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Polymorphisms in Metabolism/Antioxidant Genes May Mediate the Effect of Dietary Intake on Pancreatic Cancer Risk

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Abstract

Objectives—A source of variation for inconsistent dietary-pancreatic cancer associations may be individuals carrying constitutional metabolism/antioxidant gene variants differentially benefit compared to homozygous individuals. Seventy-six tag SNPs were genotyped in thirteen candidate genes to test differential associations with pancreatic adenocarcinoma.

Methods—A clinic-based case-control design was used to rapidly ascertain 251 cases and 970 frequency matched controls who provided blood samples and completed a 144-item food frequency questionnaire. SNPs were evaluated using a dominant genetic model and dietary categories split on controls' median intake. Logistic regression was used to calculate odds ratios and 95% confidence intervals, adjusted for potential confounders.

Results—Significant increased associations (Bonferroni corrected $P \leq 0.0007$) were observed for carriers of ≥ 1 minor allele for rs3816257 (*glucosidase, alpha; acid [GAA]*) and lower intake of deep-yellow vegetables (1.90[1.28,2.83]); and carriers of no minor allele for rs12807961 (*catalyase [CAT]*) and high total grains intake (2.48[1.50,4.09]) while those with ≥ 1 minor allele had a decreasing slope (across grains). The reference group was no minor alleles with low dietary intake.

Conclusions—Inter-individual variation in metabolism/antioxidant genes could interact with dietary intake to influence pancreatic cancer risk.

Keywords

Pancreatic cancer; dietary risk factors; interaction; case-control; genetic risk factors

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INTRODUCTION

World-wide, pancreatic cancer represents a devastating disease with high mortality among those diagnosed [1]. There is a relatively greater disease burden in more developed nations, such as the United States, where the American Cancer Society estimates there will be 43,920 new cases of pancreatic cancer and 37,390 deaths [2] in 2012. There is lack of successful early detection methods [3], and an extremely poor prognosis, with a 1-year survival rate of 25% and a 5-year survival rate of 4%[4]. An important strategy at present is to focus on prevention through identification of modifiable risk factors.

Based on an extensive literature review, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) reported that there is limited evidence to suggest that fruits protect against pancreatic cancer, and there is inconsistent evidence of a risk relationship with vegetables[5]. Since 2006, five case-control studies have reported an inverse association between pancreatic cancer and consumption of fruits[6], vegetables[7], fiber[8] and/or whole grains[9, 10]. During the same period, four cohort studies have reported overall null associations [11–15] except in high risk group sub-analyses[12, 14]. Possible explanations for inconsistency between case-control and cohort studies include information bias with respect to dietary ascertainment, homogeneous intake, and variability in histologically-verified tumor types[11].

Another suggested explanation for these diet-cancer inconsistencies involves variation of polymorphisms in genes involved in metabolizing components of fruits, vegetables, fiber, and grains or antioxidant defense. To date, there has been a limited number of epidemiologic studies that investigate pancreatic cancer risk associated with polymorphisms in antioxidant genes, glucose metabolism genes, or carcinogen metabolism genes. Among antioxidant genes, pancreatic cancer has shown null[16, 17] and increased[18] associations with SNPs of manganese superoxide dismutase (*SOD2)* with some observed significant interactions with diabeties[19], and dietary intake of vitamin E[19], lutein/zeaxanthin, lycopene, α-carotene, and α-tocopherol.[20] Among glucose metabolism genes, a SNP in glucokinase (*GCK)* has been associated with better overall survival.[21] Among carcinogen metabolism genes, a SNP in UGT1A7 has been associated with pancreatic cancer especially in younger smokers and those with chronic pancreatitis[22], but has also shown null results along with UGT1A9.[23, 24] Significant interaction effects have been observed between GSTT1 and heavy smokers,[25] and GSTP1 and older age.[26] Additional evidence exists for other cancers. In breast cancer, significant interactions have been found between consumption of fruit and vegetables and variation in *CAT*[27], *SOD2*[28, 29], or *MPO*[27, 30]; similar interactions have been reported for cruciferous vegetables and *GSTP*[31]; and fruit and *CAT*[32]. However, others reported null results when examining fruit and vegetables and *CAT*[33], *SOD2*[34], or *GSTM1*[35]; as well as vegetables and *GSTA*1 [36]. For prostate cancer, an interaction was seen between fruit and vegetable intake and *CAT*[37], while in lung cancer there was an interaction between *GSTM*1 and intake of cruciferous vegetables[38, 39].

As there has been a demonstration in several cancers that the association of fruit and vegetable intake is modified by polymorphisms in metabolism/antioxidant genes, we hypothesized that the same would be true for pancreatic cancer. Based on a literature search and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database[40–42], we identified 13 metabolism/antioxidant genes of interest: catalase (*CAT)*, glucosidase, alpha; acid (*GAA)*, glucokinase *(GCK)*, glutathione S-transferases: alpha 1 (*GSTA*1), and pi 1 (*GSTP*1), metallothionein 1E (*MT1E)*, manganese superoxide dismutase (*SOD2)*, UDP-glucuronosyltransferase 1 family, polypeptide: A6 (*UGT1A*6), A7 (*UGT1A*7), A8 (*UGT1A*8), A9 (*UGT1A*9), UDP-glucuronosyltransferase 2 family, polypeptide:B4 (*UGT2B*4), and B7 (*UGT2B7*). These genes were selected for their involvement in the

