</i>
Never	102 (26.6)	87 (27.4)	45 (32.1)	
Former	197 (51.4)	183 (57.7)	77 (55.0)	
Current	84 (21.9)	47 (14.8)	18 (12.9)	
Alcohol Consumption				<i>0.536</i>
No	41 (10.7)	28 (8.8)	11 (7.9)	
Yes	342 (89.3)	289 (91.2)	129 (92.1)	
Physical Activity (MET -h/wk/yr)				<i>0.998</i>
No	77 (20.2)	59 (18.8)	31 (22.3)	
<6.5	75 (19.9)	64 (20.4)	27 (19.4)	
6.25-13.0	78 (20.4)	61 (19.4)	27 (19.4)	
13.0-24.15	77 (20.2)	67 (21.3)	27 (19.4)	
≥24.15	75 (19.6)	63 (20.1)	27 (19.4)	
Nonsteroidal anti-inflammatory drugs				<i>0.048</i>
No	275 (72.4)	211 (67.6)	82 (61.2)	
Yes	105 (27.6)	101 (32.4)	52 (38.8)	

*p-value of Chi-square

Appendix 5 Sensitivity Analysis: Association Between Bacterial Infections and Prostate Cancer while restricting the control group to those screened in the last 2 years

	Controls		Cases				
	n=603 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections</i>[†]							
No	540 (90.3)	750 (92.4)	1.00 Reference	568 (92.1)	1.00 Reference	170 (93.4)	1.00 Reference
Yes	57 (9.6)	62 (7.6)	0.79 (0.53-1.18)	49 (7.9)	0.80 (0.52-1.22)	12 (6.6)	0.78 (0.40-1.51)
Gonorrhea							
No	548 (91.8)	759 (93.2)	1.00 Reference	574 (92.7)	1.00 Reference	173 (95.1)	1.00 Reference
Yes	49 (8.2)	55 (6.8)	0.82 (0.54-1.26)	45 (7.3)	0.86 (0.55-1.35)	9 (4.9)	0.68 (0.32-1.43)
Trichomonas							
No	587 (98.8)	803 (99.1)	1.00 Reference	613 (99.5)	1.00 Reference	177 (97.8)	1.00 Reference
Yes	7 (1.2)	7 (0.9)	0.74 (0.24-2.25)	3 (0.5)	0.31 (0.06-1.52)	4 (2.2)	2.49 (0.70-8.87)
Syphilis							
No	595 (98.8)	816 (99.6)	1.00 Reference	621 (99.7)	1.00 Reference	182 (99.5)	1.00 Reference
Yes	7 (1.2)	3 (0.4)	0.34 (0.09-1.33)	2 (0.3)	0.33 (0.07-1.59)	1 (0.5)	0.43 (0.05-3.60)
Urethritis							
No	572 (97.0)	786 (96.8)	1.00 Reference	601 (96.9)	1.00 Reference	173 (96.7)	1.00 Reference
Yes	18 (3.0)	26 (3.2)	1.03 (0.54-1.95)	19 (3.1)	0.86 (0.43-1.74)	6 (3.4)	1.25 (0.48-3.30)
Tuberculosis							
No	574 (95.4)	774 (94.6)	1.00 Reference	589 (94.5)	1.00 Reference	172 (94.5)	1.00 Reference
Yes	28 (4.7)	44 (5.4)	1.16 (0.70-1.92)	34 (5.5)	1.18 (0.69-2.01)	10 (5.5)	1.19 (0.55-2.55)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

[†]Sexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

Appendix 6 Sensitivity Analysis: Association Between Viral Infections and Prostate Cancer while restricting the control group to those screened in the last 2 years

	Controls		Cases				
	n=603 (%)	n=819 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=623 (%)	OR* (95% CI)	n=183 (%)	OR* (95% CI)
Viral Infections[†]							
No	297 (51.1)	408 (50.9)	1.00 Reference	305 (50.1)	1.00 Reference	95 (53.1)	1.00 Reference
Yes	284 (48.9)	393 (49.1)	1.03 (0.82-1.28)	304 (49.9)	1.08 (0.85-1.37)	84 (46.9)	0.94 (0.66-1.32)
Zoster Herpes							
No	520 (87.1)	713 (87.5)	1.00 Reference	542 (87.0)	1.00 Reference	158 (87.6)	1.00 Reference
Yes	77 (12.9)	102 (12.5)	1.04 (0.75-1.45)	80 (13.0)	1.11 (0.78-1.58)	22 (12.2)	0.95 (0.57-1.59)
Polio							
No	599 (99.5)	816 (99.8)	1.00 Reference	622 (99.8)	1.00 Reference	181 (99.5)	1.00 Reference
Yes	3 (0.5)	2 (0.2)	1.09 (0.15-7.99)	1 (0.2)	0.91 (0.08-10.27)	1 (0.6)	1.81 (0.15-21.93)
Dengue							
No	588 (98.2)	803 (98.4)	1.00 Reference	610 (98.2)	1.00 Reference	181 (98.9)	1.00 Reference
Yes	11 (1.8)	13 (1.6)	0.91 (0.39-2.16)	11 (1.8)	1.01 (0.41-2.49)	2 (1.1)	0.59 (0.12-2.88)
Viral Hepatitis							
No	531 (90.3)	725 (89.2)	1.00 Reference	554 (89.6)	1.00 Reference	159 (87.4)	1.00 Reference
Yes	57 (9.7)	88 (10.8)	1.08 (0.75-1.56)	64 (10.4)	1.03 (0.70-1.53)	23 (12.6)	0.64 (0.21-1.96)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

[†]Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

Appendix 7 Sensitivity Analysis: Association between Sexually Transmitted Viral Infections and Prostate Cancer while restricting the control group to those screened in the last 2 years

	Controls		Cases				
	n=603 (%)	n=819 (%)	All OR* (95% CI)	Low grade cancer** n=623 (%)	OR* (95% CI)	High-grade cancer*** n=183 (%)	OR* (95% CI)
<i>Sexually Transmitted Viral Infections</i> [†]							
No	388 (65.8)	524 (64.9)	1.00 Reference	392 (63.7)	1.00 Reference	123 (68.3)	1.00 Reference
Yes	202 (34.2)	284 (35.2)	1.02 (0.81-1.29)	223 (36.3)	1.07 (0.84-1.37)	57 (31.7)	0.89 (0.61-1.29)
Genital Herpes							
No	581 (96.8)	793 (97.3)	1.00 Reference	602 (97.0)	1.00 Reference	178 (97.8)	1.00 Reference
Yes	19 (3.2)	22 (2.7)	0.71 (0.36-1.37)	18 (3.0)	0.74 (0.37-1.49)	4 (2.2)	0.64 (0.21-1.96)
Epstein-Barr							
No	579 (97.6)	786 (97.9)	1.00 Reference	599 (97.9)	1.00 Reference	174 (97.8)	1.00 Reference
Yes	14 (2.4)	17 (2.1)	0.76 (0.36-1.59)	13 (2.1)	0.73 (0.33-1.62)	4 (2.3)	0.92 (0.29-2.96)
Herpes labialis							
No	420 (70.2)	555 (68.1)	1.00 Reference	416 (67.2)	1.00 Reference	130 (71.0)	1.00 Reference
Yes	178 (29.8)	260 (31.9)	1.12 (0.88-1.43)	203 (32.8)	1.17 (0.91-1.51)	53 (29.0)	0.96 (0.66-1.41)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

[†]Sexually Transmitted Viral Infections: Herpes labial & genital, mononucleosis, Epstein-Barr

	Controls		Cases				
	n=586 (%)	All n=591 (%)	OR* (95% CI)	Low grade cancer** n=446 (%)	OR* (95% CI)	High-grade cancer*** n=140 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections^a</i>							
No	538 (91.8)	555 (93.9)	1.00 Reference	411 (93.0)	1.00 Reference	135 (97.1)	1.00 Reference
Yes	48 (8.2)	36 (6.1)	0.73 (0.46-1.16)	31 (7.0)	0.83 (0.51-1.36)	4 (2.9)	0.35 (0.12-1.01)
<i>Viral Infections^b</i>							
No	316 (55.6)	301 (51.8)	1.00 Reference	218 (50.2)	1.00 Reference	77 (56.2)	1.00 Reference
Yes	252 (44.4)	280 (48.2)	1.17 (0.92-1.49)	216 (49.8)	1.28 (0.99-1.67)	60 (43.8)	0.94 (0.64-1.40)
<i>Sexually Transmitted Bacterial & Viral Infections^c</i>							
No	357 (62.2)	352 (60.4)	1.00 Reference	255 (58.4)	1.00 Reference	92 (67.7)	1.00 Reference
Yes	217 (37.8)	231 (39.6)	1.09 (0.86-1.40)	182 (41.7)	1.19 (0.92-1.55)	44 (32.4)	0.81 (0.53-1.23)
1	189 (32.9)	203 (34.8)	1.11 (0.86-1.43)	159 (36.4)	1.20 (0.91-1.58)	39 (28.7)	0.84 (0.54-1.29)
≥ 2	28 (4.9)	28 (4.8)	1.00 (0.86-1.43)	23 (5.3)	1.12 (0.62-2.04)	5 (3.7)	0.66 (0.24-1.81)
<i>Overall Infections^d</i>							
No	275 (48.2)	259 (44.7)	1.00 Reference	188 (43.3)	1.00 Reference	67 (49.3)	1.00 Reference
Yes	293 (51.6)	321 (55.3)	1.18 (0.92-1.50)	246 (56.7)	1.26 (0.97-1.63)	69 (50.7)	0.97 (0.66-1.44)
1	211 (37.2)	228 (39.3)	1.17 (0.90-1.52)	171 (39.4)	1.22 (0.92-1.62)	51 (37.5)	1.00 (0.65-1.52)
≥ 2	82 (14.4)	93 (16.0)	1.20 (0.84-1.71)	75 (12.3)	1.35 (0.92-1.97)	18 (13.2)	0.90 (0.50-1.65)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Sexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

