Risk of Pancreatic Cancer in Families With Lynch Syndrome

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Context Lynch syndrome is an inherited cause of colorectal cancer caused by mutations of DNA mismatch repair (MMR) genes. A number of extracolonic tumors have been associated with the disorder, including pancreatic cancer; however, the risk of pancreatic cancer in Lynch syndrome is uncertain and not quantified.

Objective To estimate pancreatic cancer risk in families with germline MMR gene mutations.

Design, Setting, and Patients Cancer histories of probands and their relatives were evaluated in MMR gene mutation carriers in the familial cancer registries of the Dana-Farber Cancer Institute (n=80), Boston, Massachusetts, and University of Michigan Comprehensive Cancer Center (n=67), Ann Arbor, Michigan. Families enrolled before the study start date (June 2008) were eligible. Age-specific cumulative risks and hazard ratio estimates of pancreatic cancer risk were calculated and compared with the general population using modified segregation analysis, with correction for ascertainment.

Main Outcome Measures Age-specific cumulative risks and hazard ratio estimates of pancreatic cancer risk.

Results Data on 6342 individuals from 147 families with MMR gene mutations were analyzed. Thirty-one families (21.1%) reported at least 1 case of pancreatic cancer. Forty-seven pancreatic cancers were reported (21 men and 26 women), with no sex-related difference in age of diagnosis (51.5 vs 56.5 years for men and women, respectively). The cumulative risk of pancreatic cancer in these families with gene mutations was 1.31% (95% confidence interval [CI], 0.31%-2.32%) up to age 50 years and 3.68% (95% CI, 1.45%-5.88%) up to age 70 years, which represents an 8.6-fold increase (95% CI, 4.7-15.7) compared with the general population.

Conclusions Among 147 families with germline MMR gene mutations, the risk of pancreatic cancer was increased compared with the US population. Individuals with MMR gene mutations and a family history of pancreatic cancer are appropriate to include in studies to further define the risk of premalignant and malignant pancreatic neoplasms and potential benefits and limitations of surveillance.

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PANCREATIC CANCER IS THE fourth leading cause of cancer deaths in the United States.[1] Although most cases are thought to be sporadic, data suggest up to 10% of ductal adenocarcinomas may be due to an inherited predisposition based on familial clustering.[2,3] For most pancreatic cancer kindreds, the causative gene has not been identified. In a subset of families, pancreatic cancer may be an integral tumor in a number of familial cancer syndromes with established germline mutations. These conditions include Peutz-Jeghers syndrome (cumulative lifetime risk of 36%),[4,5] familial atypical multiple mole melanoma syndrome (lifetime risk, 17%),[6] hereditary breast/ovarian cancer syndrome (lifetime risks, 1.2% and 2.1%, for *BRCA1* and *BRCA2* carriers, respectively),[7,8] hereditary pancreatitis (lifetime risk, 40%),[9] and the newly described familial pancreatic cancer due to mutations in the *PALB2* gene (risk not specified).[10]

Pancreatic cancer has also been observed in Lynch syndrome, an autosomal dominant condition caused by defects in the mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Colorectal cancer (CRC) and endometrial cancer are the most common cancers in this condition, with other specific neoplasms also occurring more frequently than in the general population. Evidence to include pancreatic cancer in the Lynch syndrome cancer spectrum has been difficult to inter-

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pret and an increased risk has not been convincing.[11-16] Most studies examining cancer risk in Lynch syndrome have been from families with a strong history of early onset CRCs. This lends itself to a number of problems including the overestimation of age-specific cumulative risks of component tumors due to ascertainment bias. Additionally, many published data report on a small number of cases with incomplete testing of the full pedigree. Analyses performed exclusively on observed genotypes lack power to accurately estimate uncommon events, such as cancers with lower prevalence in a given syndrome.

The goal of our study was to quantify the risk of pancreatic cancer in families with an identified pathogenic MMR gene mutation. We have used analytic tools that correct for ascertainment and provide genotype data on patients whose mutation status is unknown.

