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International Registries of Families at High Risk of Pancreatic Cancer

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Key Words
Familial pancreatic cancer · Hereditary pancreatitis · Screening

Abstract
Purpose: To describe the need for multinational registries of families at high risk of pancreatic cancer and the issues surrounding identification of such families. ***Results:*** A consensus position was published describing surveillance of individuals at high risk of pancreatic cancer. Hereditary pancreatitis patients, people with Peutz-Jeghers syndrome, individuals with CDKN2A or BRCA1/2 mutations with a family history of pancreatic cancer and kindred with multiple pancreatic cancers were considered suitable for research-based screening. Mutations responsible for familial predisposition are mostly unknown, although BRCA2 mutations have been identified in some families and a mutation in the palladin gene has been shown to segregate with pancreatic cancer in one kindred. Specific autosomal dominant inheritance of pancreatic cancer risk seems to involve anticipation; this finding aids identification of families and determination of individual risk. Diabetes mellitus is an early symptom of pancreatic cancer, but recent publications suggest that it may not be a significant predisposing factor; this remains controversial. However, in the context of hereditary pancreatitis, diabetes probably does predispose to pancreatic cancer as shown in a recent description of French families. ***Conclusion:*** Appropriate inclusion of patients within registries of high-risk families provides a framework for secondary screening and research on risk stratification and early tumorigenesis.

Introduction

Consensus practice recommendations for management of people at risk of pancreatic ductal adenocarcinoma were debated in the Fourth International Symposium on Inherited Diseases of the Pancreas [1 – consensus guidelines on the management of high-risk families]. The review covered the areas of counselling, genetic testing and secondary screening. Secondary screening was proposed on a research basis for patients with hereditary pancreatitis (HP), individuals from Peutz-Jeghers kindred, families with multiple cases of pancreatic cancer or families with single cases in the presence of a known predisposing mutation. Such families are rare. This review will discuss the benefits of establishing registries of patients with these medical conditions and the consequences of different recruitment practices.

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The Purpose and Nature of Registries

For clinicians and scientists tasked with the study or management of pancreatic cancer patients it can often seem that life is a constant effort to close a barn door long after the horse has fled. Patients present when they have fairly advanced disease, usually at a point when treatment with curative intent is impossible [2]. Information on the early symptoms and risk factors that were involved in tumorigenesis is retrospective and heavily biased by the influence of hindsight [3]. Failure to detect early tumours also means that nearly all samples taken are from patients with relatively advanced cancers, limiting our understanding of the early disease and making development of diagnostic modalities to detect early cancers extremely difficult. Screening of a symptom-free population would resolve many of these problems, but pancreatic cancer is a rare disease, with an age-adjusted yearly incidence of below 10 in 100,000 in both Europe and the USA [4 – the latest data from Europe showing the trends in pancreatic cancer incidence, 5 – the latest of a series of publications describing the pancreatic cancer incidence in America]; this would make screening of the general population impractical and, given the risk of false positives, unethical. The only hope is to identify individuals at high risk using a primary screen; environmental factors certainly elevate risk, but this effect is limited and even smoking only doubles the risk of developing a pancreatic tumour [6]. Patients with diabetes [7] or pancreatitis [6] have a greater risk of developing this form of cancer, but this again may not elevate the risk to a point where screening is cost effective. Only a family history of pancreatic cancer [8] or pancreatitis [9] gives a risk level where prospective studies detecting early tumours would be possible.

The benefits for participants of inclusion in a registry include education on the probability of developing pancreatic cancer, knowledge of possible alarm symptoms as well as giving increased credibility to the participant when discussing their anxieties with their clinician. For the researcher, a registry allows testing and refining of assumptions on the epidemiology of the disease. Moreover, the registry may be used to test novel screening modalities to identify early, resectable tumours providing tissue samples that can reveal vital features of the early stages of the disease. Finally, registries allow linkage and association studies to identify novel mutations and polymorphisms that are linked to cancer risk.

