Genomic Strategies in Cancer Prevention: A Pancreatic Cancer Perspective

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Abstract

Background: Pancreatic cancer (PC) is one of the deadliest cancers worldwide for which little clinical progress has been made in the last decades. Furthermore, increased trends of PC mortality rates have been reported in Westernised countries. PC is usually diagnosed in advanced stages, precluding patients of an effective treatment. Identifying high-risk populations and early detection markers is the first and crucial step to impact on these figures and change the PC horizon. ***Aims/Objectives:*** To discuss the published body of evidence on host and tumor genomics promising markers for primary and/or secondary personalised PC prevention, as well as the future perspectives in the field. ***Methods:*** A review of the literature was performed to identify germline and tumor DNA and RNA markers that showed potential usefulness in defining the high-risk population, diagnosing the disease early, and identifying new carcinogens associated with PC. ***Results:*** Only high-penetrance inherited mutations are used, at present, to define the high-risk PC population. Although there are some promising genomics markers to be used as

early detection tests, none has been validated adequately to be integrated into the clinics routine. ***Conclusions:*** Despite of important efforts made in the recent time, little progress has been made to better characterise high-risk PC populations and to identify genomics-based markers for its early diagnosis. PC rates continue to rise, and this disease is becoming a real public health problem in the Westernised world. International and multidisciplinary strategies to identify new markers and properly validate the promising ones are urgently needed to implement cost-efficient primary and secondary prevention interventions in PC.

Mortality from cardiovascular diseases has dramatically decreased over the last decades, while mortality from cancer has only slightly declined during the same time [1] . The divergence in these mortality trends is somewhat striking as both conditions share several risk factors. Certainly, there are examples of interventions in either avoiding risk factors (smoking and lung cancer), promoting protective factors (*Helicobacter pylori* eradication or better food conservation for stomach cancer), or increasing

Dr. N. Malats and Dr. C. La Vecchia are Chair and Vice-Chair of the EUPancreas COST Action (BM1204), respectively. resistance to disease (HPV vaccination and cervical cancer) for successful primary prevention. However, this is not a generalised situation. Secondary prevention of cancer is also challenging, population screening programs being cost-efficient only for colorectal and cervical cancers worldwide and gastric cancer in some Asian populations. What are the reasons that cancer resists to its control? The fact that carcinogenesis is a complex process dealing with two genomes, at least, that of the host and that of the tumor, that evolve at different paces may explain, to a large extent, the challenges of cancer control.

I n the field of cancer, the study of human genome has mainly been focused on the description of tumor alterations and the identification of druggable mutations towards a personalised treatment of oncological patients. At present, genomics has contributed to a very limited extent to cancer control through primary and secondary prevention. Nevertheless, considering personalised prevention based on genome information may suppose a turning point in cancer control and an efficient complementary action to treatment. Thinking about the "cancer prevention scenario," there are three main actors to consider, namely the host genomics (HG), the tumor genomics (TG), and the non-genomics (NG) factors, the latter including environmental exposure to carcinogens, lifestyle factors, infectious agents, as well as the endogenous conditions such as inflammation, hormone status, and oxidative stress (Fig. 1). While the population-attributable fraction for NG factors, the proportion of cancer that would be avoided by preventing a particular exposure, has been estimated at around 40% for all cancers combined and close to 100% for cervical cancer due to HPV [2] , the estimates for HG factors are not so well assessed, probably ranging between 0 and 42% [3] . Consequently, the population-attributable fraction resulting from the interaction between these two types of factors has seldom been estimated, and the NG × HG × TG interactions are extremely complex to address.

G enomics is a broad concept that includes not only DNA features but also transcriptomics and epigenomics.

Therefore, when considering its contribution to cancer prevention, these three areas need to be taken into account for each HG and TG. We do not consider here metagenomics and metatranscriptomics, though this is debatable. Genomics are unavoidable risk determinants; however, understanding the role of the identified HG and TG potentially translationable markers would lead to a more detailed characterization of a high-risk population that would benefit from a targeted intervention, to the identification of new carcinogens associated with TG signatures, and to increasing the early diagnosis biomarker armamentarium (T able 1).