following pathways: antioxidant, starch and sucrose, glycolysis, glutathione, and fructose. *CAT* is involved in antioxidant binding and is a major heme enzyme converting H_2O_2 to H_2O and O_2[43]. A common polymorphism in the promoter region of the *CAT* gene consists of a C to T substitution at position −262 in the 5′ region and results in lower enzyme activity[43]. *CAT* activity has been demonstrated to decline with age similar to antioxidant capacity[44–46]. *SOD2* is important to mitochondrial antioxidant defenses, as it destroys superoxide anion radicals. The protein is translated from nuclear DNA and transferred to the mitochondria[47, 48]. The polymorphism substitution of C for T changes the amino acid from alanine to valine which may decrease activity and translocation of the protein into the mitochondrial matrix as a result of structural modification[47–51]. Overexpression of *SOD2* has been shown to reverse a malignant pancreatic cancer phenotype[52]. *MT1E* interacts with glucocorticoids and heavy metals and has been linked with antioxidants[53]. *GAA* is required for the conversion of glycogen to glucose, a form of starch metabolism. *GCK* is involved with the metabolism of sugars including fructose. *GCK* catalyzes the ATP dependent phosphorylation of glucose and maintains glucose homeostasis by regulating insulin secretion[54]. *GCK* – 515G>A has been associated with reduced beta-cell function[55]. *GCK* IVS1 +9652T allele is in linkage with the −515A allele and has been associated with decreased PC risk in non-diabetics but increased PC in diabetics and reduced overall survival in PC patients[21]. There have been interindividual differences in glucuronidation, suggesting an important role for the family of UDP-glucuronosyltransferases (UGT)[56]. These genes conjugate endogenous and exogenous compounds with 5′-diphosphoglucuronic acid to form glucuronidated compounds that are more water soluble and easily excreted. Enzymes encoded by *UGT1A* conjugate estrogens, bilirubin, and xenobiotic compounds including PhIP and enzymes encoded by *UGT2B* regulate bile acids, androgens, and drugs[57]. Genetic polymorphisms have been identified that alter enzyme expression and/or activity and affect carcinogen clearance[57]. For example, *UGT1A*1*28 polymorphism with 7 thymine adenine repeats rather than 6 TA repeats result in lower promoter activity due to reduced binding of TATA binding proteins[58, 59] and may increase risk of cancer[60–63] as a result of decreased ability to excrete potential carcinogen[56, 64–67]. Glutathione S-transferase pi 1 (*GSTP*1) belongs to a family of enzymes that have a role in detoxification of many hydrophobic and electrophilic compounds with reduced glutathione, thereby protecting the cell from reactive oxygen species and products of peroxidation[40]. A polymorphism (A to G) within the binding site of *GSTP*1 causes an amino acid substitution influencing enzyme activity[68].

Given the inconsistent results of dietary analyses, positive gene-diet interaction results in several cancers, and limited research in this area for pancreatic cancer, we report our analysis of potential interactions of metabolism/antioxidant gene variants with intake of fruit, vegetable, fiber, and grain and pancreatic cancer risk.

MATERIALS AND METHODS

Study sample

This study was approved by the Institutional Review Board. Briefly, from May 2004 to December 2009, using a rapid ascertainment method[69], 1,648 of 2,473 (66.6%) pancreatic adenocarcinoma cases consented to participate in a prospective registry at time of their clinic visit. During the same time period, 1,514 of 2,708 (55.9%) potential controls (unrelated individuals without pancreatic cancer) seen in primary care clinics were consented. Controls were frequency matched to cases on age at time of recruitment (in 5-year increments), race, sex, and region of residence (Olmsted County; three-state (MN, WI, IA); or outside of area), and those with prior diagnoses of cancer except non-melanoma skin cancer were excluded. Written, informed consent was obtained from each individual for participation in the study. Both groups were asked to complete a questionnaire which collected information on

demographic characteristics and potential risk factors and to provide a peripheral blood sample. DNA was extracted from lymphocytes.

Molecular genetic analysis of polymorphism

All DNA samples were genotyped for the selected 76 SNPs in the institutional genotyping shared resource using an Illumina Golden Gate® Custom 1152-plex OPA panel as part of a larger study using standard protocols. Candidate genes were selected using a combination of literature review and the KEGG pathway database[40–42] for involvement in the metabolism of components of fruits, vegetables, fiber, or grains or in antioxidant defense. For all the candidate genes in our list, we assessed LD (r^2 = 0.9, minor allele frequency (MAF) cutoff = 5%) within the gene and included SNPs 5kb upstream and downstream. From Caucasian populations in HapMap, Seattle SNPs and NIEHS SNPs, the single source was chosen for each gene (the single source with most bins and most SNPs, with ties going to Hapmap due to its larger sample size) and tag SNP(s) were identified from these sources. The SNPPicker software[70] was used to optimize the tag SNP selection process. Genotyping was successful for 1,372 cases (1,143 Caucasian) and 1,190 controls (1,097 Caucasian) with SNP call rate and sample success rates >99%; this was the set used for testing our gene associations with pancreatic cancer. Concordance between inter- and intra-plate replicates of a CEPH family trio (http://ccr.coriell.org/sections/collections/nhgri/hapmap.aspx?PgId=266) was used for quality control.

