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Carcinogenesis of Pancreatic Cancer: Challenges, Collaborations, Progress

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Understanding the etiology of pancreatic cancer provides the best means to develop strategies for prevention, early detection, and treatment. Without a doubt, pancreatic cancer historically has been understudied. Until the past decade, efforts to understand the etiology and biology of this cancer had been hampered by the grim characteristics of the disease and lack of resources for proper study. Among the leading causes of cancer death in the United States, pancreatic cancer ranks fourth in both men and women, with an estimated 37,660 deaths in 2011. Incidence rates have increased approximately 1% per year since 1998 [1]. Worldwide, over 265,000 people die each year of this cancer [2]. Prognosis has not dramatically changed for decades, and 5-year survival is less than 5%. Treatment options are limited, while evidence-based early detection and prevention strategies are nearly non-existent. While improvements in clinical management could contribute to better survival, it is fundamental that prevention and early diagnosis of pancreatic cancer are the optimal approaches to reduce the burden of this disease.

Unlike the more common cancers of the lung, colon, prostate, and breast, the relatively modest incidence of pancreatic cancer, its later age at diagnosis, and advanced clinical presentation have hindered comprehensive accrual of patient data and biospecimens that would be sufficient for large-scale analysis. Two recent developments in etiology oriented research have played important roles in advancing our knowledge and response to the challenge of pancreatic cancer. First, a multidisciplinary approach that integrates biological understanding of the process of pancreatic carcinogenesis and molecular epidemiology, using large-scale prospective cohort and case–control studies, has gained widespread application. In particular, case–control studies have enabled timely study of pancreatic cancer patients using richly detailed risk factor and clinical datasets. A key necessity for this approach is very rapid case finding built into population-based and clinic-based methods of ascertainment. This has also facilitated the assembly of informative and comprehensive research biospecimen repositories of thousands of pancreatic cancer patients worldwide. Second, collaborations among researchers who share ideas, research data, and research-relevant tissue, have enabled us to arrive more quickly at statistically robust and meaningful answers. These collaborations can range from the informal, involving a handful of investigators, to formally chartered consortia and networks that receive infrastructural funding support [3–7].

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The Pancreatic Cancer Case–Control Consortium (PanC4) is a growing collaborative network of independently funded multidisciplinary pancreatic cancer researchers whose shared goal is to investigate the etiology of pancreatic cancer using case– control designs [6] that exploit both classic case–control samples and prospective cohort samples. In this special issue of *Molecular Carcinogenesis*, a series of papers by members of PanC4 present new data and provide comprehensive reviews of our current knowledge on the major causes of pancreatic cancer. Together, these reports provide a framework for future research directions.

Tobacco smoking, use of smokeless tobacco products, increased body mass, heavy alcohol consumption, and a personal history of diabetes mellitus or chronic pancreatitis have been demonstrated to increase the risk of pancreatic cancer. Several hereditary syndromes due to known genes (e.g., *BRCA1*, *BRCA2*, and *CDKN2A*) feature increased risk of pancreatic cancer, while ongoing research is identifying new susceptibility genes in familial pancreatic cancer. Single nucleotide polymorphisms identified through genome-wide association studies and candidate gene studies are associated with increased risk of the disease, but their effect is much more modest (e.g., *ABO*). Yet the genetic associations provide clues to mechanism and pathways that are important in pancreatic carcinogenesis. Novel directions in the study of pancreatic cancer are now possible with new molecular technologies for interrogation of genomes in biospecimens that have heretofore been difficult to assemble, and in large enough volumes to make proper inferences.

Exploration of disease mechanisms through study of environmental factors, including occupational exposures, infectious agents such as *Helico-bacter pylori*, dietary intake of mutagens from cooking meat, and immunologic-based hypotheses such as allergy and other exposures, are suspected to cause the disease but at present no final conclusions can be drawn. The overall message is that at present, the known causes of pancreatic cancer account for only a relatively modest proportion of the disease.

The limitations and challenges presented by pancreatic cancer should not, however, diminish our resolve to use fresh and existing knowledge to address modifiable risks. Curbing the epidemic of obesity and diabetes, controlling tobacco use, and reducing excessive alcohol intake all contribute to the prevention of the pancreatic cancer. While novel, effective therapeutic and early diagnosis approaches are being developed, research into the causes of pancreatic cancer should remain a high priority.

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