Table 1. The purposes of genomics markers in pancreatic cancer primary and secondary prevention

Markers	Host	Tumor
DNA mutations/ variants	Definition of a high-risk population (evidence only for hereditary pancreatic cancer)	Carcinogen identification (with few lines of evidence) Early detection markers (promising but not validated markers)
RNA markers	Definition of a high-risk population (no evidence yet)	Early detection markers (promising but not validated markers)
DNA methylation markers	Definition of a high-risk population (no evidence yet)	Early detection markers (promising but not validated markers)

P ancreatic cancer (PC) still does not benefit from the potential of genomics as this disease poses additional difficulties in primary and secondary prevention. PC incidence/mortality increases with age. Furthermore, increased trends of PC mortality rates (still equaling to incidence rates) have been reported in high-income countries. In Europe, while mortality rates for all cancers fall, rising PC death rates have been observed [4, 5] . This first observation was more evident among women in subsequent reports [6, 7] . A recent publication estimated that, by 2017, there will be more deaths from PC than breast cancer in the EU [8]. In the US, PC mortality was projected to surpass breast, prostate, and colorectal cancers, becoming the second leading cause of cancer-related deaths by 2030 [9]. Therefore, this tumor will become an increasing health problem in the aging population of the more developed countries.

P C is a complex disease with both environmental and genetic factors contributing to its development. Known NG factors explain only a third of PC cases [2] . Unfortunately, primary prevention has a limited scope due to the lack of knowledge on factors contributing to a large proportion of PC aetiology. Furthermore, for the majority of the identified risk factors, the associations are generally modest, making it difficult to identify a high-risk group that would benefit from screening. PC is one of the deadliest cancers worldwide with a 5-year survival rate of up to 7% [10]. Furthermore, this is the single common cancer for which there has been no improvement in its fatal prognosis over the last decades, despite the efforts in tertiary prevention since the tumor is overall resistant to treatment. Only 15–20% of patients undergo resection, whereas the remaining are diagnosed with metastatic or locally advanced disease due to nonspecific symptoms in the early stage of disease. The high mortality from PC is mainly due to the difficulties in early diagnosis: tumours <2 cm are generally already metastatic. Thus, the absence of specific symptoms and biomarkers of early stages, as well as the aggressive nature of the disease, makes early detection highly challenging.

In this article, we discuss the published evidence for HG and TG promising markers for primary and/or secondary personalised prevention of PC, as well as the future perspectives in the field.

Host Genomics

M ost of the HG markers that have been associated with cancer are DNA variant genotypes and 5mC levels at specific CpG islands. Individually, the magnitude of their association with cancer is small and, therefore, their benefit in defining high-risk populations is limited in cancer overall and, specifically, in PC where the number of markers identified is not large.

Host DNA Mutations/Variants

High-penetrance mutations have been reported in *STK11* , *ATM* , *P16/CDKN2A* , *PALLD* , *BRCA1/2* , *PALB2* , *APC* , *TP53* , *MSH2* , *MLH1* , *CTFR* , *PRSS1/2* , *SPINK1* , and *CTRC* , explaining about 2% of PC burden and 20% of familial aggregation of this cancer [11] . This genomics information has shown translational potential as it defines, at present, the only PC high-risk population to which screening interventions based on imaging screening tests are offered. However, the diagnostic yield of these tests has not been as efficient

as primarily thought in identifying early-stage neoplastic lesions [12] . Potential explanations are the yet unidentified PC susceptibility genes, the catastrophic progression of the disease, which narrows the window of opportunity, the extent of an individual's family history, the unknown age at onset of screening, the inadequacy of screening strategies, and the nature of the studies conducted on the evaluation of such screening strategies (short follow-up and small sample size studies). Consequently, no secondary prevention interventions are offered to these high-risk populations on a routine basis.

G enome-wide association studies (GWAS) conducted in large case-control studies and cohorts have identified >1,000 risk loci for a variety of complex diseases. The results from these GWAS have provided unprecedented insights into disease pathogenesis but – considered in isolation – known risk loci only account for a relatively small proportion (<25%) of inherited risk (i.e., ∼ 75% missing heritability). Moreover, it is poorly understood which specific variants are causal, through which biological mechanisms they act and how they interact with environmental factors.