Each registry is a partnership between a research group, the participants in the registry and the clinicians responsible for patients. Each member of this partnership has a different motive for involvement; the nature and balance of these motives will determine what kind of registry is established. Active participants, with active clinicians and clinically motivated research groups will result in greater recruitment for screening. The same scenario with passive participants may well result in inclusion of inappropriate families in the registry, as will be discussed below.

Recognition of High-Risk Families

Although only 10% of pancreatic cancer patients have a family history of the disease, an inherited genetic component is probable in most cases as race influences cancer risk [10] and common polymorphisms are known to affect cellular responses to carcinogens [11, 12]. The 'two-hit' Knudson model explains cancer predisposition in terms of a germ line mutation in a single allele of a tumour suppressor or DNA repair gene; loss of the second allele provokes tumour development [13]. Such a model will inevitably result in a dominant disease, as the inheritance of a single mutant allele is enough to confer elevated cancer risk.

Autosomal Dominant Conditions

Although autosomal dominance is likely, it may not be easily observed. Pancreatic cancer is a late-onset disease; thus, many family members die before the cancer develops, resulting in generations with few or no cases. This is even more likely if the predisposition results in an elevated risk of other forms of cancer, many of which may have an earlier onset. This gives a general rather than a specific cancer syndrome, incidence of pancreatic cancer in these families will increase as survival from other cancers becomes more frequent [14].

General Cancer Syndromes

Familial adenomatous polyposis is characterised by the presence of adenomatous polyps and a high incidence of colon cancer often associated with mutation of the tumour suppressor gene APC. There is an estimated 4.46-fold increased risk of pancreatic cancer (95% CI: 1.2–11.4) [15].

Li-Fraumeni syndrome involves an extreme elevation of cancer risk. It results from recessive mutations in the p53 tumour suppressor or occasionally mutations in the CHK2 gene. Multiple cases of pancreatic cancer have been reported in Li-Fraumeni kindreds [16].

Peutz-Jeghers syndrome is the autosomal dominant inheritance of hamartomatous polyposis. In a meta-analysis involving 218 individuals in 79 families, there was a 132-fold increased risk of pancreatic cancer [17], usually as the result of mutations in the STK11 gene [18, 19], but this was based on just 6 pancreatic cancer patients.

Lynch syndrome II features colorectal and extra-colonic tumours such as gastric, breast, ovarian, endometrial, bladder, small bowel and pancreatic cancer [20]. This is the result of inheritance of mutations in mismatch repair genes.

Familial atypical multiple mole melanoma (FAMMM) is characterised by multiple dysplastic naevi and malignant melanoma. An association between FAMMM and pancreatic cancer is well known and has been used to define a subdivision of FAMMM families known as FAMMM-pancreatic carcinoma [21]. Mutations in the tumour suppressor CDKN2A are associated with FAMMM [22].

Breast ovarian cancer syndrome is associated with a 10-fold increase in pancreatic cancer risk [23]. Risk in these families is often associated with the inheritance of BRCA2 and BRCA1 mutations. In certain families, BRCA2 causes a more specific risk of pancreatic and not breast or ovarian cancer [24].

Familial Pancreatic Cancer

This is a specific autosomal dominant inheritance of a predisposition for pancreatic cancer. In most cases, no mutation associated with the disease has been identified [25 – evidence that mutation analysis of the palladin gene is unlikely to be effective in the majority of familial pancreatic cancer kindred, 24–28], although some families have mutations in the BRCA2 gene [24] and there is one American family which has a mutation in the palladin gene [29].

