Those with the BRCA1 gene mutation may face greater risk for aggressive cancer caused by asbestos exposure

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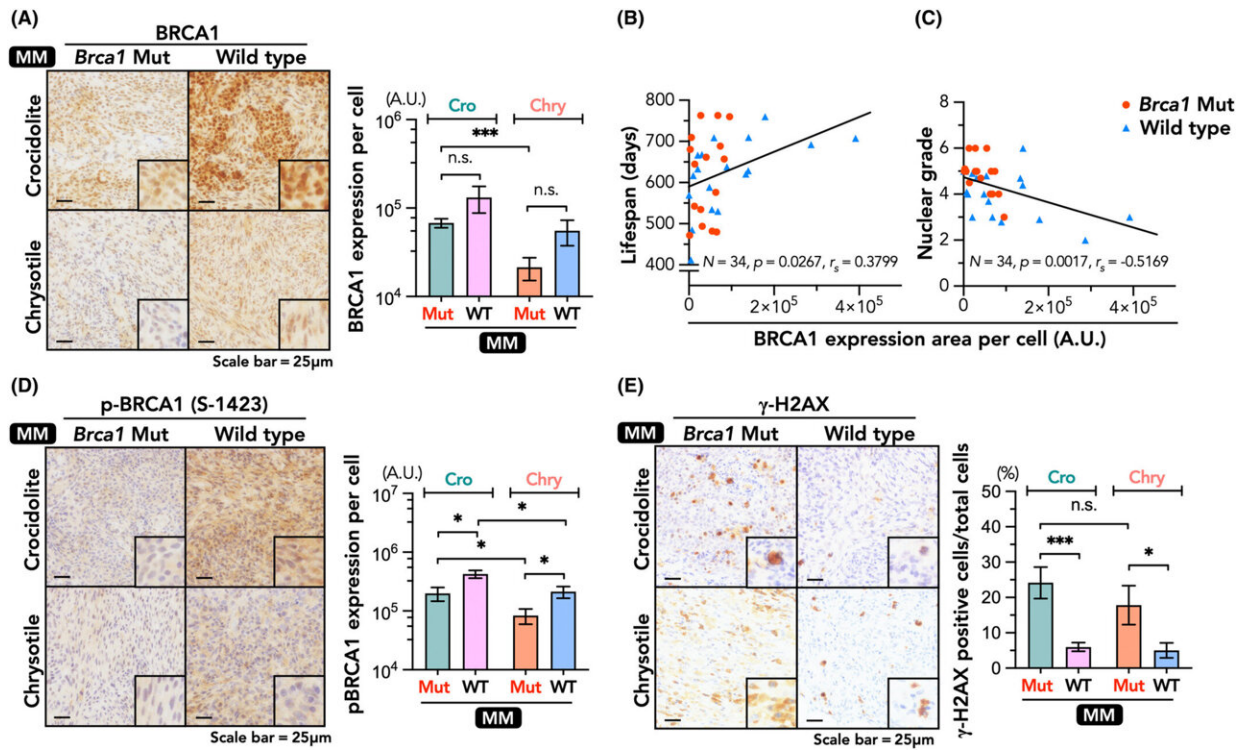

Chrysotile-induced MMs present lower expression levels of Brca1. (A) Immunohistochemistry (IHC) staining of total BRCA1 on MM samples (bar = 25 μm; N ≧ 7). (B) Correlation between the expression of total BRCA1 and survival probability (N = 34; p = 0.0267, Pearson's rank correlation coefficient = 0.3799). (C) Correlation between BRCA1 expression and nuclear grade (N = 34; p = 0.0017, Pearson's rank correlation coefficient = –0.5169). (D, E) IHC staining of phospho-BRCA1 (Ser1423) and phospho-H2AX (Ser139) on MM samples (N ≧ 7). Credit: *Cancer Science* (2022). DOI: 10.1111/cas.15705

A group of researchers from Nagoya University in Japan used a rat model to show that the BRCA1 mutation, which affects 1 in 500 people, increases the risks of malignant mesothelioma (MM), a cancer linked to asbestos exposure. Their findings were reported in *Cancer Science*.

MM is an aggressive form of cancer most commonly caused by asbestos exposure. The tumor develops in the mesothelium, a thin layer of tissue that covers most internal organs. Although there are several treatments for MM, it is often fatal.

MM is particularly dangerous because it uses the body's normal defenses to create an environment conducive to its growth. One important defense against cancer is ferroptosis, which uses iron to cause cell death and is important for tumor suppression. However, MM can accumulate iron itself, which causes breaks in the body's DNA strands, causing genomic changes in the mesothelium that favor the tumor.

The body also has a defense mechanism against these strand breaks that uses a protein encoded by the gene BRCA1. However, in people with a BRCA1 mutation, an inherited condition, the defense against these strand breaks is limited. This makes such individuals particularly susceptible to MM.

A group led by Professor Shinya Toyokuni of Nagoya University's Graduate School of Medicine and Center for Low-temperature Plasma Sciences, in collaboration with the University of Tokyo and the National Institutes for Quantum Science and Technology, studied MM caused by exposure to white asbestos in BRCA1 mutant rats.

They found that ferroptosis-related proteins were significantly reduced in BRCA1 mutant rats a few weeks after exposure to white asbestos.

Similarly, MM of mutant rats had dysregulation of iron metabolism, such as decreased stable ferric iron and expression of ferritin, both of which are important in ferroptosis. At the genetic level, they also found that the tumor had upregulated two of its genes, Slc7A11 and Gpx4, which are known to lead to ferroptosis-resistance. Taken together, these findings suggest that BRCA1 deficiency leads to earlier ferroptosis-resistance, which creates a favorable environment for tumor growth.

Although the exact mechanism is unknown, Toyokuni has a hypothesis. "Our understanding is that the mitochondria, a key organelle of iron metabolism, are more susceptible to damage, which accumulates more iron intracellularly and in the extracellular environment nearby," he said.

Although these are still early days, Toyokuni believes that their experiment has important implications for people with BRCA1 mutations. "I would recommend people with BRCA1 mutations who are exposed to asbestos to monitor chest X-rays regularly and perform regular blood donation, which showed some prevention effects in animal models. We want to emphasize that avoiding exposure to white asbestos is especially important for people with BRCA1 mutations."

More information: Yaguang Luo et al, BRCA1 haploinsufficiency impairs iron metabolism to promote chrysotile-induced mesothelioma via ferroptosis resistance, *Cancer Science* (2022). DOI: 10.1111/cas.15705

Provided by Nagoya University