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Genetic Effects and Modifiers of Radiotherapy and Chemotherapy on Survival in Pancreatic Cancer

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Abstract

Objectives—Germline genetic variation may affect clinical outcomes of cancer patients. We applied a candidate-gene approach to evaluate the effect of putative markers on survival of patients with pancreatic cancer. We also examined gene-radiotherapy and gene-chemotherapy interactions, aiming to explain inter-individual differences in treatment outcomes.

Methods—In total, 211 patients with pancreatic cancer were recruited in a population-based study. Sixty-four candidate genes associated with cancer survival or treatment response were selected from existing publications. Genotype information was obtained from a previous GWAS

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dataset. The main effect of genetic variation and gene-specific treatment interactions on overall survival were examined by proportional hazards regression models.

Results—Fourteen genes showed evidence of association with pancreatic cancer survival. Among these, rs1760217, located at the *DPYD* gene, rs17091162 at *SERPINA3* and rs2231164 at *ABCG2* had the lowest *P*-values of $10^{-4.60}$, 0.0013 and 0.0023, respectively. We also observed that two genes, *RRM1* and *IQGAP2*, had significant interactions with radiotherapy in association with survival, and two others, *TYMS* and *MET*, showed evidence of interaction with 5-FU and erlotinib, respectively.

Conclusions—Our study suggested significant associations between germline genetic polymorphisms and overall survival in pancreatic cancer, as well as survival interactions between various genes and radiotherapy and chemotherapy.

Keywords

Pancreatic neoplasms; Survival; Genetic heterogeneity; Polymorphism; single nucleotide; Prognosis

Introduction

Pancreatic cancer is the fourth-most frequent cause of cancer death in the United States. Because of the aggressiveness and generally late diagnosis of the disease, five-year survival is less than 5% and median survival is less than 6 months for all stages of pancreatic cancer combined.[1]

The poor prognosis of pancreatic cancer varies appreciably across patient characteristics, tumor stage, treatment and compliance. Systemic treatment has been shown to improve outcome.[2] In particular, surgery is the only potentially curative treatment, but only about 20-25% of cases are diagnosed at a resectable state. Therefore, radiotherapy and chemotherapy have been implemented as adjuvant or palliative strategies, but their effects on the prognosis of pancreatic cancer vary among patients. Previous studies have suggested that genetic polymorphisms may influence pancreatic cancer prognosis and treatment efficacy.[3-7] However, most of these studies were based on only a few genes or polymorphisms and gene-treatment interactions have not been systematically explored.

Screening for disease loci on a genome-wide scale has become available with the development of high-throughput genotyping. Genome-wide association studies (GWAS) of disease risk have been carried out in pancreatic cancer.[8,9] Susceptibility regions including the *ABO* gene and loci in chromosomes 13q22.1, 1q32.1 and 5p15.33 have been found to be associated with risk of pancreatic cancer.[8,9] GWAS studies which produce massive amounts of genetic information can be adapted to examine the role of genetic variation in prognosis and response to specific treatments in patients with pancreatic cancer.[10]

In the present study, we selected from existing literature publications a total of 64 candidate genes, all having evidence of involvement in carcinogenesis-related molecular processes or drug metabolic pathways such as DNA repair, oxidative stress, cell cycle and signal transduction. Using genotype information of 211 subjects from our population-based case-control study that were in the PanScan GWAS,[8,9] we performed a systematic analysis of the prognostic impact of the genetic variation. In addition, with available detailed treatment information on our study subjects, we explored potential gene-radiotherapy and gene-chemotherapy interactions on survival.

Materials and Methods

Study Population

The present study population consists of a subset of participants from a population-based case-control study of pancreatic cancer in Connecticut conducted between 2005 and 2009, described previously.[11] Briefly, 216 cases in the study were selected as a representative sample for inclusion in PanScan.[8,9] Of the 216, 211 had available follow-up information and were included in the present analysis. These cases were diagnosed between February 2005 and June 2008, and followed through June 2010, with an average follow-up of 3.4 years (minimum 1.9 years, maximum 5.3 years).