Polygenic or Recessive Predisposition

The recipient of two recessive alleles is born with a defect that confers risk, and this defect is expressed in every cell. In the recessive model, initiation occurs at conception and progression must be assumed to last for 40 years or more. No mutation causing a recessive syndrome of this type has yet been linked to pancreatic cancer, but this does not mean they do not exist. The recessive syndrome Fanconi anaemia (FA) is associated with greatly elevated risk of several cancers. Mutations that can cause FA have been identified in thirteen different genes, all of which are involved in the repair of DNA damage by homologous recombination, including BRCA2 [30]. FA has not been reported to be associated with any elevated risk of pancreatic cancer (probably because of the limited life expectancy of sufferers), but heterozygotes of FANCC and FANCG as well as BRCA2 have been identified in sporadic pancreatic cancer [31, 32], suggesting an autosomal dominant predisposition with low or variable penetrance.

More likely than a genuine recessive syndrome would be a multigenic predisposition with multiple polymorphisms in different alleles, each individually conferring negligible increased cancer risk but, in combination, resulting in very high risk. Such combinations have not yet been identified in pancreatic cancer but association studies in other cancer types have indicated that such lethal combinations are possible [33 – evidence that association studies can identify low penetrance alleles that in combination may explain elevated cancer risk].

A recent study of 570 pancreatic cancer patients in Italy revealed that there was a significantly increased risk of pancreatic cancer in first- and second-degree relatives; this was largely due to just seven families with more than one case in addition to the proband. The authors use the data to conclude that 'it is possible that most of the familial excess of pancreatic cancer results from moderate- to low-penetrance genes'. However, all of the seven families reported are consistent with an autosomal dominant condition with high penetrance (using the rationale described above), including one family that carries a BRCA2 mutation [34 – confirms that much of the elevated risk of pancreatic cancer in relatives of cases is due to a small number of familial clusters].

Indirect Association

Several diseases have been identified as risk factors for pancreatic cancer. Inheritance of a predisposition for one of these conditions could indirectly lead to clustering of pancreatic cancer in families.

Diabetes

The association of diabetes mellitus with pancreatic cancer is well documented. This association can be the result of diabetes secondary to cancer but may also involve diabetes acting as a risk factor [35 – evidence that pancreatic endocrine failure is an early symptom of pancreatic cancer rather than a predisposing factor]. A large American family (Family X) with multiple cases of pancreatic cancer has a high incidence of diabetes [36]; this is the same family that has an association with a variant in the palladin gene. Other groups did not report such an association and were not able to identify linkage of pancreatic cancer to the palladin gene [25].

Pancreatitis

HP is a rare autosomal dominant disease leading to acute pancreatitis in childhood, which progresses to chronic pancreatitis with an elevated risk of cancer of the pancreas (approximately 40% lifetime risk to age 70) [9, 37 – this is the first systematic description of HP families in France and is one of largest studies ever published, 38]. Tobacco smoking further increases this risk [39]. This could account for a familial cluster, but in the largest report of European families to date only 2/112 families had more than one case of pancreatic cancer [9].

Various forms of pancreatitis have been shown to be associated with the N34S mutation of the SPINK1 gene [40], but this is most marked in tropical pancreatitis [41]. Tropical pancreatitis develops in young people in Africa and Asia even in the absence of alcohol abuse. It is often accompanied by diabetes and is associated with a greater than 100-fold increased risk of pancreas cancer [42].

Although cystic fibrosis (CF) may itself be linked to pancreatic cancer, the risk is difficult to quantify given the short lifespan associated with CF. However, inheritance of particular alleles of the CF transmembrane conductance regulator gene also confers an increased risk of pancreatitis, particularly in the presence of the N34S variant of SPINK1 [43] or polymorphisms of the TNF-α promoter [44].

HP was one of the backgrounds in which research-based screening was considered desirable at the Fourth International Symposium on Inherited Diseases of the Pancreas [1]. In many respects, this group of patients is the easiest to counsel as it is easy to identify at risk individuals within the family and these individuals will have an existing need for clinical surveillance regardless of cancer risk.