METHODS

Selection and Description of Participants

A total of 147 families with deleterious mutations in *MLH1* (GenBank NM_000249), *MSH2* (GenBank NM_000251), and *MSH6* (GenBank NM_000179) were eligible for inclusion at the start of the study in June 2008. Families were identified from hereditary CRC registries at Dana-Farber Cancer Institute (DFCI; n=80), Boston, Massachusetts, and University of Michigan Comprehensive Cancer Center (UMCC; n=67), Ann Arbor, Michigan. Families presenting to our cancer genetics programs are either by self-referral or physician referral and are enrolled on the basis of multiple cases of CRC, CRC diagnosis at a young age, or familial association of CRC with other Lynch syndrome–associated tumors. Patients presenting for evaluation (probands) are routinely enrolled in the registries using institutional review board–approved protocols, and personal and family cancer histories and demographic data are obtained from the proband and participating relatives. Written informed consent is provided by probands for the confirmation of cancer diagnoses and deaths by review of medical records, pathology reports, or death certificates. Clinical information is updated periodically through follow-up clinic visits or telephone encounters. For this study, we selected patients with documented deleterious MMR gene mutations who were identified before June 2008. Analysis of MMR germline mutations in families was performed using standard molecular techniques for full gene sequencing and conducted on either the family member with CRC (or other Lynch syndrome–associated cancer) or an "at-risk" first-degree or second-degree relative. Reports of pancreatic cancer were confirmed either by pathology report or death certificate.

Table 1. Characteristics of Study Population and Distribution of Mutations by Gene

Characteristics	University of Michigan Comprehensive Cancer Center	Dana-Farber Cancer Institute	Combined
No. of probands[a]	67	80	147
No. of first-degree relatives	459	558	1017
Sex, No.			
Male	1395	1900	3295
Female	1265	1782	3047
Male:female ratio	1:1	1:1	1:1
No. of patients genotyped	200	232	432
No. of patients with positive mutation	144	158	302
Mutated gene, No. (%)[b]	**(n = 67)**	**(n = 80)**	**(N=147)**
MLH1	18 (26.9)	37 (46.3)	55 (37.4)
MSH2	42 (62.7)	39 (48.8)	81 (55.1)
MSH6	7 (10.4)	4 (5.0)	11 (7.5)

[a] Index patient per family presenting for genetic evaluation.
[b] Families with mismatch repair gene mutations. Because of rounding, percentages may not total 100.

Mutation Analysis Technique

DNA from white blood cells was extracted and purified from the samples of blood provided by each proband, amplified by polymerase chain reaction, and directly sequenced in forward and reverse directions. For the *MLH1* gene, approximately 2300 base pairs were sequenced, comprising 19 exons and approximately 560 adjacent noncoding intronic base pairs. For the *MSH2* gene, approximately 2800 base pairs were sequenced, comprising 16 exons and approximately 470 adjacent noncoding intronic base pairs. For the *MSH6* gene, approximately 4080 base pairs were sequenced, comprising 10 exons and approximately 290 adjacent noncoding intronic base pairs. The noncoding intronic regions of *MLH1*, *MSH2*, and *MSH6* genes that are analyzed by sequence analysis do not extend more than 20 base pairs proximal to the 5′ end and 10 base pairs distal to the 3′ end of each exon. The *MLH1* and *MSH2* genes are tested for large rearrangements that are not detected by sequence analysis. All coding exons of *MLH1* and *MSH2* and their respective promoters are examined for evidence of deletions and duplications by quantitative multiplexed end point polymerase chain reaction analysis.

