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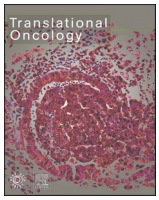

Exploring the link between low germline mutational load and low breast cancer incidence: Lessons from the Xavante Indians☆

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ABSTRACT

The study of cancer, its initiation, and its mechanisms of progression has been a focal point in science for more than a century. Despite controversies among scientists, there is a growing consensus to determine the moment when a cell gains the capacity to be transformed and whether this mechanism is to be attributed to germinal or somatic events, or possibly both. The case of the Xavante Indians is a beacon for this journey, pointing toward the importance of genetic diversity in shaping our approach to cancer research and treatment. As we incorporated these lessons into clinical practice, we embarked on a new era of personalized preventative healthcare strategies against cancer. Based on recent data, we comment on the low germinal mutational load and low cancer incidence. Statistical analyses reveal a significantly lower mutation burden in Xavante women compared to global populations ($p < 0.0001$), including rare deleterious variants in cancer-associated genes. Additionally, polygenic risk scores (PRS) for breast cancer are markedly lower in Xavante (mean PRS ~35) compared to TCGA cohorts (~80–90) ($p < 0.0001$). The absence of breast cancer cases in Xavante is statistically significant when compared to expected rates ($p < 0.001$), reinforcing the hypothesis of a protective genetic landscape.

Introduction

From Boveri to today: cancer genetics and the germinal background

The association between mutations and cancer has been a subject of discussion throughout the 20th century, marked by an interesting debate in which various perspectives and data have clashed. *Theodor Bovery* [1] was the first to draw attention to the possible role of genetic alterations in cancer with his seminal work in 1914, 'Zur Frage der Entstehung maligner Tumouren' [Concerning the Origin of Malignant Tumors].

However, in the 1950s, more data, mainly related to epidemiology, injected vitality, and productivity, were released into debate. This was evident in the work of Armitage and Doll [2,3] and the insights of Nordling [4]. The notion that *'the original cancerous cell is nothing, but an ordinary cell affected by genetic mutation of some kind'*[4] introduced the multistage model of carcinogenesis and emphasized the potential role of mutations in cancer etiology. Since then, our understanding of cancer has significantly advanced.

The tumor *'onco-genotype'*, defining the collection of cancer-related mutations, often arises mainly as *'driver mutations'*, evolving through the accumulation of various 'passenger mutations [5]. Additionally, driver and passenger mutations may display permutations as the tumor evolves, and mutations may be epigenetic or epimutations [6], that is, not as base sequence alterations, but as base modifications induced by epigenetic signals (e.g., methylation). Overall, mutations in critical genes involved in tumor progression may be effective in preventing tumor growth and metastasis [7].

In the long term, the environment and its biota affect the development of germline cells, either by promoting or protecting against cancer throughout life. As the specific gut microbiota of a population group is known to determine genetic variants [8], we must infer its role in the germinal process of cancer.

The genomic diversity across human populations is increasingly recognized as a critical factor in understanding disease susceptibility and resistance. The case of the Xavante Indians offers a unique lens to

☆ In the memory of our dear Professor José Rueff, an exceptional friend and mentor. Com amizade e carinho Professor.

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study this diversity, highlighting how distinct genetic profiles, shaped by evolutionary and environmental factors, may contribute to cancer resistance. This study explores germline mutation load as a determinant of cancer incidence, presenting novel insights that challenge existing paradigms in cancer genetics and precision medicine.

The Xavante enigma: connecting genetics and cancer susceptibility

Sporadic cancers, which constitute most human cancers, are predominantly linked to the exposome, which is the cumulative lifetime accumulation of environmental exposures that escalates the disease risk and influences disease progression. This relationship reveals an intricate link between carcinogenic and mutagenic agents. Sporadic cancers, however, are not solely driven by somatic mutations in gatekeeper genes but also stem from germline mutations in predisposed individuals. These mutations are frequent but have low penetrance, unlike those associated with familial cancer syndromes or hereditary cancers (for example, BRCA1/2 and APC), which are rare but have high penetrance. In this simple model, one should add the infidelity of DNA replication or the role of the microenvironment, resulting in the proliferation of mutant clones leading to cancer [9].