Dietary data from food frequency questionnaire (FFQ)

The FFQ was a modified form of the New England Bladder Cancer FFQ developed by the NCI. A detailed description can be found elsewhere[10]. Briefly, the scannable FFQ was used to obtain self-reported average consumption and intake frequency for 144 food and beverage items (53 pertained to fruits, vegetable, grain and fiber categories) over the 5 years prior to study entry. The NCI software DietCalc[71] was used to create food groupings and estimate average nutrient intake. FFQs were returned by 816 (49.5%) cases and 1,290 (85.2%) controls who were consented. Possible participants were excluded if they reported changing their diet within the previous 5 years (420 cases and 286 controls), or did not answer 17 or more items (12 cases and 21 controls). Therefore, the sample that was analyzed contained 384 cases and 983 controls. From this dietary analysis set, we excluded those who failed to provide a blood sample (133 cases and 76 controls), resulting in 251 cases and 907 controls for the present interaction analysis.

Statistical analysis

Seventy-six SNPs passed QC and were included in this analysis. The association between pancreatic adenocarcinoma and each SNP was evaluated using a dominant genetic model (i.e. comparisons were for 1 or 2 minor alleles vs. 0 minor alleles) and assessed using unconditional logistic regression. Sex-specific median cut-points based on the distribution of the control population were created for each dietary variable and dietary variables were created using the density method with energy-adjusted dietary items [72]. SNP-diet interactions were investigated based on the dominant genetic model for SNPs and the median dichotomized dietary variables. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% CIs, adjusting for age, sex, smoking status, BMI, family history of pancreas cancer in a first degree relative, energy intake (per 1000 kcal), and number of drinks of alcohol per week. A Bonferroni correction for the number of SNPs (0.05/76 SNPs ≤ 0.0007) was used to help control for multiple testing of main effects for these SNPs. Each dietary factor was considered as an independent hypothesis and therefore no correction was performed, similar to the approach used by Figueiredo et. al [73]. A randomization test based on resampling 10,000 times from the null distribution was run for

SNP-diet interactions meeting the Bonferroni correction (≤ 0.0007). All analyses were generated using SASreg; software (Version [9.2]) [74].

RESULTS

Demographics

For our interaction analysis set, cases compared to controls were more likely to be male, be slightly older, and have ever smoked (and if a former smoker, had tended to have quit more recently than controls). Cases were more likely to have DM, especially new onset (Table 1) and pancreatitis compared to controls. Usual BMI was similar for cases and controls.

Comparing the demographic characteristics of our analyzed participants (those who completed a FFQ and genotyping N=251) to those who completed a FFQ but who were excluded because of no genotyping (N=133) showed that our analyzed cases were more likely to be male, older, not have DM, and have been a never smoker. The 907 analyzed controls had very similar demographic characteristics compared to the 76 controls excluded because of no genotyping, with the analyzed group having a higher percentage of males and smokers (especially former smokers who quit relatively recently prior to study). A comparison between the dietary analyzed set (384 case and 983 controls) and all approached potential participants can be found in a previous publication, which showed modest differences including DM (38.1% vs. 49%), current smoker (23.6 vs. 15.6%) and former smoker status (36.9 vs. 43.4%)[10].

Dietary analysis

The median value and interquartile range is given for each food grouping by sex and case status in Table 2. We noted that the female controls have the highest intake value for most of the groupings and male cases have the lowest value. In general, female cases and male controls have similar values for each food grouping, with female cases having slightly higher median values.

Significant results (P <0.05) for inverse association between pancreatic adenocarcinoma and food groupings were citrus, melon, and berries, other fruit, total fruit, dark green vegetable, deep yellow vegetable, tomato, other vegetable, other starches, total vegetables, insoluble fiber, soluble fiber, total dietary fiber, whole grains, and orange/grapefruit juice. There was an increased association between having pancreatic adenocarcinoma and non-whole grains. The correlation between whole and non-whole grains was low (Pearson r = 0.17); therefore, this discordant association appears not to be simple dietary replacement.

Genotype analysis

There was no significant evidence (P <0.0007) of any SNPs having an association with pancreatic cancer (Table 3) with the lowest p-value (0.02) occurring for two SNPs (rs2908289 and rs2971669) in *GCK*.

Diet-gene interactions

In Table 4, we list the interactions which have $P \leq 0.0007$ based on permutation testing. There is an interaction associated with an increased risk of pancreatic cancer among the group with ≥ 1 minor allele for rs3816257 (*GAA*) and low deep-yellow vegetable intake (OR=1.90[1.28,2.83]). Also associated with increased pancreatic cancer, rs12807961 (*CAT*) interacts with total grains intake with an increasing slope (moving from low to high grain intake) for those carrying no minor alleles and decreasing slope for those with ≥ 1 minor allele.