Statistical Analysis

We used the information on diagnoses of pancreatic cancer in relatives of probands to estimate age-specific pancreatic cancer incidences in MMR mutation carriers by maximum likelihood, using a technique called modified segregation analysis. The method was implemented in MENDEL version 3.3.5.[17,18] Information on genotype in relatives was included whenever available. However, mutation status was unknown for many family members (TABLE 1). Despite missing genotypes, these individuals do contribute important information to the analysis. The segregation analysis

implemented by MENDEL automatically handles missing genotype information by maximizing the marginal likelihood by summing over all possible genotype configurations in a family.[19] Relatives were assumed to be followed from age 20 years and censored at the age at diagnosis of pancreatic cancer, at the age of death, at the age at last follow-up, or at age 70 years, whichever occurred earlier. For individuals with missing age information, the age was imputed based on relationship with proband, age of proband, or deceased status at last follow-up (dead or alive). We also performed a sensitivity analysis without imputing the age information to ensure that the age imputation did not artificially inflate estimates of penetrance and relative risk.

Our study included MMR carrier families ascertained through multiple individuals with CRC; therefore, the database potentially includes a greater representation of families with multiple CRC cases and mutation-positive probands than would be identified in population-based studies. Unless appropriate statistical methods are used, this type of ascertainment (a form of selection bias) can lead to overestimation of age-specific cumulative risks of pancreatic cancer. Using a conditional likelihood allows correction for ascertainment bias by modeling the probability of observed disease phenotypes and genotypes of the pedigrees conditional on ascertainment. This requires a model for the ascertainment probabilities, and we present results where a family was ascertained because of phenotype and genotype status of the proband and multiple-affected first-degree relatives (FDRs) with CRC. This conditioning strategy was chosen based on the typical referral pattern of families to our cancer genetics clinics, emphasizing CRC as the primary reason for the referral. We also performed additional sensitivity analyses with different alternative ascertainment mechanisms. Results are provided in the supplementary material (eAppendix; available at http://www.jama.com).

The age-specific relative risks of pancreatic cancer in carriers were obtained by using a proportional hazards regression model. We estimated the age-specific log hazard ratio (HR) parameters for 2 age intervals (<50 and ≥ 50 years). In all analyses, cancer incidences in noncarriers were assumed to follow the population cohort–specific rate as obtained through the Surveillance, Epidemiology, and End Results (SEER) 13 database (http://seer.cancer.gov). Cumulative risk (ie, penetrance) and 95% confidence intervals (CIs) were calculated from the cumulative incidence. Details of the statistical methods are provided in the supplementary material (eAppendix; available at http://www.jama.com).

RESULTS

A total of 6342 individuals were included in the analysis (147 probands, 1017 FDRs, and 5178 other relatives from the same side of the affected family with a greater than first-degree relation) (Table 1). The corresponding proportions of families carrying a mutation in 1 of 3 MMR genes were 55 of 147 families (37.4%) in *MLH1*, 81 of 147 families (55.1%) in *MSH2*, and 11 of 147 families (7.5%) in *MSH6*. The distribution of gene-specific mutations among both institutions is also shown in Table 1. Overall, a pathogenic gene mutation was detected in 302 of 6342 individuals (8.2%) and the number of patients genotyped was similar across the 2 centers (200 individuals genotyped at UMCC vs 232 individuals genotyped at DFCI). A total of 130 of the 432 individuals genotyped did not have an identified MMR gene mutation.

Description of Pancreatic Cancer Cases

Forty-seven cases of pancreatic cancer were reported among 31 families. Eighteen families reported 1 case of pancreatic cancer, 10 families reported 2 cases of pancreatic cancer, and 3 families reported 3 cases of pancreatic cancer. Thirty-one pancreatic cancer cases were reported in families with an *MSH2* gene mutation, 13 cases were in families with an *MLH1* mutation, and 3 cases were in families with an *MSH6* mutation. Of the 13 families with more than 1 case of pancreatic cancer, 62% (n=8) had a mutation in the *MSH2* gene vs 30.8% (n=4) and 7.7% (n=1) of families with mutations in the *MLH1* and *MSH6* genes, respectively.

