Press Release for article recently published in The Lancet discovery Science journal eBioMedicine

Research article Title	A genome-wide association study of buccal mucosa cancer in India and multi-ancestry meta-analysis discovers risk loci and gene-environment interactions**.**
Institution	Centre for Cancer Epidemiology, ACTREC, TMC.
Funder	Department of Health Research
Senior authors	Drs. Pankaj Chaturvedi, Nilanjan Chatterjee, Siddharth Kar, Anil Chaturvedi and Rajesh Dikshit.
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Division Website	https://tmcepi.gov.in/MolecularEpidemiologyAndPopulationGenomics/
QR code of the division website	
Link for full research article	https://www.thelancet.com/journals/EBIOM/article/PIIS2352-3964(25)00486-4/fulltext

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Agenda for Press release

Date: 29 .11.2025 Time 12:30 PM – 2.30PM

Venue: 7Th floor Seminar Room RRU Building, ACTREC, Kharghar, Navi Mumbai.

1. Registration and distribution of kit (Press release, copy of the paper, Quotes)
2. Welcome- Mr. Anand Iyer
3. Oral Cancer in India - Dr. Pankaj Chaturvedi
4. Genome Wide Association Studies: Why they are important? - Dr. Rajesh Dikshit.
5. Presentation of findings from the research paper - Dr. Sharayu Mhatre
6. Clips of Quotations from International experts
7. Question and answer
8. Vote of thanks: Ms. Grace Sarah George
9. Working Lunch

Press note:

Why Do Some Tobacco Chewers Develops Oral Cancer Early?

New Genome-Wide Study from Tata Memorial Centre Sheds Light

Mumbai, India — [29.11.2025]

A landmark **Genome-Wide Association study (GWAS)** by **Centre for Cancer Epidemiology, ACTREC at** the **Tata Memorial Centre**, Mumbai, has identified key **genetic factors** that explain why some tobacco chewers in India develop oral cancer **nearly a decade earlier** than others.

New research published in the journal eBioMedicine, part of The Lancet Discovery Science, identifies specific genetic markers that significantly increase susceptibility to oral cavity cancer, which is one of the most common and preventable cancers in India, primarily linked to tobacco use. The study compared 2,160 cases of Buccal Mucosa cancer with 2,325 controls from various geographical regions in India and conducted a genome-wide scan to understand the role of genetic susceptibility in the development of oral cancer. Researchers discovered genetic risk loci on chromosomes 5 and 6, near the genes CLPTM1L-TERT, HLA-DRB1, HLA-DQB1, and CEP43. Additionally, a meta-analysis that included data from Europe and Taiwan identified novel risk loci near the NOTCH1 gene.

The investigators calculated a polygenic risk score and found that tobacco chewers with a high polygenic risk score (indicating higher genetic susceptibility) developed Buccal Mucosa cancer 10 years earlier than those with a low polygenic risk score.

In India, there are around 141,342 cases of oral cancer, with an average age-standardized rate of 10.0 per 100,000 people. In some states, this rate ranges from 25 to 33 per 100,000. Despite similar lifestyle factors, the onset and progression of the disease can vary significantly among individuals. This study offers the first clear genetic explanation for those differences, demonstrating that genetic makeup plays a crucial role in enhancing the risk of oral cancer among tobacco chewers.

Dr. Sudeep Gupta, Director of the Tata Memorial Centre, underscored the need to examine gene-environment interactions and to develop polygenic risk scores for common cancers in India. He emphasized the importance of such studies in understanding genetic susceptibility in cancer development. Nonetheless, he reiterated that tobacco chewing is the single most preventable cause of oral cancer, with more than 80% of oral cancers potentially preventable through effective tobacco control policies.

Dr. Pankaj Chaturvedi, Director of ACTREC, emphasized that tobacco chewing is a significant risk factor for oral cancers, noting that the risk of developing oral cancer is 26 times higher among tobacco chewers, compared to non-users of tobacco. The risk attributed to genetic susceptibility markers is double for those with high genetic risk score compared to those with low genetic risk score.

