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Family history as a marker of platinum sensitivity in pancreatic adenocarcinoma

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Abstract

Purpose—Metastatic pancreatic adenocarcinoma is considered a uniformly fatal disease with a median survival of 1 year with modern chemotherapy. While a subset of patients achieve prolonged survival, few of the factors that define this group of patients are known.

Methods—For the determination of overall survival (OS), 549 patients with histologically confirmed metastatic pancreatic adenocarcinoma were evaluated. Emphasis was placed on treatment history and family history of breast, ovarian, and pancreatic cancers. To ensure a uniform metastatic population, patients treated with prior locoregional therapies (i.e., surgery or radiotherapy) were excluded as were patients with a prior history of stage I–III disease.

Results—Patients with family history or pedigree history of cancer had superior OS. This was especially true in patients with three or more relatives with either breast, ovarian, or pancreatic cancers [hazard ratio (HR) 0.49, 95 % confidence interval (CI) 0.30–0.80, $p = 0.003$]. First-line platinum chemotherapy was associated with a poor survival (hazard ratio for death 1.74, 95 % CI 1.12–2.71, $p = 0.01$) for patients without a family history of these cancers but not for those without such a history ($p = 0.31$). In fact, as the number of relatives with these cancers increased, the OS survival improved for individuals receiving first-line platinum therapy (HR 0.76, 95 % CI 0.65–0.89, $p = 0.0004$), which was not the case for those receiving other therapies ($p = 0.98$).

Conclusions—Treatment with platinum chemotherapy in patients with a family history of breast, ovarian, or pancreatic cancers was associated with a longer survival, whereas platinum use in patients without such a family history of cancer was associated with poor survival. These findings suggest that family history may serve as a predictive marker for platinum use in patients with metastatic pancreatic adenocarcinoma.

Keywords

Pancreatic adenocarcinoma; Family history; BRCA; Chemotherapy; Survival

Introduction

Adenocarcinoma of the pancreas is a devastating disease with 45,000 cases expected in the USA in 2013. Greater than 80 % of patients have metastatic disease at time of diagnosis and

have a median survival of 6 months. Until recently, the standard of care for metastatic disease had been the nucleoside analogue, gemcitabine [1]. However, this convention has been challenged by recent studies showing significant survival advantage with FOLFIRINOX (5-FU, irinotecan, and oxaliplatin) [2] and other combination chemotherapies [3–5].

Few individual patients enjoy a long-term survival benefit from chemotherapy. The clinical or molecular determinants that identify such patients are not known. However, several reports have suggested that cancers from patients with germ-line mutations in DNA repair pathways are highly sensitive to DNA-damaging agents [6–10]. The best described models show selective tumor killing with agents that generate DNA interstrand crosslinks (ICL) in tumors with loss of function mutations in the BRCA2/Fanconi Anemia pathway [11, 12]. Defects in this pathway have been well-described in familial breast, ovarian, and pancreatic cancer syndromes [13–21]. Clinical trials evaluating this approach, using ICL-inducing agents such as cisplatin or mitomycin C, have been challenging since patients with both germ-line mutations in BRCA2 and pancreatic cancer are rare.

To better define the subgroup of patients with long-term survival, we reviewed cases of metastatic pancreatic adenocarcinoma from our two institutions with an emphasis on a family history of tumors (breast, ovarian, and pancreatic) that might suggest defects in DNA repair susceptible to DNA-damaging agents such as platinum drugs and better define the ‘BRCAness’ subpopulation. We hypothesized that patients with this family history might have such defects (whether characterized or not) and would have preferential benefit from platinum-based therapy.

Methods

Study design

Patient records with a diagnosis of American Joint Committee on Cancer (AJCC) stage IV pancreatic cancer were identified from the local cancer registry at Johns Hopkins-affiliated hospitals (JHU) from 1995 to 2009 and from the M.D. Anderson Cancer Center (MDACC) tumor registries (2005–2009) and were reviewed for confirmation of clinical stage and treatment at initial presentation according to an IRB-approved protocol. The registry database contained variables reported to the local cancer registry. All patients treated with upfront modalities other than chemotherapy, such as radiation or surgery, were excluded by chart review. Patients with initial consultation records indicating non-metastatic or locally advanced disease at treatment were also excluded. Platinum chemotherapy was defined as cisplatin, carboplatin, or oxaliplatin. All pathology was reviewed centrally at Johns Hopkins or the M.D. Anderson Cancer Center. Information on grade was not routinely recorded since tissue diagnosis was made only by fine-needle aspiration sampling for some tumors.

