MEDIA RELEASE

25 May 2026
Embargoed Until 25 May 2026, 4:30pm

NEW SINGAPORE STUDY SHOWS HOW GENETICS AND METABOLIC HEALTH COMBINE TO INCREASE LIVER CANCER RISK

Men with a high-risk genetic variant face up to nine-fold higher liver cancer risk, pointing to future risk-based cancer screening using genetics and routine clinical factors

SINGAPORE — Researchers from the National University Hospital (NUH), the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), National University Cancer Institute, Singapore (NCIS) and the Genome Institute of Singapore (GIS), Agency for Science, Technology and Research (A*STAR), have found that a common genetic variant, when combined with metabolic factors such as diabetes and obesity, is associated with a significantly higher risk of liver cancer.

The findings come from a large, population-based study involving nearly 25,000 participants from the Singapore Chinese Health Study, a cohort established since 1993 for research on cancer and other chronic diseases of importance in Singapore and worldwide. This specific study has been published in *Alimentary Pharmacology & Therapeutics*[1], a leading international journal in gastroenterology.

This study is among the first large-scale prospective analyses in Asia to demonstrate a clear, dose-dependent relationship between the *PNPLA3* I148M variant and liver cancer risk. This means that risk increases progressively with the number of risk gene copies carried. Individuals with two copies of the variant faced the highest risk.

Importantly, the researchers found that genetic risk does not act in isolation. Liver cancer risk increased when combined with common metabolic conditions.

Principal investigator Adj A/Prof Daniel Huang, Senior Consultant, Division of Gastroenterology and Hepatology, Department of Medicine, NUH and Chair of the Hepato-Pancreato-Biliary Cancer Programme at NCIS said: “Our findings show that diabetes and obesity effectively “stack” on top of genetic susceptibility to further increase liver cancer risk. This highlights the importance of considering genetic factors together with routinely available clinical information, rather than viewing them separately.” On the other hand, individuals with a higher genetic risk for liver cancer may be able to meaningfully reduce their risk by adopting a healthy lifestyle, particularly by preventing diabetes and maintaining a healthy weight.

Genetics and routine clinical factors together shape liver cancer risk

[1] https://pubmed.ncbi.nlm.nih.gov/41527281/
[2]https://pubmed.ncbi.nlm.nih.gov/22258181/

Men who carried two copies of the *PNPLA3* I148M variant had up to a nine-fold higher risk of hepatocellular carcinoma (HCC), the most common form of primary liver cancer, compared with women who did not carry the variant. Elevated risks were also observed among carriers who were overweight or had diabetes, compared with non-carriers without these conditions.

Notably, the genetic association appeared more prominent among individuals without chronic hepatitis B, underscoring its relevance as liver cancer increasingly arises from non-viral causes, such as fatty liver disease and metabolic conditions.

According to the Singapore Cancer Registry Annual Report 2023, liver cancer was among the three leading contributors to cancer deaths in males between 2019 to 2023.

Implications for future practice

Liver cancer is often asymptomatic in its early stages, and many patients are diagnosed only when the disease is advanced, limiting treatment options.

With the rise of fatty liver disease as a major cause of liver cancer, these findings highlight how clinical factors – including sex, diabetes and obesity – can meaningfully influence risk when combined with genetic susceptibility.

The researchers noted that while genetic testing is not currently part of routine liver cancer screening, the findings suggest that combining genetic information with readily available clinical data may support more targeted, risk-based screening strategies in the future, helping identify individuals who may benefit from closer monitoring, including those who may not fall within traditional high-risk groups

Early detection in action: A patient's experience

The importance of identifying individuals at higher risk and detecting disease early is illustrated by the experience of Mr Foo Say Nong, 74.

Mr Foo was first diagnosed with early-stage liver cancer in 2018 after a routine follow-up for fatty liver disease. He underwent minimally invasive surgery at NUH, and the tumour was successfully removed.

"I didn't have any symptoms or pain at all. Without regular follow-ups, it could easily have gone unnoticed," Mr Foo said.

Seven years later, in 2025, Mr Foo volunteered to participate in a research study on genetics in liver cancer led by Adj A/Prof Huang. Advanced imaging performed as part of the study detected a new, unrelated liver tumour at an early stage. He underwent successful image-guided ablation and is currently in remission.