Dr. Elisabete Weiderpass, Director of the International Agency for Research on Cancer, a part of the World Health Organization, Lyon, France while noting the importance of study said that "This landmark study represents a significant advance in our understanding of the genetic and environmental factors driving buccal mucosa cancer, a disease that imposes a heavy burden in India and across South Asia. By conducting the largest genome-wide association study of its kind and integrating data from multiple ancestries, the authors have identified novel risk loci and illuminated the complex interplay between genetic susceptibility and tobacco chewing. These findings not only deepen our knowledge of oral cancer etiology but also highlight the urgent need for tailored prevention and screening strategies in high-risk populations. The work exemplifies the power of international collaboration and genomic research to address pressing public health challenges and paves the way for more personalized approaches to cancer prevention worldwide."

Dr. Rajesh Dikshit, Director of CCE, explained that the study's findings suggest that understanding genetic predisposition can lead to better prediction of oral cavity cancer development among tobacco chewers. He further highlighted that pathway analysis from the current study indicated distinct immune pathways and "highly calcium-permeable nicotine receptor-encoding genes" are involved in the development of oral cavity cancer. Further exploration of these pathways could enhance our understanding of carcinogenesis and help develop precise targets for early detection and prevention.

Dr. Nilanjan Chatterjee, Bloomberg Distinguished Professor Department of Biostatistics, Bloomberg School of Public Health Department of Oncology, School of Medicine Johns Hopkins University quoted that " This article, for the first time, provides important insights into the genes that influence susceptibility to this cancer and how they interact with the carcinogenic effects of tobacco chewing. Individuals who chew tobacco face a substantially higher risk of developing buccal mucosa cancer compared to those who do not. What is often less recognized is that genetic predisposition can further amplify this risk. We don't get to choose the genes we're born with and that makes it even more important to choose the habits that keep this really bad cancer at bay.

Dr. Sharayu Mhatre, a Scientific Officer at CCE lead author of the study, stated that while tobacco use is the strongest risk factor for developing Buccal Mucosa cancer, there is also a genetic susceptibility component involved. She noted that there is about 24% relative excess of oral cavity cancer cases among tobacco chewers with high genetic risk score compared to chewers with low genetic risk score. When compared to the European population, similarities and distinct differences in their genetic architectures were observed, highlighting the need for Indian-specific genetic data.

Dr. Preetha Rajaraman Executive Director (U.S.), Vice Chair, and Chief of Research for the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan, while stressing the importance of the study commented that "these findings provide important new insights into how behavior interacts with genetic make-up to influence the risk of buccal mucosa cancer, one of the most common cancers in India. Specifically, by considering chewing tobacco habits along with genetic predisposition, we may be able to provide more personalized screening for buccal mucosa cancer."

Dr. Siddhartha Kar, Associate Professor in the Oncology Department at Cambridge University said, "This landmark study advances our understanding of why oral cancer is so common in India, uncovering uniquely Indian genetic risk factors. By showing how inherited risk interacts with tobacco use, it lays the groundwork for targeted prevention and early detection, marking a major milestone for cancer genomics in India."

Dr. Rajesh Dikshit Director Centre for Cancer Epidemiology (CCE) told that CCE is conducting GWAS on many other common cancer sites in India which will help to estimate genetic risk score in developing cancer of these sites. Dr. Sharayu Mhatre presented the results

of the study and emphasised the requirement of large sample size to understand the genetic component responsible for causation of cancer.

Frequently asked questions:

Q1: What is burden of Oral cavity Cancer in India.

Oral cavity cancer is a significant public health issue in India. The country accounts for about one-third of global oral cancer cases, resulting in one of the highest burdens worldwide. It ranks among the top three cancers among men in India and is also prevalent in women. The high prevalence of smokeless tobacco and betel quid consumption significantly contributes to this burden. Every year, approximately 141,342 new cases of oral cavity cancer are diagnosed in India. The age-adjusted rates of oral cancer vary between 25 and 33 per 100,000 people in many Indian states. Unfortunately, oral cancers are often diagnosed at advanced stages, leading to high mortality rates and considerable challenges in treatment.