Statistical analysis

The primary outcome variable was overall survival (OS), which was calculated as the time from pathologic diagnosis to date of death from the tumor registry database, chart review, or social security death index. Patients without confirmed deaths were censored at date of last

contact. The number of family members diagnosed with pancreatic, breast, and ovarian cancers was recorded for each patient through first to third degree relatives (immediate family, grandparents, and first- and second-degree cousins). We compared demographic and clinical features between patient cohorts with Chi-square tests (or Fisher's exact tests) for categorical variables and *t* tests (or Wilcoxon rank-sum tests) for continuous variables, as appropriate. Kaplan–Meier techniques were used to estimate the survivor function, percent surviving at 1 year, and the median time to death with 95 % confidence intervals. Differences between groups were assessed using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios with 95 % confidence intervals as well as to compare groups in multivariate models, i.e., after adjusting for age, race, liver metastases, and cohort.

Results

To obtain a uniform population of patients with metastatic adenocarcinoma, charts from 1425 patients were initially screened at JHU and MDACC. Eight-hundred and seventy-six patients were excluded for histology other than adenocarcinoma, inappropriate staging of locally advanced tumors, initial treatment with cytoreductive surgery or chemoradiation, patients not treated with initial chemotherapy, or patients without family history data available.

A total of 549 individuals from Johns Hopkins and M.D. Anderson with metastatic pancreatic adenocarcinoma met the eligibility criteria (Table 1). Of the cases reviewed, 78 % had at least one family member diagnosed with cancer, while those with a family history of pancreatic, ovarian, or breast cancer represented 36 % of the cohort. A family history of pancreatic cancer specifically was seen in 15 % of the cohort. The clinical characteristics were in general well balanced between those individuals at both institutions. Exceptions were noted in race, the presence of lung and peritoneal metastases, and the year of diagnosis. In addition, platinum chemotherapy was more commonly utilized at M.D. Anderson (79 vs. 34 %). These differences may be explained by the increased use of platinum in recent years ($p < 0.0001$) and for individuals without liver metastases ($p = 0.05$) both of which were more common at M.D. Anderson. At Johns Hopkins, cisplatin was the most commonly used platinum (60 %) followed by oxaliplatin (37 %) and carboplatin (3 %). Similarly, at M.D. Anderson, patients were most commonly treated with cisplatin (60 %) followed by oxaliplatin (28 %) and carboplatin (2 %).

Of the 243 patients treated at JHU, 160 (66 %) never received platinum therapy (Table 1), 62 (26 %) received it in the first line of therapy, and 21 (9 %) received second line platinum. At MDA, 64 (21 %) of 306 patients never received platinum, while 196 (64 %) and 46 (15 %) received it in the first and second lines of treatment, respectively. Of the 549 patients enrolled in the study, 488 (89 %) had died at the time our data were assembled and analyzed.

Overall the median survival (mOS) in the 549 individuals evaluated was 8.1 months (95 % CI 7.5–9.0) with 31 % being alive at 1 year. Univariate analysis of several potential prognostic variables (Table 2) revealed that the risk of death increased with African-American race ($p = 0.008$) and in patients with liver metastases ($p = 0.003$). Prolonged

survival was observed in individuals with a family history of breast or ovarian cancers (mOS 8.5 months, HR 0.76, $p = 0.042$) and was most pronounced (mOS 14.8 months; HR 0.43; $p = 0.0003$) in patients with a family history of pancreatic cancer and breast or ovarian cancer. Survival was also strongly associated with the number of relatives with a BRCA-related malignancy (test of trend $p = 0.009$). Kaplan–Meier curves demonstrating survival for all patients (Fig. 1), patients without first-line platinum (Fig. 2), and patients who did receive first-line platinum (Fig. 3) are included.