F or the more common sporadic PC, GWAS efforts have identified about 52 SNPs significantly associated with the risk of PC [11, 13]. Genotyping and phenotyping have consistently shown that subjects of O blood group have a reduced risk of PC; the mechanisms through which this association takes place are not known. Importantly, several of the SNPs associated with PC are in the vicinity of genes involved in the development and differentiation of the exocrine pancreas: *NR5A2* (1q32) and *PDX1* (13q12) are transcriptional regulators playing a major role in pancreatic development and acinar gene expression; *KLF5* (13q22) is involved in a network in which *NR5A2* , *HNF1A* , and *GATA* proteins participate, all of them being regulators of exocrine function [14] ; *XBP1* is an eQTL at chr. 22q12 and is involved in the ER stress response, an important pathophysiological mechanism involved in acinar cell homeostasis; and *CTRB1/2* (16q23) are chymotrypsinogens, a family of proteins expressed at high levels in the exocrine pancreas and contributing to pancreatitis. The identification of rare (minor allele frequency <0.01) polymorphisms represents the next step that several groups are working on by applying next-generation sequencing strategies. This information may be translated into primary prevention interventions towards the characterisation of high-risk populations using genomics scores that would integrate several common and rare variants.

A t present, only few and partial attempts to model the prediction of PC risk based on NG and individual HG factors have been reported [15–21] . However, all of them have a limited scope regarding the number and type of factors they considered or the population to which they have been applied. The predictive ability found by Klein et al. [19] , the most comprehensive PC risk prediction score at present, was AUC = 0.58 (95% CI 0.56–0.60) for a risk model including only NG factors and AUC = 0.61 (95% CI 0.58–0.63) for a model including both HG and NG factors.

Host RNA Markers

T he levels of RNA, miRNA, or lncRNA (long-noncoding RNA) have been extensively explored in tumor tissue. While the origin of circulating RNAs is unknown, it is conceivable that they are fragments that tumor cells release to blood and, therefore, the evidence on these molecules as tumor markers will be discussed in the next section. However, normal blood cells may also release RNA fragments that may be considered as disease susceptibility markers. This scenario is gaining more interest along with the important role of tumor microenvironment and immunological status. It is therefore very early to draw any firm conclusions on its potential of translation into primary or secondary prevention of cancer, including PC.

Host DNA Methylation Markers

A growing body of research suggests that gene-environment interactions are mediated, at least in part, by epigenetic processes [22]. It has been proposed that epigenetic variation depends on external factors such as tobacco and arsenic among others, and that it may play an important role in aging and diseases such as cancer, type 2 diabetes, and metabolic disorders. There is some evidence supporting that methylation levels are potentially modifiable through diet, providing a unique opportunity for primary prevention interventions [23]. The methylomes of multiple types of tumours are currently being deciphered in the context of several worldwide consortia [24] . However, such information is not yet available for PC. The association between germline DNA methylomes and cancer has only been reported in one small study on PC, its results warranting larger explorations [25] . Similar to DNA mutations/variants, methylation levels may be used as a marker to define high-risk individuals, subjects who could adopt both primary and secondary prevention strategies only when combined with other markers since, individually, they confer very small risks.

Tumor Genomics

T his field has been extensively studied by the big consortia TCGA and ICGC, among other initiatives. The data generated at different *omics* levels assisted to better understand the genetic mechanisms and pathways underlying cancer in general, specific cancers, as well as to identify commonalities across cancer sites. PC is a molecular heterogeneity disease. Each pancreatic tumor has an average of 63 genetic alterations, which makes it difficult to develop a marker for early detection [26] . The detailed study of the molecular features of PC using nextgeneration sequencing has also shed light to understand the carcinogenesis process of this disease allowing further identification of therapeutic targets [27]. While the translational objectives of these discoveries have mainly related to treatment purposes, they also offer opportunities for primary and secondary prevention.