Q2: What are main risk factors for Oral cancer.

The major risk factors include:

- Tobacco use (smoked and smokeless forms such as Gutkha, khaini, Zarda, and betel quid with tobacco)
- Alcohol consumption
- Areca nut (supari) chewing, even without tobacco
- Poor oral hygiene.
- Long-term exposure to these factors significantly increases the risk.

Q3: What is role of genetic susceptibility in development of oral Cancer?

Genetic susceptibility means your genes make you more likely to get a certain disease, but it does not mean you will definitely get it. It only increases your risk. It plays an important role in determining who is more likely to develop oral cancer. Some people inherit genetic variations that:

- Reduce the body's ability to repair DNA damage
- Make them more sensitive to harmful chemicals from tobacco, alcohol, and areca nut
- Affect immune and inflammation pathways

These genetic differences do not directly cause oral cancer, but they increase a person's risk, especially when combined with lifestyle factors such as tobacco use. This helps explain why not everyone exposed to the same risk factors develops the oral cancer.

Q4: What is Case-Control study?

A case-control study is a type of research design used to find out what factors might be linked to a certain disease or outcome. In this approach, one group of people who already have the condition (cases) is compared with another group who do not have the condition (controls). Researchers then look back in time to see what exposures or differences existed between the two groups. This helps identify possible causes or risk factors for the particular condition.

Q5: What is DNA, and how was it extracted in this study?

DNA is the genetic material that carries the instructions for how living organisms grow, function, and inherit traits. In this study, genomic DNA was extracted from peripheral blood samples using a magnetic bead–based protocol on an automated liquid-handling platform with the QIAsymphony DNA Midi kit, following the QIAsymphony® DNA Handbook. For manual extractions, the QIAamp DNA Blood Midi kit was used.

Q6: What is GENE?

A gene is a specific segment of DNA that contains the instructions for making a functional product—usually a protein—and thereby controls hereditary traits and biological processes.

Altogether, these findings point to six biologically important genes listed i.e CLPTM1L, TERT, HLA-DRB1, HLA-DQB1, FGFR1OP, and CDKN2A (identified through the meta-analysis).

GENE	ROLE
CLPTM1L	Helps cells avoid death; linked to increased cancer risk.
TERT	Maintains telomeres; changes can raise cancer risk.
HLA-DRB1	Helps immune system recognize threats; affects cancer risk.
HLA-DQB1	Supports antigen presentation; certain types influence cancer risk.
FGFR1OP	Involved in cell division; changes may cause cell instability.
CDKN2A	Controls cell cycle; loss or mutation increases cancer risk.

Table 1. Functions of Genes Associated with Cancer Susceptibility

Q7: Difference between Allel and Allelic frequency?

An allele is a version of a gene or a specific DNA position, such as the different nucleotides (A, T, C, or G) that can appear at a SNP site. People in a population may carry different alleles at the same genetic location. The allelic frequency describes how common each allele is within that population—for example, if one allele appears 60% of the time and another appears 40%, those values represent their allelic frequencies.

Q8: What is Single Nucleotides Polymorphism?

A single nucleotide polymorphism (SNP) is a common DNA variant involving a change of one nucleotide (A, T, C, or G) at a specific genomic position, occurring in ≥1% of the population. SNPs serve as genetic markers in GWAS and can influence gene function, regulation, or disease susceptibility.

The Indian population GWAS found five important SNPs across the genome. The strongest one was rs31490 on chromosome 5p15.33, which is located 756 base pairs before the CLPTM1L gene.

Q9: What is Genome Wide Association Study.