We list additional interactions ($P \leq 0.008$) which did not meet our permutation cut-off, but still may provide interesting targets for future studies attempting to replicate results reported here (Table 5). The interactions with an increased risk of pancreatic cancer include: the group with no minor allele for rs11032703 (*CAT*) and high total grains (OR=1.62[1.15,2.28]); the group with ≥ 1 minor allele for rs3816257 (*GAA*) and low other starches (OR=1.88[1.22,2.88]); the group with ≥ 1 minor allele for rs1138272 (*GSTP1*) and high non-whole grains (OR=2.05[1.24,3.39]). The interactions with a decreased risk of pancreatic cancer include: the group with no minor allele for rs1042396 (*GAA*) and high orange/grapefruit juice (OR=0.43[0.28,0.68]). Interactions with an increased risk for low intake and decreased risk for high intake include: the group with ≥ 1 minor allele for rs17671289 (*UGT2B4*) and dry beans and peas (OR=1.43 to 0.64); the group with ≥ 1 minor allele for rs2304851 (*GAA*) and orange/grapefruit juice (OR=1.43 to 0.70). Interactions with a decreased risk for low intake and increased risk for high intake include: the group with ≥ 1 minor allele for rs1138272 (*GSTP1*) and total grains (OR=0.49 to 1.80). The interaction between rs475043 (*CAT*) and total grains has an increased risk for all 3 combinations (other than reference), constant slope across dietary category for the group with ≥ 1 minor allele, and larger positive slope for the 0 minor alleles group. The interactions between rs7403881 (*MT1E*) and total fruits and other fruits have a decreased risk for all 3 combinations (other than reference), constant slope across dietary category for the group with ≥ 1 minor allele, and larger slope across dietary category in the 0 minor allele group.

DISCUSSION

We tested the hypothesis that polymorphisms in metabolism/antioxidant genes interact with fruit, vegetable, fiber, and grain intake to modify risk of pancreatic cancer. Although none of the 76 SNP-level tests showed significant associations with pancreatic cancer, 15 of 19 dietary categories (citrus, melon, and berries, other fruits, total fruits, dark green vegetables, deep yellow vegetables, tomato, other vegetables, other starches, total vegetables, insoluble fiber, soluble fiber, total dietary fiber, whole grains, non-whole grains, total grains, and orange/grapefruit juice) were significantly ($P<0.05$) associated with pancreatic cancer. We report 2 SNP-diet interactions which had an interaction P of ≤ 0.0007 and an additional 10 which had an interaction P of ≤ 0.008.

One of the main theories on how dietary intake affects cancer risk is that dietary components reduce DNA damage/mutation by reducing oxidative stress and inflammation[75]. Fruits, vegetables and whole grains are excellent sources of exogenous antioxidants that may work either synergistically with or down-regulate endogenous antioxidant enzymes[33, 76]. Fiber has been proposed to both mechanically reduce the duration potential carcinogens spend in the digestive tract and induce digestive/antioxidant enzymes.

Our results support an interaction of *CAT* and dietary intake of grains with pancreatic adenocarcinoma. There is evidence of an increased risk for those with no minor alleles for rs12807961 (Table 4), rs11032703, and rs475043 (Table 5) and high total grains intake compared to those with no minor alleles and low total grain intake (reference group). Among those with ≥1 minor allele, higher grain intake is suggested (not significantly) to be associated with a reduced risk although significantly higher risk compared to reference group. There are no main effects seen between total grain intake and pancreatic cancer (Table 2) or between *CAT* SNPs and pancreatic cancer (Table 3). These patterns could suggest that having no minor allele increases risk with increased intake and the apparent contradictory observation among the group with ≥ 1 minor allele is a result of proportion of those with 2 minor alleles in the low vs. high intake groups. The SNPs span the gene region, suggesting they may be tagging polymorphisms which are responsible for *CAT* enzyme activity. In prior research, the CT and TT genotypes of *CAT* (at position −262 in the 5′

region, rs1001179) have been associated with lower catalase activity[33], and epidemiologic studies have shown associations between *CAT* genotype and risk of diseases related to oxidative stress[32, 37, 77]. The high activity *CAT* CC genotype has been observed to interact with fruits and vegetables exhibiting a reduced association with breast cancer[27, 32]. When considering the sum of all low-risk alleles of *CAT*, an interaction was observed with low fruit and vegetable intake to increase risk of breast cancer in a dose-dependent manner[27]. The level of mRNA *CAT* has been found to be higher in phenolic acid (found in fruits, vegetables, and whole grains) supplemented groups compared to controls[76]. Phenolic acids cause oxidative stress in the liver inducing phase II antioxidant enzymes, thereby protecting the cells from mutagenesis and oxidative damage[78, 79]. Our results combined with previous research in other cancers would suggest that the tagged *CAT* SNPs presented here are associated with increasing the negative effect of grains possibly through the activation or lack of elimination of an oxidative product.

Our results regarding *GAA* SNPs interacting with dietary intake are the first reported for any cancer. We observed those with ≥ 1 minor allele for rs3816257 and low intake of deep-yellow vegetables (Table 4) and those with ≥ 1 minor allele for rs3816257 and low intake of other starches (Table 5) increased the risk of pancreatic adenocarcinoma while those with no minor allele for rs1042396 and high orange/grapefruit juice intake had a decreased risk of pancreatic adenocarcinoma (Table 5). Those with ≥ 1 minor allele for rs2304851 had an increased risk associated with low orange/grapefruit juice intake but reduced risk associated with high orange/grapefruit juice intake (Table 5). We choose *GAA* for its involvement with starch and sucrose metabolism. The mechanism at work here is undefined, but the observations that interactions between SNPs (≥ 1 minor allele) in *GAA* and deep yellow vegetables and other starches increase the risk of pancreatic cancer suggest this gene plays a role in modifying the relationship between starch and the development of pancreatic adenocarcinoma. We observed a reduced risk of pancreatic cancer among those with ≥ 1 minor allele for orange/grapefruit juice (source of sucrose) suggesting a possible role in reducing exposure time to potential dietary carcinogens or inflammatory components.