The effect of first-line platinum treatment on survival was assessed across the different types of family history. Surprisingly, individuals without any family history of breast, ovarian, or pancreatic cancer (Table 3) fared substantially worse when treated with platinum chemotherapy as a first-line therapy (7.3 vs. 8.4 months; HR 1.42; $p = 0.005$). A significant decrease in survival was also noted when first-line platinum therapy was used in patients without a pedigree history (pedigree being comprised of both family history and personal history of cancer) of breast, ovarian, or pancreatic cancer (HR 1.39, $p = 0.008$). In both cases, the results were significantly different than those for individuals without such histories ($p = 0.01$ and $p = 0.04$, respectively, for interaction between family history and platinum variables) for whom there was no significant association between type of therapy and overall survival. The same pattern was observed for general family history, although the difference in the effect of first-line platinum therapy was not significant (test of interaction $p = 0.10$).

To determine whether the density of relatives with breast, ovarian, or pancreatic malignancies was related to platinum sensitivity, we examined the association between the number of such malignancies in the pedigree and survival (Table 4). There was a significant difference in the effects of the number of relatives with such cancers for those receiving first-line platinum therapy as compared to those who received other therapies (test of interaction $p = 0.017$). The use of first-line platinum chemotherapy was associated with superior survival in patients with two relatives (HR 0.63, $p = 0.032$) and three relatives with these cancers (HR 0.36, $p = 0.002$), but no such trend was observed in patients that did not receive first-line platinum. When comparing individuals with no history of platinum therapy versus those with platinum therapy at any point (i.e., first or second line), we observed a benefit for patients with three or more relatives harboring such cancers (mOS = 21.7 months, HR 0.41, 95 % CI 0.22–0.76, $p = 0.004$). However, the contrast with those not receiving platinum therapy was not as strong. We also note a trend toward improved survival in patients with three or more relatives who did not receive platinum, and the comparison of the two groups was no longer statistically significant (test of interaction $p = 0.19$).

Discussion

These observations provide strong evidence that patients with adenocarcinoma of the pancreas, who have a strong family history breast, ovarian, and pancreatic malignancies, may have a better overall prognosis than those patients without such histories. Additionally, we have found evidence that patients with a strong family history may also be more sensitive to platinum-based chemotherapy. Equally important is the observation that

platinum chemotherapy may be detrimental to patients without such a family history of cancer. The data are quite provocative as more than 20 % of patients in our cohort had a positive family history of breast, ovarian, or pancreatic cancers. This study, therefore, identifies a sizable population of patients that may derive substantial benefit from platinum-containing regimens and another that should avoid them.

The molecular mechanisms for this platinum sensitivity are not identified by this study, and we do not have sufficient tissue to retrospectively analyze the genetic makeup of these tumors. However, we note that mutations in the BRCA2/PALB2/Fanconi anemia pathway have been reported in approximately 10–12 % of familial pancreatic cancers. These molecular defects are also common to familial cases of breast and ovarian cancers. In each of these malignancies, a disruption of the pathway interferes with repair of DNA double-strand breaks through homologous recombination. Preclinical models have shown that cisplatin preferentially induces death of cells deficient in homologous recombination repair by generating intrastrand crosslinks in DNA. This has been validated in breast and pancreatic cancer cells lines with biallelic genetic defects in BRCA2 [22].

Multiple studies have shown clinical benefit with the use of platinum agents in BRCA mutant cancers. Case reports suggest that pancreatic cancer patients harboring BRCA2 mutations benefit from treatment with platinum agents. In one retrospective review, patients with BRCA mutant advanced pancreatic cancers lived longer if treated with platinum agents (22 vs. 9 months) [23]. Other case reports have similarly demonstrated patients with unusually long survival on treatment with these agents [9, 24, 25]. In other tumor types such as ovarian cancer, platinum sensitivity and improved survival accompany BRCA1/2 pathway mutations [25–27]. Likewise, patients with BRCA-associated breast cancer have high pathologic CR rates than non-BRCA when treated with platinum agents [28,29]. We hypothesize that the platinum-sensitive phenotype described in this report genotypically corresponds to either known or yet to be identified defects in the BRCA2/PALB2/Fanconi anemia pathway. A next logical step would be to further genotype the tumors of patients with strong family histories looking for undiagnosed BRCA, PALB2, or Fanconi gene mutations. Currently, no CLIA-certified assay for functional homologous recombination exists, but such an assay would also be helpful to identify defects in the BRCA2/PALB2/Fanconi pathway. One example of such an assay has been described by Mukhopadhyay et al. [30].

