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Pancreatic cancer

Anticipating disaster: the genetics of familial pancreatic cancer

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To be born into a family with familial pancreatic cancer, an inheritable, autosomal dominant disorder, has various implications for an individual's life—and none is fortunate. The prospects just turned even darker because of ''anticipation'', the phenomenon that successive generations are affected by an inheritable disorder at a progressively earlier age. An up to date study shows that ''anticipation'' is also operative in familial pancreatic cancer, meaning that affected children die approximately 10 years earlier than their affected parents

One of the definitions *The Oxford English Dictionary* offers for the word ''anticipation'' is: the action of looking forward to something. This is clearly the opposite of what individuals experience who have the misfortune of being born into a family that is burdened with the risk of an inheritable disorder. In genetics, ''anticipation'' describes the phenomenon that successive generations within a family are affected by an inherited disorder at either a progressively earlier age or with progressively greater severity. For example, if the malignant melanoma that affected your father at the age of 50 years was one of the inheritable variety, you have a good chance as a daughter or a son of this patient to develop malignant melanoma at the age of 30–35 years,[1] provided you have inherited the gene that places you at risk. Genetic ''anticipation'' therefore implies, indeed, nothing to look forward to. When the respective inheritable disorder is not one for which the offspring of an affected founder can be tested because no genetic assay is yet available or when a cure for this disorder is neither available nor within sight, ''anticipation'' feels like rolling dice with the devil for those at risk.

The phenomenon has been reported in families affected by Huntington's chorea,[2] familial leukaemias,[3–5] and also certain types of lymphomas.[6–8] If the diagnosis in question were to be pancreatic cancer, in which long term survival is close to zero even after technically successful surgery and no genetic test exists for most families, ''anticipation'' would truly spell disaster.

This is the question a consortium of two recruiting centres based in the UK (EUROPAC) and Germany (FaPaCa) have put to the test in a study[9] that appears in the present issue of *Gut* ***(see page 252)***. For a number of years, both registries have been actively searching for kindreds affected by familial pancreatic cancer[10] and other inherited disorders of the pancreas[11 12] and have pooled their impressive resources of 1223 patients at risk for pancreatic cancer from 106 familial pancreatic cancer kindreds for the purpose of this trial.

For the uninitiated or the statistically naïve, the question of ''anticipation'' in this setting would be straightforward: all you have to do is compare the age of onset in the 80 available child-parent pairs of the study and, provided the parents were older than the children when pancreatic cancer was diagnosed, the difference in age will tell you the extent of anticipation. That approach alone however would likely be fraught with error because of recruitment bias and the way affected families are generally identified. As the sporadic variety of pancreatic cancer is much more

common (at least a 100-fold), only families with two or more members affected by pancreatic cancer would be recognised as such and included—meaning that a father of 70 years and a son of 50 years of age, both with pancreatic cancer, would readily be recognised as a familial pancreatic cancer family. On the other hand, when the genetic founder of a familial pancreatic cancer family who is diagnosed at the age of 50 years as having pancreatic cancer has passed the disease gene onto his 30 year old daughter, who will develop pancreatic cancer, say, at the age of 70 years, this kindred could not be identified as suffering from familial, rather than sporadic, pancreatic cancer until 40 years after the father's death. Also, when two sons of a founder, who is diagnosed with pancreatic cancer at the age of 70 years, both develop the disease, but one at the age of 60 years and the other at age 80 years, this results in a period of 20 years over which the second son will appear to be unaffected and therefore an anticipation of 10 years will appear obvious—although there clearly is none if the age at diagnosis of both sons could be taken into account. All this stacks the odds in favour of finding genetic anticipation no matter what inherited disease an investigator looks at and the statistical methods needed to avoid this bias are rather complex. After initial evidence of anticipation in familial pancreatic cancer had been reported,[13] the authors of the study in this issue of *Gut* have gone to great lengths to avoid such a bias in favour of anticipation—the statistical tools and details of which are found in their methods section and not discussed here.[9] As a result, they demonstrated in the most extensive and carefully conducted analysis to date that in familial pancreatic cancer families, a child affected by this seemingly autosomal dominant disease dies approximately 10 years earlier than his or her affected parent.

The groups from the UK and Germany went on to identify factors that could possibly determine such a devastating fate. While genetic, epigenetic, as well as environmental causes could theoretically be responsible for the phenomenon of ''anticipation'', a most likely culprit would be smoking. Not only is smoking one of the few exogenous risk factors, other than alcohol, that has been associated with the progression of chronic pancreatitis,[14] it is also the single most important precipitating agent for pancreatic cancer in patients with hereditary pancreatitis[15] where it doubles the absolute cancer risk and reduces life expectancy by 20 years. However, smoking is not responsible for genetic ''anticipation'' as McFaul and Greenhalf *et al* quite clearly—and almost apologetically—show in their present study.[9] Unfortunately, no other factor emerged from their study and the ultimate cause of anticipation needs to be identified in future trials.

How could anyone benefit from such a pessimistic finding? Firstly, the information may benefit research into familial pancreatic cancer for which no genetic test or disease causing gene has yet been established. With ''anticipation'' established as a fact rather than a hypothesis, it will be easier to distinguish potential carriers from controls in pancreatic cancer families and for the purpose of controlled trials. Moreover, a project on which several groups are presently moving forward is the search for a strategy to detect pancreatic cancer at its earliest (that is, potentially curable) stage in a high risk population such as those with familial pancreatic cancer. It is still unclear whether imaging techniques or molecular markers will eventually emerge as the most effective tool to identify those family members who will profit most from total pancreatectomy in order to eliminate the risk of dying from pancreatic cancer. It was previously assumed that screening would have to begin at an age that is 10 years earlier than the age at which the index relative was diagnosed with pancreatic cancer. What the present study[9] shows rather clearly is that, whatever screening strategy aimed at preventing pancreatic cancer deaths will ultimately be used, it will have to begin much earlier in individuals' lives to be effective than previously anticipated.

However dire the outlook for affected patients and relatives remains, it is comforting to see that large research consortia are now pooling their resources and that investigations into the causes and genetic background of pancreatic cancer are rapidly progressing.

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