Note Interdisciplinaire de Synthèse (NID)

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

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Abstract

Prostate cancer remains a major global public health issue, with rising incidence, particularly in high-income countries. While age, ethnicity, and family history are well-established risk factors, the role of chronic inflammation and infections in prostate carcinogenesis remains poorly understood. This Note explores the association between chronic inflammation, infections, kidney stones, gallbladder stones, and prostate cancer, using data from the EPICAP case-control study conducted in France.

My findings demonstrate that kidney stones are significantly associated with an increased risk of prostate cancer, particularly for less aggressive forms. Furthermore, the combination of kidney stones and pyelonephritis further strengthens this risk. On the genetic front, the A allele of the rs4648261 polymorphism in the COX-2 gene was found to be associated with a higher risk of high-grade prostate cancer, highlighting the role of inflammation in the development of aggressive disease.

The perspectives outlined in this Note focus on enhancing targeted screening programs for high-risk individuals, managing inflammatory conditions in primary care, implementing public awareness campaigns, and integrating genetic screening into clinical practice. These interventions aim to reduce the incidence and mortality associated with prostate cancer through personalized prevention strategies and strengthened public health policies.

Introduction

Prostate cancer remains a significant global public health issue, consistently ranking as the second most common cancer affecting men worldwide. According to GLOBOCAN, approximately 1.4 million new cases of prostate cancer were diagnosed globally in 2022, accounting for 15.3% of all cancers in men, excluding non-melanoma skin cancers [1]. In developed countries, where life expectancy is higher and access to healthcare more robust, the incidence rates are particularly elevated. For example, in Northern Europe, prostate cancer incidence is as high as 82.8 per 100,000 men. In contrast, in less developed regions such as Southeast Asia and North Africa, the incidence rates are significantly lower, around 12.7 and 16.1 per 100,000 men, respectively. Despite these geographic variations, the global burden of prostate cancer is rising, driven in part by aging populations and improved detection methods, such as the prostate-specific antigen (PSA) test [1–3].

In France, prostate cancer poses an acute public health challenge. In 2022, 57,357 new cases were reported, representing 21.8% of all male cancer diagnoses [1]. The standardized incidence rate in France is 82.3 per 100,000, with the highest rates observed in men aged 65 and older (1). Mortality rates have improved due to advances in screening and treatment, yet prostate cancer still caused 9,264 deaths in France in 2022 [1–3]. This highlights the persistent lethality of the disease, especially in its more aggressive forms, which often evade early detection and carry a poorer prognosis.

The exact etiology of prostate cancer remains largely unknown, but certain risk factors are well established. Age is the most significant non-modifiable risk factor, with the majority of cases occurring in men over the age of 65. Ethnicity also plays a crucial role, as African American men and men of African descent are more likely to develop prostate cancer compared to their Caucasian and Asian counterparts. Family history is another important factor, with men who have a close relative with prostate cancer being twice as likely to develop the disease. These factors, however, account for only part of the picture, and much of the variability in prostate cancer incidence and progression remains unexplained [4–9].

The growing body of research suggests that environmental and lifestyle factors, including chronic inflammation, infections, dietary habits, and metabolic conditions, may also play critical roles in prostate cancer development [10]. Chronic inflammation, in particular, has emerged as a key player in the development of many cancers, including prostate cancer [11, 12]. Chronic inflammation is characterized by the prolonged activation of the immune system,

which can lead to DNA damage, disrupt normal cell growth, and create a tumor-promoting environment [12, 13]. Unlike acute inflammation, which resolves after a short period, chronic inflammation can persist for months or even years, contributing to various stages of carcinogenesis [14].

While the cause behind prostatic inflammation remains unclear, several inflammation-related factors might be potential agents contributing to the onset of prostate cancer. In fact, inflammatory infiltrates located near areas of prolifera- tive inflammatory atrophy (PAI) and prostatic intraepi- thelial neoplasia (PIN), considered precancerous prostate lesions, strengthen the hypothesis of a possible link be- tween chronic inflammation and prostate cancer [4]. Potential causes of prostatic inflammation include infections, hormonal fluctuations, urine reflux, dietary patterns, and genetic predisposition [4].

In my research, I sought to explore the relationship between chronic inflammation and prostate cancer, focusing on infections, urinary stones, and genetic predispositions. This interdisciplinary approach allowed me to assess the interaction between biological, genetic, and environmental factors, offering new insights into the role of inflammation in prostate cancer. By examining infections such as sexually transmitted diseases (STDs), non-STD infections, and chronic inflammatory conditions like kidney and gallbladder stones, I aimed to identify potential inflammatory triggers that may increase prostate cancer risk. Additionally, I investigated the role of single nucleotide polymorphisms (SNPs) in inflammatory genes, such as COX-2, and their interaction with environmental factors to better understand how genetic predispositions might modulate prostate cancer risk.

