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First interim report

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Project title:
Aligning competitive morbidities and causes of early onset deaths integrating new algorithms using the genetic variability.

Objectives:
- Integration of genetic markers in the estimation of competitive morbidity and mortality using data from cohorts of men followed for twenty years. Define subsets of genetic markers and predictive algorithms useful for personalized screening, and interventional prevention.
- Define strategies useful for causal inference in prostate diseases.

Context:
Comprehensive integration of mesological and genetic risks into predictive models allows defining individual risk profiles for targeted screening, prevention and treatment. These models can improve cost effectiveness and individual prevention schedule. They have been established as proof of concept by some healthcare companies, for example in the screening of breast cancer. Scientific evidence informing clinical policy and environmental decision-making often comes from observational studies, due to ethical concerns or feasibility of randomized clinical trials. However, the impact of selection bias on inferences from observational studies could be considerable and explain opposite results and controversies (this has been recently shown and stigmatized in the context of COVID-19) (Griffith 2020, PMID: 33184277). So, long term observational studies and introduction of new causal models using genetic markers could provide more reliable evidence for decision making and policy makers.

Results :

Our first approach was methodological, as studies of causal factors of prostate cancer risk are often contradictory and controversial. When randomised studies are not possible, epidemiological studies performed on prostate cancer or the interpretation of real data on the results of interventions are subject to selection bias based on confounding factors or controls defined by PSA measurement, despite complex statistical designs, including the use of genetic markers for a Mendelian randomisation-type approach. In this sense, in an article by Cussenot et al published in European Urology in 2024 [1], we reported a typical misinterpretation based on the analysis of real-world cohort data. Additionally, we showed in Current Opinion in Urology in 2023 [2], that understanding selections using directed acyclic graphs and the use of genetic markers could mitigate misinterpretation of causal risk factors. In this paper, we proposed new rules for the use of genetic causal factors to highlight erroneous causal factors and reduce the risk of misinterpretation.

We also reported the results of a national survey on the diagnosis and management of prostate cancer, and their regional and temporal disparities in France [3]. This descriptive analysis of a large population of 4,936,750 men is the first step towards new types of analyses concerning comorbidities and mortality competing with prostate cancer, and their alignment using genetic markers.

1. Cussenot O, Chambaz A, Hamdy FC. Re: Annika Herlemann, Janet E. Cowan, Samuel L. Washington 3rd, et al. Long-term Prostate Cancer-specific Mortality After Prostatectomy, Brachytherapy, External Beam Radiation Therapy, Hormonal Therapy, or Monitoring for Localized Prostate Cancer. Eur Urol. 2024 Mar 15:S0302-2838(24)02139-0.
2. Cussenot O, Fromont G, Cancel-Tassin G, Hamdy FC, Martin RM. Endemic statistical paradoxes in epidemiologic studies distort knowledge on prostate cancer: mitigation and caution of fallacies in prostate cancer causal epidemiological studies. Curr Opin Urol. 2023 Nov 1;33(6):421-427.
3. Cussenot O, Taille Y, Portal JJ, Cancel-Tassin G, Roupret M, de la Taille A, Ploussard G, Mathieu R, Hamdy FC, Vicaut E. A Comprehensive National Survey of Prostate-specific Antigen Testing and Prostate Cancer Management in France: Uncovering Regional and Temporal Disparities. Eur Urol Oncol. 2024 Mar 11:S2588-9311(24)00053-1. comments on https://www.urotoday.com/recent-abstracts/urologic-oncology/prostate-cancer/150441-a-comprehensive-national-survey-of-prostate-specific-antigen-testing-and-prostate-cancer-management-in-france-uncovering-regional-and-temporal-disparities.html)

Perspectives:

In line with the aims of our project, two publications are in progress that will present results on "the impact of the use of drugs against cardiovascular and metabolic disorders on prostate cancer outcomes in real practice" and "competitive cancer mortality and shared heritability between cancers". We will then decipher the genetic factors involved in the components of metabolic syndromes in order to estimate their causality on the risk of benign and malignant prostate pathologies and their impact on their evolution.