^b Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

^c Sexually Transmitted Bacterial & Viral Infections: Herpes labial & genital, Mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Urethritis

^d Overall Infections: Herpes labial & genital, mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Polio, Viral Hepatitis, Dengue, Zona, Urethritis, tuberculosis

Appendix 9 Sensitivity Analysis including cases only from Private hospitals

	Controls		Cases				
	n=871 (%)	n=659 (%)	All	Low grade cancer**		High-grade cancer***	
			OR* (95% CI)	n=529 (%)	OR* (95% CI)	n=121 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections^a</i>							
No	792 (90.9)	603 (9.1)	1.00 Reference	484 (92.4)	1.00 Reference	112 (92.6)	1.00 Reference
Yes	79 (9.1)	50 (7.7)	0.87 (0.59-1.28)	40 (7.6)	0.84 (0.55-1.27)	9 (7.4)	0.94 (0.45-1.97)
<i>Viral Infections^b</i>							
No	443 (52.7)	329 (51.2)	1.00 Reference	257 (49.8)	1.00 Reference	67 (56.8)	1.00 Reference
Yes	398 (47.3)	314 (48.8)	1.09 (0.88-1.35)	259 (50.2)	1.18 (0.93-1.48)	51 (43.2)	0.84 (0.56-1.26)
<i>Sexually Transmitted Bacterial & Viral Infections^c</i>							
No	511 (60.0)	390 (60.5)	1.00 Reference	306 (59.0)	1.00 Reference	79 (67.5)	1.00 Reference
Yes	340 (40.0)	255 (39.5)	0.99 (0.80-1.24)	213 (41.0)	1.06 (0.84-1.33)	38 (32.5)	0.73 (0.48-1.12)
1	287 (33.7)	211 (32.7)	0.97 (0.77-1.23)	178 (34.3)	1.06 (0.83-1.35)	29 (24.8)	0.64 (0.40-1.02)
≥ 2	52 (6.2)	44 (6.8)	1.11 (0.71-1.74)	35 (6.7)	1.06 (0.65-1.71)	9 (7.7)	1.29 (0.59-2.78)
<i>Overall Infections^d</i>							
No	383 (45.6)	284 (44.3)	1.00 Reference	223 (43.3)	1.00 Reference	57 (48.7)	1.00 Reference
Yes	457 (54.4)	357 (55.7)	1.08 (0.88-1.35)	292 (56.7)	1.14 (0.91-1.44)	60 (51.3)	0.90 (0.60-1.34)
1	317 (37.7)	243 (37.9)	1.06 (0.84-1.34)	198 (38.5)	1.12 (0.87-1.44)	40 (34.2)	0.84 (0.54-1.31)
≥ 2	140 (16.7)	114 (17.8)	1.15 (0.84-1.56)	94 (18.3)	1.20 (0.87-1.66)	20 (17.1)	1.03 (0.59-1.80)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Sexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

^b Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

^c Sexually Transmitted Bacterial & Viral Infections: Herpes labial & genital, Mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Urethritis

^d Overall Infections: Herpes labial & genital, mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Polio, Viral Hepatitis, Dengue, Zona, Urethritis, tuberculosis

Appendix 10 Sensitivity Analysis including cases only from public hospitals

	Controls		Cases				
	n=879 (%)	All n=160 (%)	OR* (95% CI)	Low grade cancer** n=94 (%)	OR* (95% CI)	High-grade cancer*** n=62 (%)	OR* (95% CI)
<i>Sexually Transmitted Bacterial Infections^a</i>							
No	792 (90.9)	146 (92.4)	1.00 Reference	84 (90.3)	1.00 Reference	58 (95.1)	1.00 Reference
Yes	79 (9.1)	12 (7.6)	0.77 (0.39-1.49)	9 (9.7)	0.89 (0.41-1.94)	3 (4.9)	0.59 (0.18-1.96)
<i>Viral Infections^b</i>							
No	443 (52.7)	79 (50.0)	1.00 Reference	48 (51.6)	1.00 Reference	28 (45.9)	1.00 Reference
Yes	398 (47.3)	79 (50.0)	1.17 (0.82-1.65)	45 (48.4)	1.07 (0.69-1.66)	33 (54.1)	1.44 (0.84-2.47)
<i>Sexually Transmitted Bacterial & Viral Infections^c</i>							
No	511 (60.0)	86 (54.4)	1.00 Reference	52 (55.9)	1.00 Reference	32 (52.5)	1.00 Reference
Yes	340 (40.0)	72 (45.6)	1.32 (0.93-1.88)	41 (44.1)	1.16 (0.75-1.81)	29 (47.5)	1.62 (0.94-2.79)
1	287 (33.7)	66 (41.8)	1.44 (1.00-2.07)	38 (40.9)	1.29 (0.82-2.03)	26 (42.6)	1.71 (0.98-2.98)
≥ 2	53 (6.2)	6 (3.8)	0.69 (0.29-1.69)	3 (3.2)	0.52 (0.16-1.76)	3 (4.9)	1.13 (0.33-3.91)
<i>Overall Infections^d</i>							
No	383 (45.6)	67 (42.4)	1.00 Reference	41 (44.1)	1.00 Reference	24 (38.3)	1.00 Reference
Yes	457 (54.4)	91 (57.6)	1.19 (0.84-1.69)	52 (55.9)	1.04 (0.67-1.62)	37 (60.7)	1.50 (0.86-2.62)
1	317 (37.7)	62 (38.2)	1.14 (0.78-1.68)	34 (36.6)	0.96 (0.59-1.56)	26 (42.6)	1.49 (0.82-2.71)
≥ 2	140 (16.7)	29 (18.4)	1.30 (0.80-2.11)	18 (19.4)	1.23 (0.68-2.23)	11 (18.0)	1.54 (0.72-3.29)

*ORs adjusted for age, family history of prostate cancer, ethnicity, Physical Activity, NSAIDs, Waist circumference, Education

** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

^a Sexually Transmitted Bacterial Infections: Trichomonas, Syphilis, Gonorrhea

^b Viral Infections: Herpes Zoster, Dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, Polio, Viral hepatitis

^c Sexually Transmitted Bacterial & Viral Infections: Herpes labial & genital, Mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Urethritis

^d Overall Infections: Herpes labial & genital, mononucleosis, Epstein-Barr, Trichomonas, Syphilis, Gonorrhea, Polio, Viral Hepatitis, Dengue, Zona, Urethritis, tuberculosis

