The New York Times

October 27, 2010

Strides Made Toward Early Diagnosing of Pancreatic Cancer

By **NICHOLAS WADE**

Researchers have made significant progress in understanding the biology of pancreatic tumors, suggesting that there may be ways of identifying the usually fatal cancer at a much earlier and more treatable stage.

A principal finding is that pancreatic tumors are not aggressive cancers. To the contrary, they grow slowly, taking an average of 21 years to become fatal. This creates an opportunity for detecting and removing the cancers at an early stage. At present they are diagnosed far too late, when a patient has on average only two more years to live and the cancer has already spread from the pancreas to other tissues.

The new advances, reported online Wednesday in Nature, have been made by two cooperating groups, one led by Shinichi Yachida and Christine Iacobuzio-Donahue at the Johns Hopkins Medical Institutions in Baltimore, and the other by Peter Campbell and Andrew Futreal at the Sanger Institute near Cambridge, England. Both teams used a new method for decoding DNA very rapidly. This means that instead of studying one gene at a time, researchers can now afford to look across the whole genome, tracking all the mutations that occur in cancer cells.

The Johns Hopkins team was able to identify a long series of mutations that had accumulated in the original tumors of seven patients, as well as in the secondary cancers that had spread from the pancreas to the liver, lung and peritoneum, the membrane that lines the abdominal cavity.

The mutations were then arranged in a family tree.

Since the rate at which DNA-level mutations clock up is well known, the researchers could date the development of the patients' pancreatic tumors from the length of the branches in the tumor's family tree, said Bert Vogelstein, a leading cancer researcher and member of the Johns Hopkins team.

It turns out that at least 10 years elapse between the first cancerous cell and the emergence within the tumor of the first cell with the ability to spread to other tissues, a process known as metastasis. At least five more years are required for this cell to develop metastatic ability.

Both the Johns Hopkins team and the Sanger group are now looking for specific DNA changes that might help diagnose pancreatic tumors. A leading candidate is a gene called KRAS (pronounced kay-rass), which is involved in transmitting messages inside a cell. "Almost all of the pancreatic cancers have mutations in KRAS, so that's an ideal situation from a screening point of view," Dr. Vogelstein said.

Scientists at the Sanger Institute have analyzed the same tumors as the Johns Hopkins group with a view to reconstructing the biological history of pancreatic tumors. They find that after the initial damage, possibly in the KRAS signaling gene, the natural controls on cell division are lost. "That unleashes a maelstrom of genetic instability," Dr. Campbell said. The cell divides so many times that it uses up its telomeres, the mechanism at the tip of every chromosome that forces a cell to self-destruct if it divides too many times. A few cells evidently dodge this mechanism and learn how to survive in the tumor environment. These survivors find that it is now in their interest to stabilize their genome and switch on the genes that rebuild the telomeres.

The stabilized cancer cells now start to spread but must develop a further set of mutations that help them adapt to the specialized environment of the tumor's target tissues.

"That is in some ways ominous for the treatment of cancer, because all the metastasized tumors are slightly different and would need different treatments," Dr. Campbell said.

There is some chance of picking up the KRAS mutation in stool, which is hard to do at present. "But the techniques are getting better all the time," Dr. Campbell said.