A GWAS is a research approach that scans the entire genome of many individuals to identify genetic variations associated with a disease or trait. It helps pinpoint genes that may influence a person's risk of developing specific conditions. In a GWAS, researchers:

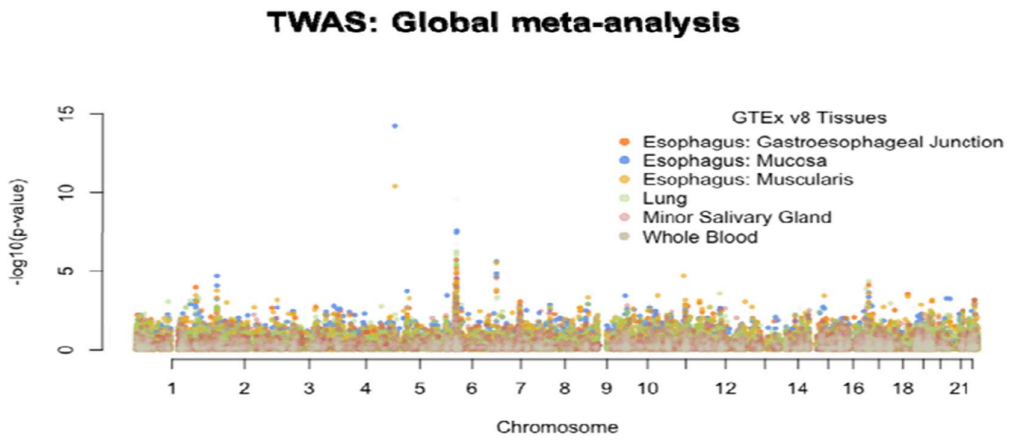
- Scan the entire genome of thousands of people
- Compare genetic data between individuals with a disease (cases) and those without it (controls)
- Look for specific genetic markers, called single-nucleotide polymorphisms (SNPs), that occur more often in people with the disease

Finding these markers helps scientists understand which genes may influence disease risk, how the disease develops, and who may be more susceptible. GWAS has been widely used to discover genetic risk factors for many conditions, including oral cancer.

Q10: What is Transcriptome-Wide Association Study?

A TWAS (Transcriptome-Wide Association Study) is a research method that links genetic variants to predicted gene expression to find genes whose activity may influence disease risk. It complements GWAS by highlighting biologically relevant genes and potential mechanisms. In the multi-ancestry TWAS described, esophageal tissues showed the strongest signals, and two genes outside known oral-cancer regions—GPN1(mainly in Europeans) and MS4A4A (consistent across Indian and multi-ancestry data)—were identified as potential risk-related genes.

Figure 1: Transcriptome-wide association study (TWAS) using the multi-ancestry meta-analysis



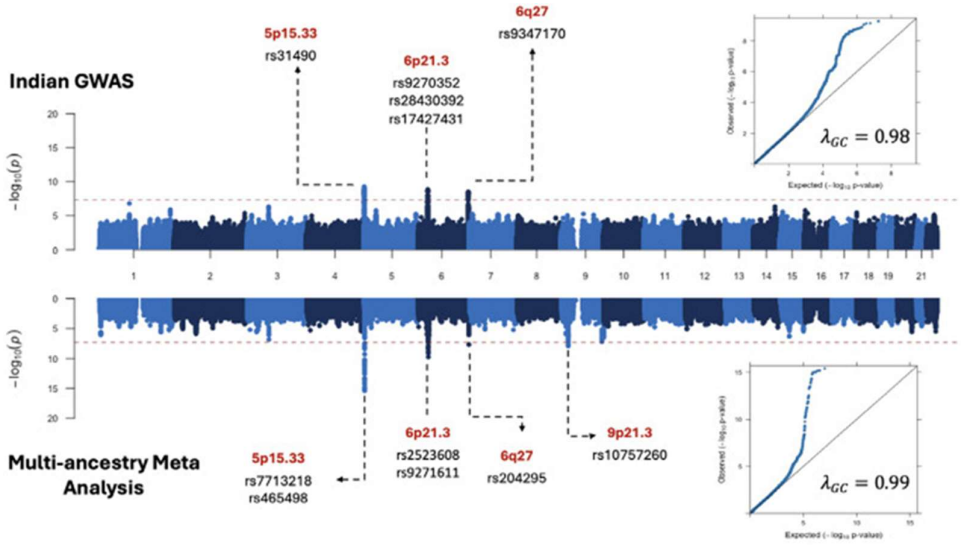
Q11: Difference between GWAS and TWAS?