	Controls		Cases				
	n=783 (%)	All		Low grade cancer**		High-grade cancer***	
		n=732 (%)	OR* (95% CI)	n=566 (%)	OR* (95% CI)	n=155 (%)	OR* (95% CI)
rs6658482							
AA	546 (69.7)	515 (70.4)	1.00 reference	405 (71.5)	1.00 reference	101 (65.2)	1.00 reference
GA	217 (27.7)	199 (27.2)	0.98 (0.78-1.23)	150 (26.5)	0.92 (0.72-1.18)	47 (30.3)	1.22 (0.82-1.79)
GG	20 (2.6)	18 (2.4)	0.94 (0.49-1.81)	11 (1.9)	0.71 (0.32-1.48)	7 (4.5)	2.00 (0.75-4.77)
rs2383513							
AA	591 (75.5)	556 (76.0)	1.00 reference	431 (76.1)	1.00 reference	116 (74.8)	1.00 reference
GA	180 (23.0)	163 (22.3)	0.96 (0.75-1.21)	128 (22.7)	0.97 (0.75-1.26)	34 (21.9)	0.98 (0.63-1.50)
GG	12 (1.5)	13 (1.8)	1.18 (0.53-2.65)	7 (1.2)	0.82 (0.30-2.07)	5 (3.2)	2.07 (0.63-5.93)
rs10911902							
GG	571 (72.9)	536 (73.2)	1.00 reference	418 (73.8)	1.00 reference	107 (69.0)	1.00 reference
AG	194 (24.8)	181 (24.7)	1.00 (0.79-1.27)	140 (24.8)	0.98 (0.76-1.26)	41 (26.5)	1.15 (0.76-1.72)
AA	18 (2.3)	15 (2.0)	0.89 (0.44-1.78)	8 (1.4)	0.60 (0.24-1.3)	7 (4.5)	2.20 (0.82-5.33)
rs689470							
GG	735 (94.2)	684 (93.5)	1.00 reference	533 (94.2)	1.00 reference	141 (91.0)	1.00 reference
AG	44 (5.6)	46 (6.3)	1.11 (0.72-1.71)	31 (5.5)	0.96 (0.59-1.54)	14 (9.0)	1.66 (0.82-3.15)
AA	2 (0.3)	1 (0.2)	0.47 (0.02-4.97)	1 (0.2)	0.66 (0.03-7.18)	0	-
rs4648292							
CC	718 (92.7)	682 (94.4)	1.00 reference	530 (94.8)	1.00 reference	141 (91.3)	1.00 reference
GC	0 (0.0)	1 (0.1)	-	-	-	-	-
GG	56 (7.3)	41 (5.6)	0.85 (0.54-1.31)	29 (5.2)	0.81 (0.49-1.31)	12 (7.7)	1.04 (0.49-2.06)
rs5275							
AA	327 (41.8)	288 (39.3)	1.00 reference	228 (40.4)	1.00 reference	56 (36.1)	1.00 reference
GA	306 (39.1)	312 (42.6)	1.18 (0.94-1.48)	240 (42.5)	1.14 (0.90-1.46)	65 (41.9)	1.25 (0.84-1.87)
GG	83 (10.6)	85 (11.6)	1.20 (0.85-1.69)	64 (11.3)	1.13 (0.77-1.63)	21 (13.5)	1.47 (0.81-2.58)
rs4648268							
GG	644 (82.2)	605 (82.2)	1.00 reference	466 (82.3)	1.00 reference	130 (83.9)	1.00 reference
AG	135 (17.2)	118 (16.1)	0.93 (0.70-1.22)	94 (17.6)	0.95 (0.71-1.27)	22 (14.2)	0.85 (0.51-1.37)
AA	4 (0.5)	9 (1.2)	2.58 (0.83-9.62)	6 (1.1)	2.31 (0.65-9.15)	3 (1.9)	4.51 (0.82-2.23)

*OR: adjusted to Age, PC1 → PC7, Waist Circumference, Education, Physical Activity, ** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

Appendix 12 Non-Significant Results for genotypes from each SNP of the COX-2 gene using the Co-dominant Model

	Controls		Cases				
	n=783 (%)	n=732 (%)	All	Low grade cancer**	High-grade cancer***		
			OR* (95% CI)	n=566 (%)	OR* (95% CI)	n=155 (%)	OR* (95% CI)
rs5277							
CC	519 (66.4)	502 (68.8)	1.00 reference	382 (67.4)	1.00 reference	111 (71.6)	1.00 reference
GC	241 (30.8)	206 (28.1)	0.86 (0.69-1.08)	167 (29.6)	0.91 (0.72-1.16)	37 (23.9)	0.73 (0.48-1.10)
GG	22 (2.8)	23 (3.1)	1.05 (0.57-1.94)	17 (3.0)	0.99 (0.51-1.91)	6 (3.9)	1.27 (0.45-3.14)
rs20424							
GG	757 (96.7)	713 (97.4)	1.00 reference	549 (97.0)	1.00 reference	153 (98.7)	1.00 reference
CG	26 (3.3)	19 (2.6)	0.78 (0.42-1.42)	17 (3.0)	0.88 (0.46-1.64)	2 (1.3)	0.41 (0.07-1.43)
rs689466							
AA	525 (67.0)	517 (70.6)	1.00 reference	400 (70.8)	1.00 reference	108 (69.7)	1.00 reference
GA	225 (28.7)	196 (26.8)	0.87 (0.69-1.09)	151 (26.5)	0.86 (0.67-1.10)	43 (27.7)	0.97 (0.65-1.43)
GG	33 (4.2)	19 (2.6)	0.60 (0.33-1.07)	15 (2.7)	0.62 (0.32-1.14)	4 (2.6)	0.68 (0.65-1.43)
rs964570							
GG	694 (88.6)	643 (87.8)	1.00 reference	493 (87.1)	1.00 reference	139 (89.7)	1.00 reference
AG	85 (10.9)	85 (11.6)	1.05 (0.76-1.45)	70 (12.4)	1.12 (0.80-1.58)	15 (9.7)	0.80 (0.42-1.42)
AA	4 (0.5)	4 (0.5)	1.13 (0.26-4.82)	3 (0.5)	1.08 (0.21-4.97)	1 (0.6)	1.45 (0.07-10.58)
chr1_186685095_C_T							
TT	690 (88.1)	656 (89.6)	1.00 reference	510 (90.3)	1.00 reference	135 (87.1)	1.00 reference
CT	26 (3.3)	21 (2.9)	0.82 (0.45-1.47)	16 (2.8)	0.81 (0.42-1.52)	5 (3.2)	0.87 (0.28-2.20)
NA	67 (8.6)	55 (7.5)		40 (6.9)		15 (9.7)	
rs4650701							
AA	695 (88.8)	638 (87.2)	1.00 reference	490 (86.5)	1.00 reference	137 (88.4)	1.00 reference
GA	84 (10.7)	90 (12.3)	1.14 (0.83-1.57)	73 (12.9)	1.19 (0.85-1.68)	17 (11.0)	0.95 (0.52-1.65)
GG	4 (0.5)	4 (0.5)	1.1 (0.27-4.87)	3 (0.5)	1.09 (0.21-5.01)	1 (0.6)	1.48 (0.07-10.79)

*OR: adjusted on Age, PC1→PC7, NSAIDs, Waist Circumference, Education, Physical Activity, ** Gleason ≤ 7 (3+4) *** Gleason ≥ 7 (4+3)

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 première 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 dernière 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 première 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 dernière 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=2 ou NSP)

I13. Avez-vous déjà fait une urétrite ?

ENQ : Citer

Oui une1

Oui plusieurs2

Non3

NSP4

Si I13=1 ou 2

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 première urétrite)?

Infection sexuellement transmissible1

Urétrite à gonocoque2

Urétrite à chlamydiae trachomatis3

Urétrite à ureaplasma urealyticum4

Autres5

NSP6

Si I14=1 ou 2

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 dernière 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	

BLOJ - INFECTIONS VIRALES

Consignes montage

D'abord

1^{er} temps : Citer toutes les maladies en Oui/Non

2^{ème} temps : Afficher les maladies en Oui + précisions

Ensuite :

3^{ème} temps : Vous m'avez dit vous aviez eu (afficher) , A quel âge ou en quelle année ?

4^{ème} temps : si plusieurs épisodes alors âge au 1^{er} puis âge au dernier

A tous

J1. Un médecin vous a-t-il déjà diagnostiqué l'une des maladies suivantes (Attention nous parlons bien de la maladie et non du vaccin) ?

ENQ : CITEZ en oui/non

A monter en simple (Oui/Non/NSP)

Attention : Mettre l'article devant chaque maladie

1. La rougeole
2. La rubéole
3. Les oreillons

Si oui, poser J2 dans la foulée

J2. Suite à vos oreillons, avez-vous eu une atteinte testiculaire ?

- Oui1
- Non2
- NSP

4. La scarlatine
5. La coqueluche
6. La varicelle
7. Un zona

Si oui, poser J3 dans la foulée

J3. Combien d'épisodes de zona avez-vous connu ?

- Un1
- 2-32
- 4-53
- 5 et plus4
- NSP

8. La polio
9. La tuberculose
10. Le paludisme
11. La dengue
12. Un herpès labial

Si oui, poser J4 dans la foulée

J4. Combien d'épisodes d'herpès labial avez-vous connu ?

- 11
- 2 à 42
- 5-93
- 10-144
- 15 ou plus5
- NSP

13. un herpès génital ou rectal

Si oui, poser J5 dans la foulée

J5. Combien d'épisodes d'herpès génital ou rectal avez-vous connu ?

- 11
- 2 à 42
- 5-93

10-144

15 ou plus5

NSP

14. Une mononucléose infectieuse
15. une infection par le virus d'Epstein Barr
16. Une hépatite virale
17. une cirrhose ou autre problème au niveau du foie
18. une pancréatite ?

Jrecap. Variable de vérification

A toutes les J1SQ1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 14, 15, 16, 17, 18 citées, J3=1, J4=1, J5=1

J6.Vous m'avez dit vous aviez eu (afficher) . , A quel âge ou en quelle année ?