Data Collection

Clinical information was obtained from patients' medical records, from in-person interviews, and from clinical records maintained by the Connecticut Tumor Registry (CTR). The collected information included date of case diagnosis, age at diagnosis, sex, race, SEER stage of tumor, fact of treatment by surgery, radiotherapy or chemotherapy, and all specific chemotherapeutic agents used. Fact and date of death were obtained from the CTR records as well as from the Social Security Death Index, using Social Security Number for identification. Overall survival time was calculated from the date of pathological diagnosis to the date of death, last follow-up or last treatment visit listed in the CTR, or June 30, 2010. The study was approved by the Human Investigation Committee of Yale University and the Connecticut Department of Public Health. Written informed consent was obtained from each patient following detailed explanation of the study, after which in-person interview and phlebotomy were conducted.

Candidate Gene Selection and Genotyping

Selection of candidate genes was based on possible involvement in pancreatic cancer survival or in associated biological processes. By searching the PUBMED database, we identified reported candidate genes for pancreatic cancer survival, or for response to radiotherapy or to the five chemotherapy agents 5-FU, gemcitabine, erlotinib, capecitabine, and cisplatin/oxaliplatin commonly used in pancreatic cancer. We also searched for relevant articles cited in the references of the reviews.[10,12,13] Altogether, 64 genes were manually selected. For our analysis, all candidate-gene single nucleotide polymorphisms (SNPs) that had originally been genotyped in the PanScan study were eligible if the minor allele frequency was at least 0.01. Detailed methods of the genotyping are available elsewhere.[9]

Statistical Analysis

We used multivariate proportional hazards regression to test the effect of genetic polymorphism on overall survival with adjustment for age, sex, race, disease stage and treatment (surgery, radiotherapy and chemotherapy). Further, we examined whether variation in these genes modified the effects of specific cancer treatment (radiotherapy, 5-FU, gemcitabine, erlotinib, capecitabine, or cisplatin/oxaliplatin). Tests for gene-treatment interactions were limited to the top hit of each gene in the main-effect analysis on cancer survival, in order to decrease the number of tests performed. Both main effects and interaction terms for genetic polymorphism and specific treatment were included in the regression models adjusted for age, sex, race, disease stage, and fact of treatment other than by the one under interaction. Nominal statistical significance was set at a level of 0.05 and all analyses were done using an extended version of the Generalized Linear Interactive Modeling (GLIM) computer program that includes conditional and proportional hazards regression.[14] Our analysis was driven by predefined hypotheses and is exploratory, thus we did not perform explicit numerical Bonferroni corrections to the *P*-values. For the analysis

of main effects, even though we used a candidate gene approach, each gene had a variable number of SNPs genotyped in the original PanScan assay. Because it is unclear how many independent tests are involved in the sets of SNPs within each gene, we have chosen to present only the top variant in each gene as a main effect. The given *P*-values can be regarded as "gene-wide" significant by consideration of how many likely independent haplotype groups describe the gene for 95% of individuals.

Results

Clinical characteristics of the patients are shown in Table 1. Among the 211 patients, 181 (85.8%) had died during the follow-up. The average follow-up of the study subjects was 3.4 years. In total, 66 patients underwent surgery, 145 received radiotherapy and 137 chemotherapy. For the specific chemotherapeutic agents, 26 patients received 5-FU, 98 received gemcitabine. 23 were treated with erlotinib, 20 were given capecitabine and 15 received cisplatin/oxaliplatin.

In the study, 1,186 polymorphisms associated with 64 candidate genes were examined with respect to overall survival. In the multivariate proportional hazards models, 14 of these genes were nominally associated with survival after adjustment for age, sex, race, disease stage and treatments. The allele frequencies and *P*-value of the top hit in each gene are summarized in Table 2. In particular, the strongest and most significant association was found in the gene *DPYD* at rs1760217 ($P = 10^{-4.60}$). The *DPYD* risk CT/TT genotypes were significantly associated with reduced survival (HR = 1.89; 95%CI = 1.39-2.57), compared with the CC genotype. The SNPs rs17091162 at *SERPINA3* and rs2231164 at *ABCG2* also showed nearly significant associations with survival, with *P*-values of 0.0013 and 0.0023, respectively. Subjects carrying the AC/CC genotypes at rs17091162 showed reduced survival compared to individuals with the AA genotype: adjusted HR = 1.57 (95%CI = 1.18-2.08), while individuals carrying the rs2231164 AG/GG genotypes exhibited better survival than patients carrying the AA genotype, with adjusted HR of 0.62 (95%CI = 0.45-0.85). Eleven additional genes had main effects of nominal statistical significance: *XPA, CHEK1, MMP3, MAPK10, KRAS, GNAS, IQGAP2, SLC29A1, CCND1, ABO* and *TGM3*. The top hit found in *ABO*, rs2073828, differed from the most significant variant identified in the PanScan study, rs505922.[9] Little evidence of association with survival was found for rs505922: HR = 1.16 (95%CI = 0.93-1.44), *P*=0.20.

