

Healthcare industry BW

Pancreatic cancer and its resistance to therapy

Pancreatic tumours are among the cancers with the worst prognosis. In many cases they are resistant to treatment. Prof. Dr. Andreas Trumpp and his colleagues from the DKFZ and the Heidelberg Institute for Stem Cell Technology and Experimental Medicine HI-STEM have discovered that the reason why some pancreatic tumours are so resistant to treatment is down to larger quantities of the enzyme CYP3A5 in subtypes of pancreatic cancer. Molecular markers to differentiate the subtypes improve the diagnosis of the disease and enable the development of more successful individual therapies.



“It is thanks to the global effort in the fight against cancer that cancer patients now survive for much longer than they did around ten years ago. For all common types of cancer, the five-year survival rate following diagnosis has increased,” said Prof. Dr. Hermann Brenner, head of the Division of Clinical Epidemiology and Ageing Research at the German Cancer Research Center (DKFZ) at a German Cancer Congress press conference in February 2016. In its fifty years of existence, the DKFZ has made significant contributions to this success. However, success levels for different types of cancer differ significantly.

Pancreatic tumours are extremely aggressive

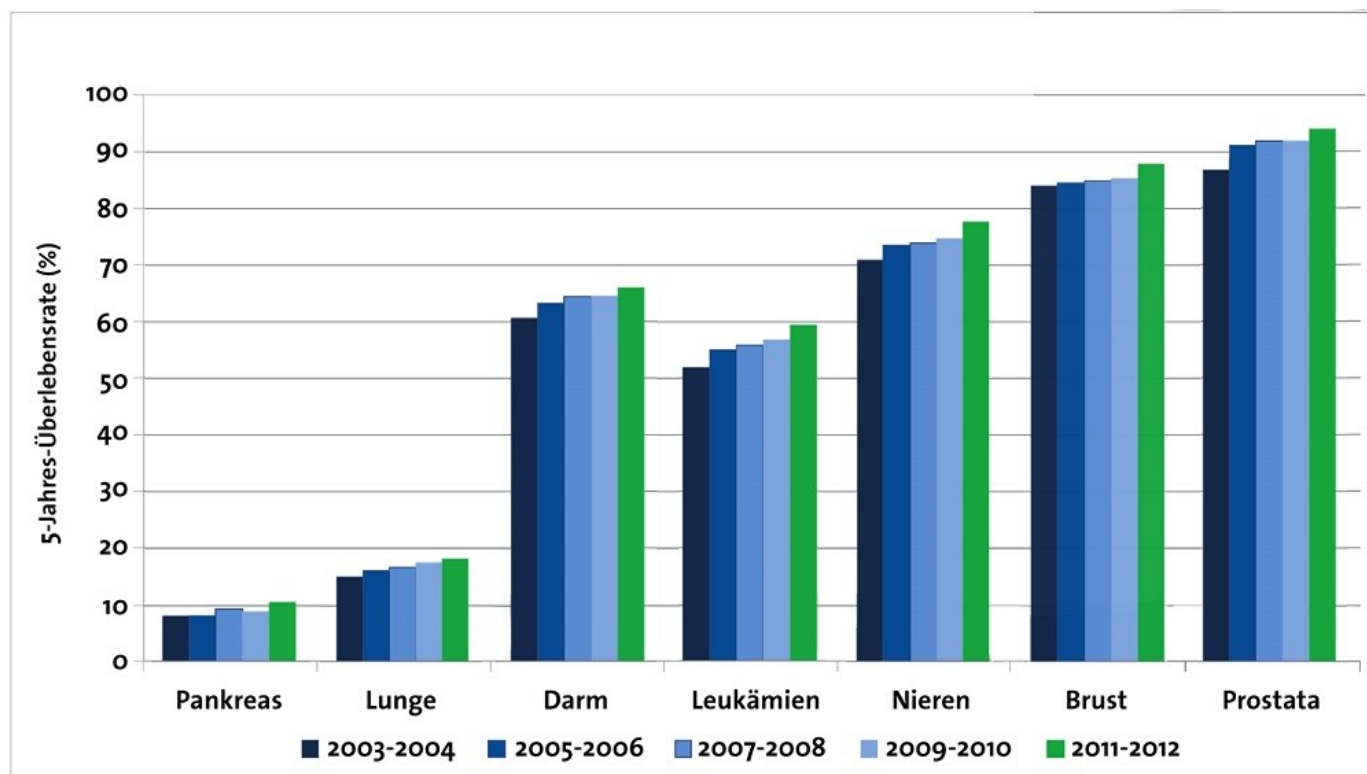
In 2012, whereas the five-year survival rate for breast and prostate cancer patients (the two most commonly diagnosed cancers in Germany) was 88 and 94 percent, respectively, the survival rate for pancreatic cancer patients was only 11 percent. This depressing figure increased only slightly against the decade before the period under review (2003 - 2012).