ENQ : si plusieurs fois, la dernière en date

ENQ : Si à la naissance ou moins de 7 jours, noter un

1. La rougeole/*afficher si Oui en J1*/
2. La rubéole /*afficher si Oui en J1*/
3. Les oreillons /*afficher si Oui en J1*/
4. La scarlatine /*afficher si Oui en J1*/
5. La coqueluche /*afficher si Oui en J1*/
6. La varicelle /*afficher si Oui en J1*/
7. Un zona /*afficher si Oui en J1*/
8. La polio /*afficher si Oui en J1*/
9. La tuberculose /*afficher si Oui en J1*/
10. Le paludisme /*afficher si Oui en J1*/
11. La dengue /*afficher si Oui en J1*/
12. Un herpès labial /*afficher si Oui en J1*/
13. un herpès génital ou rectal /*afficher si Oui en J1*/
14. Une mononucléose infectieuse /*afficher si Oui en J1*/
15. une infection par le virus d'Epstein Barr /*afficher si Oui en J1*/
16. Une hépatite virale /*afficher si Oui en J1*/
17. une cirrhose ou autre problème au niveau du foie /*afficher si Oui en J1*/
18. une pancréatite ? /*afficher si Oui en J1*/

1. Saisie âge : J6b.1 : Age:__\ \ AN Refus : 97 et NSP : 99

J6b.2 : Mois __\ \ mois Refus : 97 et NSP : 99

J6b.3 : semaine __\ \ mois Refus : 97 et NSP : 99

2. Saisie année : J6b.4: Année ____\ \ Refus : 9997 et NSp : 9999

3. Nsp

4. Refus

Si J6 = NSP ou J6b.1=NSP ou J6b.2=NSP ou J6b.3=NSP ou J6b.4=NSP

J6C. Vous diriez que vous aviez ... ?

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 |
| NSP | |
| Refus | |

J6brecap et Jrecap.2 . Variables de vérification

Si J3>1, J4>1, J5>1

J7. Vous m'avez dit que vous aviez eu plusieurs épisodes de (afficher)?

A quel âge ou en quelle année avez-vous connu le premier ?

1. Saisie âge : J7b.1 : Age:__\ AN Refus : 97 et NSP : 99

J7b.2 : Mois __\ mois Refus : 97 et NSP : 99

J7b.3 : semaine __\ mois Refus : 97 et NSP : 99

2. Saisie année : J7b.4: Année ____\ Refus : 9997 et NSp : 9999

3. Nsp

4. Refus

Si J7 = NSP

J7C. Vous diriez que vous aviez ... ?

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

NSP7

Refus8

J7brecap. Variable de vérification

Si J3>1, J4>1, J5>1

J8. Vous m'avez dit que vous aviez eu plusieurs épisodes de (afficher)?

A quel âge ou en quelle année avez-vous connu le dernier épisode ?

1. Saisie âge : J8b.1 : Age:__\ AN Refus : 97 et NSP : 99

J8b.2 : Mois __\ mois Refus : 97 et NSP : 99

J8b.3 : semaine __\ mois Refus : 97 et NSP : 99

2. Saisie année : J8b.4: Année ____\ Refus : 9997 et NSp : 9999

3. Nsp

4. Refus

Si J8 = NSP

J8C. Vous diriez que vous aviez ... ?

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

NSP7

Refus8

J8brecap. Variable de vérification

BLOC L - MALADIES CHRONIQUES, INFLAMMATOIRES ET AUTO-IMMUNES

L1. Un médecin vous a-t-il déjà diagnostiqué

ENQ : CITER

Pour chaque sous-questions suivante :

Oui¹

Non²

NSP³

1. une poly-arthrite rhumatoïde ?
2. de l'arthrose avec des crises d'arthrite aiguë ?
3. une spondylarthropathie ?
 - **L1C. Si oui, est-ce que vous êtes HLA B27 positif ?**
 - ⇒ Oui¹
 - ⇒ Non²
4. un lupus ?
5. une maladie cœliaque ?
6. une maladie de Crohn / recto-colite hémorragique (RCH) ?
7. un problème à la thyroïde ?

Si oui L2. Pouvez-vous me préciser ? Avez-vous eu :

ENQ : PLUSIEURS REPONSES POSSIBLES

- ⇒ La maladie de Basedow¹
 - ⇒ Une thyroïdite²
 - ⇒ Une hyperthyroïdie³
 - ⇒ Une hypothyroïdie⁴
 - ⇒ Un goître⁵
 - ⇒ Un nodule⁶
 - ⇒ Un goitre Multi Nodulaire⁷
 - ⇒ NSP⁸
8. un reflux gastro-oesophagien ?
 9. un ulcère à l'estomac ?
 10. des calculs dans la vésicule biliaire ?
 11. des calculs rénaux ?
 12. une maladie rénale chronique
- Si Oui L3. Avez-vous déjà fait une dialyse ?**
- ⇒ Oui¹
 - ⇒ Non²
 - ⇒ NSP³
13. une sclérose en plaque ?
 14. une maladie de Parkinson ?
 15. un vitiligo, des zones de dépigmentation de la peau ?
 16. une maladie de Gilbert, c'est-à-dire une augmentation de la bilirubine dans le sang ?
 17. un adénome de la prostate ?
 18. une angine de poitrine ?
 19. un infarctus du myocarde ?
 20. un accident vasculaire cérébral ?
 21. une phlébite / embolie pulmonaire ?

Pour chacune des SQ citée : Faire un déroulement horizontale de L5 et jusqu'à L7 pour chaque maladie de L1sq1à sq21 = 1

L5. A quel âge ou en quelle année vous a-t-on diagnostiqué (afficher)?

1. Saisie âge : L5b1 : Age:__\ AN Refus : 97 et NSP : 99

L5b2 : Mois __\ mois Refus : 97 et NSP : 99

L5b3 : semaine __\ mois Refus : 97 et NSP : 99

2. Saisie année : L5b4: Année ____\ Refus : 9997 et NSp : 9999

3. Nsp

4. Refus

Si L5 = NSP

L5C. Vous diriez que vous aviez ... ?

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

NSP

Refus

L5brecap. Vérification des L5

RESEARCH ARTICLE

Sexually and non-sexually transmitted infections and the risk of prostate cancer: Results from the EPICAP study

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Abstract

Introduction: Prostate cancer (PCa) is by far the most common type of cancer among men in western countries. However, relatively little is known about its etiology despite the high morbidity and mortality. It has been suggested that chronic inflammation may be involved in prostate carcinogenesis. We investigated the role of sexually and non-sexually transmitted infections in prostate cancer risk with a specific interest in the aggressive types.

Methods: We used data from epidemiological study of prostate cancer (EPICAP), a population-based case–control study. A total of 819 incident cases and 879 controls were interviewed face-to-face using a standardized questionnaire gathering information on known or suspected risk factors of prostate cancer and personal history of specific sexually and non-sexually transmitted infections: gonorrhea, syphilis, trichomonas, herpes, mononucleosis, Epstein–Barr virus, varicella-zoster, and dengue. Odds ratios (OR) and their 95% confidence interval were estimated using multivariate unconditional logistic regression.

Results: There was no significant association between gonorrhea (OR: 0.90, 95% CI: 0.61–1.33), trichomonas (OR: 0.74, 95% CI: 0.27–2.07), genital herpes (OR: 0.69, 95% CI: 0.38–1.27), and the risk of prostate cancer. No association emerged for overall sexually transmitted bacterial and viral infections (OR 1.05, 95% CI: 0.86–1.29) and overall non-sexually transmitted viral infections (OR 1.11, 95% CI: 0.90–1.35) and the risk of prostate cancer.

Conclusion: Our results showed that sexually or non-sexually transmitted infections, either bacterial or viral, were not associated to prostate cancer. Therefore, further investigation is needed to help advance our understanding of the role of chronic inflammation in the etiology of prostate cancer, with a particular focus on its most aggressive types.