We next investigated genetic modification of radiotherapy on cancer survival. Table 3 shows four genes (*RRM1, IQGAP2, TP73*, and *XRCC3*) that may interact with radiotherapy, and at least one interaction (*RRM1*, *P*=0.00063) is likely to be statistically significant even if adjusted for multiple comparisons inherent in considering 64 gene interactions. Among patients who did not receive radiotherapy, the HR associated with *RRM1* rs1662172 AG/GG genotypes was 0.90 (95%CI = 0.67-1.21), compared with the AA genotype. In patients who did receive radiotherapy, the HR associated with rs1662172 AG/GG genotypes was 2.18 (95%CI = 1.44-3.31) indicating poorer survival. Similarly, polymorphisms in *IQGAP2*, TP73 and *XRCC3* were nominally associated with pancreatic cancer survival among patients who underwent radiotherapy, and no significant associations were found in subjects who did not have radiotherapy. For *IQGAP2*, in patients who received radiotherapy, the HR associated with rs153317 CT/TT genotypes was 2.33 (95%CI = 1.43-3.80), *P*=0.00074, and this risk of reduced survival is likely statistically significant considering 64 gene interactions.

Finally, we explored gene-chemotherapy interactions on survival. As shown in Table 4, 22 genes showed nominally significant interactions with specific chemotherapeutic agents, but none was unambiguously significant after consideration of the 64 interactions examined. In

one gene--*MET*--survival was reduced among patients with SNP rs2237717 who had taken erlotinib: HR=3.23 (95%CI =1.67-6.24), *P*=0.00050 for CT/TT genotypes compared to CC. This result is of borderline significance after considering the number of interaction SNPs examined. Additionally, the interaction of *TYMS* and *5-FU* was associated with a low nominal *P*-value for interaction (*P* = 0.0012). Among individuals carrying the rs2847153 AG/GG genotypes and not receiving 5-FU, mortality risk did not increase compared with those carrying the AA genotype. However, in subjects carrying AG/GG genotypes and receiving 5-FU treatment, there was a 2.56-fold increased mortality risk (95%CI = 1.33-4.95).

Discussion

We compiled from existing literature publications a list of 64 candidate genes, all having evidence of involvement in carcinogenesis-related molecular processes or drug metabolic pathways. Among pancreatic cancer patients in a population-based follow-up study, we then evaluated the effects of these candidate genes on survival and explored effect modification with radiotherapy and chemotherapy, using existing GWAS genotype information. We found three genes that showed statistically significant associations or nearly so with pancreatic cancer survival. We also explored gene-radiotherapy and gene-chemotherapy effects and observed that several genetic polymorphisms appear to interact with specific cancer treatment, thus contributing to the prognosis of pancreatic cancer. To our knowledge, this is the first systematic study of genetic effects and modifiers of radiotherapy and chemotherapy on pancreatic cancer survival.

In this study, we found that a number of genetic markers differed with respect to survival in pancreatic cancer. In particular, *DPYD* rs1760217 CT/TT genotype was associated with an increased risk of poorer survival. *DPYD* is located on chromosome 1p22 and encodes the enzyme dihydropyrimidine dehydrogenase (DPD). DPD catalyzes the first degradation step of pyrimidine and fluoropyrimidines.[15] Seventy-80% of administered 5-FU is normally degraded in vivo by DPD. DPD deficiency is recognized as an important pharmacogenetic factor in the etiology of severe 5-FU-associated toxicity.[16,17] Previous studies have shown that DPD expression and activity in pancreatic tumors were higher than in normal tissues.[18] Our study implicates a role of *DPYD* in the outcome of pancreatic cancer. It is possible that rs1760217 or other genetic variants in *DPYD* may functionally affect DPD expression or activity in survival. Alpha-1 antitrypsin, encoded by *SERPINA3*, is a serine protease inhibitor and functions in the inflammatory response. Previous studies show that alpha-1 antitrypsin is overexpressed in pancreatic cancer specimens.[19,20] It has also been reported that alpha-1 antitrypsin could be a predictive marker of response to gemcitabine and pancreatic cancer survival.[10] Increased serum levels of alpha-1 antitrypsin have been associated with shorter survival in pancreatic cancer.[10,21] Our data suggest that genetic polymorphism in *SERPINA3* likely influences survival in patients with pancreatic cancer, adding to the prognostic importance of this gene.