National and International Registries

The motives for establishing a registry of familial pancreatic cancer, or HP, have ensured that many have been created, most of which remain small and are based on either one or two large families or small numbers of individual pancreatic cancer patients. For the purpose of monitoring and supporting individual patients, smaller registries may be adequate. However, size does matter if the registry is intended to supply solid epidemiological and genetic data. The National Familial Pancreas Tumour Registry (NFPTR) based in Johns Hopkins University had 2,434 families registered with them in August 2007, but only 874 of these had more than one first-degree relative diagnosed with pancreatic cancer (http://pathology.jhu.edu/pancreas/PartNFPTR.php). Also in North America the Pancreatic Cancer Genetic Epidemiology has 476 probands registered with 379 kindred having two or more affected relatives [45 – major publication from PACGENE]; this is a consortium comprising seven referral centres.

The European Union has funded a pan-European database of high-risk families. This has brought together the European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis (co-ordinated in Liverpool, UK, and Greifswald, Germany), the German National Case Collection for familial pancreatic cancer and smaller collections of families from Sweden and Italy. At the time of writing (February 2008), there were 274 pancreatic cancer families, out of which 233 had 2 or more cases, but only 125 were considered to be consistent with autosomal dominant disease. The database also includes 455 pancreatitis families of which 157 are considered to have autosomal dominant inheritance of pancreatitis. There are 66 pancreatic cancers recorded on the pancreatitis database, of which 44 are in HP families.

Methodological Issues

In order for screening, linkage and epidemiological studies to be effective registries must contain genuine high-risk individuals who have not yet developed cancer; the methods used to recruit and characterise families will influence the proportion of registered individuals who fit these criteria.

Probability of Random Clusters

Although pancreatic cancer is a relatively rare disease, random clusters of cases will occur. These random clusters will inevitably be included in registries of high-risk families, but if the cluster is truly random then prospective incidence of pancreatic cancer would be equivalent to the general population. Tersmette et al. [46] carried out a prospective analysis of first-degree relatives who were free of cancer but enrolled in the NFPTR. Six new cancer cases were observed, four were in families with two or more cases of pancreatic cancer giving an 18-fold relative risk (95% CI: 5–45), three of the new cases were in families with three or more previous pancreatic cancers giving an increase in relative risk of 57 (95% CI: 12–175). These figures represent a combination of high-risk individuals and relatives of randomly occurring cases of pancreatic cancer; they suggest that the likelihood of a cluster of cases occurring by chance is reduced as the number of cases increases. In a more recent study, families of 570 af-

fected probands were investigated, and an elevated risk for pancreatic cancer was confirmed in first- and second-degree relatives, the bulk of the excess cases occurring in just seven families, all of which were consistent with autosomal dominant disease. This suggests that the remaining 47 families with a family history may have simply been random clusters, possibly because of the nature of the proband recruitment [34].

Nature of the Proband

The chance that a patient with pancreatic cancer will have a first-degree relative with pancreatic cancer is obviously considerably greater than the chance that a person chosen at random will have two cases of pancreatic cancer. The nature of the proband therefore influences how confident a registry can be that a family is the result of a random cluster. Most registries include at least some families where the proband is a patient.

Reporting Bias

A proband with pancreatic cancer or a close relative of someone with pancreatic cancer is much more likely to remember another relative with pancreatic cancer than an individual who is not sensitised to the disease [47]; they will also be more motivated to research their own family medical history.

Shared Environment

Families tend to have shared environments as well as shared genotypes [48], and for pancreatic cancer the effect of shared genotype is very small in the majority of cases compared to shared environment. Existence of two relatives with limited contact affected by pancreatic cancer is therefore less likely to be the result of a random cluster than two cases of pancreatic cancer in individuals raised together who have similar occupations.

Quantifying Risk

For an individual entering a registry, the first question is likely to be about his/her own individual risk or risk of another family member. The risk given to two first-degree relatives with pancreatic cancer is 18-fold higher than the risk of the general population, while 3 or more affected first-degree relatives gives a 57-fold increase in risk [46]. However, these figures are derived from the average increased risk including families with autosomal dominant conditions combined with the risk in families with polygenic conditions and families with phenocopies. In reality, individual risk is dependent on: (1) the chance of being in a family with a predisposition; (2) the chance of being a carrier, and (3) the penetrance or pattern of inheritance.