Although it may be impossible to ascertain the extent to which both DNA replication infidelity or the interface of landscaper genes and the microenvironment of the initiated cells contribute to cancer incidence, it is clear that germline mutation load decisively determines cancer incidence. Indeed, recent work by Selvan et al. [10], extending and widening previous studies on the contribution of the accumulation of deleterious variants to cancer incidence [11–15], sheds new light on the importance of the inherited culprit of DNA variations in cancer.

At this stage, indicating the unavoidable role of germline mutation load in the cancer process, additional evidence could be contraposition proof, or at least an indication that low or non-existent cancer incidence is associated with a low germline mutation load. This indication could be derived from the observation of Castro and co-workers, who worked for over ten years as a *pro bono* physician in Xavantes' Indian reserve in Brazil. This is one of the best-studied human populations in terms of human biology, as Salzano et al. described and reported in 1997. They are hunter-gatherers with a low degree of miscegenation, remain genetically isolated over the past decade, and provide advantages for genome-wide mapping studies of inherited disorders [16]. The patients did not develop breast cancer during their lifetime (Fig. 1**a**). This absence of breast cancer among Xavante women aligns with their significantly lower germline mutation burden. Whole-exome sequencing of 14 Xavante individuals revealed an average of ~269 mutated genes per person (SD ≈ 13.7), which is notably lower than in European and African populations (300–400+ mutated genes per person). Furthermore, statistical comparisons show that the Xavante mutation burden is significantly lower than that of other ethnic groups ($p < 0.0001$). Given the observed breast cancer incidence in global populations, a chi-square test comparing Xavante to expected global rates confirms that the near-zero cancer incidence in Xavante is statistically significant ($p < 0.001$).

To clarify the possible basis of this observation, sequencing of the exomes of Indians who volunteered to 179 participate in the study was performed. Despite the huge agricultural developments in the region, where they reside within the reserves, the Xavante ethnic group preserved their culture and social behavior, growing their population from 1100 inhabitants in 1958 to 22,556 in 2020 [17], adopting cross-breeding with patrilineal rotation, according to the Iroquois model described by Maybury-Lewis (1984). After obtaining legal authorization from the Brazilian Government and informed consent signed by each Xavante woman, Castro administered a questionnaire, measured, weighed, and collected 168 blood samples from 179 volunteer participants, as shown below in the examples in Fig. 2. All samples revealed a