Evidence of interaction between intake of fruit, vegetable, grains, or fiber and polymorphisms in *SOD2* is limited. There are studies demonstrating that blueberries are able to upregulate *SOD2* in a mouse model[80]. The *SOD2* Val genotype (CT or CC) is associated with decreased risk of breast cancer with low gamma-tocopherol intake[81], and the Ala/Ala genotype (TT) is associated with higher risk of aggressive prostate cancer with low intake of lycopene[82]. A possible proposed explanation for these observations is that in the presence of Ala and low antioxidant intake, an excess amount of H_2O_2 is produced, which results in higher expression of matrix metalloproteinase (MMP) and metastatic activity[47, 83, 84]. This metastatic activity is prevented in the presence of Val because the *SOD2* enzyme is restricted from entering the mitochondria, creating a buildup of ROS within the mitochondria resulting in induction of programmed cell death[85]. We did not find evidence of an interaction between our tag SNP for *SOD2* and dietary intake with pancreatic cancer.

Phase II detoxification enzymes, including GST and UGT, have been shown to be induced by a component of vegetables (isothiocyanate) in human cell lines and rats[86]. Liver GST or UGT activity was shown not to be affected by dietary treatments with cabbage or brassica[87], in contrast to other studies which showed a two-fold increase in liver GST and UGT activity in rats fed cabbage[88], brassica[89–91], or freeze-dried brussel sprouts[91–93]. Our results provide evidence that those with ≥ 1 minor allele for the missense polymorphism rs1138272 in *GSTP*1 and higher intakes for the categories: total grains and non-whole grains have an increased risk of pancreatic cancer (Table 5). This result is consistent with evidence that dietary fiber intake induces antioxidant/detoxification enzymes including *GSTP*1[94]. We

observed that those with ≥ 1 minor allele for the gene *UGT2*B4 (rs17671289) and intake of dry beans and peas had reduced pancreatic cancer risk (Table 5).

MT1E is predicted to be involved in the detoxification of carcinogens[53]. The antioxidant Genistein upregulates transcription of *MT1E*[95], avoiding depletion of *MT1E* and associated decreased cell proliferation[53]. Our study shows that those with no minor alleles for *MT1E* rs7403881 and high total fruit and other fruit intake have a reduced risk of pancreatic adenocarcinoma (Table 5). Results here and from previous literature would suggest that, mechanistically, *MT1E* and fruit are working synergistically to eliminate potentially harmful carcinogens from the body and that those with a polymorphism associated with rs7403881 are not as effective in this capacity.

This clinic based case-control study has several strengths. All adenocarcinoma cases were pathologically confirmed, allowing for a well-defined case population. The unique recruitment protocol enabled rapid ascertainment of cases, increasing the probability of self completion and enrollment of cases at all stages of disease as well as biospecimen collection. The hypothesis was evidence driven using a combination of KEGG database information on pathways and previous metabolism/antioxidant gene-diet interaction studies. Tagging SNPs were selected to cover the entire gene + 5kb upstream and downstream.

There are limitations that affect retrospective designs requiring participant recall of past events and behavior. Differential misclassification and recall of dietary patterns between cases and controls could contribute to biased risk estimates. However, within this study, cases were rapidly enrolled and completed the FFQ at the time of diagnosis, potentially reducing the effect of such bias. In retrospective population-based studies of rapidly fatal disease, bias can occur due to demise of eligible cases (with a higher proportion of later stage disease). There is a risk of false-positive findings due to multiple comparisons. Given our small sample size, the power to detect interactions is rather limited since tests for an interaction require even larger sample sizes than tests for main effects in order to be adequately powered to detect clinically meaningful effects. This is an observational study; therefore, additional studies, as well as functional work, need to be completed to confirm results of gene-diet interactions on risk of pancreatic cancer reported here. Even though when crudely adjusting for reported diabetes we did not see significant changes in reported results, there could be unmeasured effect on reported results. Diabetes was self-reported and there is a level of bias associated with both self-reporting and being diagnosed. Since diagnosed diabetics are consulted to modify their diets, there could be an unmeasured effect on the reported result as a result of either intentional or unintentional dietary modification.

We have provided evidence that supports our hypothesis that metabolism/antioxidant genes modify the association dietary intake of fruits, vegetables, fiber and grains have on pancreatic cancer risk. At least one SNP from each of 5 genes and 8 dietary categories showed potential interaction. Results need to be confirmed with other studies, and functional work linking these metabolism/antioxidant genes to dietary intakes would be informative. If confirmed, our observations provide the potential for more effective dietary prevention strategies aimed at reducing the risk of pancreatic cancer.

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Table 1

Characteristics of pancreatic adenocarcinoma cases and controls used in the analysis (no recent diet change), and all adenocarcinoma cases and controls who completed FFQs.