Prof. Dr. Andreas Trumpp, head of the Division of Stem Cells and Cancer at the German Cancer Research Center (DKFZ) and managing director of HI-STEM gGmbH, a public-private partnership between the DKFZ and the Dietmar Hopp Foundation.

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Poor diagnosis and the exceptional aggressiveness of pancreatic tumours is seen in the large number of deaths from this type of cancer. The number of deaths is almost as high as the number of people diagnosed with pancreatic cancer every year. In absolute terms, more than 16,000 people died of

pancreatic cancer in 2012.



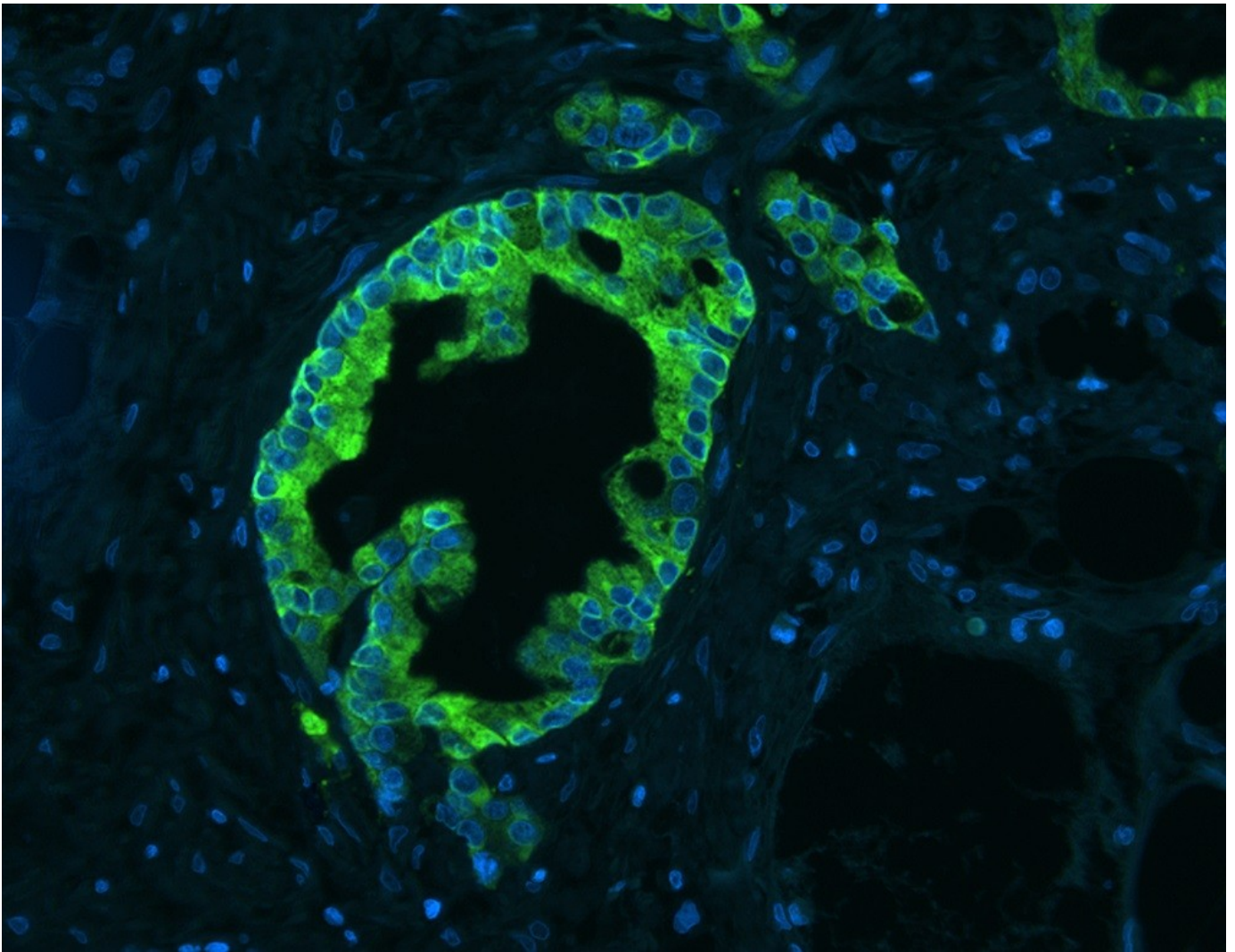
Five-year survival rate for the most common types of cancer (tumour location) in Germany between 2003 and 2012.
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Far more people die of pancreatic cancer than prostate cancer, even though the latter is around four times more common than the former. The figures given above relate to the organs in which tumours have been observed rather than cancer types, as different types of cancer or metastases can occur in one and the same tissue or organ. Hermann Brenner, who presented these figures at a press conference given by the DKFZ at this year's German Cancer Congress, therefore prefers to use the term tumour location rather than cancer type. Pancreatic cancer is a highly malignant type of cancer, also known as ductal pancreatic adenocarcinoma.