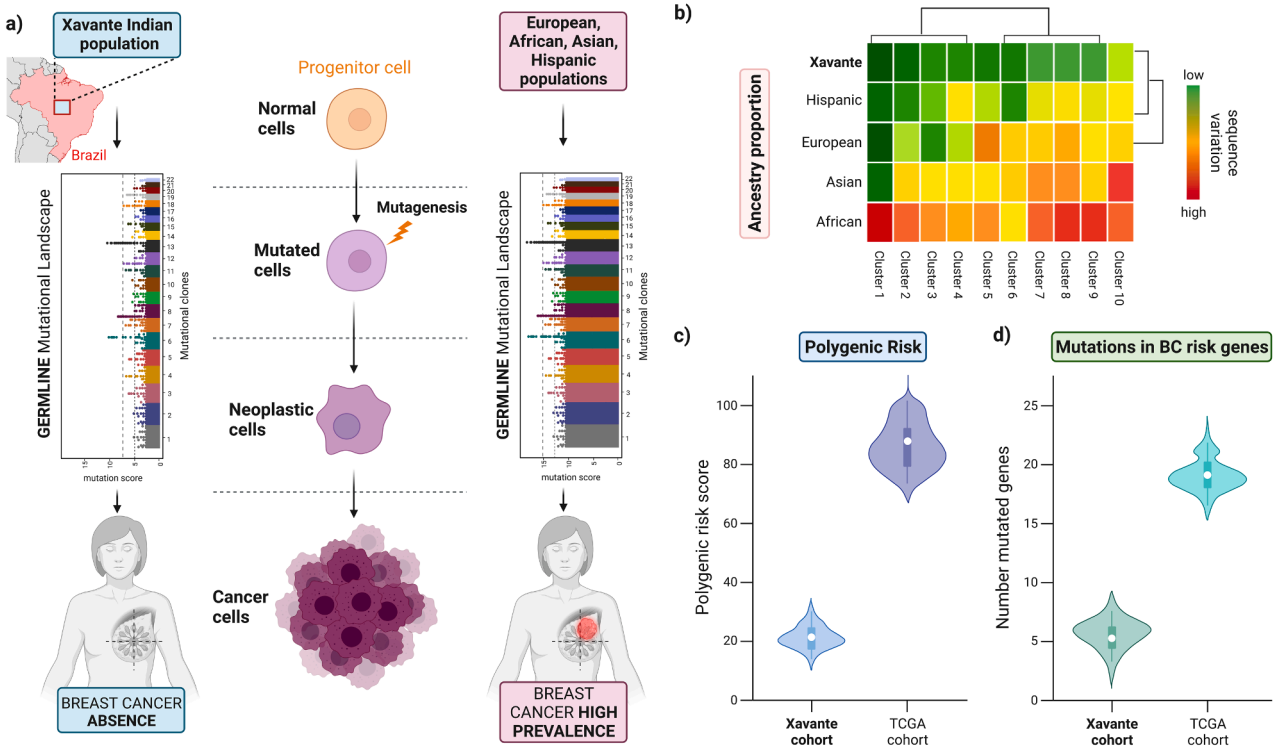

Fig. 1. Absence of breast cancer in Xavante Indians: A case study of germline genetic factors. (a) Germline mutational landscape of the Xavante population compared with other ethnic groups from the 1000 Genomes Project, which includes European, African, Asian, and Hispanic populations. (b) Ancestral genetic composition and sequence variation across different populations, including Xavante, Hispanic, European, Asian, and African. (c) Polygenic risk scores for breast cancer in the Xavante and TCGA cohorts, indicating lower risk in the Xavante population. (d) Number of mutations in breast cancer risk genes in the Xavante and TCGA cohorts, with fewer mutations observed in the Xavante population.