	Cases		Controls	
	Genotyped (N=251)	**Not Genotyped (N=133)**	**Genotyped (N=907)**	**Not Genotyped (N=76)**
Sex				
Female	102 (40.6%)	61 (45.9%)	440 (48.5%)	60 (78.9%)
Male	149 (59.4%)	72 (54.1%)	467 (51.5%)	16 (21.1%)
Age when approached				
N	251 (100.0%)	133 (100.0%)	907 (100.0%)	76 (100.0%)
Mean (SD)	67.5 (10.0)	65.9 (11.4)	65.9 (10.5)	64.4 (14.4)
Median	67.0	66.0	67.0	69.0
Q1, Q3	60.0, 75.0	59.0, 74.0	59.0, 74.0	57.5, 73.5
Range	(43.0–91.0)	(31.0–92.0)	(28.0–94.0)	(24.0–86.0)
Diabetes Mellitus type 2				
Yes	106 (48.8%)	56 (54.4%)	64 (7.1%)	4 (6.2%)
≥ 3 years ago	45 (45.0%)	21 (42.0%)	46 (75.4%)	3 (100.0%)
< 3 years ago	55 (55.0%)	29 (58.0%)	15 (24.6%)	0 (0.0%)
Missing	6	6	3	1
No	111 (51.2%)	47 (45.6%)	842 (92.9%)	61 (93.8%)
Missing	34	30	1	11
Race				
American Indian/ Alaskan Native	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (3.9%)
Asian/Asian-American	1 (0.4%)	2 (1.5%)	3 (0.3%)	5 (6.6%)
Black/African American	0 (0.0%)	4 (3.0%)	1 (0.1%)	0 (0.0%)
White/Caucasian	247 (98.4%)	126 (94.7%)	901 (99.3%)	65 (85.5%)
Multiracial	3 (1.2%)	1 (0.8%)	1 (0.1%)	3 (3.9%)
Smoking				
Current	35 (13.9%)	23 (17.4%)	35 (3.9%)	2 (2.7%)
Former	110 (43.8%)	55 (41.7%)	378 (41.7%)	28 (37.3%)
Quit < 10 years ago	17 (16.0%)	3 (5.5%)	33 (8.9%)	1 (3.8%)
Quit 10+ years ago	89 (84.0%)	52 (94.5%)	336 (91.1%)	25 (96.2%)
Missing	4	0	9	2
Never	106 (42.2%)	54 (40.9%)	494 (54.5%)	45 (60%)
Usual BMI				
N	248 (98.8%)	131 (98.5%)	884 (97.5%)	70 (92.1%)
Mean (SD)	27.5 (5.1)	27.8 (5.7)	26.7 (4.2)	25.9 (4.3)
Median	26.6	27.1	26.4	25.3
Q1, Q3	24.0, 30.1	23.9, 31.1	23.7, 29.1	23.3, 27.4
Range	(15.3–53.0)	(17.0–45.7)	(14.0–49.0)	(19.1–40.7)

Abbreviations: SD, standard deviation; Q1, quintile 1; Q3, quintile 3

Table 2

Median and Interquartile Range (Q1–Q3) for Food Grouping Intake by Sex and Case Status.

	Male		Female		
	Cases	**Controls**	**Cases**	**Controls**	***P****
Citrus, Melon, and Berries (svg/1000 kcal)	0.40 (0.2–0.8)	0.54 (0.3–0.9)	0.68 (0.3–1.0)	0.71 (0.4–1.1)	<0.0001
Other Fruits (svg/1000 kcal)	0.53 (0.3–0.9)	0.71 (0.4–1.1)	0.80 (0.5–1.1)	0.96 (0.6–1.4)	<0.0001
Total Fruits (svg/1000 kcal)	1.09 (0.5–1.70	1.36 (0.8–1.9)	1.49 (1.0–2.1)	1.73 (1.2–2.4)	<0.0001
Dark-green Vegetables (svg/1000 kcal)	0.06 (0.0–0.1)	0.09 (0.1–0.1)	0.09 (0.1–0.1)	0.12 (0.1–0.2)	<0.0001
Deep-yellow Vegetables (svg/1000 kcal)	0.06 (0.0–0.1)	0.09 (0.05–0.14)	0.09 (0.06–0.15)	0.12 (0.07–0.19)	<0.0001
Tomato (svg/1000 kcal)	0.21 (0.1–0.3)	0.23 (0.2–0.3)	0.23 (0.2–0.3)	0.24 (0.2–0.3)	0.0173
Other Vegetables (svg/1000 kcal)	0.41 (0.3–0.6)	0.49 (0.3–0.7)	0.52 (0.4–0.7)	0.61 (0.5–0.8)	<0.0001
Dry Beans and Peas (svg/1000 kcal)	0.04 (0.0–0.1)	0.05 (0.0–0.1)	0.04 (0.0–0.1)	0.05 (0.0–0.1)	0.059
White Potato (svg/1000 kcal)	0.41 (0.2–0.6)	0.33 (0.2–0.5)	0.39 (0.2–0.6)	0.33 (0.2–0.5)	0.0757
Other Starches (svg/1000 kcal)	0.13 (0.1–0.2)	0.16 (0.1–0.2)	0.17 (0.1–0.3)	0.19 (0.1–0.3)	<0.0001
Total Vegetables (svg/1000 kcal)	1.46 (1.1–1.9)	1.65 (1.2–2.1)	1.67 (1.4–2.2)	1.84 (1.5–2.4)	<0.0001
Insoluble Dietary Fiber (g/1000 kcal)	5.78 (4.6–7.5)	6.70 (5.5–8.1)	6.68 (5.3–7.8)	7.51 (6.3–9.0)	<0.0001
Soluble Dietary Fiber (g/1000 kcal)	2.88 (2.4–3.5)	3.20 (2.7–3.7)	3.18 (2.7–3.7)	3.50 (3.0–4.1)	<0.0001
Total Dietary Fiber (g/1000 kcal)	8.59 (7.1–11.1)	9.88 (8.1–11.7)	10.03 (8.2–11.1)	11.17 (9.4–13.0)	<0.0001
Non-whole Grains (svg/1000 kcal)	1.85 (1.5–2.3)	1.79 (1.4–2.2)	1.84 (1.5–2.2)	1.69 (1.3–2.1)	0.0097
Whole Grains (svg/1000 kcal)	0.65 (0.4–1.0)	0.75 (0.5–1.1)	0.69 (0.5–1.0)	0.79 (0.5–1.1)	0.0119
Total Grains (svg/1000 kcal)	2.64 (2.0–3.3)	2.62 (2.1–3.2)	2.61 (2.1–3.2)	2.52 (2.1–3.1)	0.4760
Orange/Grapefruit Juice (g/1000 kcal)	5.33 (1.6–17.0)	5.06 (1.9–24.9)	2.95 (0.8–14.1)	8.01 (1.8–38.7)	0.0088
Tomato/Vegetable Juice (g/1000 kcal)	2.45 (0.0–7.9)	3.34 (0.0–7.3)	2.63 (0.2–4.5)	2.80 (0.0–6.7)	0.5726