Understanding the value of research in improving early detection, Mr Foo also encouraged family members to take part in the study.

Today, he is enjoying retirement, spending time with his grandchildren and practising meditation and qigong.

Advancing care through research

At the National University Health System (NUHS), the findings reflect ongoing efforts to translate population-based research into insights that can inform future clinical practice. As liver cancer increasingly arises from metabolic and non-viral causes, there is a growing need for more precise, risk-stratified approaches to early detection.

By improving the understanding of how genetic and metabolic factors interact, such research contributes to NUHS's broader commitment to advancing evidence-based, patient-centred care, with the long-term goal of improving early diagnosis and outcomes.

Chinese Glossary

National University Hospital	国立大学医院(国大医院)
National University Cancer Institute, Singapore (NCIS)	新加坡国立大学癌症中心
NUS Yong Loo Lin School of Medicine	新加坡国立大学杨潞龄医学院（国大杨潞龄医学院）
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About the National University Hospital

The National University Hospital (NUH) is Singapore's leading university hospital. While the hospital at Kent Ridge first received its patients on 24 June 1985, our legacy started from 1905, the date of the founding of what is today the NUS Yong Loo Lin School of Medicine. NUH is the principal teaching hospital of the medical school.

Our unique identity as a university hospital is a key attraction for healthcare professionals who aspire to do more than practise tertiary medical care. We offer an environment where research and teaching are an integral part of medicine, and continue to shape medicine and transform care for the community we care for.

We are an academic medical centre with over 1,200 beds, serving more than one million patients a year with over 50 medical, surgical and dental specialties. NUH is the only public and not-for-profit hospital in Singapore to provide trusted care for adults, women and children under one roof, including the only paediatric kidney and liver transplant programme in the country.

The NUH is a key member of the National University Health System (NUHS), one of three public healthcare clusters in Singapore. For more information, visit www.nuh.com.sg

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About the National University Cancer Institute, Singapore (NCIS)

The National University Cancer Institute, Singapore (NCIS) is an academic, national specialist centre for cancer under the National University Health System (NUHS), and is the only public cancer centre in Singapore that treats both paediatric and adult cancers in one facility.

As one of two national cancer centres in Singapore, NCIS (pronounced as "n-sis") offers a broad spectrum of cancer care and management from screening, diagnosis and treatment to rehabilitation and survivorship, as well as palliative and long-term care. NCIS' strength lies in the multi-disciplinary approach taken by our clinician scientists and clinician-investigators to develop a comprehensive and personalised plan for each cancer patient.

NCIS provides the full suite of specialised oncology and haematology services at the NUH Medical Centre at Kent Ridge, Singapore, including those by the NCIS Chemotherapy Centre, NCIS Radiotherapy Centre and NCIS Cellular Therapy Centre.

NCIS also offers cancer services at other hospitals in Singapore:

- NCIS Cancer & Blood Clinic @ Ng Teng Fong General Hospital
- NCIS Radiotherapy Centre @ Tan Tock Seng Hospital
- NCIS Radiotherapy Clinic @ Khoo Teck Puat Hospital

To bring cancer care even closer to our patients, our NCIS on the Go programme delivers a range of cancer services at clinics within the community for their convenience.

For more information, please visit www.ncis.com.sg.

About National University of Singapore (NUS)

The National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education, research and entrepreneurship, with a focus on Asian perspectives and expertise. We have 15 colleges, faculties and schools across three campuses in Singapore, with more than 40,000 students from 100 countries enriching our vibrant and diverse campus community. We have also established our NUS Overseas Colleges programme in more than 15 cities around the world.
Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, 30 university-level research institutes, research centres of excellence and corporate labs focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

For more information on NUS, please visit www.nus.edu.sg.

About the NUS Yong Loo Lin School of Medicine (NUS Medicine)

The NUS Yong Loo Lin School of Medicine is Singapore's first and largest medical school. Our enduring mission centres on nurturing highly competent, values-driven, and inspired healthcare professionals to transform the practice of medicine and improve health around the world.

Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2026 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2026).

For more information about NUS Medicine, please visit https://medicine.nus.edu.sg/