KEYWORDS

cancer prevention, cancer risk factors, epidemiology, prostate cancer

1 | INTRODUCTION

Prostate cancer (PCa) is by far the most common type of cancer among men in western countries, with an estimate of 1,414,295 new cases and roughly 375,000 deaths worldwide in 2020.¹ More than 60,000 new cases in France were diagnosed, with approximately 9000 deaths in 2020, making it the second leading cause of cancer-related mortality.^{2,3}

Relatively little is known about the etiology of prostate cancer despite the high morbidity and mortality rates, where only advanced age, ethnicity, and family history of prostate cancer are well-established non-modifiable risk factors.⁴ However, according to studies done on migrants, Asian men living in the United States had a much higher incidence rate of prostate cancer compared to those living in their native countries, suggesting the role of lifestyle and environmental factors.⁵

Chronic inflammation has been associated with a wide range of malignancies, such as liver, kidney, and lung, via a specific infectious or environmental agent.^{6,7} It has been suggested through several epidemiological studies that inflammation of the prostate may also be involved in the development of prostate carcinogenesis.^{8,9} In fact, inflammatory infiltrates located near areas of proliferative inflammatory atrophy (PAI) and prostatic intraepithelial neoplasia (PIN), considered precancerous prostate lesions, strengthen the hypothesis of a possible link between chronic inflammation and prostate cancer.^{9,10}

While the cause behind prostatic inflammation remains unclear, several inflammation-related factors might be potential agents contributing to the onset of prostate cancer.⁹ Notably, infectious agents, including bacteria and viruses, have been observed to infect the prostate and trigger an inflammatory response and therefore are potential contributors to prostate carcinogenesis.⁹ While infectious agents can be classified into non-sexually and sexually transmitted infections (STIs), it is worth noting that the latter has received more extensive attention over the years compared to the former. For instance, the role of *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, syphilis, herpes simplex virus (HSV), herpes papillomavirus (HPV) 16 and 18, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) in the occurrence of prostate cancer has been studied, yet the findings were inconsistent.¹¹ Case-control studies¹²⁻¹⁵ and prospective cohort studies¹⁶⁻¹⁹ mainly focused on gonorrhoea, syphilis, genital herpes and did not find any association with a history of gonorrhoea,^{12-14,18} syphilis,¹²⁻¹⁵ trichomonas,¹⁴ or genital herpes,^{12,14,18,20} and prostate cancer. Similarly, investigations into blood-borne viral infections such as hepatitis B and C known for their liver-related impact, yielded inconsistent results.^{21,22} Given the often asymptomatic nature

of STIs, additional resources have been established, like blood collection and serological detection, allowing the prospective examination of STIs and their associated risk with prostate cancer.²³ The role of HSV-1 and HSV-2 viruses,^{24,25} CMV,^{25,26} *Trichomonas vaginalis*,²⁷⁻²⁹ and EBV³⁰ were studied through serological essays with varying results.

Among non-sexually transmitted infections, significant attention has been directed toward genitourinary infections, particularly prostatitis³¹ and various other genitourinary infections, such as urethritis, orchitis, epididymitis, and pyelonephritis.^{32,33} Herpes zoster, on the other hand, often known as shingles, is caused by the reactivation of the varicella-zoster virus (VZV) previously latent after primary infection with VZV has been suggested to directly affect the development of cancer, including prostate cancer.³⁴ However, the existing body of research on this topic is limited and inconclusive.^{35,36} Importantly, and beyond varicella-zoster, it is noteworthy to mention that non-sexually transmitted infections, such as polio, tuberculosis, and dengue, have yet to be explored in relation to prostate cancer.

To date, very few studies have considered the aggressiveness of cancer while studying chronic inflammation and/or infection.^{14,18}

In this context, the main objective of this study was to examine the association of sexually and non-sexually transmitted infections, whether bacterial or viral, in the occurrence of prostate cancer, with a particular interest on the aggressive types using data from the EPICAP study.

2 | METHODS

2.1 | Study population

EPICAP (Epidemiological study of prostate cancer) is a population-based case-control study conducted in the department of Hérault located in the south of France between 2012 and 2014 to investigate the role of environmental and genetic factors in the occurrence of prostate cancer. Details of the EPICAP objectives and study design have been previously described.³⁷ Eligible cases were men newly diagnosed with prostate cancer between 2012 and 2013 who were under the age of 75 and living in the department of Hérault at the time of diagnosis. All cases included in the study were histologically confirmed. The identification of cases was done by clinical research nurses, specifically trained for the study, by active search in all public and private cancer care centers of the department. Controls were randomly selected from the general population in the department of Hérault that were not diagnosed with prostate cancer and living in the same

department at the time of inclusion. To achieve frequency-matching, quotas by age were established as a preliminary to yield a control group similar to the case group in terms of age (5-year age group). Quotas on socioeconomic status were also set a priori to yield a control group comparable to the general male population of the same age in the department of Hérault.

In total, EPICAP had 1098 prostate cancer cases, and 1109 population-based controls that were eligible, of which 819 cases and 879 controls were included, with a participation rate of 75% and 79%, respectively.

2.2 | Data collection

Cases and controls were interviewed face-to-face by a well-trained clinical research nurse, using a standardized computer-assisted questionnaire (CAPI). Information on sociodemographic and lifestyle characteristics (Tobacco, alcohol consumption, and physical activity), occupational and residential history, personal medical history and drug use, family history of prostate cancer, and anthropomorphic measurements (weight, height, abdominal, and hip perimeter) were collected.

For tobacco consumption, men were asked during the interview whether they are smokers, non-smokers, or former smokers. Therefore, it was classified into three categories: former, current, and non-smoker.

For alcohol consumption, men were asked during the interview whether they drink or not. Therefore, it was classified into two categories: drinkers and non-drinkers.

For physical activity it was assessed using Metabolic Equivalent Task (MET-hour/week/year) for each activity practiced for a minimum of 1 h per week over a year. The variable was then later categorized into quartiles based on calculations from the control population.

Important health metrics, including abdominal circumference and body mass index (BMI) were measured by a clinical research nurse.

For non-steroidal anti-inflammatory drugs it was categorized into users and non-users.

Self-reporting of a personal history of sexually or non-sexually transmitted infections, whether bacterial (gonorrhea, syphilis, trichomonas, tuberculosis) or viral (herpes, Epstein–Barr, zoster herpes, dengue, polio, viral hepatitis), and their conditions such as urethritis and mononucleosis were collected. In addition, the number of infections for each type during their lifetime and age/year at the time of infection was also collected.

Clinical medical information for each case, such as Gleason scores and prostate specific antigen (PSA), were extracted from the patient's medical records at the time of diagnosis and validated by the Hérault cancer registry.

2.3 | Statistical analysis

All analyses were performed using the statistical analysis software SAS (9.4 version).

Personal history of each sexually or non-sexually transmitted bacterial or viral infection and their conditions (gonorrhea, syphilis, trichomonas, urethritis, tuberculosis, zoster herpes, mononucleosis, Epstein–Barr, zona, polio, dengue, herpes genital and non-genital, mononucleosis, viral hepatitis) were defined separately by ever having an infection before the reference date (date of diagnosis for the cases and date of interview for the controls).

Similar types of infections were combined in different groups to have an overall view of the association between all types of infections and prostate cancer.

Sexually Transmitted Bacterial Infections were defined by having at least one type of bacterial infection (gonorrhea, syphilis, trichomonas) before the reference date.

Viral infections were defined by having at least one type of sexually or non-sexually transmitted viral infection or their condition (zoster herpes, polio, dengue, herpes genital and non-genital, Epstein–Barr, viral hepatitis, mononucleosis) before the reference date.

Sexually transmitted viral infections were defined by having at least one type of sexually transmitted viral infection or their condition (mononucleosis, herpes, Epstein–Barr) before the reference date.

Sexually transmitted bacterial & viral infections were defined by having one type of sexually transmitted infection or their conditions before the reference date (gonorrhea, syphilis, trichomonas, urethritis, mononucleosis, Epstein–Barr, herpes genital and non-genital, and mononucleosis) or having two or more types of infections before the reference date.

Overall infections were defined by having one type of infection or their conditions (bacterial or viral) or having two or more types of infections before the reference date.

Regarding the reference group, each was defined as having no personal history of the infection or conditions concerned in each group except for all infections, where the reference group is defined as never having any type of infection or condition in their lifetime.

Odds ratios (OR) and their 95% confidence intervals (95% CI) were computed using unconditional logistic regression to investigate the association between sexually and non-sexually transmitted infections and the risk of prostate cancer.

The analysis was systematically adjusted to the non-modifiable risk factors: age, ethnicity (Caucasians, others), and family history of prostate cancer in first-degree relatives as well as potential confounding factors such as education, physical activity, non-steroidal anti-inflammatory drugs (NSAIDs), and waist circumference (WC).

Logistic regression models were performed to assess the relationship based on the aggressiveness of prostate cancer (PCa) using the Gleason score at the time of diagnosis. For non-aggressive or low-grade cancer, the Gleason score was ≤ 7 [including 3+4], which is considered a low or intermediate score; for aggressive or high-grade cancer, the Gleason score was ≥ 7 [including 4+3], which is regarded as a high score.

3 | RESULTS

The characteristics of prostate cancer cases and controls are presented in Table 1. Among cases, 183 (22.7%) were classified as aggressive or high-grade cancer. The study population was predominantly of Caucasian origin, with 97.1% among cases and 97.7% among controls. Age in a five-year group ($p=0.144$), education level ($p=0.609$), lifestyle factors such as smoking ($p=0.288$), alcohol consumption ($p=0.591$), physical activity ($p=0.11$), and anthropomorphic measurements such as Body Mass Index ($p=0.534$) and waist circumference ($p=0.086$) were similarly distributed between cases and controls. Non-steroidal anti-inflammatory drugs were more frequent among controls than in cases ($p=0.043$). As expected, the family history of prostate cancer in first-degree relatives was more frequent in cases (22%) than in controls (9%) ($p<0.0001$).