Abbreviations: g = grams; svg = servings; kcal = kilocalories; mg = milligrams; mcg = micrograms; Q1, quintile 1; Q3, quintile 3

*P for sex combined cases versus controls

Table 3

SNPs in selected metabolism/antioxidant genes and association with pancreatic adenocarcinoma.

rsID	Chromosome	Gene	Location	bp	MAF	Minor	OR	Lower 95% CI	Upper 95% CI	χ^2 *P*
rs208682	11	*CAT*	5′upstream	34412517	0.17	A	0.96	0.80	1.14	0.6086
rs12807961			5′upstream	34412684	0.37	G	1.08	0.91	1.27	0.3831
rs10836233			5′upstream	34414148	0.09	A	0.95	0.77	1.18	0.6699
rs769214			5′upstream	34416293	0.32	G	1.01	0.86	1.18	0.9400
rs484214			intron	34423848	0.27	G	1.03	0.88	1.22	0.6982
rs11032702			intron	34424699	0.04	A	1.14	0.85	1.53	0.3788
rs11032703			intron	34426232	0.13	A	0.97	0.80	1.17	0.7607
rs7933285			intron	34433701	0.26	A	0.96	0.82	1.13	0.6226
rs769217			synonymous	34439484	0.22	A	0.96	0.82	1.14	0.6677
rs10488736			intron	34445828	0.30	A	1.03	0.88	1.21	0.7020
rs566979			intron	34447223	0.36	C	1.03	0.87	1.21	0.7316
rs16925614			intron	34448885	0.12	A	0.95	0.79	1.15	0.6238
rs475043			3′downstream	34450377	0.42	G	1.06	0.90	1.26	0.4792
rs12952612	17	*GAA*	synonymous	75685647	0.25	A	0.98	0.83	1.15	0.7963
rs2304854			synonymous	75688157	0.46	G	0.96	0.80	1.15	0.6667
rs2304851			3′UTR	75688355	0.36	C	1.05	0.90	1.24	0.5223
rs3816257			5′upstream	75689041	0.39	C	1.04	0.88	1.23	0.6321
rs12450199			intron	75691187	0.38	C	1.07	0.90	1.26	0.4462
rs12600845			intron	75692309	0.48	A	0.91	0.76	1.10	0.3336
rs1042396			synonymous	75699364	0.28	A	1.07	0.91	1.25	0.4351
rs12452616			intron	75704676	0.27	A	1.07	0.91	1.26	0.3948
rs2229221			3′UTR	75707816	0.07	A	1.00	0.80	1.27	0.9730
rs8132			3′UTR	75707948	0.28	A	1.01	0.86	1.18	0.9333
rs4889970			3′downstream	75710681	0.25	A	0.99	0.84	1.16	0.8762
rs11150846			3′downstream	75713115	0.27	A	1.08	0.92	1.27	0.3327
rs2908277	7	*GCK*	3′downstream	44149958	0.13	A	1.00	0.83	1.20	0.9783
rs2268575			intron	44155799	0.20	G	0.99	0.84	1.17	0.8924
rs2971676			intron	44161007	0.09	A	1.03	0.84	1.27	0.7676
rs2268572			intron	44161076	0.15	A	1.00	0.84	1.20	0.9666