How will these data affect future clinical care and clinical trial design for patients with pancreatic cancer? Certainly, the benefit of other DNA-damaging agents in patients with a family history of cancer should be explored. For example, one patient in our study who did not receive platinum therapy, but who had a dense pedigree (3 + relatives) for pancreatic, breast, and ovarian cancers, survived for >2 years when treated with irinotecan, a topoisomerase inhibitor (Table 3). Other compelling therapies include radiation therapy and inhibitors of PARP [poly(ADP-ribose) polymerase], the latter which appears to be selectively active in BRCA mutations carriers [7].

In our analysis, we did not review objective responses to therapy; however, previous studies using platinum-containing regimens have reported a number of major responses, which

would have clear implications not only for metastatic patients, but also in the neoadjuvant setting for resectable or borderline resectable patients. Of note, no individual prospective study has shown a significant survival benefit to platinum-containing regimens in pancreatic cancer. It is possible that the benefit that might have been obtained in patients with BRCA history might have been diluted by an absence of benefit in patients without such history. Subgroup analysis by family history was not performed in those studies [31, 32].

One limitation of our analysis is that we did not include patients treated with the FOLFIRINOX regimen, a recently published oxaliplatin-containing regimen that has demonstrated improved survival over single agent gemcitabine in pancreatic cancer patients treated for metastatic disease, as this regimen had not come into use during the time frame of our review [2]. Likewise, we have not been able to include patients treated with the gemcitabine and nab-paclitaxel regimen, also recently described [3]. Both have demonstrated increased efficacy in the metastatic setting as compared to gemcitabine alone. Clinicians currently have no biologic marker to suggest which of the two regimens might be more effective for any given patient. It may therefore be fruitful to repeat our analysis, focusing on patients treated with these regimens, in order to discern whether family history remains relevant for prognosis or prediction with these newer treatments.

An interesting question is whether our broad definition of family history introduced many sporadic cases of breast, ovarian, and pancreatic cancers into our analysis, which potentially weakened the described survival benefit. For instance, we observed little difference between patients with no or one family member affected by BRCA tumors. A more stringent and prospective evaluation of our observations will likely result in fewer patients meeting the criteria for a familial cancer syndrome, but would likely improve the statistical significance and size of the observed survival benefit.

Future comparisons will more rigorously compare biological markers of DNA repair deficits with family history and overall survival. However, for the immediate moment, we believe that family history might serve as an inexpensive and easily obtained biomarker for sensitivity to platinum agents among patients with metastatic adenocarcinoma of the pancreas.

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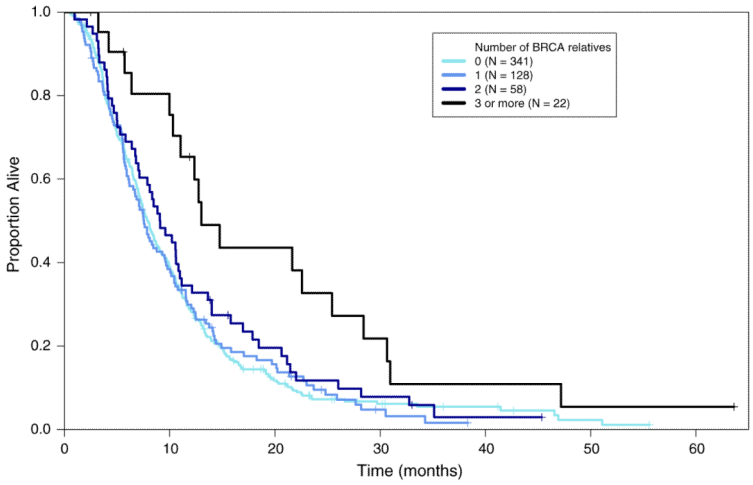