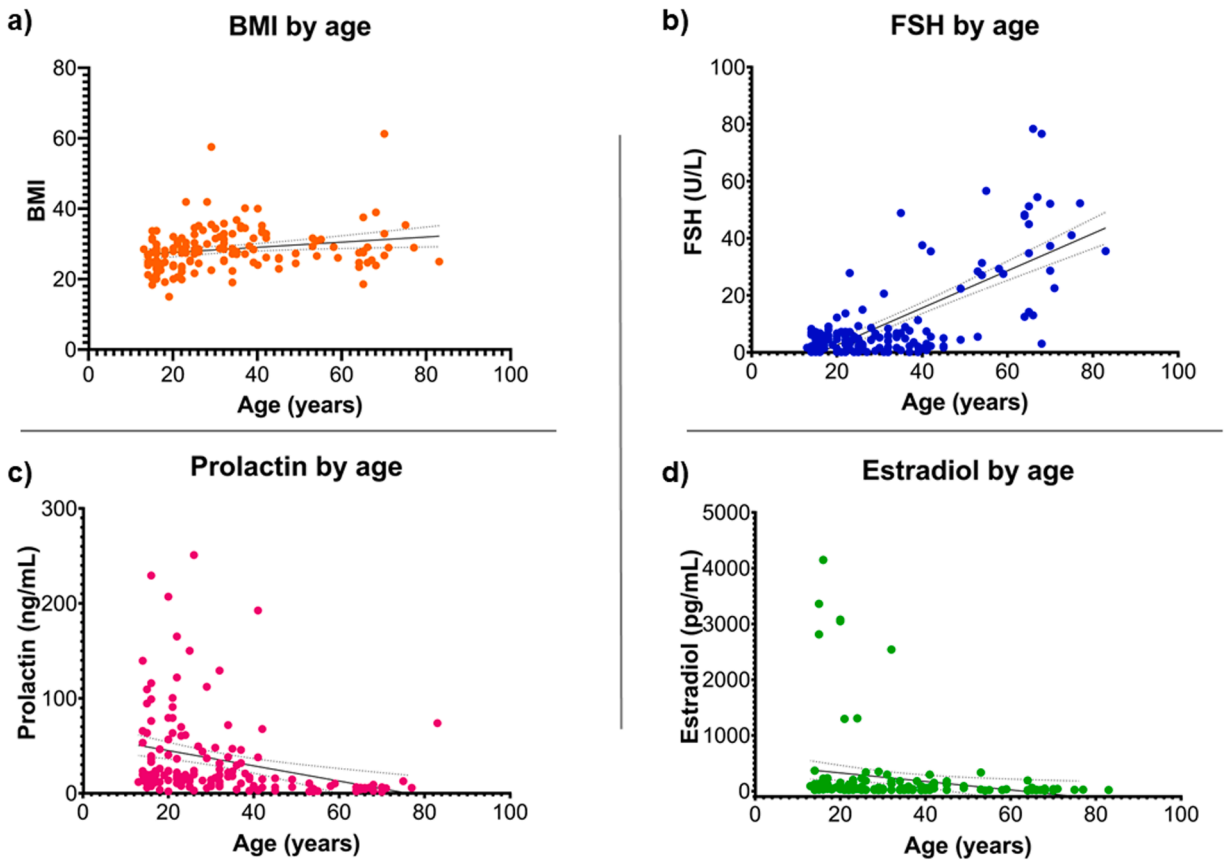

Fig. 2. Analysis of 168 blood samples from Xavante women living in Sangradouro Indian Reserve, Mato Grosso, Brazil by age of **(a)** Average high BMI (Body Mass Index), **(b)** Follicle-stimulating Hormone (FSH), **(c)** Prolactin and **(d)** Estradiol levels.

unique blood type, "O" Rh Positive, corresponding to the study published by Salzano in 1961 [18].

The hormone levels observed in Xavante women were compared to global reference ranges. Prolactin levels, with a range of 10–250 ng/mL, exhibited some higher values compared to the global standard range for non-pregnant women (3–27 ng/mL). Estradiol levels varied widely, with some reaching up to 4500 pg/mL, exceeding the global follicular phase range (20–350 pg/mL). FSH levels, which ranged from 5 to 80 IU/L, also showed higher values compared to the expected global ranges for reproductive phases (3–25 IU/L). A statistical comparison between Xavante hormone levels and global reference values indicates significant differences in prolactin (mean: 45.2 ng/mL, SD: 67.8, $p < 0.01$) and estradiol (mean: 1120 pg/mL, SD: 1950, $p < 0.05$). These findings suggest potential ethnic-specific hormonal regulation patterns that may contribute to unique reproductive health profiles among Xavante women. These results indicate that while Xavante women show certain hormone levels within global norms, others deviate significantly. For example, prolactin and estradiol levels in some individuals were markedly higher than those observed globally. These deviations may point to ethnic-specific biological patterns, environmental factors, or dietary influences unique to the Xavante population. Notably, Xavante women's hormonal profiles appear unaffected by BMI in ways distinct from global populations where BMI above 25 is typically associated with altered reproductive hormone levels and fertility outcomes [19]. This lack of association may reflect genetic adaptations or lifestyle factors influencing endocrine health. Further studies are needed to investigate whether these findings are indicative of broader population-level trends or unique to the Xavante community. By contextualizing the hormone data with global standards, this study highlights the importance of considering ethnic diversity in understanding reproductive health and lays the groundwork for future research on the interplay between genetics, environment, and health outcomes.