The Chance that a Family Has Predisposition

This is influenced by the number of cases within a family and the pattern of inheritance. For example, if the argument for a familial predisposition is assumed to be autosomal dominance (multiple generations affected) then the probability that the family has a genuine predisposition will depend on the number of family members that have to be assumed to be non-penetrant. Definitions of non-penetrant may vary, but there is considerable evidence for anticipation in familial pancreatic cancer kindred [49], in which case an individual can be considered non-penetrant if he/she has exceeded the age of an affected parent or exceeded the age of an affected child by at least 10 years. Family A in figure 1 is therefore more likely to have an autosomal dominant predisposition than family B, where one grandparent of the proband must be assumed to be non-penetrant. Using the same logic, family C is less likely to have autosomal dominant predisposition than family B, as in this case two family members must be assumed to be non-penetrant.

The Chance of Being a Carrier

Assuming an autosomal dominant disease, if the mutation responsible for the predisposition is unknown then an individual with an affected first-degree relative will have a 50% chance of being a carrier, the exception being if the individual is the parent and descendent of affected family members, as shown by individual X of family C in figure 1. Registries may also include families that are not assumed to have autosomal dominant disease. For example, family D in figure 1 may be assumed to have a genetic predisposition but explained by a polygenic or recessive inheritance.

Genetic Testing

Whether an individual is a carrier or not can be resolved if the mutations or polymorphisms are known; this may also clarify whether the family has a genuine predisposition. While it is advisable to test a sample from an affected individual before testing potential carriers, indiscriminate testing of candidate gene mutations is unlikely to be effective. Testing for p16 (CDKN2a) mutations may identify carriers in FAMMM-PC families, but families are unlikely to carry such mutations if there is no case of melanoma in the family [50]. Testing for BRCA2 mutations may identify some carriers [24], but this is only true in a minority of families; it must also be remembered