Associations between sexually transmitted bacterial infections (gonorrhea, trichomonas, and syphilis) and prostate cancer risk in all its grades are shown in Table 2. Having a history of gonorrhea (OR: 0.90, CI: 0.61–1.33), trichomonas (OR: 0.74, CI: 0.27–2.07), or syphilis (OR: 0.39, CI: 0.11–1.46) was not associated with the risk of prostate cancer, either for low-grade or high-grade cancer in all three bacterial infections. Neither bacterial infections (OR: 0.85 CI: 0.59–1.22) nor their conditions (OR: 0.87 CI: 0.62–1.21) were associated with the risk of prostate cancer in all its grades.

Associations between sexually (genital herpes, mononucleosis, Epstein–Barr) and non-sexually transmitted viral infections (zoster herpes, dengue, herpes labialis, polio, viral hepatitis) and prostate cancer risk in all its grades are shown in Table 3. We did not find any association between having a history of zoster herpes (OR:1.04 CI: 0.77–1.41), dengue (OR:0.92 CI: 0.42–2.03), herpes labialis (OR: 1.21 CI 0.97–1.50), genital herpes (OR: 0.69 CI: 0.38–1.27) Epstein–Barr (OR: 0.92 CI: 0.46–1.86), or viral hepatitis (OR:1.18 CI:0.85–1.65), and the risk of prostate cancer. Similarly, the association did not change as well among low-grade and high-grade cancer in all of the viral infections. The overall viral infections group was also not associated to PCa, whether for all viruses (OR: 1.11 CI:

0.90–1.35) or only for sexually transmitted viral infections (OR: 1.12 CI: 0.91–1.38), even for low-grade and high-grade PCa. Finally, the association between overall bacterial and viral infections combined and prostate cancer is shown in Table 4. For sexually transmitted bacterial and viral infections combined, there was no association in all prostate cancer cases (OR: 1.05 CI: 0.86–1.29). In regard to the overall infections having one infection, whether bacterial or viral, in their lifetime yielded an OR of 1.07 (CI: 0.86–1.34), and it increased to OR: 1.17 (CI: 0.88–1.56) when having more than one type of infection, though it was not significantly associated with prostate cancer even for low-grade and high-grade cancer.

4 | DISCUSSION

Our findings are based on a large, carefully designed population-based case–control study conducted to address environmental and genetic factors in prostate cancer risk with a specific interest on the aggressive types of prostate cancer.

Our study yielded no evidence of an association between personal history of both sexually and non-sexually transmitted bacterial and viral infections and the risk of developing prostate cancer. These findings remained consistent even when analyzing the aggressiveness of prostate cancer cases. Therefore, infections may not play a significant role in influencing prostate cancer risk.

Chronic inflammation has been linked to several types of human malignancies. Around 20% of malignancies are caused by chronic infection or chronic inflammatory states. Within the prostate, chronic inflammation may be triggered by infectious agents known as inflammation-related factors that eventually contribute to the onset of prostate cancer.^{8,9} Data from meta-analyses^{38,39} are supportive of the role of STIs in the occurrence of prostate cancer. A pooled analysis based on 17 studies were in favor of the role of STI in the occurrence of prostate cancer with an SRR = 1.19 (95% CI: 1.05–1.92).¹¹ Similar results were observed in another meta-analysis yielding an OR = 1.30 (95% CI: 1.30–1.61).³⁹ When overall STIs were considered together in studies based on self-reporting of STIs, two studies^{40,41} found a possible link yielding an OR = 1.7 (95% CI: 1.1–2.5) and OR = 1.68 (95% CI: 1.05–2.7), respectively, and another two^{12,18} found no association yielding an OR = 1.0 (95% CI: 0.7–1.5) and OR = 1.02 (95% CI: 0.91–1.15), respectively, between STIs and prostate cancer which was similar to our results. Our null findings were also consistent with studies that focused on particular types of STIs, such as gonorrhea,^{12,16–18} syphilis,^{12,18,26} trichomonas,^{14,29} and herpes.^{12,18,20,24} They differed from several studies^{13,42}

TABLE 1 Study population characteristics of epidemiological study of prostate cancer.

	Cases n = 819 (%)	Controls n = 879 (%)	p-Value
Gleason score			
Low-grade cancer ≤7 (3 + 4)	623 (77.3)	–	
High-grade cancer ≥7 (4 + 3)	183 (22.7)	–	
Age (years)			
<55	48 (5.9)	59 (6.7)	0.144
[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			
Caucasian	795 (97.1)	859 (97.7)	0.396
Other	24 (2.9)	20 (2.3)	
Family history of prostate cancer			
No	633 (77.8)	799 (91.2)	<0.001
Yes	181 (22.2)	77 (8.8)	
Education			
Primary	179 (21.9)	193 (22.0)	0.609
Secondary	380 (46.4)	425 (48.4)	
University	260 (31.8)	260 (29.6)	
Body mass index (kg/m²)			
<25 – normal	231 (28.5)	248 (29.1)	0.534
[25–30] – overweight	399 (49.1)	397 (46.6)	
≥30 – obese	182 (22.4)	207 (24.3)	
Waist circumference (cm)			
≤94	209 (25.9)	254 (29.6)	0.086
>94	599 (74.1)	603 (70.4)	
Smoking status			
Never	240 (29.3)	246 (28)	0.288
Former	455 (55.6)	476 (54.2)	
Current	123 (15.0)	157 (17.9)	
Alcohol consumption			
No	72 (8.8)	84 (9.6)	0.591
Yes	746 (91.2)	795 (90.4)	
Physical activity (MET^a-h/wk/yr)			
No ^b	177 (20.1)	191 (23.3)	0.11
<6.25	174 (19.8)	151 (18.4)	
6.25–13.0	174 (19.8)	138 (16.8)	
13.0–24.15	175 (19.9)	147 (17.9)	
≥24.15	174 (19.8)	187 (22.8)	
Non-steroidal anti-inflammatory drugs			
No	596 (73.0)	593 (68.6)	0.043
Yes	220 (27.0)	272 (31.5)	

^aMET: metabolic equivalent task.^bNo: Less than 1 h/week during at least 1 year.

for gonorrhea and for syphilis.^{43,44} Similar to our results, a large prospective study on health professionals was conducted to investigate the role of STIs and prostate cancer which did not find any association for neither gonorrhea nor syphilis.¹⁷ Extensive research has been dedicated to investigating the impact of prostatitis on the development of prostate cancer. A meta-analysis of 16 studies revealed an odds ratio (OR) of 1.83 (95% confidence interval: 1.43–2.35), indicating a higher risk of developing prostate cancer among individuals with a history of prostatitis [54]. However, it is important to acknowledge that the possibility of a detection bias cannot be dismissed as a potential explanation for these results.⁴⁵ Even though herpes zoster was studied the least among infections, two studies were consistent with our results.^{30,46} On the contrary, two other studies with an HR = 1.42 (95% CI: 1.06–1.92) and HR = 1.97 (95% CI: 1.27–3.06) showed that having herpes zoster infection is a suggestive risk factor for later developing prostate cancer.^{35,36} Hepatitis B and C have been studied in recent years and were inversely associated with prostate cancer,^{21,47} while a cohort study showed that viral hepatitis of HCV and HBV combined were not associated with prostate cancer which was consistent with our study.⁴⁸ The observed inconsistency in results may be attributed, in part, to the varying impact of racial differences among Latino, Black, and Caucasian populations where the rate of STD reporting is higher among Latinos and Africans in comparison to Caucasians.¹⁸ In addition, among individuals from diverse racial, ethnic, socioeconomic, or educational backgrounds, a history of gonorrhea may be indicative of multiple episodes or coinfections, which may result in a stronger association with prostate cancer risk.⁴³ Another possible explanation for varying results is for example, in the case of gonorrhea, which often denotes a longer duration of untreated infection due to challenges in medical access, lack of proper or effective treatments, or even non-compliance with treatment leading to prolonged inflammation. The frequency and timing of infection events can influence their overall effect on prostate cancer risk.

Within the literature, a significant body of evidence highlights intriguing associations between human papillomavirus (HPV), human immunodeficiency virus (HIV), and Mycoplasma infections, suggesting compelling connections that warrant further exploration. However, our EPICAP study did include data pertaining to these infections. While these infectious agents have garnered significant attention in the context of prostate cancer research, their inclusion in studies has yielded inconsistent results. Two meta-analysis showed that the risk of prostate cancer increased when having a history of HPV or when being infected with certain species of

TABLE 2 Associations of bacterial infections and prostate cancer risk.