An article by Ventura Santos [20] revealed the transition in the health profile among the Xavante population within half a century, changing their behavior and nutritional patterns and getting similar health issues as populations living in developed countries, such as diabetes, high blood pressure, and heart diseases. The endocrinologist Joao Paulo Botelho Vieira-Filho, from the University of São Paulo (UNIFESP) wrote in 2000, "*The Xavante, who were slim before contact…have become overweight or obese, because of dietary changes that came with the Government rice-growing project…(and) high consumption of rapidly absorbed carbohydrates* [21].

Even though there have been several changes in Xavante corporeal biology, there is no record of breast cancer among them, even if cancers in other organs are currently reported, such as lung, colon, gastric, head and neck, leukemia, and cervix. "*The five main sites in men were the stomach, liver, colon, rectum, leukemia, and prostate. The five main sites in women are the uterine cervix, stomach, liver, leukemia, and uterus. In indigenous men there was an excess of deaths from stomach cancer compared to the populations of Goiânia (SMR = 2.72; 2.58–2.87), Acre State (SMR = 2.05; 1.94–2.16) and North region (SMR = 3.10; 2.93–3.27)*" [22].

After verification by PCA, a unique genetic cluster using 291,984 SNVs shared by other populations in the 1000 Genomes Project Phase 3 was performed to calculate the polygenic risk score using 2171 variants for that population and compared with the risk score from TCGA blood samples with breast cancer, which showed a much lower risk for Xavantes (Fig. 1**b**). Polygenic risk score (PRS) analysis further supports this trend. Xavante individuals exhibit a significantly lower PRS for breast cancer than TCGA individuals, with mean PRS values of ~35 vs. ~80–90, respectively ($p < 0.0001$). The distribution of PRS in Xavante is tightly clustered, suggesting a consistently low genetic predisposition across individuals. Notably, a Wilcoxon–Mann–Whitney test comparing

PRS distributions between Xavante and TCGA groups indicates a highly significant difference ($p < 0.0001$), reinforcing the hypothesis that low PRS contributes to the near-absence of breast cancer in Xavante. A comparison was also performed on the mutation burden on the whole exome of 1296 females from the 1000 Genome Project Phase 3 reference population and 200 randomly selected TCGA normal blood samples (100 from women with ductal breast cancer and 100 from ductal breast cancer), which showed a much lower mutation burden (Fig. 1**c-d**) [23]. Statistical analyses further confirm these observations. The Xavante mutation burden remains significantly lower than global populations ($p < 0.0001$), supporting the hypothesis that reduced germline mutational load is linked to decreased cancer risk. These results support the multifactorial nature of cancer development, emphasizing the role of germline mutations and inherited genetic variations in predisposing individuals to cancer. Beyond qualitative observations, statistical analyses further support these findings. The Xavante mutation burden is significantly lower than that observed in global populations ($p < 0.0001$). A chi-square test comparing observed breast cancer incidence (0 cases in 168 women) to expected rates (~12 % lifetime risk in global populations) yields a highly significant result ($p < 0.001$), rejecting the null hypothesis that Xavante cancer incidence follows global patterns. Correlation analyses suggest an inverse relationship between germline mutation load and breast cancer incidence, where populations with higher deleterious variant loads tend to exhibit greater cancer prevalence. Spearman rank correlation analyses confirm a strong negative association between inherited mutation burden and cancer occurrence, emphasizing the role of genetic predisposition in shaping cancer susceptibility. These data align with the current understanding that while some populations may carry a higher burden of mutations linked to cancer risk, others may have a genetic makeup that confers a lower risk. This information is crucial for precision medicine as it could lead to population-specific cancer screening and prevention strategies. This highlights the importance of studying diverse populations, as most genetic studies have historically been Eurocentric. This illustrates the complex interplay among genetic ancestry, germline mutations, and cancer risk. This underscores the potential of unique genetic profiles to inform cancer epidemiology and develop tailored approaches for cancer prevention and treatment.