Fig. 1.
First-line platinum status: overall

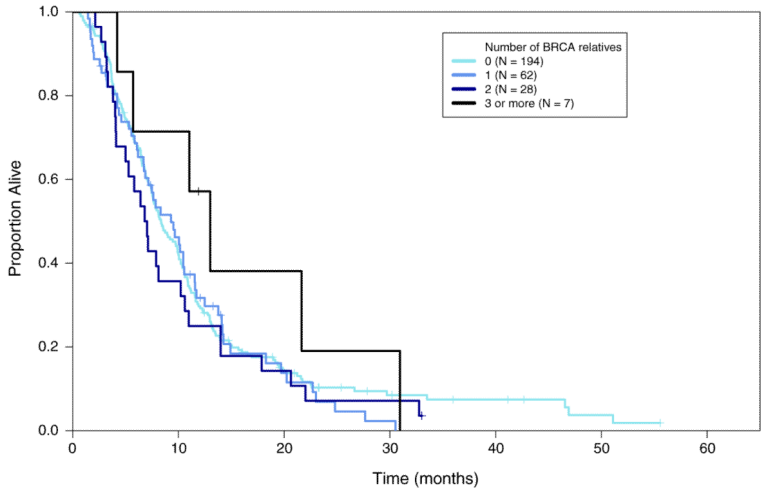

Fig. 2.
First-line platinum status: none

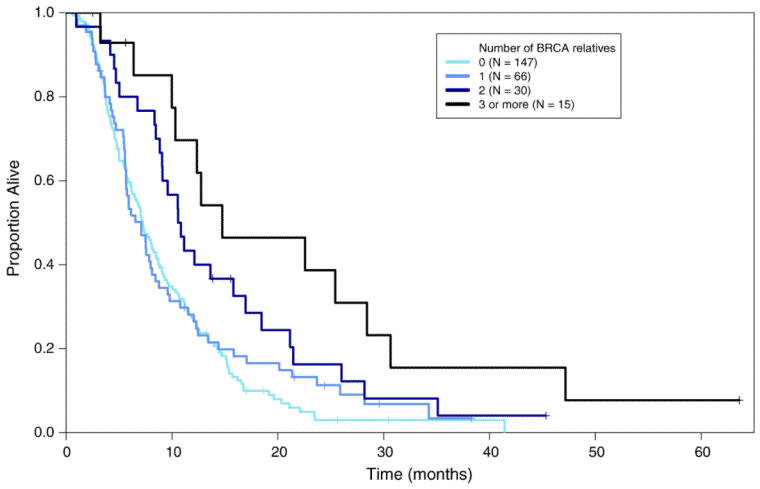

Fig. 3.
First-line platinum status: present

Table 1

Comparison of patients in the Johns Hopkins and MD Anderson cohorts

	Overall (*N* = 549)	Johns Hopkins (*N* = 243)	MD Anderson (*N* = 306)	*p* value
Age (years)				
Median (range)	62 (30–89)	62 (30–89)	62 (34–87)	0.30
Gender				
Female	235 (43 %)	113 (47 %)	122 (40 %)	0.14
Male	314 (57 %)	130 (53 %)	184 (60 %)	
Race				
White	452 (82 %)	209 (86 %)	243 (79 %)	0.004
Black	57 (10 %)	26 (11 %)	31 (10 %)	
Other	40 (7 %)	8 (3 %)	32 (10 %)	
Year of diagnosis				
1995–1999	13 (2 %)	13 (5 %)	0 (0 %)	<0.0001
2000–2005	74 (13 %)	65 (27 %)	9 (3 %)	
2005–2010	462 (84 %)	165 (68 %)	297 (97 %)	
Liver metastases				
No	122 (22 %)	45 (19 %)	77 (25 %)	0.064
Yes	427 (78 %)	198 (81 %)	229 (75 %)	
Lung metastases				
No	434 (79 %)	202 (83 %)	232 (76 %)	0.045
Yes	115 (21 %)	41 (17 %)	74 (24 %)	
Peritoneal metastases				
No	437 (80 %)	205 (84 %)	232 (76 %)	0.014
Yes	112 (20 %)	38 (16 %)	74 (24 %)	
Family history of cancer[a]				
None	122 (22 %)	61 (25 %)	61 (20 %)	0.45
Pancreatic	57 (10 %)	21 (9 %)	36 (12 %)	
Breast or ovarian	118 (21 %)	48 (20 %)	70 (23 %)	
Pancreatic and breast or ovarian	25 (5 %)	12 (5 %)	13 (4 %)	
Other	227 (41 %)	101 (42 %)	126 (41 %)	
Personal history of breast, ovarian, or pancreatic cancer				
No	533 (97 %)	237 (98 %)	296 (97 %)	0.62
Yes	16 (3 %)	6 (2 %)	10 (3 %)	
Platinum therapy				
None	224 (41 %)	160 (66 %)	64 (21 %)	<0.0001
First line	258 (47 %)	62 (26 %)	196 (64 %)	
Second line	67 (12 %)	21 (9 %)	46 (15 %)	

[a] Family history of cancer excludes personal history of cancer

Table 2

Summary of risk factors associated with overall survival in the combined Johns Hopkins and MD Anderson cohorts