Tumor DNA Mutations

T here are sound lines of evidence that both external and internal carcinogens can leave specific marks in the tumor DNA, both at the individual gene level and at the genome level [28] . A recent large study identified tissuespecific mutational and methylation signatures associated with tobacco smoking [29]. These observations pave the road for further explorations into the genomics to identify new carcinogen signatures. The study by Alexandrov et al. [29] , however, provided intriguing results from PC sample analysis showing no elevated mutation burden in smokers versus nonsmokers and presenting a different mutational profile from other smoking-related cancers with a higher proportion of indels and a lower proportion of transversions. Other recent studies reported interesting data on the presence of squamous-like tumours on the basis of their molecular profile with highly similarities across tumours, including pancreatic, breast, and bladder cancers [30, 31]. These observations may point to common risk factors across cancer sites.

Tumor molecular alterations may also be present and can be found in circulating tumor DNAs (ctDNAs), also known as liquid biopsy, becoming a potential early diagnosis marker [32]. However, the amount of ctDNA at early stages of the disease is very low (0.1–1%), requiring highly sensitive techniques to provide adequate sensitivity and specificity. However, ctDNA detection techniques still present some limitations. This jointly with a lack of sample technical standardisation makes it a premature marker. While PC would benefit from ctDNA early diagnosis markers, same challenges apply to this disease [33] .

Tumor RNA Markers

T he PC tumor transcriptome has extensively been characterised mainly through RNA microarrays that have identified several tumor markers as therapeutic potential targets. Recently, an RNA sequencing assessment has complemented the list of the previous differently expressed genes in PC tumor samples in comparison to benign pancreatic tissue [34] . These data have been used for PC taxonomy purposes and clinical trial design. Based on the transcriptional profile, three subgroups of PC were proposed (classical, quasi-mesenchymal and exocrinelike) that were further associated with their clinical outcomes and treatment response [35] . Additional work is needed to translate these findings into the early detection field of this disease.

miRNAs are involved in several altered PC signaling pathways. As promising early diagnosis biomarkers, circulating miRNA overexpression has been identified associated with diagnosis, prognosis, and treatment response of PC. Huang et al. [36] published a thorough revision of the evidence of miRNA in PC. According to this review, 5 studies identified diagnostic miRNA profiles in serum/plasma with AUC ranging from 0.82 to 0.99 when comparing PC with normal subjects. However, work is still needed to assess their final clinical value before implementing them into the hospital routine. lncRNA have also been observed dysregulated in PC in comparison to normal tissue, though their promising clinical potential needs to be validated before they are translated into the clinics, too [37] .

Tumor DNA Methylation Markers

Both hypermethylation and hypomethylation CpG islands have been identified in PC. Kisiel et al. [38] identified a methylomics profile in pancreatic juice that discriminated well PC from chronic pancreatitis and normal pancreas with AUCs up to 0.92 for *CD1D* . Unfortunately, the collection of pancreatic juice requires an aggressive maneuver that cannot be implemented in a population screening program. While the evidence is still scarce, ctDNA methylation is a promising marker for all cancers [32] . PC would largely benefit from it, too.

Future Perspectives

P C diagnosis is almost invariably a death sentence, representing a devastating impact for the affected patients, families, society, and the work-related issues. It is a cancer for which little clinical progress has been made in the last decades. A failure we cannot afford. The progress derived from a multidisciplinary and international effort will contribute to change this scenario

by reducing PC incidence and mortality. Identifying the population at high risk of developing PC is the first and crucial step to impact on these figures and change the PC horizon. Similar approaches have been developed and implemented in other medical, cancer, and non-cancer areas. As for cancer, there is a large body of research that has rarely been translated in great part because integrative approaches and risk algorithms are not in practice. This is unlike the cardiovascular disease field, where the Framingham risk score and all its derivatives have efficiently discriminated the fraction of the population at a higher risk allowing them to benefit from prevention measures [39] . Few risk scores have been proposed for PC, yet they suffer from methodological caveats and/or the fact that their discriminative capacity is not enough to be applied in the healthcare systems. It is crucial to improve the preexisting tools by tuning them with genomics biomarkers selected through an appropriate methodology.

This approach will impact on a broad sector of the Westernised population because the main PC risk factors are of high prevalence in our aging population: type 2 diabetes (>15%), obesity (23%), smoking (>20%), alcoholism (20%), blood group A/B (>60%), among others, without taking into account the protective factors such as asthma and allergic rhinitis with the prevalence of 4 and 23%, respectively [http://www.euro.who.int/en/healthtopics; 40]. The affected population for targeted intervention needs to be narrowed down not only by combining these factors but also by tuning the model with proved and validated genomics biomarkers.