Twenty-one of 47 pancreatic cancer cases (45%) were reported among men, who had a median age of 51.5 years at the time of diagnosis (range, 19-85 years). There was no sex-related difference in median age of pancreatic cancer diagnosis (51.5 vs 56.5 years for men and women, respectively). However, 50% of men with pancreatic cancer were younger than 50 years at the time of diagnosis compared with only 22% of women diagnosed at younger than 50 years (TABLE 2).

Of the 47 cases of pancreatic cancer, we were able to verify diagnoses with additional records in 3 of 23 cases from UMCC and 7 of 24 cases from DFCI. In 20 of 23 UMCC cases and 17 of 24 DFCI cases, the diagnosis was based on family report alone. Pathology review was available for 2 of 23 cases from UMCC and 4 of 24 cases from DFCI, whereas other documentation (clinical report, death certificate) was obtained in 1 of 23 UMCC cases and 3 of the DFCI families. We were unable to verify the remaining pancreatic cancer cases due to patient confidentiality issues. We did not have permission to contact the next-of-kin of the reported cases of pancreatic cancer who were often biologically unrelated to the proband.

Estimates of Age-Specific Cumulative Risk

Among the 147 families with identified pathogenic MMR gene mutations, approximately 4% were diagnosed with pancreatic cancer by the age of 70 years. The increase in risk was more pronounced after age 40 years. The estimated decade-specific cumulative risks of pancreatic cancer for carriers of any of the 3 MMR genes compared with the

Table 2. Age of Diagnosis for Pancreatic Cancer Cases Stratified by Sex

	Men			Women		
	University of Michigan Comprehensive Cancer Center	Dana-Farber Cancer Institute	Combined	University of Michigan Comprehensive Cancer Center	Dana-Farber Cancer Institute	Combined
Total No. of pancreatic cancer cases (No. of cases with known ages at diagnosis)	13 (8)	8 (8)	21 (16)	10 (6)	16 (12)	26 (18)
Proportion of cancers diagnosed at age <50 y, No./ total No. (%)[a]	6/8 (75.0)	2/8 (25.0)	8/16 (50.0)	1/6 (16.7)	3/12 (25.0)	4/18 (22.2)
Age at diagnosis, median (range)[a]	42.5 (19.0-75.0)	65.0 (40.0-85.0)	51.5 (19.0-85.0)	55.0 (36.0-73.0)	62.0 (27.0-79.0)	56.5 (27.0-79.0)

[a]Calculated from cases with known ages at diagnosis of pancreatic cancer.

general population are shown in TABLE 3 and the FIGURE.

There was an approximately 9-fold increase in risk of developing pancreatic cancer among families with pathogenic MMR gene mutations compared with the general population (HR, 8.6; 95% CI, 4.7-15.7). Table 3 also depicts the HRs for mutation carriers stratified by age (≥50 or <50 years). The estimated relative risk of pancreatic cancer was higher for individuals aged between 20 and 49 years (HR, 30.5; 95% CI, 14.2-65.7) and then decreased with increasing age (ages 50-70 years: HR, 5.1; 95% CI, 2.2-11.8). The absolute cumulative risk of developing pancreatic cancer in MMR gene mutation carriers at 50 years was 1.31% (95% CI, 0.31%-2.32%) and at 70 years was 3.68% (95% CI, 1.45%-5.88%). These risks are significantly higher than the population-based, cumulative age-specific incidences reported in SEER 13, which were 0.04% and 0.52% for ages 50 and 70 years, respectively.

MLH1 and *MSH2* mutation carriers had a similar increase in risk of developing pancreatic cancer compared with the general population. For carriers of mutations in *MLH1*, the overall HR was estimated at 7.5 (95% CI, 2.4-23.0) compared with 10.9 (95% CI, 5.5-21.9) for *MSH2* carriers. Given the small number of pancreatic cancer cases among *MSH6* carriers, risk estimates were not calculated for these mutation carriers. The HRs were obtained from a proportional hazard regression model with a single log(HR) parameter across all ages. The 2 parameter models could not be fitted due to lack of data strength in each gene category.