	Number at risk	Number of events	Median overall survival in months (95 % CI)	Hazard ratio (95 % CI)	*p* values	*p* values test of trend
Overall	549	488	8.1 (7.5–9.0)			
Age (years)						
<50	70	59	9.7 (7.5–11.7)	1.00		0.080
50–59	147	132	8.5 (7.4–10.1)	1.00 (0.73–1.37)	0.99	
60–69	200	175	8.2 (7.0–9.9)	1.08 (0.08–1.45)	0.62	
70 or greater	132	122	7.5 (6.1–8.6)	1.25 (0.91–1.72)	0.15	
Gender						
Female	235	207	8.1 (7.4–9.8)	1.00		
Male	314	281	8.1 (7.1–9.1)	1.04 (0.86–1.25)	0.70	
Race						
White	452	402	8.3 (7.6–9.4)	1.00		
Black	57	53	6.1 (5.0–10.0)	1.48 (1.10–1.98)	0.008	
Other	40	33	8.3 (6.4–11.2)	1.01 (0.70–1.45)	0.95	
Year of diagnosis						
1995–1999	13	13	10.6 (8.5–Inf)	1.00		
2000–2005	74	74	8.0 (7.2–10.7)	0.94 (0.52–1.71)	0.84	
2005–2010	462	401	8.1 (7.3–9.1)	0.99 (0.56–1.72)	0.96	
Liver metastases						
No	122	105	10.6 (9.0–12.6)	1.00		
Yes	427	383	7.6 (7.1–8.5)	1.38 (1.11–1.72)	0.003	
Lung metastases						
No	434	387	8.1 (7.4–9.0)	1.00		
Yes	115	101	8.57 (7–10.61)	0.97 (0.77–1.21)	0.78	
Peritoneal metastases						
No	437	389	8.1 (7.5–9.2)	1.00		
Yes	112	99	7.6 (6.4–10.6)	1.00 (0.79–1.25)	0.97	
Family history of cancer						
None	122	109	7.5 (5.6–8.9)	1.00		
Pancreatic	57	53	7.1 (5.5–10.1)	0.86 (0.61–1.20)	0.37	
Breast or ovarian	118	102	8.5 (7.1–10.5)	0.76 (0.57–1.00)	0.042	
Pancreatic and breast or ovarian	25	22	14.8 (10.5–28.4)	0.43 (0.26–0.68)	0.0003	
Other	227	202	8.4 (7.3–9.9)	0.75 (0.59–0.95)	0.015	
Personal history of breast, ovarian, or pancreatic cancer						
No	533	473	8.1 (7.4–9.0)	1.00		
Yes	16	15	10.6 (5.4–20.3)	0.98 (0.58–1.64)	0.93	
Pedigree history of malignancy[a]						

	Number at risk	Number of events	Median overall survival in months (95 % CI)	Hazard ratio (95 % CI)	*p* values	*p* values test of trend
No	119	106	7.5 (5.6–8.90)	1.00		
Other cancer	222	197	8.4 (7.3–9.9)	0.76 (0.59–0.97)	0.022	
BRCA-related	208	185	8.8 (7.5–10.4)	0.72 (0.56–0.92)	0.008	
Number of relatives with a breast, ovarian, or pancreatic						
0	341	303	7.9 (7.2–8.8)	1.00		0.009
1	128	113	7.6 (6.5–9.6)	1.01 (0.81–1.26)	0.92	
2	58	54	9.1 (7.1–11.2)	0.85 (0.63–1.14)	0.26	
3 or more	22	18	13.0 (11.0–30.7)	0.49 (0.30–0.80)	0.004	
Platinum therapy: First line						
No	291	259	8.3 (7.5–10.0)	1.00		
Yes	258	229	8.0 (7.1–9.1)	1.04 (0.87–1.25)	0.65	

[a]After adjusting for age, African-American race, liver metastases, and cohort, only BRCA-related malignancies were significantly associated with overall survival ($p = 0.488$)

