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Multiple primaries in pancreatic cancer patients: indicator of a genetic predisposition?

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Background The genetic basis of several familial cancers including breast and colon cancers has been identified recently. The occurrence of multiple cancers in one individual is also suggestive of a genetic predisposition. To evaluate inherited predisposition in pancreatic cancer we compared the clinical data of pancreatic cancer patients with and without multiple primaries as well as the frequency of malignancies among their relatives.

Methods Detailed data on 69 pancreatic cancer patients included survival time and TNM-classification. Index case data were separated into two groups. The first group (group 1) developed only pancreatic cancer during their lifetime, whereas the second group (group 2) developed additional primary tumours. A systematic family history was taken from 59 of these pancreatic cancer patients using a standardized questionnaire. The pancreatic cancers and the multiple primaries of the 59 patients were histologically proven.

Results Of the 69 pancreatic cancer patients, 13 (18.8%) had multiple primaries. Neither the clinical data nor the survival data of the index cases revealed differences between the two groups (all nominal *P*-values >0.05). In the family history study blood relatives developed a malignancy in 51% (24 of 47) of the families in group 1 compared to 75% (9 of 12) in group 2. The risk of relatives in group 2 of developing a malignant tumour was significantly higher ($P = 0.034$) than in group 1 after adjustments for family size and age of disease onset of the index case. The cancer spectrum of the 59 families mainly included tumours of the digestive tract and the reproductive organs.

Conclusions A multiple primary cancer history is a common condition among pancreatic cancer patients. Relatives of these patients seem to have an increased risk for the development of distinct malignant solid tumours, which might be caused by an inherited predisposition. Clinical and genetic investigation of pancreatic cancer patients with multiple primaries and their families might lead to the identification of predisposing gene defects providing a new goal for the understanding of a shared genetic basis of different solid tumours.

Keywords Multiple primaries, pancreatic carcinoma, family history method, genetics

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A familial aggregation of the same cancer indicates a hereditary predisposition for the development of these tumours. For some of these the causative gene defect has already been identified. For example, familial breast and ovarian cancer is associated with germline mutations in the *BRCA1* or *BRCA2* tumour suppressor genes and germline mutations in the *APC* gene cause familial adenomatosis polyposis coli.[1–3] In some families a clustering of pancreatic cancer has also been observed although the responsible gene defect has yet not been identified.[4,5] Lynch[6] hypothesized that 5% of pancreatic cancers are based on a genetic predisposition. Ghardirian *et al.*[7] and Fernandez *et al.*[8] reported a positive family history for this cancer in 3.9% and 7.8% of pancreatic cancer patients, respectively. In some families with an aggregation of pancreatic cancer and malignant melanomas germline mutations in the $p16^{INK4a}$ tumour suppressor gene have been identified.[9,10] Goggins *et al.*[11] detected germline mutations in the *BRCA2* tumour suppressor gene in 7% of apparently sporadic pancreatic cancer patients. In addition, Phelan *et al.*[2] described an aggregation of pancreatic

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cancers in breast cancer families associated with distinct *BRCA2* germline mutations.

The appearance of different primaries in particular individuals may also indicate a genetic predisposition to different neoplasms resulting in an aggregation of tumours among their relatives.[4] The term 'second primary' is not used homogeneously in the literature. In the Connecticut Tumor Registry only tumours following pancreatic cancers are registered as second or multiple primaries,[12] whereas Hruban *et al.* [4] count simultaneous and metachronous cancers as second primaries. Due to the short survival time of most pancreatic cancer patients these different definitions lead to different frequencies of second primaries in patients with pancreatic cancer. Hoar *et al.*[12] reported less than 1% of second primaries in pancreatic cancer patients, while Hruban *et al*.[4] observed almost 20% of second primaries in patients without a family history of pancreatic cancer. Furthermore, data of the National Familial Pancreatic Tumor Registry in the US showed 23.8% of familial pancreatic cancer patients with one relative who also developed a pancreatic cancer and 36.8% with more than one relative with pancreatic cancer developed second primaries.[4]

In the present study we hypothesized that multiple primaries in patients with ductal pancreatic carcinoma coincides with an increased risk of malignancies among their first- and second-degree relatives, possibly indicating a shared genetic predisposition.

