

Random Chronic Stress Is a Major Cause of Pancreatic Cancer

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Nat Pernick, M.D., Nat@PathologyOutlines.com

Context: Pancreatic cancer is the #3 cause of US cancer death, projected to become #2 by 2030. Patients have a 5 year relative survival rate of only 10% with minimal recent improvements. Many cases have no apparent risk factors.

Design: We analyzed the population attributable fraction (PAF) of known risk factors and estimated the proportion due to random chronic stress or bad luck. We then analyzed possible mechanisms of action for malignant progression.

Results: Random chronic stress (i.e. no risk factor malignancies) accounts for 25-35% of US pancreatic cancer cases, calculated as 100% minus the PAF of known risk factors. It causes 2 cases per 100,000 people per year (age-standardized), accounting for 13,360 age-adjusted cases.

Causes include: (a) errors in DNA replication, organization or epigenetic modification; (b) errors in distributing cell components during or restoring contact inhibition after cell division; (c) immune system dysfunction; (d) classification errors due to undiscovered cancer risk factors or subclinical pancreatitis. Based on self-organized criticality, small disturbances in cellular networks may rarely disturb physiologic attractor states and initiate long periods with accumulations of minor network changes followed by bursts of activity leading to obvious premalignant or malignant changes. Gradualism (linear stepwise change) does not accurately describe malignant progression in pancreatic cancer.

Conclusions: Further study is needed to determine if "no risk factor" pancreatic cancer patients have different clinical and molecular characteristics, as exists for lung cancer with and without smoking, and whether their accompanying premalignant disease is more limited because risk factors with field effects are not present.