	Controls		Cases				
	<i>n</i> = 586 (%)	<i>n</i> = 591 (%)	OR ^a (95% CI)	<i>n</i> = 623 (%)	OR ^a (95% CI)	<i>n</i> = 183 (%)	OR ^a (95% CI)
Sexually transmitted bacterial infections ^d							
No	792 (90.9)	750 (92.4)	1.00 Reference	568 (92.1)	1.00 Reference	170 (93.4)	1.00 Reference
Yes	79 (9.1)	62 (7.6)	0.85 (0.59–1.22)	49 (7.9)	0.85 (0.57–1.25)	12 (6.6)	0.83 (0.44–1.58)
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 (0.61–1.33)	45 (7.3)	0.93 (0.62–1.41)	9 (4.9)	0.73 (0.35–1.52)
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)	0.74 (0.27–2.07)	3 (0.5)	0.31 (0.07–1.53)	4 (2.2)	2.53 (0.76–8.39)
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)	0.39 (0.11–1.46)	2 (0.3)	0.37 (0.08–1.73)	1 (0.5)	0.51 (0.06–4.15)
Urethritis							
No	836 (97.0)	786 (96.8)	1.00 Reference	601 (96.9)	1.00 Reference	173 (96.7)	1.00 Reference
Yes	26 (3.0)	26 (3.2)	1.04 (0.58–1.88)	19 (3.1)	0.88 (0.46–1.69)	6 (3.4)	1.25 (0.49–3.19)
Tuberculosis							
No	835 (95.2)	774 (94.6)	1.00 Reference	589 (94.5)	1.00 Reference	172 (94.5)	1.00 Reference
Yes	42 (4.8)	44 (5.4)	1.11 (0.70–1.74)	34 (5.5)	1.14 (0.70–1.86)	10 (5.5)	1.07 (0.51–2.23)

^aORs adjusted for age, family history of prostate cancer, ethnicity, physical activity, NSAIDs, waist circumference, education.

^bGleason <7 (3+4).

^cGleason ≥7 (4+3).

^dBacterial Infections: trichomonas, syphilis, gonorrhea.

mycoplasma.^{39,49} On the contrary, for HIV infection, the results showed a decreased risk of prostate cancer, which could be explained by the altering testosterone levels in men with HIV.⁵⁰

Moreover, and to our knowledge, there were no studies that specifically studied the role of Dengue or Polio or tuberculosis in the occurrence of prostate cancer.

Case identification was made in all private and public cancer centers in the department of Hérault. In 2011, the Hérault cancer registry observed 770 new cases of prostate cancer in men, of which 75% were less than 75 years old. Considering that the number of cases observed in 2012–2013 will be similar, approximately 1150 new cases were expected during the study period.⁵¹ The recruitment of cases was quite exhaustive since the identified eligible cases were 1098 over the study period, thus limiting the potential of having selection bias. Controls were randomly selected from the general population of the department of Hérault using quotas defined by age (5 years) to reflect the age distribution of the cases. Moreover, the SES distribution of the control group reflects the SES distribution of the entire department of Hérault to yield a control

group similar to the general population of men to avoid selection bias. After the selection process, the distribution by SES between the control group and the general male population of the department of Hérault was compared. No significant difference was found, indicating that no major selection bias by SES had occurred in the control population.

Acknowledging the potential for recall bias in our study is essential, particularly when the data collection method relies on self-reporting of exposure. This introduces the possibility of differential classification bias. In our case, the study involved self-reporting a history of sexually transmitted infections (STIs). It is important to note that STIs are often stigmatized and can be asymptomatic, which may result in underestimation of their prevalence due to reluctance to answer, lack of awareness, or inadequate knowledge about the nature of the infection. However, the data collection was done face-to-face by a trained research clinical nurse using a standardized questionnaire and was carried out identically in both cases and controls. In addition, several questions regarding the variables of interest were also formulated

TABLE 3 Associations of viral infections and prostate cancer risk.

	Controls n = 879 (%)	Cases		Low-grade cancer ^b		High-grade cancer ^c	
		All n = 819 (%)	OR ^a (95% CI)	n = 623 (%)	OR ^a (95% CI)	n = 183 (%)	OR ^a (95% CI)
Viral infections ^d							
No	443 (52.7)	408 (50.9)	1.00 Reference	305 (50.1)	1.00 Reference	95 (53.1)	1.00 Reference
Yes	398 (47.3)	393 (49.1)	1.11 (0.90–1.35)	304 (49.9)	1.16 (0.93–1.44)	84 (46.9)	1.02 (0.73–1.42)
Zoster herpes							
No	761 (87.6)	713 (87.5)	1.00 Reference	542 (87.0)	1.00 Reference	158 (87.6)	1.00 Reference
Yes	108 (12.4)	102 (12.5)	1.04 (0.77–1.41)	80 (13.0)	1.11 (0.80–1.53)	22 (12.2)	0.96 (0.58–1.58)
Polio							
No	872 (99.5)	816 (99.8)	1.00 Reference	622 (99.8)	1.00 Reference	181 (99.5)	1.00 Reference
Yes	4 (0.5)	2 (0.2)	1.46 (0.20–10.58)	1 (0.2)	1.18 (0.11–13.21)	1 (0.6)	2.51 (0.21–30.44)
Dengue							
No	858 (98.3)	803 (98.4)	1.00 Reference	610 (98.2)	1.00 Reference	181 (98.9)	1.00 Reference
Yes	15 (1.7)	13 (1.6)	0.92 (0.42–2.03)	11 (1.8)	1.03 (0.45–2.34)	2 (1.1)	0.62 (0.13–2.88)
Viral hepatitis							
No	780 (90.7)	725 (89.2)	1.00 Reference	554 (89.6)	1.00 Reference	159 (87.4)	1.00 Reference
Yes	80 (9.3)	88 (10.8)	1.18 (0.85–1.65)	64 (10.4)	1.13 (0.7–1.62)	23 (12.6)	1.56 (0.93–2.62)
Sexually transmitted viral infections ^e							
No	575 (66.9)	524 (64.9)	1.00 Reference	392 (63.7)	1.00 Reference	123 (68.3)	1.00 Reference
Yes	284 (33.1)	284 (35.2)	1.12 (0.91–1.38)	223 (36.3)	1.17 (0.93–1.47)	57 (31.7)	0.98 (0.69–1.40)
Genital Herpes							
No	847 (96.8)	793 (97.3)	1.00 Reference	602 (97.0)	1.00 Reference	178 (97.8)	1.00 Reference
Yes	28 (3.2)	22 (2.7)	0.69 (0.38–1.27)	18 (3.0)	0.73 (0.38–1.39)	4 (2.2)	0.62 (0.21–1.83)
Epstein-Barr							
No	849 (98.0)	786 (97.9)	1.00 Reference	599 (97.9)	1.00 Reference	174 (97.8)	1.00 Reference
Yes	17 (2.0)	17 (2.1)	0.92 (0.46–1.86)	13 (2.1)	0.89 (0.42–1.90)	4 (2.3)	1.08 (0.34–3.41)
Herpes labialis							
No	615 (70.9)	555 (68.1)	1.00 Reference	416 (67.2)	1.00 Reference	130 (71.0)	1.00 Reference
Yes	253 (29.1)	260 (31.9)	1.21 (0.97–1.50)	203 (32.8)	1.26 (0.99–1.59)	53 (29.0)	1.05 (0.73–1.52)

^aORs adjusted for age, family history of prostate cancer, ethnicity, physical activity, NSAIDs, waist circumference, education.

^bGleason ≤ 7 (3 + 4).

^cGleason ≥ 7 (4 + 3).

^dViral infections: herpes zoster, dengue, Herpes labial & genital, mononucleosis, Epstein-Barr, polio, viral hepatitis.

^eSexually transmitted viral infections: Herpes labial & genital, Epstein-Barr.

differently multiple times, allowing cross-referencing and thus limiting potential classification bias. It is noteworthy to consider the prevalence of controls, and in our study, the prevalence of controls was found to be 7.7% for gonorrhea. Comparatively, in the general population of France, the prevalence of gonorrhea among men aged greater than 45 is approximately 6% indicating a relatively similar prevalence, which helps minimize the potential impact of classification bias in our findings. However, we should consider that the prevalence of syphilis observed in EPICAP is around 1% which is lower than the

prevalence of syphilis in the population of France which is around 4%⁵² indicating a potential underestimation of our results. When considering cases, we cannot entirely rule out the possibility of recall bias, potentially resulting in underreporting and subsequent underestimation of the true impact.

Our results remained unchanged after adjusting to non-modifiable risk factors and major potential confounding variables such as level of education, physical activity, waist circumference, and non-steroidal anti-inflammatory drugs.

TABLE 4 Overall association of sexually and non-sexually transmitted infections and prostate cancer risk.