Patients and Methods

At the Department of General Surgery of the Philipps University of Marburg 72 pancreatic resections were performed for ductal pancreatic cancer from 1 April 1992 to 30 September 1998. The data base was closed at 31 March 1999 so that the minimum follow-up of each patient was 6 months.

One aim of our study was to investigate the survival rate of patients with and without multiple primary tumours. For this reason, we *a priori* excluded those three patients from our study who died of postoperative complications. Thus detailed data including gender, age at resection, survival, TNM-classification and UICC-stage were collected for 69 patients and their tumours. The TNM-classification was based on the 5th edition of the TNM-classification of malignant tumours.[4] These patients were asked to participate in our family history study, if they were still alive. If they were deceased, we tried to contact their first-degree relatives or their spouses. If none of these individuals could be contacted successfully, the patient was excluded from the study (10). Hence, the total sample consisted of 59 (81.9%) pancreatic cancer cases (index cases) with a follow-up of at least 6 months.[13]

The family history of the index cases was collected by one surgeon (BG) in a telephone interview or at outpatient attendance. A standardized questionnaire was used with information on pedigree structure covering first- and second-degree blood relatives in a family with 25–100% of genes shared[15] including their children with offspring, grandparents, parents, uncles and aunts, siblings, nieces, and nephews. Since the precise determination of the age of disease onset for family members seems to be problematic, we refrained from calculating person-years of risk. Smoking data was not collected because we did not expect good validity using the family history method.

The data of the 69 index cases were separated into two groups. The first group (group 1) consisted of index cases who developed only pancreatic cancer during their lifetime, whereas the second group (group 2) developed additional primary cancers. We defined the term 'second primaries' analogously to Hruban *et al.* [4] who included all additional primaries in the whole lifetime of pancreatic cancer patients. Group 2 encompassed 13 of the 69 (18.8%) index cases. All primary tumours of the index cases were verified histologically by an experienced pathologist (AR).

The main aim of this study was to investigate whether family members of pancreatic cancer patients with multiple primaries had an increased risk for the development of cancer compared with family members of pancreatic cancer patients without multiple primaries. For this purpose, we applied the Independence Estimating Equations (IEE[16]) with logit link and binomial variance function. This method adequately deals with the relationship of family members and allows a one-sided Wald-test of our hypothesis. Furthermore, we computed an asymptotic two-sided 95% CI for the corresponding odds ratio (OR). All reported *P*-values except for this test are considered as nominal. Adjustments for age of disease onset of the index cases and family size were performed. Since the quality of the family history information is likely to be better for first-degree relatives than for second-degree relatives, we also examined the data based on the inclusion of only first and both first- and second-degree relatives of the index patients.

Contingency table analyses were performed as follows: If the expected frequency within each cell was >5, the asymptotic Yates-corrected χ^2 test was applied, otherwise Pearson's exact test was used. The survival time was compared for patients of group 1 and group 2 using the log-rank test. Analogously, the Mann-Whitney test was applied to compare age of patients in group 1 and group 2.

Results

Of the 69 pancreatic cancer patients, 13 (18.8%) suffered from second primaries (Table 1). One of the 13 patients developed four cancers originating at discordant sites. He developed a vocal cord cancer and a basal cell carcinoma 4 years before pancreatic cancer. One year following pancreatic cancer he developed an anaplastic thyroid carcinoma, which caused his death. The other 12 patients developed two primary cancers until 31 March 1999. The period between pancreatic cancer and the detection of the additional primaries ranged from 24 years before the occurrence of pancreatic carcinoma (–24) to 2 years after this cancer (+2).

No difference in the median age was detected between patients of group 2 (mean ± SD 67.33 ± 8.36 years) and group 1 (63.77 ± 9.68 years; $P = 0.29$). Furthermore, no gender difference was observed in index cases of groups 1 and 2 ($P = 0.40$). The survival time in both groups was similar ($P = 0.23$). Table 2 shows that the two groups did not differ with regard to TNM-classification (T with $P = 0.59$; N with $P = 0.39$; M with $P = 0.35$) and UICC-stage ($P = 0.25$).