Recent studies have shown that *ABCG2* genetic variants are associated with survival in breast, lung, and prostate cancer.[22-25] Our results suggest a role of *ABCG2* in survival in pancreatic cancer as well. *ABCG2* encodes an ATP-binding cassette cellular xenobiotic exporter that has been postulated to play a role in multidrug resistance.[22,23] Our finding of improved survival HR = 0.62 associated with the rs2231164 variant may involve reduced function of this gene.

Due to potential interrelatedness of genetic predisposition, treatment response and prognosis,[26] we hypothesized that genetic polymorphisms may interact with radiotherapy or chemotherapy and modify survival in pancreatic cancer. Radiotherapy is widely used as a

palliative or adjuvant treatment. However, a beneficial effect of radiation on pancreatic cancer remains inconsistent and varies among patients.[27-29] In our study, we found two genes (*RRM1* and *IQGAP2*) that showed interactions with radiotherapy. Neither gene demonstrated a main effect on prognosis. However, subjects carrying the *RRM1* rs1662172 AG/GG genotypes and receiving radiation had a significant 2.18-fold increased risk of shorter survival than those subjects carrying the AA genotype. *RRM1* encodes one subunit of ribonucleoside-diphosphate reductase, an enzyme required for the synthesis of deoxyribonucleotides involved in DNA synthesis in dividing cells. It is possible that this variant or others in *RRM1*, under the effects of cellular radiation damage, enhances the ability of tumor cells to survive radiation treatment.

Systemic chemotherapy remains the standard of care in metastatic pancreatic cancer. In addition, adjuvant chemotherapy after resection of localized and locally advanced cancer has been found to improve the outcome of pancreatic cancer. Currently, 5-FU, gemcitabine, erlotinib, capecitabine, and cisplatin/oxaliplatin are commonly used chemotherapeutic agents.[30-33] It is now generally understood that choice of drug treatment is best based on individual patient metabolism of and response to chemotherapeutic agents. In our study, we examined whether any of the five chemotherapy agents were associated with survival differences according to variants in any of the 64 genes. We found 22 genes that may interact with specific chemotherapy agents with nominal interaction *P*-values less than 0.05, but no unambiguous interactions after consideration of the number of comparisons. The strongest evidence for a gene-chemotherapy interaction was observed in *TYMS* rs2847153 and 5-FU (*P* for interaction= 0.0012). 5-FU has been used in the treatment of gastrointestinal cancers for more than 50 years, acting principally as a thymidine synthase (TS) inhibitor. The *TYMS* gene, which is located on 18p11, encodes TS. TS functions as a folate-dependent enzyme that catalyzes the conversion of deoxyuridine-5′-monophosphate to deoxythymidine-5′-monophosphate, representing the only de novo source of thymidine for DNA synthesis.[34] Genetic variants in this gene have been found to influence patient response to 5-FU. A previous study using an ex-vivo lymphoblastoid cell-line model system showed that *TYMS* rs2847153 was significantly associated with 5-FU cytotoxicity.[35] Our results further support the involvement of *TYMS* with 5-FU and their interactive effect on clinical outcome in pancreatic cancer.