Our findings reveal that Xavante Indians exhibit a markedly low germline mutation burden, correlating with the absence of breast cancer. Beyond this observation, our analysis suggests that non-coding regulatory regions, rather than coding regions traditionally associated with breast cancer, may play a pivotal role in resistance. This has shifted the focus of cancer research towards underexplored genomic elements, providing a novel framework for understanding cancer etiology in diverse populations. Furthermore, the Xavante case exemplifies how genetic isolation, and unique evolutionary pressures can inform population-specific approaches for cancer prevention and treatment.

Integrative analysis of germline mutation load across studies: bridging genomic and cancer incidence

Overall, the available data seem to support the view that germline mutational load is associated with cancer incidence, and as a contraposition proof, a population with a very low mutational load does not appear to have breast cancer, indicating an almost direct role of mutation load in cancer incidence.

Cancer is chiefly a disease with mutations, as suggested by Boveri's view, whether inherited or somatic. The relative role in cancer incidence was sought to determine their quantitative effect on cancer incidence, with the relevant fact that many inherited mutations may affect the rate of occurrence of somatic mutations that lead to tumor growth and metastases. The lower the inherited mutational load, the lower the incidence risk. Thus, germline mutation load is a possible main mechanism explaining the different susceptibilities to cancer in different populations and paves the way for a new paradigm in understanding genetic predisposition to cancer.

The comparison of genetic data from the Xavante Indians with that of TCGA cohorts revealed insights into the landscape of cancer genetics. Interestingly, when comparing the number of mutated genes in the whole exome of Xavantes' Indians to the 1000 Genomes reference population, they had a significantly lower number of mutated genes. However, if such a comparison is made only for genes known to be relevant to breast cancer (e.g. BRCA1, BRCA2, CASP8, RAD51, TERT, and TP53), Xavante did not seem to differ (Fig. 3 [23]), suggesting that the mutation load essential for cancer development may rely on non-coding genes such as those involved in the network circuitry of non-coding RNAs (e.g., microRNAs and long ncRNAs). This indicates that the genes involved in regulatory networks may be of crucial importance in cancer development [24]. Xavante data, indicating a lower burden of mutations in these non-coding regions, open new avenues for research on non-coding genetic contributions to cancer. These analyses suggest that Xavante Indians with lower polygenic risk scores and mutation burden in known breast cancer genes may indicate genetic resistance to cancer development or a distinct evolutionary path in their genomic landscape. This led us to discuss how these findings underscore the complex interplay between genetics and the exposome in shaping cancer susceptibility. This could prompt the re-evaluation of current cancer risk models, especially in populations with unique genetic backgrounds. Moreover, the minimal germline mutation burden in Xavante might indicate a broader spectrum of genetic factors involved in cancer protection that are not yet fully understood, including regulatory elements and non-coding RNA sequences, which are increasingly recognized as significant players in gene expression and disease manifestation. These comparisons not only provide valuable data for the scientific community but also have significant implications for precision medicine. This could lead to the development of tailored screening and prevention programs that consider the diverse genetic makeup of different population groups. Understanding the genetic factors that contribute to Xavante's lower cancer rates could lead to novel therapeutic targets and preventive strategies, reinforcing the need to expand research efforts to encompass the full breadth of human genetic diversity.

These results were also confirmed by a genome-wide analysis in Xavante Indians [16], showing that Xavante has a distinct genetic profile that may contribute to the reduced incidence of cancer. This could be because of a combination of factors including lifestyle, a limited number of germline mutations, and a unique evolutionary pathway that has equipped them with genetic variants that provide a protective effect against cancer development. In the context of cancer genetics, the Xavante case study provides a unique opportunity to understand how certain populations may have a lower predisposition to cancer. This could offer new avenues for research on cancer prevention and treatment, specifically identifying genetic markers that could be used for early detection and prevention strategies in other populations. Furthermore, this low incidence of cancer may challenge existing theories about the inevitability of cancer as a disease of aging, suggesting that genetic factors play a more significant role than previously thought. The lessons learned from Xavante could influence future research on germline mutations and their contributions to oncogenesis, potentially leading to advances in understanding 140 and in approaching the genetic basis of cancer.