Table 3

Interaction between family history of cancer and first-line platinum therapy

	Number at risk	Number of deaths	Median overall survival (95 % CI)	Adjusted hazard ratio[a] for stratified models (95 % CI)	Adjusted stratified *p* value[a]	Adjusted interaction *p* value[a]
No family history of breast, ovarian, or pancreatic cancer						
No first-line platinum	198	176	8.4 (7.5–10.1)	1	0.005	0.017
First-line platinum	151	135	7.3 (6.1–8.6)	1.42 (1.11–1.80)		
Family history of breast, ovarian, or pancreatic cancer						
No first-line platinum	93	83	7.9 (6.8–10.4)	1	0.314	
First-line platinum	107	94	9.1 (7.5–11.5)	0.85 (0.61–1.18)		
No pedigree history of breast, ovarian, or pancreatic cancer						
No first-line platinum	194	172	8.3 (7.5–10.0)	1	0.008	0.047
First-line platinum	147	131	7.3 (6.1–8.8)	1.39 (1.08–1.77)		
Pedigree history of breast, ovarian, or pancreatic cancer						
No first-line platinum	97	87	8.1 (6.8–10.5)	1	0.474	
First-line platinum	111	98	8.8 (7.5–10.8)	0.89 (0.64–1.23)		
No family history of cancer						
No first-line platinum	71	63	8.2 (7.4–10.7)	1	0.013	0.101
First-line platinum	51	46	5.0 (4.2–8.1)	1.74 (1.12–2.71)		
Family history of cancer						
No first-line platinum	220	196	8.3 (7.3–10.1)	1	0.384	
First-line platinum	207	183	8.5 (7.4–10.3)	1.10 (0.88–1.37)		

[a]Models are adjusted for age, African-American race, liver metastases, and cohort (JHH vs. MDA)

Table 4

Interaction between the strength of family history of breast, ovarian, or pancreatic cancers and first-line or any platinum therapy

	Number at risk	Number of deaths	Median overall survival (95 % CI)	Adjusted hazard ratio[a] for stratified models (95 % CI)	Adjusted *p* value[a]	Adjusted interaction *p* value[a]
No first-line platinum therapy						
Number of relatives with breast, ovarian, or pancreatic cancer						
0	194	172	8.3 (7.5–10.0)	1		0.017
1	62	54	9.3 (6.8–11.6)	1.04 (0.76–1.42)	0.78[b]	
2	28	27	6.8 (4.9–11.0)	1.21 (0.80–1.82)	0.36	
3 or more	7	6	13.01 (5.7–Inf)	0.63 (0.27–1.45)	0.28	
First-line platinum therapy						
Number of relatives with breast, ovarian, or pancreatic cancer						
0	147	131	7.3 (6.1–8.8)	1		
1	66	59	7.1 (5.6–8.5)	0.89 (0.65–1.23)	0.47[c]	
2	30	27	10.6 (9.0–18.5)	0.63 (0.41–0.97)	0.032	
3 or more	15	12	14.8 (10.3–Inf)	0.36 (0.18–0.68)	0.002	
No platinum therapy (*any line*)						
Number of relatives with breast, ovarian, or pancreatic cancer						
0	151	140	7.5 (6.4–8.8)	1		0.19
1	45	40	6.9 (5.5–9.6)	1.13 (0.78–1.63)	0.50[d]	
2	22	21	5.3 (4.0–11.0)	1.12 (0.70–1.78)	0.64	
3 or more	6	5	12.0 (5.7–Inf)	0.65 (0.26–1.60)	0.35	
Platinum therapy (*any line*)						
Number of relatives with breast, ovarian, or pancreatic cancer						
0	190	163	8.3 (7.3–10.1)	1		
1	83	73	8.0 (6.5–11.5)	0.97 (0.73–1.30)	0.87[e]	
2	36	33	10.6 (9.0–17.0)	0.82 (0.56–1.20)	0.30	
3 or more	16	13	21.7 (12.3–47.2)	0.41 (0.22–0.76)	0.004	

[a] Models are adjusted for age, African-American race, liver metastases, and cohort (JHH vs. MDA)

[b] Test for trend among individuals not receiving first-line platinum therapy: HR 0.99, 95 % CI 0.85–1.17, $p = 0.98$

[c] Test for trend among individuals receiving first-line platinum therapy: HR 0.76, 95 % CI 0.65–0.89, $p = 0.0004$

[d] Test for trend among individuals not receiving any-line platinum therapy: HR 0.99, 95 % CI 0.83–1.18, $p = 0.94$

[e] Test for trend among individuals receiving any-line platinum therapy: HR 0.83, 95 % CI 0.72–0.96, $p = 0.0076$