GWAS and TWAS both help find genes related to a disease, but they look at different things. GWAS checks the DNA to see which SNPs are more common in people with the disease. TWAS checks which genes are more active or less active by using both DNA data and gene-expression data. In simple words, GWAS looks at DNA changes, while TWAS looks at gene activity to understand what may cause the disease.

Q12: What is Manhattan plot?

A Manhattan plot shows the p-values of all SNPs in a GWAS, with each dot representing how strongly a SNP is linked to the disease—the higher the dot, the stronger the association. In GWAS, we test whether a SNP appears more often in people with the disease than in healthy individuals. This test produces a p-value, which tells us the chance that the result happened randomly; a smaller p-value means the SNP is more likely to be genuinely associated with the disease. A SNP is a common change in a single DNA letter, while a mutation is a rarer change that can sometimes affect health.

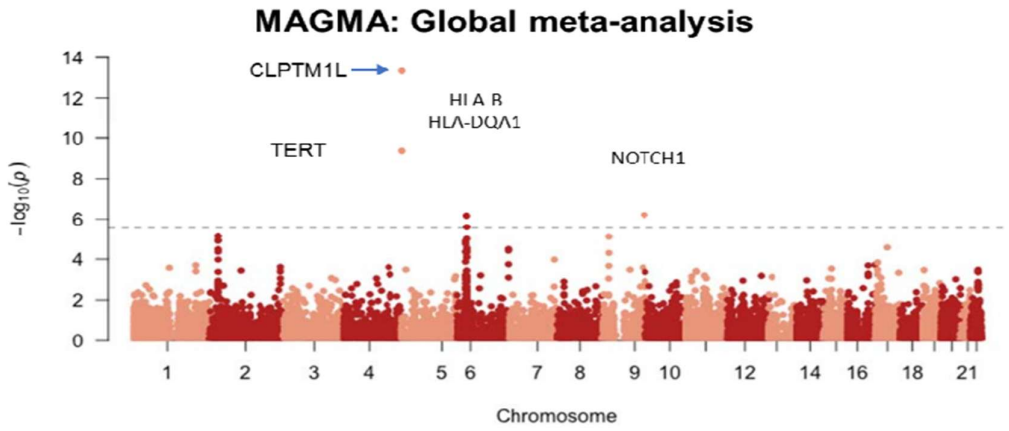
Figure 2: Genome-wide association study of BMC. The Miami Plot illustrating the Genome-wide significant SNPs ($p < 5 \times 10^{-8}$) identified in multicentre study on Indian Buccal Mucosa Cancer. The lower panel illustrates a Genome-wide significant SNPS in multi-ancestry meta-analysis with Indian, Taiwanese, European population. Top and bottom inset shows the quantile–quantile (QQ) plot for the corresponding GWAS with the estimated genomic inflation factor.



Q13: What is MAGMA?

MAGMA is a statistical method that evaluates whether sets of SNPs within a gene are significantly linked to a disease or trait. Using this approach, the Indian GWAS identified four key genes, while the multi-ancestry analysis detected five gene-level associations.

