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New study aims to uncover some of the unknown causes of oesophageal squamous cell carcinoma by using mutational signatures

Lyon, France, 26 October 2021 – Oesophageal cancer is the sixth most frequent cause of cancer deaths worldwide, and oesophageal squamous cell carcinoma (ESCC) is the most common subtype. ESCC shows remarkable variation in incidence globally, and the majority of cases occur in low- and middle-income countries. This variation in incidence is not fully explained by known lifestyle and environmental risk factors, and it has been speculated that an unknown exogenous exposure could be responsible.

A new global collaborative study by researchers from the International Agency for Research on Cancer (IARC) and partners, published in *Nature Genetics*,[1] aims to uncover some of the unknown causes of ESCC by using mutational signatures, i.e. patterns left in DNA by factors linked to cancer development.

This study focused on the analysis of 552 whole genomes of patients with ESCC from eight countries with varying incidence rates. Contrary to expectation, the mutational profiles were strikingly similar across all countries studied. Associations between specific mutational signatures and ESCC risk factors were identified for tobacco use, alcohol consumption, opium consumption, and germline variants, with modest impacts on mutation burden. The study showed no evidence of a mutational signature indicative of an exogenous exposure capable of explaining the observed differences in ESCC incidence rates.

“The lack of any mutational signature between the countries would seem to indicate that whatever is driving the difference in incidence is not leaving its trace in the tumour genome,” says Dr Paul Brennan, Head of the Genomic Epidemiology Branch at IARC. “This is surprising because we have been assuming that lifestyle factors cause cancer by damaging DNA. If they are causing cancer by some other mechanism, then we will have to change our research strategies for how we identify potential new causes of cancer.”

“This study takes advantage of the important recent progress in the field of mutational signatures, applicable not only in tumour tissues but also in normal tissues,” explains Dr Sergey Senkin, a postdoctoral scientist at IARC. “It paves the way for new research combining mutational signatures and cancer epidemiology, and suggests other avenues for future studies, such as sequencing the normal tissue in order to elucidate the disparities in cancer incidence.”

[1] Moody S, Senkin S, Islam SMA, Wang J, Nasrollahzadeh D, Cortez Cardoso Penha R, et al. Mutational signatures in esophageal squamous cell carcinoma from eight countries with varying incidence. *Nat Genet*. Published online 18 October 2021. https://doi.org/10.1038/s41588-021-00928-6

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Note to Editors

This study is part of a major Cancer Research UK (CRUK) Grand Challenge project combining the fields of mutational signature analysis with cancer epidemiology. It is included in a broader initiative led by IARC, the Wellcome Sanger Institute (United Kingdom), and the University of California San Diego (USA), aiming to discover how unusual patterns of mutation are induced by different cancer-causing events, and to elucidate the remarkable differences in incidence of many cancer types around the globe.

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release emailing list, please write to com@iarc.fr.

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