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# Loss of function in key Y-chromosome genes increases cancer risk in men

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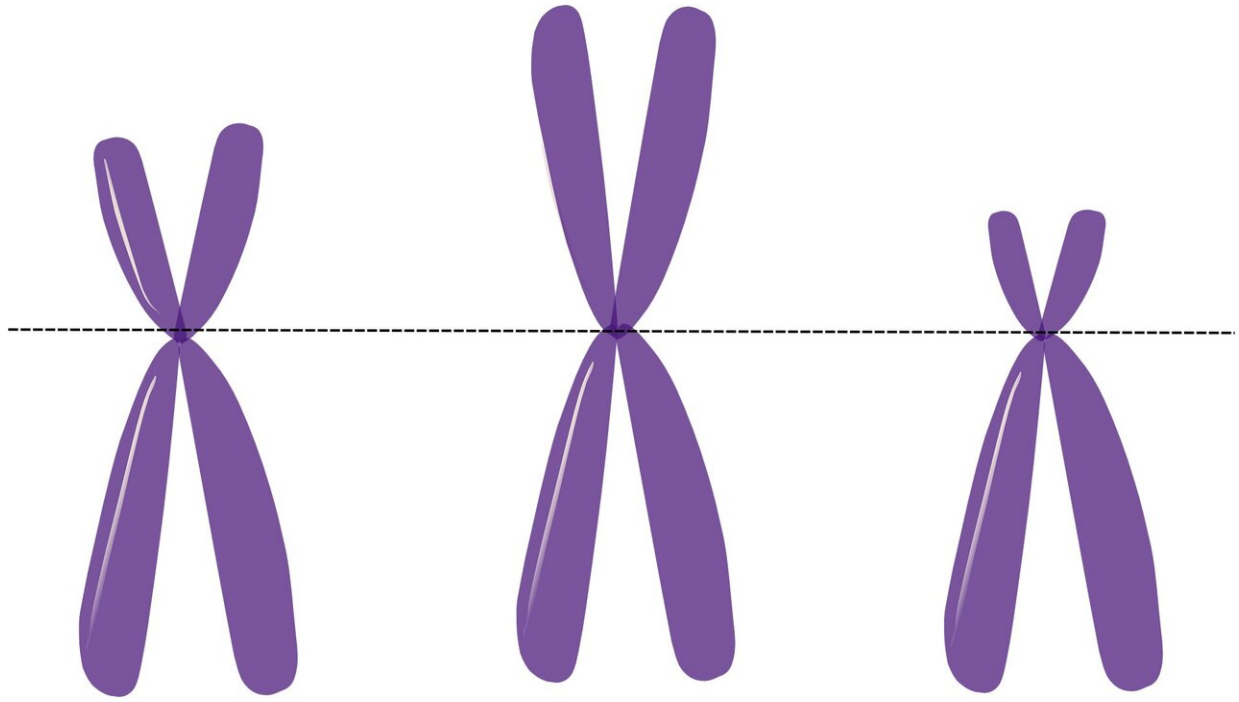

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Numerous studies have shown that men are more susceptible to cancer than women; however, the reason for this difference remains poorly understood. A new study by researchers from the Barcelona Institute for Global Health (ISGlobal) has identified a key biological mechanism that puts men at higher risk of cancer: loss of function in certain genes of the sex-determining Y chromosome. 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 fetal sex differentiation, occurs, with aging, in the cells of some men," said 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 tumor development. "Interestingly, these genes are matched by a similar copy on the X chromosome," said 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."

Understanding the biological differences between men and women in cancer is crucial for the development of personalized 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," said González. "Our findings open the door for the development of targeted detection methods and specific therapies for men with cancer."

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

Provided by Barcelona Institute for Global Health