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Discovery could help docs identify those at high risk of stomach cancer

Study shows age, smoking, oral bacteria and genetic mutations together can amplify risk

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While it is well known that age, smoking, oral bacteria and genetic mutations can individually cause stomach cancer, a recent study has found that when they occur together in one person, the risk is amplified.

This discovery by scientists from Duke-NUS Medical School and the National University Health System (NUHS), together with an international team of researchers, provides a peek into the earliest biological changes in the stomach lining that precede the cancer and allows doctors to identify those at high risk.

"It is about finding the right people, at the right time, with the right interventions before cancer takes hold," said Professor Yeoh Khay Guan, chief executive of NUHS and co-senior author of the study.

Published in Cancer Discovery, a monthly peer-reviewed scientific journal by the American Association for Cancer Research, the study highlighted several red flags in people with intestinal metaplasia (IM), a condition where there are changes in the mucous lining of the stomach in patients with chronic gastritis or acid reflux.

Using advanced genetic analyses, the researchers identified 47 significantly mutated genes in IM cells after analysing more than 1,500 samples collected across six countries. Mutated genes, including the loss of a key tumour suppressor gene called ARID1A, age-related blood mutations in stem cells as people grow older, and a distinct pattern of DNA damage known as SBS17, result in an increased risk of gastric cancer and poorer prognosis.

This large, geographically diverse dataset enabled the team to compare genetic changes across populations with differing levels of stomach cancer risk.

Speaking to ST, Professor Patrick Tan, dean of the Duke-NUS Medical School and co-senior author of the study, said genes are not equal in their effects.

"ARID1A stands out because it provides crucial growth control and is the second-most frequently mutated driver gene in gastric cancer, occurring in 17 to 27 per cent of cases... When ARID1A is lost, the stomach's protective safeguards are weakened and IM is more likely to progress, which is why this gene gets special attention among the many mutations detected," he said.

The scientists found that SBS17, linked to oxidative stress, can be further damaged by smoking.

"Now that we know about these, we can aim to use them to identify people who are at high risk and who need closer follow-up. Conversely, we offer reassurance to people who are at low risk and do not need excessive investigations," said Prof Yeoh, who is also a senior consultant with the Division of Gastroenterology and Hepatology at the National University Hospital.

Stomach or gastric cancer remains one of the world's deadliest cancers because it has no symptoms during the early stages, often leading to late diagnosis when the disease has already spread.

It is among the top 10 causes of cancer-related deaths and claims between 300 and 500 lives in Singapore every year.

The cancer typically develops over many decades, beginning with chronic inflammation in the stomach lining, which can progress to IM. Over time, these changes progress to more severe tissue damage and cancer.

Professor Patrick Tan (left), dean of Duke-NUS Medical School, and Professor Yeoh Khay Guan, National University Health System chief executive, are co-senior authors of the study. PHOTO: NATIONAL UNIVERSITY HEALTH SYSTEM

Unfortunately, doctors have limited ability to predict which individuals with the condition are most likely to progress to gastric cancer.

To address this gap, studies were conducted under the Singapore Gastric Cancer Consortium (SGCC), a multidisciplinary national research programme comprising clinicians and scientists from various academic medical centres, universities and research institutes working in gastric cancer research and management.

The longitudinal study – started in 2007 with pre-cancerous patients – looked at over 1,100 tissue samples to study genetic material one cell at a time and see where specific genes are being expressed within tissues or organs. It also provided insight into the communication between cells in their actual location within the tissue.

In 2023, researchers from SGCC discovered that patients with IM face a six times increased risk of developing stomach cancer, which could help with early detection of the cancer.

"That study, however, was confined to Singapore patients, and it was unclear how generalisable our findings were and if they could be extended to other countries. For findings to have true clinical value, international validation is required, preferably across multiple countries," Prof Yeoh said.

"Our new results, demonstrated across six countries, reinforce IM as a true pre-cancerous lesion in the development of gastric cancer, and an actionable checkpoint for its prevention. The new results also add crucial nuance: IM is heterogeneous and only a subset appears poised to progress," he added.

Unexpectedly, the team discovered that pyrvinium, a drug currently used to treat intestinal pinworms, can slow down the growth and transformation of stomach lining cells into intestinal-type IM cells that cause cancer.

Prof Yeoh said: "When we were searching the literature for clinically approved compounds that can inhibit a specific molecular pathway that is often activated in IM... we zeroed in on pyrvinium as a promising candidate.

"Our colleagues in the US have also performed pre-clinical studies in mice and organoids, and (found) that pyrvinium suppresses cancer-driving chemical signalling and reverses metaplasia in the stomach."

Prof Yeoh said clinical trials are needed to establish dosage, safety and efficacy for use to slow or prevent IM progression.

The SGCC is embarking on clinical studies to test pyrvinium's effect on IM and, if approved, early-phase trials may take about one to two years.

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