A total of 1436 blood relatives were identified in the 59 pancreatic cancer patients who participated in our family study, 1171 in group 1 and 265 in group 2. Sixty-nine tumours (Table 3) developed among these relatives (4.8%), 48 (4.1%)

Table 1 Occurrence of multiple primaries in relationship to the occurrence of the pancreatic cancer[a]

No.	SP[b]	Time difference PC[c]-SP (years)	Age of diagnosis of SP (years)
1	Basal cell carcinoma	–4	77
2	Bladder cancer	–1	65
3	Prostate cancer	–4	66
4	Uterine cancer	–11	67
5	Bladder cancer	–5	61
6	Breast cancer	–23	43
7	Oropharyngeal cancer	–10	61
8	Endometrial cancer	+1	77
9	Colon cancer	+2	60
10	Thyroid cancer (anaplastic)	+1	69
	Vocal cord cancer	–4	64
	Basal cell carcinoma	–4	64
11	Cervical cancer	–24	31
12	Basal cell carcinoma	+1	57
13	Colon cancer	0	70

[a] + = second primary follows pancreatic cancer, – = second primary before pancreatic cancer.

[b] Second primary.

[c] Pancreatic cancer.

Table 2 Comparison of TNM-stage and UICC-stage in pancreatic cancer patients with and without second primaries

	Second primary		Row
T-stage	No	Yes	Totals
1	6 (10.7%)	2 (15.4%)	8
2	8 (14.3%)	1 (7.7%)	9
3	39 (69.6%)	8 (61.5%)	47
4	3 (5.4%)	2 (15.4%)	5
Totals	56	13	69
	Second primary		**Row**
N-stage	No	Yes	Totals
0	27 (48.2%)	8 (61.5%)	35
1	29 (51.8%)	5 (38,5%)	34
Totals	56	13	69
	Second primary		**Row**
M-stage	No	Yes	Totals
0	50 (89.3%)	13 (100%)	63
1	6 (10.7%)	0 (0%)	6
Totals	56	13	69
	Second primary		**Row**
UICC-stage	No	Yes	Totals
1	10 (17.9%)	2 (15.4%)	12
2	13 (23.2%)	5 (38.4%)	18
3	25 (44.6%)	4 (30.8%)	29
4a	2 (3.6%)	2 (15.4%)	4
4b	6 (10.7%)	0 (0%)	6
Totals	56	13	69

Table 3 Distribution of tumours in families of patients with pancreatic cancer without (group 1) and with (group 2) a second primary history

Type of tumours in the families of pancreatic cancer patients	Malignancies among relatives of patients with pancreatic cancer		
	Total		
	Group 1[a]	Group 2	Total
Aerodigestive tract	**17**	**8**	**25**
Oropharyngeal cancer	0	1	1
Oesophageal cancer	1	0	1
Gastric cancer	5	1	6
Pancreatic cancer	2	1	3
Colorectal cancer	5	5	10
Hepatocellular cancer	1	0	1
Non-small cell lung cancer	3	0	3
Reproductive organs	**19**	**3**	**22**
Breast cancer	13	2	15
Prostate cancer	1	1	2
Cervical cancer	1	0	1
Endometrial cancer	3	0	3
Testicular cancer	1	0	1
Others	**12**	**10**	**22**
Urinary bladder cancer	3	0	3
Lymphoma	1	1	2
Plasmocytoma	0	2	2
Leukaemia	2	1	3
Gall bladder cancer	1	1	2
Malignant melanoma	2	0	2
Basal cell carcinoma	0	1	1
Cancer of the eye	1	0	1
Unknown cancer	2	4	6
Total	**48**	**21**	**69**

[a] Three relatives in different families of group 1 developed multiple primary cancers: one developed colon cancer, breast cancer and endometrial cancer, a second relative developed endometrial cancer and breast cancer and a third developed pancreatic cancer and oesophageal cancer. Thus, 69 tumours developed in 65 relatives of pancreatic cancer patients.

and 21 (7.9%) in groups 1 and 2, respectively. Relatives of pancreatic cancer patients developed malignant tumours in 33 of the 59 families (55.9%). There was a tendency for malignancies to occur more frequently in families of group 2 (75.0% of the families) than in group 1 (51.1%; $P = 0.07$).

