Surprise finding: Pancreatic cancers progress to lethal stage slowly

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Pancreatic tumors are one of the most lethal cancers, with fewer than five percent of patients surviving five years after diagnosis. But a new study that peers deeply into the genetics of pancreatic cancer presents a bit of good news: an opportunity for early diagnosis. In contrast to earlier predictions, many pancreatic tumors are, in fact, slow growing, taking nearly 20 years to become lethal after the first genetic perturbations appear.

"There have been two competing theories explaining why pancreatic cancers are so lethal," says Bert Vogelstein, the Howard Hughes Medical Institute investigator who helped lead the new study. "The first is that pancreatic tumors are aggressive right from the get-go and spread to other organs very quickly. The second theory is that pancreatic tumors are, in fact, not more aggressive than other tumors, but that symptoms appear so late in the process that patients have little chance of surviving. We were surprised and pleased to discover that this second theory is correct, at least for a major fraction of tumors. It means that there is a window of opportunity for early detection of pancreatic cancer."

The new work is published in the October 28, 2010, issue of the journal *Nature*. Christine Iacobuzio-Donahue, a pathologist at Johns Hopkins University School of Medicine, is the senior author of the paper.

Working with Iacobuzio-Donahue, Vogelstein obtained samples of primary pancreatic tumors from seven autopsied patients, as well as metastatic lesions from their lungs, liver, and other organs. Their team

sequenced the DNA of every gene in each metastatic tumor as well as in the primary tumor. These genetic read-outs provided data to compare the genetic mutations found in each patient's metastatic lesions with the mutations found in the primary tumor.

The investigators found that each metastatic lesion contained, on average across all patients, 61 cancer-related genetic mutations. Further, the majority of these mutations – 64 percent on average – were also present in the primary tumor. The researchers then worked with Martin Nowak, an evolutionary biologist at Harvard, to estimate how long it took these mutations to accumulate. Using a "molecular clock" technique commonly used in evolutionary biology, it is possible to generate a hypothesis about when a mutation occurred. By comparing the genomes of, say, monkeys and man, evolutionary biologists can estimate how long ago the two species diverged.

Similarly, each genetic mutation seen in a cancer cell represents a tick of the molecular clock. Because such mutations accumulate at a steady rate – as observed in cancer cells growing in petri dishes - Vogelstein and his colleagues could estimate how long it took for all of the mutations seen in each metastatic lesion to appear.

The technique showed that it took a surprisingly long time – 11.7 years on average – for a mature pancreatic tumor to form after the appearance of the first cancer-related mutation in a pancreatic cell. Another 6.8 years passed, on average, before the primary tumor sent out a metastatic lesion to another organ. From that point, another 2.7 years went by, on average, before the patient died. In total, more than 20 years elapsed between the appearance of the first mutated pancreatic cell and death.

"This time scale is similar to what we've previously seen in colorectal cancers," says Vogelstein. "These tumors evolve over long periods --decades."

Unlike other cancers, though, pancreatic tumors usually produce no symptoms until they've spread. Jaundice is often the first symptom, but that arrives only after a pancreatic tumor has metastasized to the liver. But Vogelstein says the new data suggest that a blood or stool test might be able to pick up early cancer-causing mutations. His team is already examining the efficacy of such tests for detecting early signs of colorectal cancer.

"For disease control in the future, this finding is paramount," Vogelstein says. "It gives us hope that we will eventually be able to reduce morbidity and mortality from pancreatic cancer through earlier detection."

The research also provided a glimpse into how pancreatic tumors evolve. In the pancreatic tumors of two of the patients, Iacobuzio-Donahue sectioned the tumors into smaller pieces, and then examined the genetics of each section. Surprisingly, she found that each tumor comprised genetically distinct sub-tumors. That is, the tumor continued to accumulate genetic mutations after the tumor first appeared.

"We saw a whole lot of evolution within the primary tumor, producing what looked like a series of generations of tumor clones – fathers, grandfathers, great-grandfathers, you could say," Vogelstein says. "The primary tumor is, in fact, not a single tumor but an accretion of several genetically distinct tumors. Moreover, we could find a subclone within the primary tumor that gave rise to each metastasis," Vogelstein says. "That's fascinating from a basic science perspective and gives us some deep insights into how these tumors evolve."

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