



## Pancreatic Cancer Formation is Gradual

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### Abstract

It is widely accepted that cancer development requires the sequential accumulation of DNA changes over years or decades. In a recent study published in *Nature*, Notta, *et al.* challenge this dogma [1]. They analysed the genomes of more than 100 pancreatic tumours and found that many DNA changes occur simultaneously as a consequence of massive genomic rearrangements associated with catastrophic mitotic events. The authors discuss that the formation of advanced pancreatic cancers is not gradual, and propose a new model in which the simultaneous accumulation of genetic alterations arising from mitotic errors rapidly leads to the development of invasive disease. However, cancer incidence data by age indicate that the time frame required for the formation of invasive pancreatic cancers is similar from other cancers in which these mitotic errors are rare, thereby indicating that the high frequency of catastrophic mitotic events in pancreatic tumours may be a consequence of the disease rather than a cause. In addition, the extremely low rates of pancreatic cancer in young people and the striking increase in its incidence with age strongly suggests that the formation of most invasive pancreatic cancers requires the gradual accumulation of DNA changes over several decades. This means that there is time and opportunity to detect and stop pancreatic carcinogenesis before the development of advanced disease.

**Keywords:** Pancreatic Cancer; Carcinogenesis; Cancer Development; Chromothripsis; Cancer Models

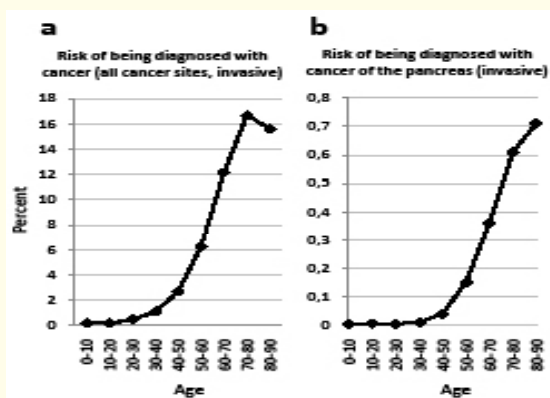
Analyses of cancer statistics by age carried out in the 1950s showed that cancer mortality increased exponentially with age [2,3]. These studies revealed that cancer was the end-result of several successive cellular changes. If cancer were caused by only one cellular change, or by several changes occurring simultaneously or in a short period of time, these changes could occur at any moment in life, and cancer mortality would be rather similar in different age groups after an age corresponding to the length of the latency period [3]. Because DNA is the only cellular component that can accumulate changes throughout life, it soon became accepted that carcinogenesis required the multistep accumulation of DNA changes.

According to a prevailing model of carcinogenesis, generally referred to as the somatic mutation theory, these DNA changes are mutations in oncogenes and tumour-suppressor genes. The multistep accumulation of mutations in three of these genes in a specific order would suffice for a cell to evolve into an advanced cancer [4-6]. Pancreatic cancer would initiate when a mutation in *KRAS* confers a proliferative advantage to a normal cell. A second mutation in *CDKN2A* would then give rise to a benign tumour. Finally, a third mutation in *SMAD4* or *TP53* would cause tumour invasion and metastasis [6]. Most of the mutations required for carcinogenesis would arise during DNA replication [7].

In a study published in October 2016 in *Nature*, Notta, *et al.* challenge this model of pancreatic cancer and propose a new one [1]. The authors performed an in-depth analysis of more than 100 whole genomes from primary and metastatic pancreatic tumours and found that 65.4% of them harboured at least one chromothripsis event. Chromothripsis is a phenomenon characterized by the formation of tens to hundreds of genomic alterations in one or few chromosomes. A single catastrophic mitotic event results in the formation of multiple chromosome fragments that are repaired by error-prone mechanisms leading to massive genomic rearrangements. Chromothripsis can generate multiple mutations simultaneously, which can affect genes involved in cancer development [1,8,9]. Because chromothripsis occurs very frequently in pancreatic tumours [1], the authors challenge the established idea that pancreatic cancer formation evolves slowly and presents at a late stage. They propose that the accumulation of the genetic alterations required for pancreatic cancer development is not gradual [1]. This proposal has an important implication: the time frame available for stopping pancreatic carcinogenesis would be shorter than currently accepted.