Contextualizing in Public Health

The rising incidence of prostate cancer, particularly in aging populations, presents a significant challenge for public health systems worldwide. The economic burden of prostate cancer is considerable, both in terms of direct medical costs and indirect costs, such as lost productivity and caregiving expenses. In the European Union, the economic burden of prostate cancer was estimated to account for 7% of all cancer-related costs, second only to lung, breast, and colorectal cancers [15]. In France alone, the total cost of prostate cancer care was estimated at 8.43 billion euros in 2009, a figure that has likely risen since [15]. These costs are exacerbated by the fact that prostate cancer often requires long-term treatment, particularly for those with advanced or metastatic disease [15, 16].

From a public health perspective, the identification of modifiable risk factors for prostate cancer could lead to more effective prevention strategies. Chronic inflammation, which has been implicated in up to 20% of all cancers, represents one such modifiable factor [17]. Conditions such as prostatitis, urinary stones, and infections can lead to persistent inflammation in the prostate, potentially increasing the risk of malignancy. In addition to its role in cancer, chronic inflammation is a major contributor to other chronic diseases, such as cardiovascular disease and diabetes, further underscoring its relevance as a public health issue [18].

Addressing chronic inflammation in clinical practice and public health policy could have far-reaching benefits. By focusing on early detection and treatment of inflammatory conditions, healthcare providers could reduce the incidence of prostate cancer and other inflammation-related diseases. Public health initiatives aimed at reducing infection rates and improving the management of conditions like kidney stones could also help lower prostate cancer risk. These efforts should be complemented by ongoing research into the genetic and environmental factors that contribute to chronic inflammation and cancer.

Interdisciplinary Approach

The interdisciplinary nature of my research is reflected in the diverse methods and analytical tools employed. **Epidemiology** and **biostatistics** were essential in analyzing the EPICAP study, which provided a comprehensive dataset for examining the relationship between infections, urinary stones, and prostate cancer risk. Using statistical models, I was able to account for potential confounders, such as age, family history, and lifestyle factors, ensuring that the associations observed were robust and reliable. I was also able to take into account the aggressivity of prostate cancer in my analysis.

The incorporation of **genetic analysis** further enriched the study. By examining SNPs in inflammatory genes, such as COX-2, I was able to explore how genetic variations might influence an individual's susceptibility to inflammation-related prostate cancer. This approach allowed me to investigate potential **gene-environment interactions**, shedding light on how genetic predispositions interact with external factors, such as infections and urinary stones, to influence cancer risk.

Moreover, the use of **data science and modeling** was critical in managing the large dataset and performing complex multivariate analyses. By integrating epidemiological, genetic, and

clinical data, I was able to develop a comprehensive understanding of the interplay between various risk factors and prostate cancer.

Finally, my research has important implications for **public health policy** and **health economics**. The identification of modifiable risk factors, such as chronic inflammation and infections, provides a basis for developing targeted prevention strategies. By addressing these factors through public health interventions, we could potentially reduce the incidence of prostate cancer and lower the associated healthcare costs. Furthermore, the genetic component of my research highlights the need for personalized medicine approaches, where individuals at high risk of prostate cancer could benefit from tailored screening and prevention programs.

Problem Statement and Interventions

The central focus of my research was to investigate the role of chronic inflammation in prostate cancer, with a specific emphasis on infections, urinary stones, and genetic predispositions. The findings from the EPICAP study provided important insights into how these factors contribute to prostate cancer risk.

1. **Infections and Prostate Cancer**: My analysis revealed no significant associations between individual infections, such as gonorrhea, herpes, and prostatitis, and prostate cancer risk. Additionally, considering the cumulative effect of multiple infections did not strenghten the hypothesis of chronic inflammation and its role in prostate cancer.
2. **Kidney and Gallbladder Stones**: A significant association was found between kidney stones and prostate cancer, particularly in cases of low-grade tumors. This finding supports the hypothesis that chronic inflammation caused by urinary stones may contribute to the development of prostate cancer. Additionally, the combination of kidney stones and pyelonephritis was associated with an even higher risk, indicating that co-existing inflammatory conditions may exacerbate cancer risk. Gallbladder stones, while not directly associated with prostate cancer in my analysis, may still contribute to inflammation that could influence cancer risk among individuals with hypertriglyceridemia.
3. **Genetic Factors (SNPs)**: The genetic analysis focused on polymorphisms in the COX-2 gene, which plays a critical role in the inflammatory response. The A allele of SNP rs4648261 was found to be significantly associated with high-grade prostate cancer, suggesting that genetic variations in inflammatory pathways may predispose

individuals to more aggressive forms of the disease. This finding highlights the potential for genetic screening to identify individuals at higher risk of prostate cancer, particularly those with a family history of the disease.