Table 3. Age-Specific Cumulative Risk of Pancreatic Cancer[a]

	Cumulative Risk		Hazard Ratio (95% CI)	
Age, y	Population, %[b]	Families With MMR Gene Mutation, % (95% CI)		
20	0	0		
30	0	0.03	30.5 (14.2-65.7)[c]	
40	0.01	0.23		8.6 (4.7-15.7)[e]
50	0.04	1.31 (0.31-2.32)		
60	0.18	1.98	5.1 (2.2-11.8)[d]	
70	0.52	3.68 (1.45-5.88)		

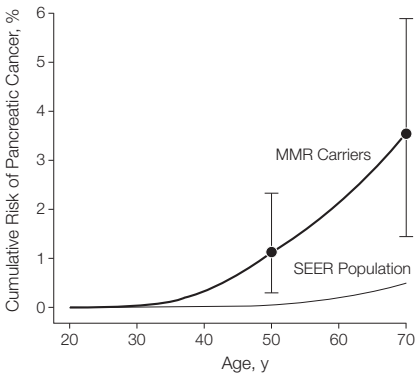
Abbreviations: CI, confidence interval; MMR, mismatch repair.
[a]Two age-specific hazard ratios in proportional hazards regression model (<50 y, ≥50 y), corrected for ascertainment by conditioning on genotype and phenotype of proband and phenotype of all colorectal cancer–affected first-degree relatives.
[b]1992-2005 Surveillance, Epidemiology, and End Results (SEER) 13 (http://seer.cancer.gov).
[c]For age range, 20 to 49 years.
[d]For age range, 50 to 70 years.
[e]For age range, 20 to 70 years.

COMMENT

Among 147 families with germline MMR gene mutations, we found that the risk of developing pancreatic cancer was increased compared with the general population. The cumulative risk of developing pancreatic cancer was 3.68% by age 70 years, with cases among families with Lynch syndrome occurring at an earlier age than sporadic cases.

The statistical methods used in this study afford many advantages.[20,21] Segregation analysis accounts for relatives who have undergone mutation analysis and those who have not. The probability of being a mutation carrier is calculated for all relatives whose mutation status is unknown and used to estimate the overall cumulative risk of cancer among family members with a germline alteration. Segregation analysis also minimizes ascertainment bias by conditioning the analysis on available phenotypic information provided for individual pedigrees. We chose a priori to exclude from the risk estimate calculation all pancreatic cancers in probands and their FDRs with CRC, which yields a conservative estimate for pancreatic cancer risk and best corrects for how patients were ascertained at both centers. Data from the 2 registries provide a large sample of families who have undergone mutation analysis with identified MMR gene mutations.

Figure. Age-Specific Cumulative Risk of Pancreatic Cancer in Families With Pathogenic Mutations in *MLH1*, *MSH2*, or *MSH6* Genes



MMR carriers indicates families with mismatch repair gene mutation carriers (*MLH1*, *MSH2*, *or MSH6*); SEER, Surveillance, Epidemiology, and End Results. The penetrance curves were generated by plotting the age-specific cumulative risks of pancreatic cancer (Table 3) for a set of discrete ages from 20 to 70 years at 5-year intervals and then applying a smoothing spline function. The 95% confidence intervals (error bars) corresponding with the age-specific cumulative risk of pancreatic cancer for MMR carrier families were also plotted at 50 and 70 years. Population estimates of age-specific cumulative risks of pancreatic cancer are given by pancreatic cancer incidence rates reported in 1992-2005 SEER 13 (http://seer.cancer.gov).

