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New insights into cancer evolution help define screening window of opportunity

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A new appreciation of how cancer cells evolve could help scientists design better screening methods to catch cancer before it advances.

Researchers at Fred Hutchinson Cancer Research Center studying the precancerous condition Barrett's esophagus have shown that rather than resulting from a steady accumulation of small genetic mutations, cancer arises a few years after cells begin to undergo large, drastic mutations. This insight could help researchers detect cells on the cusp of becoming malignant and distinguish benign from dangerous pre-cancerous conditions.

"Cancer's a frightening word," said Brian Reid, M.D., a cancer geneticist at Fred Hutch who led the study. But the results should reassure patients, Reid said, because researchers are gaining a better understanding of how to increase the window of opportunity to detect potentially dangerous cancers before they're hard to treat. The findings are published online in *Cancer Prevention Research*.

Most tumors are benign and slow-growing, posing little risk to patients. According to the standard cancer model, cells acquire mutations at a relatively steady rate, and a faster rate results in a faster-developing and more dangerous cancer. But this model couldn't explain why regular screening reliably detects benign tumors while often missing aggressive ones. Reid's work helps explain this phenomenon. He studies Barrett's esophagus (BE), a precancerous condition caused by chronic heartburn.

Only about 5 percent of BE patients progress to cancer, but often their tumors are not identified early enough for successful treatment, even with regular screenings.

To understand the genome changes distinguishing BE cells that progress to cancer from those that don't, Reid and his team examined esophageal tissue samples taken from BE patients at regular intervals. They found that despite the highly mutagenic nature of acid reflux, the cells from non-progressing patients acquired almost no mutations — even after years of exposure to stomach acid.

But in patients who ultimately progressed to esophageal cancer, Reid and his colleagues saw a sudden change about four years prior to cancer diagnosis. These cells seemed to tip suddenly toward a cancerous path, undergoing large, catastrophic mutations such as deletions of long stretches of chromosomes or doubling of entire genomes. This was contrary to what Reid expected to find. "We thought we'd find a fast rate of mutation [in progressors] and a slow rate [in non-progressors]," he said, noting that the striking findings are in keeping with recent observations by other researchers. Other studies examining ovarian, prostate, breast, and colon cancer have observed a pattern of drastic mutations and genome doubling.

Because the findings seem to be generalizable to other types of cancers, Reid is optimistic that they are a first step toward better screening and prevention strategies. The four-year window in which BE cells take a turn for the malignant should reassure patients, Reid said. It gives physicians plenty of time to identify cancerous cells, and findings like Reid's and others' are giving researchers a better picture of how to detect premalignant cells as they begin to progress toward cancer.

It may be that researchers will identify even earlier, smaller mutations that presage these cells' malignant future, extending the window of

opportunity by several years. Additionally, research into less invasive screening tests may well make invasive screening methods like endoscopies a thing of the past.

Ideally, Reid noted, researchers will discover ways to stop precancerous cells before the tipping point. Such interventions may be as simple as popping a few aspirin, as research by Reid and his colleagues has already demonstrated that high-risk BE patients who use aspirin and non-steroidal anti-inflammatories cut their esophageal cancer risk by about half. "If something like that could be implemented, it would be a huge victory for patients," Reid said.

The good news, he said, is that "most Barrett's esophagus patients won't get cancer in their lifetime"— and less invasive tools to increase the window of detection are on the horizon.

Provided by Fred Hutchinson Cancer Research Center

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