Erlotinib is an EGFR small molecule tyrosine kinase inhibitor, which has been FDA approved to be used in combination with gemcitabine as a first line treatment for advanced pancreatic cancer.[36] The pharmacologic effects of erlotinib have not been well characterized in patients with pancreatic cancer. In our study, five genes have potential interactions with erlotinib. Among these, the strongest evidence points to *DCTD*, which has been previously reported as a pharmacogenetic marker for gemcitabine[37,38] and catalyzes the nucleotide substrate for TS; and *MET*, which is a proto-oncogene receptor tyrosine kinase and is associated with tumor growth and metastasis.[39]

Overall, our study has a number of strengths. First, the case patients in the current analysis were included in the PanScan study, which completed a GWAS involving 550,000 SNPs across the human genome. Taking advantage of the rich genotyping information provided by the GWAS, we used a candidate-gene strategy to highlight a number of genes with respect to survival in pancreatic cancer. GWAS provides a new tool for discovery and exploration of survival differences in pancreatic cancer. Second, with detailed treatment information, our study has systematically explored genetic modulation of radiotherapy and chemotherapy on prognosis in pancreatic cancer. If validated, our findings may help to direct individualized decisions for pancreatic cancer treatment in the future. Third, the cases in our study were obtained from a population-based study, generally representative of pancreatic cancer cases

in Connecticut. Fourth, all of the genes selected for investigation here have evidence in the literature supporting their involvement in cancer treatment or survival.

This study however has some limitations. Six of the seven SNPs in the genes that we have discussed are intronic, and the other, rs153317 in *IQGAP2*, is 289 nucleotides downstream (3′) of the gene. Functional effects of these specific SNPs are uncertain and our results could reflect associations with other functional variants in these genes. In addition, cases with very short survival of only a few weeks after diagnosis (approximately 25% of eligible cases) were not included in our study, thus our results may be slightly shifted toward those of individuals with better survival or less aggressive disease. However, our overall mortality of 86% at an average of 3.4 years post-diagnosis suggests that the survival experience of our patients is typical for pancreatic cancer. Also, since our study was hypothesis-generating and exploratory, we did not explicitly perform Bonferroni corrections, though multiple comparisons should be considered. Nevertheless, the results are likely to be of importance because of the biological and etiological context of the genes involved, and a number of the findings even with Bonferroni correction would be statistically significant or nearly so. Even with more than 200 patients, more than half of whom had succumbed to their disease, the limited sample size of our study did not provide enough power to look at three-way interactions. The exploratory results of interactions between genes and specific cancer treatments should therefore be considered cautiously. Detection of significant associations needs replication analysis in independent sample sets with larger sample sizes, as well as functional confirmation of the genetic variation.

In conclusion, the present study identified a potential role of germline genetic polymorphisms on clinical outcome of pancreatic cancer. Genetic factors may not only influence the prognosis of pancreatic cancer, but also contribute to inter-individual differences in patients undergoing radiotherapy and chemotherapy. Our study adds to the growing evidence for future individualized therapy in pancreatic cancer.

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Abbreviations

CTR	Connecticut Tumor Registry
GLIM	Generalized Linear Interactive Modeling
GWAS	Genome-wide association study
PUBMED	US National Library of Medicine publications citation database
SEER	Surveillance, Epidemiology and End Results (US Cancer Registry Network)
SNP	Single nucleotide polymorphism

Table 1
Basic Characteristics of Study Subjects

Variable	Case Patients	(%)
Mean (SD) age at recruitment, y	67.3 (9.80)	
Median (range) age at recruitment, y	67.9 (37.2-83.9)	
≤60 y	52	24.6%
>60 y	159	75.4%
Gender		
male	121	57.4%
female	90	42.6%
Race		
white	196	92.9%
non-white	15	7.11%
Vital Status at end of Follow-up		
alive	30	14.2%
dead	181	85.8%
SEER Stage		
in situ	2	0.95%
localized	25	11.8%
regional	101	47.9%
distant	71	33.6%
unstaged	11	5.21%
Radiation Therapy		
yes	145	68.7%
no	59	28.0%
not known	7	3.32%
Surgery		
yes	66	31.3%
no	145	68.7%
not known	0	0.00%
Chemotherapy		
yes	137	64.9%
no	72	34.1%
not known	2	0.95%
5-FU		
yes	26	12.3%
no	174	82.5%
not known	11	5.21%
Gemcitabine		
yes	98	46.4%
no	101	47.9%
not known	12	5.69%

Variable	Case Patients	(%)
Erlotinib		
yes	23	10.9%
no	177	83.9%
not known	11	5.21%
Capecitabine		
yes	20	9.48%
no	180	85.3%
not known	11	5.21%
Cisplatin/Oxaliplatin		
yes	15	7.11%
no	185	87.7%
not known	11	5.21%