Furthermore, another study on the Xavante Indian population highlighted a lower frequency of specific genetic polymorphisms in estrogen-metabolizing genes, which may contribute to their notably low breast cancer incidence [25]. This study explored genetic polymorphisms in estrogen-metabolizing genes and their associations with breast cancer risk. Specifically, it examines MnSOD gene polymorphisms, which have a potential protective role, especially in women who have never breastfed. This finding aligns with the broader notion that reduced germline mutational load could be linked to decreased cancer susceptibility. These findings provide a valuable perspective on

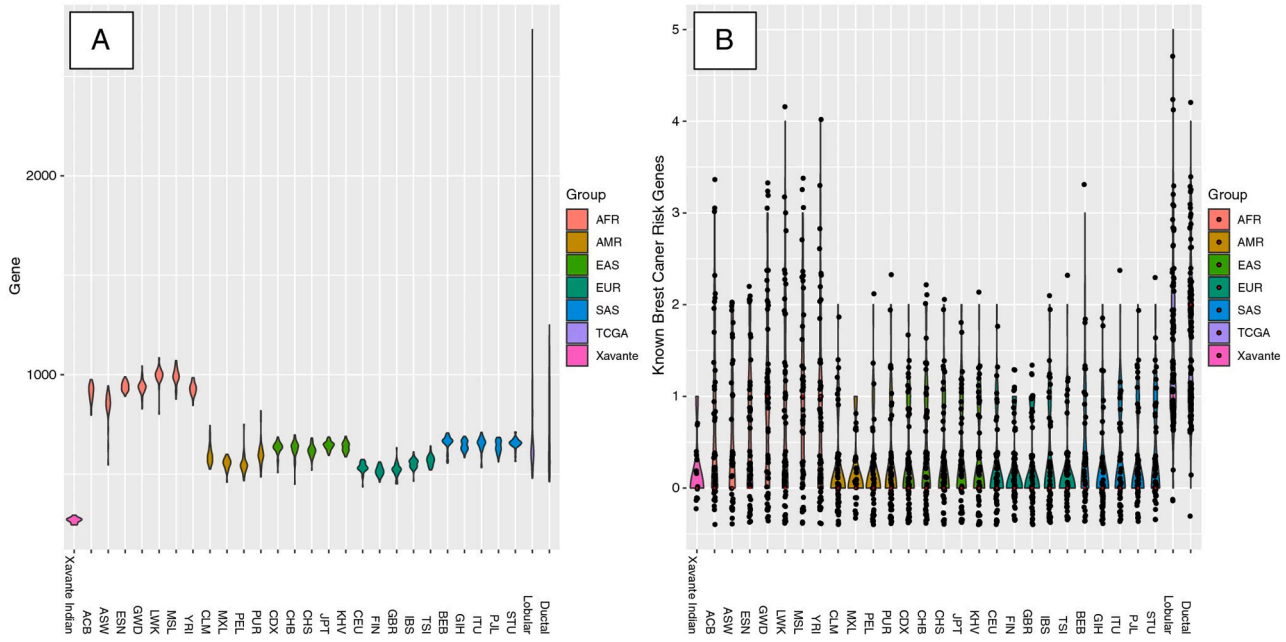

Fig. 3. The number of mutated genes affected by rare damaging variants in different populations, including Xavante Indians, normal populations from the 1000 Genome Project, and normal samples from the TCGA breast cancer dataset. (A) The number of mutated genes in the whole exome ($p < 0.0001$ for all groups against Xavante Indians). (B) Number of mutated genes among the known breast cancer risk genes ($p < 0.0001$ for Xavante Indians vs. TCGA breast normal control groups). Adapted with permission from [23].

the genetic underpinnings of cancer resistance, emphasizing the significance of germline genetic diversity in disease prevalence and offering potential avenues for personalized cancer prevention strategies.