The risk of relatives in group 2 (second primary) of developing a tumour was significantly higher ($P = 0.014$) than in group 1 (no second primary) (OR = 2.09, 95% CI : 1.08–4.04). It was significant even after adjustment for family size and age of disease onset in the index patients (one-sided $P = 0.034$; OR = 1.83, 95% CI : 0.96–3.51). The results were similar when only first-degree and both first- and second-degree relatives of the index cases were included in the analyses. The effect remained significant when both first- and second-degree relatives were considered ($P = 0.012$ with n = 872 relatives; OR = 1.99; 95% CI : 1.10–3.62), however, due to the low number of relatives (n = 444), it was not significant when only first-degree relatives were included ($P = 0.12$). The risk of relatives for developing a tumour increased significantly with decreasing family size

($P = 0.010$). There was, however, no dependency between the risk of relatives for developing a tumour and the age of disease onset in the index patient ($P = 0.97$).

The tumour spectrum in both groups mainly encompassed tumours of the aerodigestive tract and the reproductive organs (Table 3). Three basal cell carcinomas and two bladder cancers were observed among the primaries of the index patients (Table 1). Nevertheless, none of the families showed the characteristic tumour spectrum of known cancer syndromes (e.g. hereditary non-polyposis colorectal carcinoma (HNPCC), familial atypical multiple mole-melanoma (FAMMM), Peutz-Jeghers, Li-Fraumeni) that are associated with pancreatic cancer. However, an atypical phenotype of one of these syndromes could not be excluded. Three female relatives of different families in group 1 suffered from multiple primary cancers: one developed colon cancer, breast cancer and an endometrial cancer, one endometrial cancer and breast cancer and the third had a pancreatic cancer and an oesophageal cancer.

Discussion

The occurrence of multiple primary cancers in particular individuals has intrigued clinicians and scientists for more than a century. The earliest case reports were published in the 19th century. Since then numerous works have appeared summarizing data that have been collected over many years on simultaneous and metachronous cancers.[17]

First we surmised that the prognosis of patients with a positive cancer history (group 2) is better than in sporadic cancer patients (group 1) due to an observational bias.[17] Curtis described this phenomenon in prostate cancer which was detected more frequently in patients who were under observation because of a former diagnosed cancer. However, about 80% of pancreatic cancer patients suffer from advanced tumours at the time of diagnosis since no screening markers are currently available.[18] Thus, no difference in the two groups could be identified concerning TNM-classification, UICC-stage and survival in our study. Secondly, this retrospective study focused on differences in the family history between pancreatic cancer patients with (group 2) and without (group 1) second or multiple primaries. A positive cancer family history for cancers at different sites could be detected in 75.0% of the families of group 2 in comparison to 51.1% of the families of group 1 (mean 55.9%) in this study. Similarly, Dergham *et al.*[19] detected a family history of cancer in 52% of pancreatic cancer patients. According to our study, multiple primaries in ductal pancreatic cancer patients coincide with an increased risk of malignancies among their close relatives (OR = 1.83), since significantly more tumours developed among relatives of patients with multiple primaries compared to patients without multiple primaries ($P = 0.034$) even after adjustment for family size and age of disease onset in the index cases. The results were similar when only first- and both first- and second-degree relatives were included in the analysis. Information on the occurrence of malignancies among relatives was, however, obtained by the family history method, which is a methodological limitation of our study. Nevertheless, our findings lead to the hypothesis that multiple primaries in pancreatic cancer patients with a positive family history for cancer might be caused by an inherited predisposition.