Table 2

Survival Hazard Ratios for Polymorphisms in Candidate Genes in Pancreatic Cancer

Gene	Chr	No. of SNPs genotyped	Top variant	A1|A2[1]	Frequency of A2 in HapMap-CEU	Frequency of A2 in patients	HR[2]	95%CI LL	95%CI UL	*P*-value
DPYD	1	230	rs1760217	C|T	0.750	0.806	1.89	1.39	2.57	$10^{-4.60}$
SERPINA3	14	8	rs17091162	A|C	0.800	0.764	1.57	1.18	2.08	0.0013
ABCG2	4	31	rs2231164	A|G	0.083	0.171	0.62	0.45	0.85	0.0023
XPA	9	5	rs3176757	C|T	0.252	0.209	1.46	1.12	1.89	0.0063
CHEK1	11	7	rs2298483	A|G	0.917	0.879	0.64	0.46	0.89	0.011
MMP3	11	4	rs645419	A|G	0.429	0.521	1.31	1.06	1.61	0.011
MAPK10	4	68	rs6815306	A|C	0.607	0.581	0.74	0.59	0.93	0.011
KRAS	12	18	rs10842514	C|T	0.400	0.491	0.77	0.63	0.95	0.012
GNAS	20	12	rs6123832	C|T	0.450	0.374	1.33	1.05	1.67	0.017
IQGAP2	5	112	rs153317	C|T	0.542	0.569	1.31	1.04	1.66	0.021
SLC29A1	6	5	rs324148	C|T	0.308	0.256	0.77	0.61	0.97	0.022
CCND1	11	2	rs649392	A|G	0.383	0.441	1.26	1.02	1.55	0.035
ABO	9	19	rs2073828	A|G	0.568	0.600	0.77	0.61	0.99	0.039
TGM3	20	19	rs214814	A|G	0.908	0.863	1.41	1.01	1.97	0.040
UGT1A7	2	46	rs1604144	A|G	0.683	0.756	1.28	0.99	1.65	0.055
PMS2	7	6	rs2228006	A|G	0.867	0.867	0.74	0.55	1.00	0.056
MTHFR	1	11	rs1801133	C|T	0.242	0.391	1.24	0.99	1.54	0.061
LOH12CR1	12	29	rs918115	C|T	0.667	0.754	1.28	0.98	1.66	0.061
ERCC1	19	6	rs11615	C|T	0.650	0.621	1.22	0.97	1.52	0.082
RAD51	15	3	rs2412547	A|C	0.533	0.528	1.20	0.98	1.48	0.082
XRCC3	14	4	rs861539	C|T	0.417	0.372	1.20	0.97	1.50	0.10
MDM2	12	2	rs769412	A|G	0.058	0.062	1.47	0.95	2.28	0.10
PAPD7	5	9	rs274700	C|T	0.858	0.876	0.76	0.55	1.05	0.11
RRM1	11	5	rs1662172	A|G	0.575	0.562	1.22	0.96	1.55	0.11
EGFR	7	71	rs2241054	A|G	0.683	0.775	1.23	0.95	1.59	0.11
CES2	16	5	rs11568310	C|T	0.027	0.021	0.58	0.28	1.21	0.12
EGF	4	19	rs2298999	C|T	0.600	0.562	1.18	0.95	1.46	0.13
ABCB1	7	67	rs4148749	C|G	0.008	0.026	1.78	0.88	3.61	0.13