The Xavante study underscores the importance of integrating underrepresented populations into genomic research. Historically, most genetic studies have focused on Eurocentric cohorts, overlooking the vast diversity of genetic profiles worldwide. The lower mutation burden observed in the Xavante population emphasizes the need to re-evaluate current cancer risk models. These findings pave the way for tailored screening and prevention strategies that align with the principles of precision medicine. Expanding such studies could uncover additional protective genetic mechanisms and provide novel therapeutic targets.

Overall, the view on the importance of germinal mutation load could help identify people to be included in an out-and-out program of surveillance according to a high risk of cancer, discharging a large number of others at low risk when using this algorithm. The identification of individuals with a high germline mutation burden can enhance targeted screening and early intervention. Conversely, recognizing low mutation burden profiles could spare individuals from unnecessary screening procedures, aligning cancer prevention strategies with ideals of precision medicine.

The genetic road ahead

As we have explored the complex interplay between genetics and cancer, our journey from Boveri's foundational work to today's advanced genomic analyses illuminates a path forward in cancer research. The intriguing case of Xavante Indians, demonstrating a notably low incidence of breast cancer correlated with a minimal germline mutation burden, opens new avenues for our understanding of cancer susceptibility and prevention. The insights gained from these unique population studies underscore the need to broaden the scope of this research. Future studies should aim to encompass diverse genetic backgrounds and environmental contexts, allowing for a more holistic understanding of cancer etiology. This approach promises to reveal the intricate genetic and epigenetic mechanisms underlying the development of cancer.

Furthermore, the genetic profile of Xavante Indians, particularly the low mutation burden in non-coding regions associated with regulatory networks, is a key area for future research. This highlights the potential role of ncRNAs and other regulatory elements in cancer pathogenesis, which remains relatively unexplored. In the clinical field, these findings could revolutionize cancer screening and prevention strategies. Targeted surveillance programs that enhance early detection and intervention can be developed by identifying individuals with high germline mutation loads. Conversely, recognizing those with a low mutation burden could reduce unnecessary interventions, aligning them with personalized medicine principles. Moreover, an emerging understanding of the impact of germline mutation load calls for re-evaluation of current cancer treatment protocols. Therapies tailored to individual genetic profiles, considering both coding and non-coding mutations, could significantly improve the treatment efficacy and patient outcomes.

The lessons learned from Xavante Indians present a compelling case for the importance of genetic factors in cancer susceptibility. Their distinct genetic profile, characterized by a lower mutation burden in germline cells and fewer mutations in known breast cancer risk genes, contrasts sharply with data from other populations, including TCGA. This suggests that genetic diversity and evolutionary history play crucial roles in determining disease prevalence. Such findings emphasize the need for the inclusion of diverse genetic backgrounds in research, which can illuminate previously unknown protective mechanisms against cancer and may lead to novel therapeutic targets and strategies for cancer risk assessment. The continued exploration of germline mutations in diverse populations, such as Xavante Indians, coupled with advancements in genomic technology, has led to innovative discoveries in cancer research. Now it is essential to integrate these insights into clinical practice to transform the landscape of cancer prevention, diagnosis, and treatment. This evolution in our understanding and approach marks a new era in the fight against cancer, one that holds promise for more effective, personalized, and preventive healthcare strategies.

This study reinforces the importance of genetic diversity in the understanding of cancer susceptibility. The unique genomic profile of Xavante Indians challenges conventional theories about cancer

development and highlights the potential of non-coding regulatory regions in conferring cancer resistance. These findings have profound implications for cancer epidemiology, precision medicine, and the development of population-specific prevention strategies, demonstrating the critical need to expand research beyond the traditionally studied populations.

CRediT authorship contribution statement

José Rueff: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **João Conde:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Guilherme Castro:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

J.C. is a co-founder and shareholder of TargTex S.A. – Targeted therapeutics for Glioblastoma Multiforme. J.C. is a member of the Global Burden Disease (GBD) consortium of the Institute for Health Metrics and Evaluation (IHME), University of Washington (US) and is in the Scientific Advisory board of Vector Bioscience Cambridge. The other authors have no conflicts of interest to declare.

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