While individual risk factors are of low/moderate magnitude with risks of about 2, the risk of PC increases by considering together several known risk factors/comorbidities concomitantly [41]. The reality, however, is more complex since the number of risk factors is larger and several of them strongly correlate. In addition, the proportion of subjects with multiple risk factors becomes small in the population. Furthermore, new actors have appeared on the scene such as (epi)genetics and microbes/ microbiome. Therefore, new efforts should be done to assess in an integrated manner these individual risk factors and their interactions by applying cutting-edge research.

This vision is based on technology, methods, and data integration [42]. This endeavour requires developing novel interdisciplinary tools for collaborative research to improve our understanding of PC and its prevention, diagnosis, and treatment. This would have a relevant public health impact on a large number of citizens, in particular in the face of an aging population. Involvement of pancreas research multidisciplinary teams integrating stateof-the art technology, methods, and data requires a strong commitment towards a new approach for PC control focusing in primary and secondary prevention. We have paved the way to identify the real limitations of current (single factor) approaches in PC control and set up realistic future steps to provide a chance for integrative approaches to gain a wide acceptance by clinical and public health domain, with an impact on the citizens.

T he public national health services will hardly be able to afford personalised chemotherapy of an increasing number of cancer patients, including those with PC, with such very costly treatments. By decreasing the incidence of cancer through primary prevention interventions and its mortality through primary and secondary prevention strategies (early diagnosis and screening), we can accomplish decreases in costs in health services and health care. Genomics efforts will also have a strong impact on national societies and economies. Improving early detection from 20 to 40% would have an impact on 5-year survival by doubling the number of subjects who are candidates to receive surgical treatment. In 2014, this policy was adopted by the US Congress which defined PC as a “recalcitrant cancer” and launched a 5-year effective Pancreatic Cancer Research and Education Act involving research for biomarkers of early detection [43] . EUPancreas (COST Action BM1204, www.eupancreas.com) also supports this mission. The Action aims to unite groups across Europe interested in pancreas cancer research, by providing an innovative and unique platform for collaborating and sharing information, ideas, and experience. It hosts more than 250 multidisciplinary members from 22 European countries, private companies, and governmental institutions. It has a broad scope covering by integrating knowledge and experience in a multidisciplinary way “from cell to society,” fostering collaborative research to improve our understanding of pancreas cancer and its prevention, early diagnosis, and treatment under the personalised medicine umbrella, promoting the application of uniform study tools and protocols and their optimal use by researchers, enhancing the mobility and training of researchers, and disseminating the results produced to the broader society. EUPancreas addresses questions related to the aetiology, early detection, evidence-based, personalised treatment, and health management for PC. The Action aims to foster PC research in Europe and to coordinate this effort with international initiatives to reduce disease incidence and mortality such as Pancreatic Cancer Europe, PCE (www.pancreaticcancereurope.eu). Created in 2014, PCE is a European multistakeholder platform which aims at bringing together experts from all over Europe

including academics, physicians, politicians, patient groups, journalists, and industry to work towards the development of targeted EU and national policies on PC, to raise awareness of the condition at national level, to improve its diagnosis, to foster data collection and to support research. The commitment of EUPancreas and PCE to PC control will guarantee the timely and effective translation of the findings into the European health care systems through the involvement of all relevant stakeholders (e.g., industry, policy makers, patients, clinicians, third-party payers).

While improving health and developing innovation strategies are the ultimate goals, first it is important to create and integrate knowledge that can be applied to both goals. The strategy to stimulate innovation requires ensuring close and productive interactions between groups with expertise in a range of areas that are central to progress in cancer research and medicine, as well as in biotechnology. Integrative research should first lead to define the tools that are needed, which then could be used by the biotechnology groups to implement risk scores, bioinformatics devices, and biomarker arrays.

Despite important efforts done in the recent time, little progress has been made to better characterise PC highrisk populations and to identify genomics-based markers for its early diagnosis. PC rates continue to rise, and this disease is becoming a real public health problem in the Westernised world. International and multidisciplinary strategies to identify new markers and properly validate the promising ones are urgently needed to implement cost-efficient primary and secondary prevention interventions in PC.

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