

EMBARGOED UNTIL 16 JANUARY 2020 AT 6.01 PM ET

Loss of Function in Key Y-Chromosome Genes Increases Cancer Risk in Men

Study identifies key biological mechanism that puts men at higher risk of cancer than women

Barcelona, 17 January 2020. Numerous studies have shown that men are more susceptible to cancer than women; however, the reason for this difference remains poorly understood. A new study by researchers from the Barcelona Institute for Global Health ([ISGlobal](#)), a centre supported by "la Caixa", has identified a key **biological mechanism that puts men at higher risk of cancer: loss of function in certain genes of the sex-determining Y chromosome**, which is present only in men. The study, published in the *Journal of the National Cancer Institute*, was carried out in collaboration with Pompeu Fabra University, the University of Adelaide and the Estonian Genome Centre.

Using data from 9,000 individuals, the researchers studied Y-chromosome gene function in patients with various types of cancer. The findings showed that cancer risk increases with loss of function of **six key Y-chromosome genes** in various types of cells. "Recent studies have shown that complete loss of the Y chromosome, which is essential to foetal sex differentiation, occurs, with aging, in the cells of some men," commented **Juan Ramón González**, coordinator of the study and head of the Bioinformatic Group in Genetic Epidemiology at ISGlobal. "Although the loss of the Y chromosome has previously been associated with higher incidence of cancer, the causes of this association are poorly understood."

These six Y-chromosome genes are involved in cell-cycle regulation, the failure of which can lead to tumour development. "Interestingly, these genes are matched by a similar copy on the X chromosome," explained **Alejandro Cáceres**, lead author of the study. "If, as demonstrated, the X-chromosome copy also mutates in the same cells, the protection against cancer that these genes might otherwise provide is lost completely."

A High-Priority Line of Research

Understanding the biological differences between men and women in cancer is crucial for the development of personalised lines of treatment and prevention. "Men are not only at higher risk of cancer than women, they also **face a worse prognosis**," commented González. "In fact, these differences partially account for the **lower life expectancy** of men."

Identifying the factors that make men more vulnerable to cancer is an important line of research that has the potential to mitigate risk in this population. "Although men may be more exposed to carcinogens due to the type of work they do and at higher risk because they are less likely to consult a doctor, our study has shown that there are also biological factors that increase cancer

risk among men,” commented Cáceres. In fact, it seems that one of these factors can be found in the Y chromosome, the very essence of maleness.”

According to the authors of the study, suppression of the Y chromosome can occur as a result of loss of function in the chromosome, which would explain previous findings, or as a result of other mechanisms mediated by the chemical (epigenetic) inactivation of the same regions.

“Certain environmental exposures, for example to **tobacco or other harmful substances, could affect chromosome function** and lead to epigenetic modifications,” commented González. “Our findings open the door for the development of **targeted detection methods and specific therapies** for men with cancer.”

Reference

Alejandro Cáceres, Aina Jene, Tonu Esko, Luis A Pérez-Jurado, Juan R González. *Extreme down-regulation of chromosome Y and cancer risk in men*. Journal of the National Cancer Institute, January 2020.

About ISGlobal

The Barcelona Institute of Global Health (ISGlobal) is the result of an innovative alliance between “la Caixa” and academic and government institutions. The Institute was set up to contribute to the work undertaken by the international community to address global health challenges. The Barcelona Institute of Global Health (ISGlobal) is the result of an innovative alliance between “la Caixa” and academic and government institutions. The Institute was set up to contribute to the work undertaken by the international community to address global health challenges. ISGlobal has consolidated a hub of excellence in research and medical care that has its roots in work first started in the world of health care by the Hospital Clínic and the Mar Health Park and in the academic sphere by the University of Barcelona and Pompeu Fabra University. ISGlobal is accredited as a Severo Ochoa Centre of Excellence and is a member of CERCA, the Catalan Government’s network of research centres.

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