Catastrophic mitotic events in pancreatic cancer are much more frequent than in other cancers; chromothripsis can be seen in 65.4% of pancreatic tumours [1] and in 2-3% of all cancers [9]. Be-

cause chromothripsis can lead to multiple mutations simultaneously, the time required for pancreatic carcinogenesis would be shorter than for other cancers. If the model of Notta, *et al.* [1] is correct and the formation of invasive pancreatic cancer is driven by mitotic errors, the percentage of invasive pancreatic cancers diagnosed at younger ages would be higher than for all cancers combined. However, the trend for the increase in pancreatic cancer incidence with age is very similar than that of overall cancer (Figure 1), thereby indicating that the period of time required for pancreatic carcinogenesis is not shorter than for other cancers. The high frequency of chromothripsis in pancreatic cancer does not seem to accelerate the development of the disease in relation to other cancers in which chromothripsis is rare. This suggests that chromothripsis may be a consequence of pancreatic cancer development rather than a cause, and therefore does not support the model of pancreatic cancer proposed by Notta, *et al.* [1].



**Figure 1:** Risk of being diagnosed with cancer or with pancreatic cancer by age. The risk of being diagnosed with any invasive cancer (a) or with invasive pancreatic cancer (b) is very low during the first decades of life and increases dramatically with age. This indicates that the development of most invasive cancers, including pancreatic cancers, requires the gradual accumulation of DNA changes over several decades (see text for details). According to Notta, *et al.* [1], the high rates of catastrophic mitotic events found in pancreatic tumours (65.4%) result in the simultaneous accumulation of genetic alterations, which leads to the rapid development of invasive disease. However, the extremely low rates of invasive pancreatic cancer during the first decades of life indicate that the time required for the development of this cancer is not shorter than for the development of other invasive cancers, in which catastrophic mitotic events are rare (2 - 3%) [8]. This does not support the model proposed by Notta, *et al.* [1], and suggests that the high frequency of catastrophic events observed in pancreatic tumours may be a consequence of the disease rather than a cause. Data were taken from SEER Cancer Statistics Review 1975-2013, United States of America ([http://seer.cancer.gov/csr/1975\\_2013/](http://seer.cancer.gov/csr/1975_2013/), accessed October 2016).

During the first two decades of life, the cells of the pancreas have already accumulated many mitosis and DNA alterations as a result of the high division rates required for organ development and growth. If a subset of pancreatic cancers developed rapidly after a catastrophic mitotic event, this event could occur before adulthood in some people, and pancreatic cancer would be relatively common before the age of 30. However, the risk of being diagnosed with pancreatic cancer during the first decades of life is very low in the United States of America (Figure 1). Similar data are observed in other countries. In the United Kingdom, the average number of new cases of pancreatic cancer per year is 9,618 for the 2012 - 2014 period, and only 17 cases per year are diagnosed in people under 30 years old [10]. The extremely low incidence of pancreatic cancer during the first decades of life and the striking increase in the incidence of this cancer with age strongly suggest that the formation of most pancreatic cancers requires the gradual accumulation of DNA changes over several decades.

Carcinogenesis is the process by which a normal cell gives rise to a malignant tumour; invasion and metastasis occur in the final stages of this process. Although pancreatic tumour invasion and metastasis can evolve abruptly, pancreatic cancer incidence by age indicates that the whole process is gradual and takes decades to complete. Therefore, even if chromothripsis were a driver of the late stages of carcinogenesis rather than a consequence, the model proposed by Notta, *et al.* [1] would not invalidate the accepted idea that there is time and opportunity to detect and stop pancreatic carcinogenesis before the development of advanced disease.

In summary, Notta, *et al.* [1] demonstrate that the mutations found in pancreatic tumors do not necessarily occur independently or in a specific order. Their results also indicate that these mutations do not always originate during DNA replication but also during mitosis. However, cancer incidence data by age challenge their model of pancreatic cancer and their central conclusion that invasive pancreatic cancer formation is not gradual.

### Conflicts of Interest

The author declares no conflict of interest.

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