Several hereditary cancer syndromes coincide with an increased risk of pancreatic cancer. Patients with HNPCC have an increased risk of pancreatic cancer as well as stomach, breast, small bowel, endometrial and renal pelvis cancer.[20–22] Among the index patients in the present study 3 of 16 multiple primaries and 9 of 21 tumours in their families fell into the HNPCC tumour spectrum (Tables 1 and 3). Furthermore 3 of the 13 index patients of group 2 had additional basal cell carcinomas, that may occur in a subset of HNPCC families (Muir-Torre syndrome).[23,24] None of the families in group 2, however, fulfilled the Amsterdam criteria.[25] It is well known that not all HNPCC families with detectable germline mutations in the *mismatch repair* genes meet the Amsterdam criteria.[26] Furthermore, an increased risk of synchronous and metachronous tumours of the colorectum and other organs in HNPCC patients has been described.[20] Therefore, it seems possible that one of the HNPCC causing *mismatch repair* genes may underlie the tumour development in some of the presented families. Several other well-characterized genetic syndromes have been shown to predispose affected family members to the development of pancreatic cancers.[21] Syndromes associated with pancreatic cancer include hereditary pancreatitis, ataxia teleangiectasia, a subset of FAMMM syndrome and Peutz-Jeghers syndrome. The history of the patients in this study did not indicate one of these rare syndromes in any case. No patient was a member of a family with a hereditary pancreatitis. Multiple melanomas did not occur in any index patient nor in one of their relatives.

Familial breast cancer has also been associated with pancreatic cancer in some families.[5] Tulinius found more cases of pancreatic cancer than expected in male first-degree relatives of breast cancer patients (relative risk 1.66).[27] Phelan could show an excess of pancreatic cancer in some families with *BRCA2* germline mutations.[2] In the present study, there was one breast cancer among the second primary cancers in group 2, which had occurred 23 years before the pancreatic cancer of this female patient when she was 43 years old. Since no family member of this patient has developed breast cancer an inherited predisposing *BRCA2* germline mutation is not likely, although a *de novo* mutation might be possible.

Another cancer syndrome associated with an increased risk of pancreatic cancer was described by Li and Fraumeni. In those families tumours such as different sarcomas, adrenocortical carcinomas, breast cancers, brain tumours, leukaemias, pancreatic cancers, carcinomas of the lung and others were described.[28,29] The occurrence of neoplasms originating at discordant sites is caused by a predisposing gene defect of *TP53* tumour suppressor gene in those families. Epidemiological studies have confirmed that the neoplasms in Li-Fraumeni syndrome often tend to develop as multiple primaries in affected individuals.[30] A follow-up study of the original four families found that over a 12-year period 10 of the 31 surviving family members had developed 16 additional cancers, in comparison with less than one expected from general population rates.[28] In addition, a multicentre study in 59 patients with multiple primaries has shown that four of the 59 patients (6.8%) carried germline mutations in the *TP53* tumour suppressor gene, although they did not have a family history suggestive for the Li-Fraumeni syndrome.[31] Since some of the tumours in the Li-Fraumeni tumour spectrum appeared among the index patients of

group 2, it seems to be worthwhile to determine the role of *TP53* in these patients and their families by genetic analysis.

Patients with genetically caused cancers such as familial colon cancer and familial breast cancer are frequently characterized by younger age of onset of the disease.[4] In some of the patients in group 2 the second primary occurred as an early onset cancer (breast cancer at age 43 and cervical cancer at 31 years). We investigated whether pancreatic cancer patients with multiple primaries were younger than those patients without a cancer history when pancreatic cancer occurred, however, no difference was found ($P = 0.29$). This is not surprising, since it is known that familial pancreatic cancer is not characterized by early onset.[4]

In summary, the data of the present study and the literature imply that multiple primaries in some pancreatic cancer patients might be caused by a genetic predisposition. Thus, a careful clinical and genetic analysis of pancreatic cancer patients with multiple primaries and their families, including analyses of known cancer predisposing genes (e.g. *TP53*, *p16*, *BRCA2* and *Mismatch-Repair*-genes) and allelotyping should be performed to verify or negate this hypothesis. Such an approach may be useful for identifying predisposing gene defects for the development of different solid neoplasms and thus understanding the shared genetic alterations of different tumour types.

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