	Controls <i>n</i> = 879 (%)	Cases		Low-grade cancer ^b		High-grade cancer ^c	
		All <i>n</i> = 819 (%)	OR ^a (95% CI)	<i>n</i> = 623 (%)	OR ^a (95% CI)	<i>n</i> = 183 (%)	OR ^a (95% CI)
Sexually transmitted bacterial & viral infections ^d							
No	511 (60.1)	476 (59.3)	1.00 Reference	358 (58.5)	1.00 Reference	111 (62.4)	1.00 Reference
Yes	340 (40.0)	327 (40.7)	1.05 (0.86–1.29)	254 (40.5)	1.06 (0.85–1.32)	67 (37.6)	0.97 (0.69–1.38)
1	287 (33.7)	277 (34.5)	1.05 (0.85–1.30)	216 (35.2)	1.07 (0.85–1.35)	55 (30.9)	0.93 (0.65–1.35)
≥2	53 (6.2)	50 (6.2)	1.04 (0.67–1.59)	38 (6.2)	0.97 (0.61–1.56)	12 (6.7)	1.23 (0.62–2.43)
All infections ^e							
No	383 (45.6)	351 (43.9)	1.00 Reference	264 (43.4)	1.00 Reference	81 (45.5)	1.00 Reference
Yes	457 (54.4)	448 (56.1)	1.10 (0.90–1.35)	344 (56.6)	1.11 (0.89–1.38)	97 (54.5)	1.07 (0.77–1.50)
1	317 (37.7)	305 (38.2)	1.07 (0.86–1.34)	232 (37.7)	1.07 (0.84–1.35)	66 (37.1)	1.03 (0.71–1.49)
≥2	140 (16.7)	143 (17.9)	1.17 (0.88–1.56)	112 (18.4)	1.21 (0.89–1.64)	31 (17.4)	1.18 (0.73–1.89)

^aORs adjusted for age, family history of prostate cancer, ethnicity, physical activity, NSAIDs, waist circumference, education.

^bGleason ≤7 (3+4).

^cGleason >7 (4+3).

^dSexually transmitted bacterial & viral infections: Herpes labial & genital, mononucleosis, Epstein–Barr, trichomonas, syphilis, gonorrhea, urethritis.

^eAll infections: Herpes labial & genital, mononucleosis, Epstein–Barr, trichomonas, syphilis, gonorrhea, Polio, viral hepatitis, dengue, zona, urethritis, tuberculosis.

5 | CONCLUSION

We found no association between sexually transmitted and non-sexually transmitted infections in the occurrence of prostate cancer. Therefore, our results do not indicate an essential role for infectious agents in the etiology of prostate cancer. Due to the inconsistency in the results of previous studies, additional research is warranted to ascertain the role of inflammatory or infectious agents with a particular interest on sexually transmitted infections and the onset of prostate cancer to adjust and implement the proper preventive strategies to limit its occurrence.

AUTHOR CONTRIBUTIONS

Melissa Sawaya: Formal analysis (lead); writing – original draft (lead); writing – review and editing (equal). **Emilie Cordina-Duverger:** Data curation (equal); formal analysis (supporting); project administration (equal); resources (supporting); validation (supporting); writing – review and editing (supporting). **Pierre-Jean Lamy:** Conceptualization (supporting); data curation (equal); funding acquisition (supporting); investigation (equal); project administration (supporting); writing – review and editing (supporting). **Xavier Rébillard:** Conceptualization (supporting); data curation (equal); funding acquisition (supporting); methodology (supporting); project administration (equal); writing – review and editing (supporting). **Brigitte Trétarre:** Conceptualization (supporting); data curation (equal); funding acquisition (supporting);

investigation (equal); methodology (supporting); project administration (equal); writing – review and editing (equal). **Florence Menegaux:** Conceptualization (lead); data curation (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); supervision (lead); validation (lead); writing – original draft (equal); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

All authors have no financial disclosures to report.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB-Inserm n° 01-040 – November 2010) and by the French Data Protection Authority (CNIL N° 910,485 – April 2011).

CONSENT TO PARTICIPATE

Each subject included in EPICAP signed a written informed consent.

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Titre: L'inflammation chronique et le cancer de la prostate: Rôle des infections, des calculs, du gène COX-2 et de leurs interactions GxE

Mots clés : Facteurs de l'inflammation, génétique, cancer de la prostate, études cas-témoins

Introduction : L'inflammation chronique a été suggérée comme un facteur contribuant à la carcinogenèse prostatique. Divers facteurs liés à l'inflammation, tels que les infections, les calculs rénaux et biliaires, ainsi que la susceptibilité génétique impliquant des gènes de l'inflammation comme COX-2, ont été étudiés, mais les résultats restent souvent contradictoires ou limités. Peu d'études ont également examiné l'impact de ces facteurs sur l'agressivité du cancer.

Objectifs : 1) Étudier le rôle des infections, 2) des calculs et le cancer de la prostate ; 3) Analyser l'influence des SNPs du gène COX-2 et l'interaction gènes-environnement sur le risque de cancer de la prostate.

Méthodes : Les données de l'étude EPICAP, une étude cas-témoins en population menée dans le département de l'Hérault en France, ont été utilisées pour analyser les infections et les calculs, avec 819 cas et 879 témoins. Des informations ont été collectées sur l'historique de ces facteurs, ainsi que sur les scores de Gleason pour différents grades de cancer. Pour l'analyse génétique, les données sur le gène COX-2 provenant des 732 cas et 783 témoins ayant des données obtenues à partir d'échantillons de sang ou de salive, ont été utilisées après contrôle qualité, avec un total de 20 SNPs analysés.

Résultats : Aucune association significative n'a été observée entre les infections sexuellement ou non sexuellement transmissibles (bactériennes ou virales) et le risque de cancer de la prostate.

Les calculs rénaux, en particulier en présence d'un antécédent de pyélonéphrite, et les calculs biliaires, notamment chez les individus avec une hypertriglycéridémie, ont été associés à un risque accru de cancer de la prostate. Des associations significatives ont été observées entre plusieurs SNPs du gène COX-2 et le cancer de la prostate, avec l'allèle A du rs4648261 lié aux cancers de haut grade. Les interactions entre les variations génétiques du COX-2 et les facteurs environnementaux comme les infections et les calculs n'ont pas eu d'influence significative sur le risque de cancer de la prostate.

Conclusion : Ces résultats soulignent le rôle important des processus inflammatoires dans la carcinogenèse prostatique et mettent en lumière la nécessité de poursuivre les recherches sur les facteurs liés à l'inflammation. Il est important d'étudier la durée d'exposition à ces facteurs et l'efficacité des traitements pour mieux comprendre l'impact de l'inflammation chronique sur le risque de cancer. Les résultats génétiques, basés sur une approche préliminaire par SNP, suggèrent des associations potentielles qui nécessitent des recherches supplémentaires pour être confirmées et approfondies. Enfin, étant donné l'importance du cancer de la prostate agressif et son pronostic souvent défavorable, il est essentiel que les futures recherches se concentrent sur les facteurs génétiques et environnementaux qui l'influencent, afin de mieux comprendre les mécanismes sous-jacents et d'élaborer des stratégies de prévention et de traitement plus efficaces.

Title: Chronic Inflammation and The Risk of Prostate Cancer: Role of Infections, Calculi, COX-2 gene and their GxE Interaction

Keywords: Inflammation-related factors, Genetic Susceptibility, Prostate Cancer, Case-Control Study

Introduction: Chronic inflammation has been suggested to contribute to prostate carcinogenesis. Inflammation-related risk factors, such as infections, kidney and gallbladder stones, and genetic susceptibility involving inflammatory genes like COX-2, have been studied, but results are often contradictory or limited. Few studies have considered how these factors impact the aggressiveness of the cancer as well.

Objectives: 1) Study the role of infections and calculi in the occurrence of prostate cancer 2) Study the role of COX-2 SNPs and the GxE interaction and Prostate Cancer.

Methods: Data from the EPICAP, a population-based case-control study carried out in the department of Herault in France, was used for the analysis of infections and calculi, including 819 cases & 879 controls. Information was collected on the history of these factors along with Gleason scores for various grades of cancer. For genetic analysis, EPICAP provided data on the COX-2 gene, including 732 cases and 783 controls derived from blood or saliva samples, after quality control checks, with 20 SNPs analyzed in total.

Results: No significant associations between sexually and non-sexually transmitted infections (STIs) whether bacterial or viral and the risk of prostate cancer. Kidney stones, particularly with a history of pyelonephritis, and gallbladder stones, especially in

individuals with hypertriglyceridemia, were associated with an increased risk of prostate cancer.

Significant associations were observed between several SNPs in the COX-2 gene and prostate cancer, with the A allele of rs4648261 linked to high-grade cancer. Interactions between COX-2 genetic variations and environmental factors like infections and stones did not significantly influence prostate cancer risk.

Conclusion: The findings underscore the significant role of inflammatory processes in prostate carcinogenesis and highlight the need for further research into inflammation-related factors. Investigating the duration of these factors and the effectiveness of treatments is crucial to see how chronic inflammation can impact cancer risk. The genetic results based on a preliminary SNP-by-SNP approach, indicate potential associations that require further investigation to confirm and expand upon these findings. Finally, given the importance of aggressive PC and its associated poor prognosis, future research should specifically explore the genetic and environmental factors influencing it and understand the underlying mechanisms for better prevention strategies and more effective treatments.