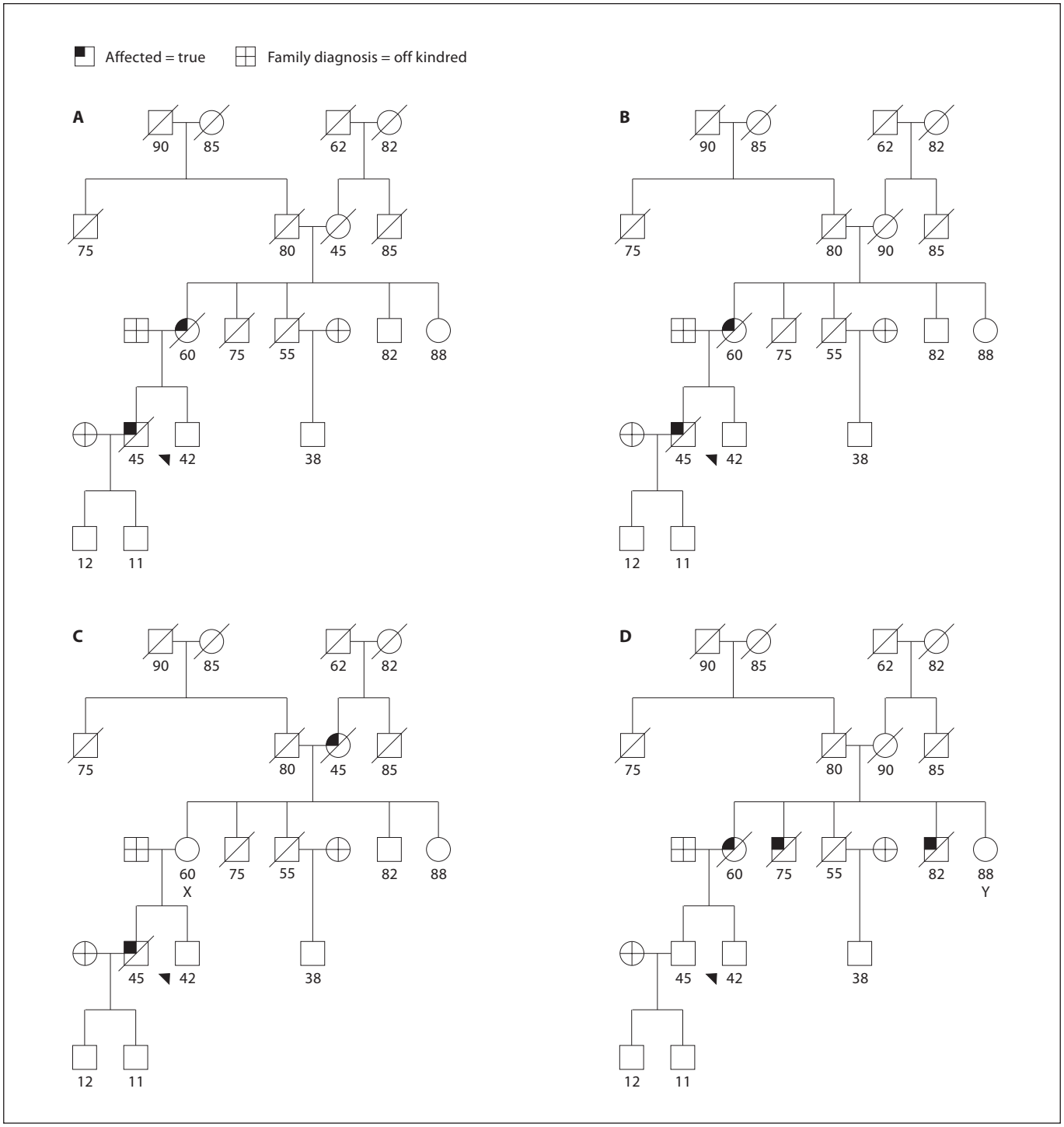

Fig. 1. Four similar families are shown. In family A, the proband has an affected sibling and parent, neither of his maternal grandparents were affected but one died of other causes aged 45; this is younger than the age of the affected mother so we cannot tell whether this grandparent is non-penetrant. Family B is identical to family A except that both grandparents died over 20 years after the affected mother. It is reasonable to say that in this family one great grandparent is non-penetrant. In family C, in order to assume autosomal dominance individual X must be assumed to be non-penetrant as well as at least one great grandparent. In family D, there are three cases of pancreatic cancer, but there is no evidence for autosomal dominance as the affected cases are restricted to a single generation. If this pattern is the result of a recessive or polygenic predisposition, individual Y has a greater chance of having the same combination of alleles that conferred risk on her siblings than any of her nephews.

that BRCA2 in the absence of family members with pancreatic cancer does not in itself indicate a greatly elevated pancreatic cancer risk [23]. In most families, testing for mutations in palladin is unlikely to be productive as the majority of familial pancreatic cancer families tested to date have proved to be wild type for this gene [25].

Penetrance

In defining a family as having autosomal dominant predisposition to pancreatic cancer, assumptions on penetrance will already have been made, as described above. If the family is assumed to have a polygenic or recessive predisposition, then penetrance may depend on the combination of alleles inherited. The chance that individual Y in family D has the same combination of alleles that gave risk to her siblings would (under this assumption) be relatively low, for a single gene recessive syndrome 25%. The chance that any of her nephews has this combination would be even lower.

Conclusion

Multinational registries of high-risk families of pancreas cancer will provide a basis for a pilot screening program. These registries will inevitably contain 'false-positive families', merely a random cluster of pancreatic cancer cases, where there is no elevated risk of pancreatic cancer for close relatives. Success of screening trials will require that the majority of participants have a genuinely high risk; this would be greatly facilitated if causative mutations could be identified; failing this, it will require a careful analysis of the joint influence of genetic predisposition and environmental risk factors.

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