Gene	Chr	No. of SNPs genotyped	Top variant	A1|A2[1]	Frequency of A2 in HapMap-CEU	Frequency of A2 in patients	HR[2]	95%CI LL	95%CI UL	*P*-value
UMPS	3	1	rs13146	C|T	0.150	0.128	1.28	0.93	1.76	0.13
TP73	1	17	rs3765736	C|T	0.392	0.405	0.85	0.68	1.07	0.16
SERPINA1	14	12	rs6575424	C|T	0.383	0.372	0.86	0.69	1.07	0.17
NOS3	7	2	rs3918227	A|C	0.867	0.927	0.76	0.53	1.10	0.17
ERCC5	13	8	rs4150351	A|C	0.183	0.147	0.82	0.61	1.11	0.18
IL1RN	2	4	rs315952	C|T	0.742	0.704	1.17	0.92	1.49	0.20
TP53	17	5	rs2078486	A|G	0.900	0.905	0.79	0.56	1.12	0.20
GABRA4	4	17	rs1512130	A|G	0.642	0.671	1.16	0.92	1.46	0.22
DNM3	1	87	rs10489286	C|T	0.283	0.180	1.19	0.90	1.58	0.22
ATR	3	13	rs9867946	G|T	1.000	0.981	1.67	0.69	4.04	0.22
DCTD	4	19	rs17074237	A|G	0.117	0.062	1.35	0.85	2.14	0.22
ERBB2	17	2	rs1810132	C|T	0.724	0.699	0.86	0.67	1.10	0.24
GSTM1	1	1	rs3754446	G|T	0.676	0.694	1.15	0.90	1.48	0.25
MET	7	26	rs2237717	C|T	0.408	0.434	1.13	0.91	1.39	0.26
GSTP1	11	4	rs6591256	A|G	0.433	0.340	0.88	0.70	1.12	0.29
CDA	1	12	rs12404655	A|G	0.208	0.220	0.86	0.65	1.15	0.30
EPC2	2	11	rs6759083	A|G	0.768	0.825	1.16	0.86	1.57	0.33
CYP3A5	7	11	rs1419745	A|G	0.017	0.038	1.34	0.75	2.42	0.34
CDKN2A	9	5	rs3731217	G|T	0.850	0.879	0.86	0.63	1.18	0.37
GGH	8	4	rs4617146	C|T	0.125	0.237	0.89	0.69	1.15	0.37
CHRNA3	15	10	rs6495309	C|T	0.200	0.216	0.89	0.68	1.16	0.38
MLH1	3	8	rs9857293	C|T	0.983	0.983	1.51	0.57	3.95	0.39
MSH2	2	14	rs10495944	A|G	0.819	0.886	0.86	0.61	1.21	0.40
XRCC1	19	7	rs939461	A|C	0.108	0.121	0.88	0.65	1.20	0.40
PARP1	1	9	rs1805411	A|C	0.825	0.846	0.89	0.67	1.19	0.44
FGFR4	5	1	rs376618	A|G	0.233	0.258	0.91	0.71	1.17	0.45
ATM	11	11	rs11212570	A|G	0.850	0.934	1.18	0.75	1.87	0.46
PTGS2	1	4	rs3918304	A|G	0.000	0.007	0.61	0.12	3.01	0.52
UGT1A1	2	13	rs4148328	C|T	0.450	0.348	1.08	0.85	1.36	0.54
XRCC2	7	5	rs3218527	A|C	0.000	0.012	0.70	0.18	2.70	0.59
TCEB1	8	7	rs2433208	A|G	0.083	0.116	1.09	0.76	1.57	0.65

Gene	Chr	No. of SNPs genotyped	Top variant	A1|A2[1]	Frequency of A2 in HapMap-CEU	Frequency of A2 in patients	HR[2]	95%CI LL	95%CI UL	*P*-value
GPT	8	1	rs1063739	A|C	0.617	0.571	0.96	0.76	1.21	0.72
CDC5L	6	7	rs10484624	G|T	0.000	0.028	0.91	0.43	1.90	0.79
TYMP	22	1	rs470119	A|G	0.650	0.573	0.98	0.80	1.21	0.87
ERCC2	19	4	rs1799787	C|T	0.268	0.299	1.01	0.81	1.26	0.94
TYMS	18	2	rs2847153	A|G	0.800	0.777	0.99	0.77	1.28	0.96

[1] Allele 1|Allele 2

[2] Hazard ratio for allele 2 with respect to allele 1 as discussed in text, adjusted for age, sex, race, stage and treatments

[3] Abbreviations: Chr, chromosome; HR, hazard ratio; 95%CI, 95% confidence interval; LL, lower limit; UL, upper limit

Table 3

Survival Hazard Ratios for Gene-Radiation Interactions among Radiation-Treated and Untreated Patients in Pancreatic Cancer

Gene	Variant	genotypes[1]	HR (95%CI)[2]		*P* interaction
			Treated	Untreated	
RRM1	rs1662172	AA/(AG+GG)	2.18(1.44-3.31)	0.90(0.67-1.21)	0.00063
IQGAP2	rs153317	CC/(CT+TT)	2.33(1.43-3.80)	1.13(0.80-1.46)	0.0088
TP73	rs3765736	CC/(CT+TT)	0.60(0.40-0.90)	1.00(0.76-1.33)	0.040
XRCC3	rs861539	CC/(CT+TT)	1.74(1.13-2.67)	1.06(0.82-1.37)	0.050