The heterogeneity of pancreatic tumours

Although they are usually treated as single disease, pancreatic tumours can be very heterogeneous. Andreas Trumpp and his team from the DKFZ and HI-STEM gGmbH have shown that three different pancreatic cancer subtypes can be differentiated based on aggressiveness and response to drugs.

Around a fifth of all cases (primarily resistant pancreatic carcinomas) do not respond to cancer drugs such as erlotinib, a tyrosine kinase inhibitor, and paclitaxel, a drug made from the bark of



Immunohistochemical detection of the enzyme CYP3A5 (green) in pancreatic cancer cells. The cell nuclei are stained blue. Healthy cells do not stain.

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the Pacific yew. In their recent publication in the renowned journal *Nature Medicine*, Trumpp and his team showed that cells of this tumour subtype express higher levels of CYP3A5, an enzyme that usually occurs in the liver and degrades many drugs. As a result, the aforementioned anti-cancer drugs are broken down before they can exert their effect. The second subtype, which affects a much greater number of people, initially responds relatively well to paclitaxel treatment. However, drug resistance can also occur during treatment. The researchers found that if paclitaxel is given for a prolonged period of time, tumour cells that were initially responsive to treatment start producing increasing quantities of CYP3A5 and stop responding to therapy.

The researchers also found that secondary CYP3A5-mediated resistances to the anti-cancer drugs also appear in other tumours such as gastric carcinoma and liver cancer. In experiments with tumour cells and mice with tumours, the researchers were able to show that resistance to the drug could be overcome by specific inhibition of the enzyme, making the cancer cells responsive to the drug again. "We now hope to find compounds that can be used for human cancer patients," says Dr. Martin Sprick, group leader at HI-STEM gGmbH.

Diagnostic markers

In order to find out the tumour subtype a patient has contracted, the HI-STEM researchers, in

cooperation with researchers from the European Pancreas Center and the Department of Pathology at the Heidelberg University Hospital, have screened a large number of pancreatic tumours for the presence of diagnostic markers. Depending on the tumour subtype, the cultured cell lines from these tumours either produced the proteins KRT81, HNF1A or none of them. The scientists are now able to identify these markers in patient samples quickly and reliably using immunohistochemical procedures. "These markers can now be used to differentiate different pancreatic tumour subtypes in routine diagnostics and potentially also adapt treatment," says Andreas Trumpp. "The goal is to offer patients more successful individualised treatment through better diagnostics."

Reference:

Elisa M Noll, Christian Essen, Albrecht Stenzinger, Elisa Espinet, ..., Andreas Trumpp & Martin R Sprick: CYP3A5 mediates basal and acquired therapy resistance in different subtypes of pancreatic ductal adenocarcinoma. *Nature Medicine* 22, 278-287 (2016)

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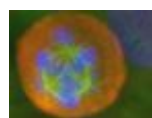
Further information

- ▶ [German Cancer Research Center \(DKFZ\), Heidelberg](#)
- ▶ [HI-STEM gGmbH](#)
- ▶ [European Pancreas Center](#)

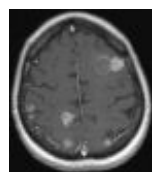
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