War on pancreatic cancer is showing progress in worst cases

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Just seven years from now, pancreatic cancer is projected to become this country's second-leading cancer killer, surpassed only by lung cancer and claiming 48,000 lives a year.

Now No. 4, pancreas cancer will climb in the ranking partly by becoming more common, but mostly because it is ferociously difficult to detect and treat, according to an analysis by the Pancreatic Cancer Action Network.

"The dramatic increase in the anticipated number of deaths ... is a wake-up call to the research and health-care systems in the United States," senior author Lynn M. Matrisian, a molecular biologist, wrote last month in the journal *Cancer Research*.

The hopeful counterpoint to this dire prediction is that the call has already been heard. A war on pancreas cancer is underway, and it is improving the outlook, at least a little, for patients with the grimmest common malignancy.

The war is being driven by unconventional players who want to get new treatments into the clinic now. That includes the entertainment industry's Stand Up to Cancer initiative, family philanthropies such as the Lustgarten Foundation, the advocacy group Pancreatic Cancer Action Network (PanCan), and the PanCan-inspired federal "recalcitrant cancer" law.

The result is that medical centers across the country are testing chemotherapies, targeted therapies, immunotherapies, and much more, as they reshape the understanding and treatment of pancreatic cancer.

"We're not declaring victory. We're declaring progress," said Jeffrey A. Drebin, chair of surgery at the University of Pennsylvania's Abramson Cancer Center and a member of the SU2C "dream team."

The survival rate for cancer overall has steadily improved since war was declared in 1972. Today, 67 percent of all patients live five years, and the rate is over 90 percent for the most common cancers, breast and prostate.

In contrast, five-year survival for pancreatic cancer is 6 percent. Only one in four patients live a year. (Apple founder Steve Jobs had a neuroendocrine tumor of the pancreas, a rare and less aggressive form with a five-year survival rate of about 60 percent.)

In 2012, pancreatic cancer was diagnosed in 44,000 Americans, and killed 37,000. Lung cancer, which was responsible for more than 150,000 deaths that year, will remain the No. 1 killer by far, but last month's paper projects that pancreatic cancer will edge past colorectal, breast, and prostate for the No. 2 spot by 2021.

There are many reasons for the disparity in lethality. The pancreas - a six-inch-long flattened gland vital to digestion - lies deep in the abdomen, tough to image and access. Cancer rooted there spreads early and without symptoms. Less than 20 percent of patients are eligible for surgery, and the disease is notoriously resistant to standard chemotherapies.

So far, there is no drug that targets mutations in RAS genes, which underlie 95 percent of pancreas cancers. The genes regulate cellular

signaling that controls growth, and some current therapies actually aggravate RAS-driven malignancies.

Finally, pancreatic tumor cells are shrouded in - and shielded by - the stroma, a dense network of fibrous tissue, immune system cells, and scarring caused by inflammation.

Inflammation also plays a role in diabetes - which is linked to obesity, which is epidemic among Americans. Obesity and diabetes are factors behind the rising incidence of pancreatic cancer, although the connections are unclear.

The National Cancer Institute in March outlined plans to investigate the link between diabetes and pancreatic cancer, and to develop drugs that target mutated RAS genes. Both initiatives are the result of the Recalcitrant Cancer Research Act, signed into law by President Barack Obama last year, which requires the institute to step up research on cancers with low survival rates.

"We absolutely need to figure it out," said Penn oncologist Robert Vonderheide. "It's a medical emergency."

In April, Vonderheide and Johns Hopkins University oncologist Elizabeth M. Jaffee were named co-leaders of a Stand Up to Cancer team that is marshaling nine institutions and $8 million over three years to find ways to activate the immune system to effectively attack pancreatic cancer.

One promising approach supported by the entertainment industry effort involves an experimental protein being developed by Roche. It binds to immune cells that then tell macrophages - cells that gobble up cellular debris - to eat the stroma surrounding the tumor. Normally, the tumor's powerful chemical signals call in macrophages, but keep them on tight

protective leashes.

"It is something of a Trojan horse approach," Vonderheide said. "The tumor is still calling in macrophages, but now we've reeducated them to attack - not promote - the tumor."

In a small study of 21 patients who got the experimental protein plus the standard chemotherapy gemcitabine, four saw their tumors temporarily shrink.

The team is also doing human tests of "step on the gas" approaches that activate T cells, the elite soldiers of the immune system, and "cut the brakes" approaches that use novel drugs to slip through immune system checkpoints.

Vonderheide's team complements the original, four-year-old Stand Up to Cancer pancreatic brigade of 28 researchers at five centers. They are working on ways to starve tumor cells by depriving them of nutrients. Pancreas tumor cells have massive energy needs, so they leach nutrients from healthy cells - one reason patients often waste away.

Albumin, a common blood protein, has turned out to be a key. Albumin serves both as a taxi, carrying molecules such as calcium around the body, and as a fuel that cells can break down for energy.

Clinical trials headed by team co-leader Daniel Von Hoff, physician in chief at the Translational Genomics Research Institute in Scottsdale, Ariz., showed a survival advantage for patients who combined gemcitabine with Abraxane, a drug that binds tiny particles of albumin to the widely used chemotherapy paclitaxel.

The advantage wasn't big; patients lived a median of 8.5 months with the two drugs, compared with 6.7 for gemcitabine alone. Folfirinox, a

combination of four existing chemotherapy drugs, had a longer median survival, 11.1 months, in a study published in 2011 - although it also is far more toxic.

Still, the advantage was an inroad. With evidence that albumin helps penetrate the stroma, the team conducted mouse studies that revealed that albumin also feeds the tumor cells.

"The tumor cells suck up the albumin," said Drebin, the Penn surgeon and member of the SU2C brigade.

That, in turn, has set the stage for testing drugs that may block this intake. The team has found a ready candidate - an antimalaria drug called hydroxychloroquine.

Another pilot study is testing whether adding a vitamin D analog to the gemcitabine/Abraxane combo can inhibit inflammation and the progression of fibrosis in the stroma, a hypothesis supported by preclinical research.