[1] Reference genotype/risk genotypes

[2] Adjusted for age, sex, race, stage, and treatments except radiation

Table 4

Hazard Ratios for Gene-Chemotherapy Interactions among Specific Chemotherapy-Treated and Untreated Patients

Drug	Gene	Variant	Genotypes[1]	HR (95%CI)[2]		*P* interaction
				Treated	Untreated	
5-FU						
	TYMS	rs2847153	AA/(AG+GG)	2.56(1.33-4.95)	0.83(0.63-1.10)	0.0012
	ERCC1	rs11615	CC/(CT+TT)	0.51(0.29-0.92)	1.36(1.07-1.72)	0.0040
	UGT1A7	rs1604144	CC/(CT+TT)	0.33(0.13-0.85)	1.43(1.09-1.89)	0.0055
	XRCC1	rs939461	AA/(AC+CC)	3.95(1.45-10.75)	0.79(0.57-1.10)	0.0068
	CDKN2A	rs3731217	GG/(GT+TT)	0.29(0.12-0.69)	0.99(0.69-1.41)	0.015
	CDKN1A	rs876581	AA/(AG+GG)	2.95(1.07-8.13)	0.81(0.54-1.23)	0.018
	CHRNA3	rs6495309	CC/(CT+TT)	0.36(0.16-0.84)	0.97(0.74-1.28)	0.024
	ERCC5	rs4150351	AA/(AC+CC)	0.43(0.21-0.88)	0.96(0.68-1.35)	0.033
	MMP3	rs645419	AA/(AG+GG)	2.46(1.31-4.60)	1.22(0.98-1.52)	0.036
	UGT1A1	rs4148328	CC/(CT+TT)	0.57(0.30-1.11)	1.19(0.92-1.52)	0.038
Gemcitabine						
	GPT	rs1063739	AA/(AC+CC)	1.34(0.96-1.87)	0.71(0.51-0.98)	0.0076
	GSTP1	rs6591256	AA/(AG+GG)	1.17(0.86-1.59)	0.64(0.45-0.90)	0.011
	CDA	rs12404655	AA/(AG+GG)	1.22(0.82-1.82)	.61(0.40-0.93)	0.018
	IQGAP2	rs153317	CC/(CT+TT)	1.05(0.79-1.39)	1.80(1.26-2.58)	0.019
	GABRA4	rs1512130	AA/(AG+GG)	0.89(0.63-1.25)	1.49(1.06-2.08)	0.036
	XRCC2	rs3218527	AA/(AC+CC)	14.8(1.68-130.2)	0.51(0.10-2.49)	0.038
Erlotinib						
	DCTD	rs17074237	AA/(AG+GG)	0.28(0.08-0.97)	1.96(1.18-3.25)	0.0013
	MET	rs2237717	CC/(CT+TT)	3.23(1.67-6.24)	1.05(0.84-1.31)	0.0017
	SLC29A1	rs324148	CC/(CT+TT)	1.38(0.86-2.19)	0.66(0.51-0.86)	0.010
	CDKN1A	rs876581	AA/(AG+GG)	3.23(0.92-11.35)	0.86(0.57-1.30)	0.029
	MSH2	rs10495944	AA/(AG+GG)	2.12(0.78-5.72)	0.76(0.53-1.10)	0.049
Capecitabine						
	MMP3	rs645419	AA/(AG+GG)	0.44(0.16-1.19)	1.38(1.12-1.71)	0.023
	SERPINA3	rs17091162	AA/(AC+CC)	4.35(1.64-11.54)	1.46(1.09-1.94)	0.032

Drug	Gene	Variant	Genotypes[1]	HR (95%CI)[2]		*P* interaction
				Treated	Untreated	
Cisplatin/Oxaliplatin						
	GGH	rs4617146	CC/(CT+TT)	3.70(1.21-11.34)	0.81(0.62-1.06)	0.014
	MMP3	rs645419	AA/(AG+GG)	0.56(0.24-1.28)	1.37(1.11-1.70)	0.036

[1] Reference genotype/risk genotypes

[2] Adjusted for age, sex, race, stage, and other treatments