Henry Lynch first reported pancreatic cancer in adenocarcinoma-prone families more than 40 years ago[22] and additional studies have described families with Lynch syndrome and pancreatic cancer.[11-16] Pancreaticobiliary cancers are often included in the spectrum of Lynch syndrome–associated malignancies, but data on the prevalence and risk of developing pancreatic cancer have been conflicting. A limitation of most existing data are that risk estimates were derived from families ascertained for a strong history limited to CRC.[11,12,14] Additionally, studies that have not found an increased risk of pancreatic cancer were from homogeneous populations that have a preponderance of founder mutations and possibly a limited spectrum of tumors.[12]

However, emerging data support that pancreatic tumors are a component of Lynch syndrome. Medullary carcinomas of the pancreas are a distinct variant of pancreatic adenocarcinoma associated with microsatellite instability (MSI), loss of protein expression of MMR genes, family history of cancer in an FDR, and germline MMR gene mutation.[23,24] We recently reported on a known *MSH2* gene mutation carrier who developed an intraductal papillary mucinous neoplasm of the pancreas; the lesion showed MSI and loss of expression of *MSH2* and *MSH6* gene proteins.[25] A number of small studies suggest that MSI in sporadic pancreatic cancers offers a survival benefit similar to that observed in other Lynch syndrome tumors. To determine if long-term survival in pancreatic cancer was attributed to defective MMR, Maple et al[26] ascertained its prevalence in patients with pancreatic cancer who survived 3 or more years after surgery. The data suggest that immunohistochemistry for pancreatic cancer is both sensitive and specific for the MSI phenotype. A study of 130 families with MMR mutations reported 22 pancreatic cancers with many early onset cases[27]; however, lifetime risks of developing pancreatic cancer were not calculated.

Our study has several limitations. As in most Lynch syndrome registries, our families were ascertained through an affected proband with a classic Lynch syndrome tumor, notably CRC. To reduce ascertainment bias, our analysis of pancreatic cancer cases specifically excluded these probands, as well as any FDRs who also had CRC. We also relied in large part on the probands' report of pancreatic cancers in their families, which may be inaccurate.[28-31] The majority of patients with pancreatic cancer were deceased and not available for mutation analysis; therefore, it was not possible to accurately determine those cases that may have been sporadic and whose inclusion in the analysis may have overestimated risk. Recall bias may also occur when family members without a personal history of cancer are underreported by the proband.

Although family structure was completely enumerated for a 3-generation pedigree at both sites by certified genetic counselors during the retrospective review and construction of the pedigrees, it is possible the selective expansion of branches of the family with cancer might lead to this type of recall bias. In our study, this bias may be present but is likely minimal for 2 reasons. First, pedigree structures are routinely verified by multiple relatives who undergo genetic evaluation, increasing the chances of completely enumerating all affected and unaffected members. Second, because the majority of relatives with pancreatic cancer were identified in FDRs and second-degree relatives, the standardized construction of 3-generation pedigrees is likely to reduce the magnitude of this potential recall bias. Another potential limitation reflects our choice to impute missing ages; however, this was performed conservatively and is unlikely to inflate risk as shown in the supplemental sensitivity analyses. Despite these potential limitations, the increased risk of pancreatic cancer was similar at both study sites, lending credence to the results.

Our findings have implications regarding the care of patients and families with a known MMR gene mutation. Information on cancer risk is important in planning cancer prevention and determining the efficacy of proposed prevention strategies.[32-38] Several screening trials aimed at identifying early pancreatic neoplasia through radiographic and endoscopic imaging are currently under way in patients with genetic syndromes associated with high incidence of pancreatic cancer.[32,33] MMR gene mutation carriers with a family history of pancreatic cancer may need to be screened in a similar manner to these individuals. Ongoing screening programs will provide information on the risks and benefits of early detection of pancreatic neoplasms and allow further study on the spectrum of pancreatic lesions in families with Lynch syndrome.

CONCLUSION

Families with an identified pathogenic MMR gene mutation have an increased lifetime risk of developing pancreatic cancer compared with the

general US population. Further studies are necessary in individuals with Lynch syndrome to further define the risk of premalignant and malignant pancreatic neoplasms and the potential benefits and limitations of surveillance. Pancreatic cancer is a clinically relevant component of Lynch syndrome and quantifying this risk for gene carriers should be incorporated into clinical management.

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