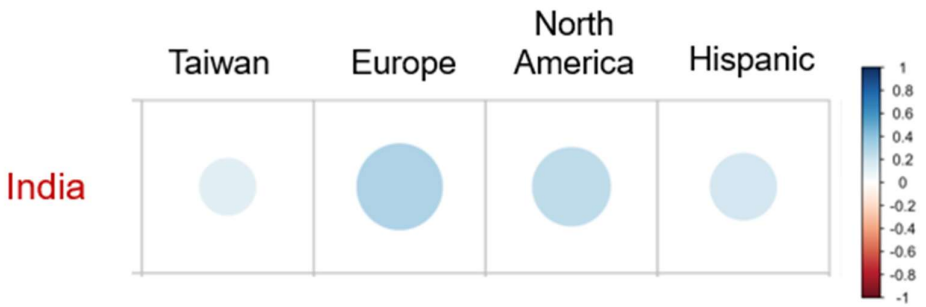
Figure 3: gene-level statistical association tests using MAGMA



Q14: What is Popcorn Analysis?

Popcorn analysis is a method used to compare how similar the genetic risk of a disease is across different populations. Using this approach, the study estimated that the genetic risk for BMC in the Indian population and oral cancer in the European population has a correlation of 0.53, meaning they share some common genetic factors but also show clear differences. In simple words, Popcorn helps us understand how much the genetics of a disease in one population matches or differs from the genetics of the same disease in another population.

Figure 4: Popcorn Analysis

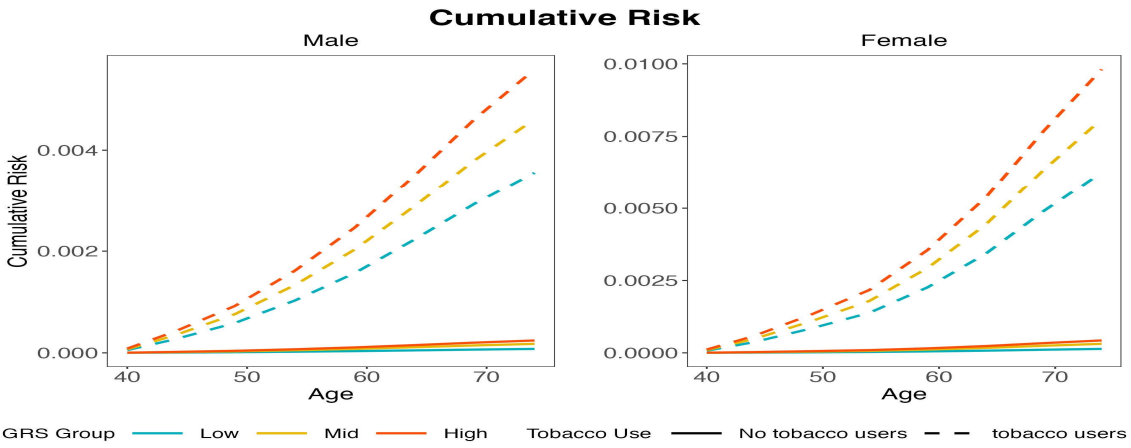


Q15: What is the major finding of the current study.

The current study identified several genetic susceptibility loci associated with the development of oral cancer. While tobacco remains a significant risk factor for oral cavity cancer, there is also a notable genetic component contributing to its development.

A polygenic risk score was calculated by summing all the statistically significant genetic risk loci. The findings revealed that tobacco chewers with a high polygenic risk score (indicating greater genetic susceptibility) tend to develop buccal mucosa cancer a decade earlier than those with a low polygenic risk score.

Figure 5: Cumulative risk of BMC for interaction between Tobacco Chewers and Polygenic risk score.



Q16: What is Centre for Cancer Epidemiology (CCE)

The Centre for Cancer Epidemiology (CCE) is part of the Tata Memorial Centre and is located on the ACTREC campus in Kharghar, Navi Mumbai. Established in 2015, the CCE focuses on studying the burden and causes of cancer, as well as methods for preventing and detecting cancer early in the population. The centre evaluates new cancer screening techniques, conducts molecular and genetic research, and fosters strong national and international research collaborations.

Additionally, CCE is committed to raising cancer awareness, providing expert epidemiological support to research groups, and offering educational and training programs such as the Master

of Public Health in Epidemiology (MPHE) and PhD in Epidemiology. The centre has developed large community cohorts and maintains an automated biobank for storing biological samples.