Perspectives

The findings from my thesis have several important implications for public health policy and clinical practice. By identifying chronic inflammation as a potential modifiable risk factor for prostate cancer, we can develop targeted interventions aimed at reducing inflammation and, consequently, cancer risk.

1. **Targeted Screening and Prevention Programs**: One of the key areas for improvement lies in enhancing early detection through **targeted screening programs**. Current prostate cancer screening primarily relies on PSA testing, which has its limitations, especially in differentiating between indolent and aggressive forms of the disease. Screening efforts could be refined by identifying individuals at higher risk due to chronic inflammatory conditions. This personalized approach could help distinguish between men at higher and lower risk of aggressive prostate cancer, allowing for more focused use of PSA testing and other diagnostic tools.

   Additionally, genetic factors could be incorporated into screening programs to further stratify risk. Men with genetic predispositions to aggressive prostate cancer could benefit from more frequent screenings or advanced diagnostic methods, ensuring that cases of aggressive cancer are caught early, when treatment is most effective.
2. **Management of Chronic Inflammation in Primary Care**: Another potential improvement lies in the **management of chronic inflammatory conditions**, such as prostatitis, kidney stones, and infections, in primary care settings. Healthcare providers could implement more aggressive monitoring and treatment strategies for men with a history of these conditions. For example, patients with recurrent kidney stones might benefit from more frequent check-ups, dietary changes, or medication to manage inflammation, reducing their long-term risk of developing prostate cancer. Furthermore, my findings suggest that men with co-existing inflammatory conditions, such as pyelonephritis alongside kidney stones, are at even greater risk. This highlights the need for a more integrated approach to managing urological health, where comorbid conditions are treated holistically to prevent chronic inflammation from escalating into more serious health issues.

3. **Public Health Campaigns Focused on Inflammation Prevention**: **Public health campaigns** could play an essential role in raising awareness about the connection between chronic inflammation and cancer risk. Educating the public about the importance of managing infections, dietary choices, and inflammation could lead to earlier intervention and reduced prostate cancer incidence. For instance, public health messaging could emphasize the importance of timely treatment for urinary tract infections, as prolonged untreated infections can lead to chronic inflammation, potentially increasing cancer risk. Campaigns could also focus on lifestyle changes that reduce inflammation, such as promoting physical activity, healthy diets rich in anti-inflammatory foods, and weight management. Such initiatives would not only benefit prostate cancer prevention but also reduce the risk of other inflammation-related conditions like cardiovascular diseases.
4. **Incorporation of Genetic Testing in Clinical Practice**: Men with genetic susceptibility to prostate cancer could be counseled on personalized prevention strategies, including more frequent screenings and specific anti-inflammatory interventions. In the long term, this could reduce both the incidence and mortality of prostate cancer, especially for high-risk groups. The combination of genetic and environmental factors suggests that a multi-faceted prevention strategy would be the most effective. By addressing both the genetic predispositions and the environmental triggers of chronic inflammation, healthcare providers could better tailor prevention efforts to individual patients, improving outcomes and reducing the burden on healthcare systems.

Conclusion

Prostate cancer is a complex disease with a multifactorial etiology, involving interactions between genetic, environmental, and lifestyle factors. The findings from my thesis contribute to a better understanding of the role of chronic inflammation in prostate cancer risk, highlighting the importance of inflammatory-related factors in the development of prostate cancer.

From a public health perspective, my research underscores the need for a multi-pronged approach to prostate cancer prevention, combining targeted screening, improved management of chronic inflammatory conditions, and public health campaigns aimed at reducing inflammation. Additionally, the identification of genetic risk factors, such as COX-2

polymorphisms, opens the door to more personalized prevention strategies, allowing healthcare providers to tailor interventions based on an individual's genetic profile.

Looking forward, further research is needed to confirm these findings in larger, more diverse populations and to explore additional genetic and environmental factors that may contribute to prostate cancer. As we continue to unravel the complexities of this disease, the ultimate goal is to develop more effective strategies for prevention, diagnosis, and treatment, ultimately improving outcomes for men at risk of prostate cancer.

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