rsID	Chromosome	Gene	Location	bp	MAF	Minor	OR	Lower 95% CI	Upper 95% CI	χ^2 *P*
rs2070971			intron	44164108	0.14	A	1.05	0.87	1.26	0.6377
rs17832252			intron	44166624	0.13	A	1.00	0.83	1.21	0.9595
rs2041547			intron	44167409	0.48	A	1.00	0.84	1.20	0.9765
rs2080033			intron	44170847	0.49	G	0.98	0.82	1.18	0.8293
rs12535229			intron	44172130	0.14	A	1.03	0.85	1.23	0.7871
rs12673242			intron	44174019	0.14	G	0.94	0.79	1.13	0.5143
rs2908292			intron	44177235	0.23	A	1.08	0.91	1.27	0.3786
rs2908290			intron	44182662	0.37	A	0.99	0.84	1.17	0.9140
rs758988			intron	44188106	0.16	A	1.05	0.88	1.26	0.5794
rs758985			intron	44188996	0.17	A	1.02	0.86	1.21	0.8268
rs2908289			intron	44190467	0.17	A	1.22	1.02	1.46	0.0262
rs2268569			intron	44193545	0.08	A	1.13	0.90	1.42	0.3008
rs1476891			5′upstream	44196493	0.32	G	0.99	0.84	1.16	0.8831
rs2971669			5′upstream	44198303	0.20	A	1.22	1.03	1.44	0.0216
rs735670			5′upstream	44199870	0.08	T	1.03	0.82	1.29	0.8219
rs7927381	11	*GSTP*1	5′upstream	67103319	0.08	A	0.81	0.65	1.01	0.0617
rs614080			5′upstream	67103863	0.49	A	1.10	0.91	1.32	0.3287
rs6591256			5′upstream	67106475	0.43	G	0.95	0.80	1.12	0.5306
rs1138272			missense	67110155	0.08	A	0.99	0.80	1.24	0.9553
rs2758329	6	*SOD2*	3′downstream	1.6E+08	0.48	G	0.87	0.73	1.05	0.1445
rs7403881	16	*MT1E*	5′upstream	55212672	0.48	C	0.94	0.78	1.13	0.4976
rs2070836			intron	55217621	0.08	G	1.11	0.89	1.40	0.3470
rs6759892	2	*UGT1A*6	missense	2.34E+08	0.41	C	1.04	0.88	1.24	0.6173
rs1105879			missense	2.34E+08	0.35	C	1.14	0.96	1.34	0.1261
rs7577677	2	*UGT1A*7	synonymous	2.34E+08	0.38	A	1.01	0.85	1.19	0.9251
rs17863778			synonymous	2.34E+08	0.06	C	0.99	0.77	1.28	0.9483
rs17863762	2	*UGT1A*8	missense	2.34E+08	0.03	A	0.71	0.49	1.02	0.0642
rs3832043	2	*UGT1A*9	intron	2.34E+08	0.36	T	0.99	0.84	1.17	0.9331
rs1569343	4	*UGT2B*4	3′downstream	70376052	0.43	C	1.00	0.84	1.19	0.9931
rs13119049			missense	70381154	0.25	A	0.92	0.78	1.09	0.3417
rs11249442			intron	70384946	0.31	G	0.95	0.81	1.12	0.5379

rsID	Chromosome	Gene	Location	bp	MAF	Minor	OR	Lower 95% CI	Upper 95% CI	χ^2 *P*
rs1826690			intron	70386855	0.25	G	0.99	0.84	1.17	0.9249
rs2013573			intron	70389067	0.21	A	0.88	0.74	1.04	0.1284
rs1845556			intron	70389473	0.44	A	1.07	0.90	1.28	0.4488
rs3822179			intron	70390784	0.09	A	1.02	0.825627	1.27	0.8407
rs17671289			intron	70393434	0.25	C	1.14	0.971302	1.34	0.1074
rs7441743			intron	70394283	0.39	A	1.01	0.851418	1.19	0.9316
rs17614939			intron	70394818	0.21	G	0.88	0.742708	1.04	0.1260
rs941389			5′upstream	70396330	0.36	C	0.94	0.795146	1.10	0.4364
rs7662029	4	*UGT2B7*	5′upstream	69996501	0.47	G	1.01	0.842836	1.21	0.9289
rs7668258			5′upstream	69996667	0.47	G	1.05	0.841951	1.20	0.9395
rs10028494			intron	70005526	0.21	C	0.94	0.799725	1.11	0.4949
rs3924194			intron	70005681	0.16	C	0.98	0.823617	1.18	0.8629
rs7435335			intron	70005924	0.12	A	1.12	0.925358	1.36	0.2421
rs4356975			intron	70007052	0.35	A	1.00	0.849551	1.18	0.9988
rs6600894			3′downstream	70017681	0.19	A	0.97	0.82	1.15	0.7277

Table 4

Significant metabolism/antioxidant gene SNP – fruit, vegetable, fiber, and grain intake category interactions that are associated with pancreatic adenocarcinoma. Interactions in this table are determined significant based on the interaction and permutation test *P*s ≤ 0.0007.

				Minor Allele Frequency (Control %/Case %)		Odds Ratio (95% CI)		*P*	
Gene	**Influence**	**number**	**Nutrient**	**0**	**≥ 1**	**0**	**≥ 1**	**tion**	**tion**
CAT	5′upstream	rs12807961	Low total grains	20.18/12.35	29.77/35.46	1.00 (ref)	2.05 (1.28,3.28)	***0.0007***	***0.0003***
			High total grains	20.07/24.70	29.99/27.49	2.48 (1.50,4.09)	1.74 (1.07,2.83)		
GAA	5′upstream	rs3816257	Low deep-yellow vegetables	20.95/18.40	29.22/48.40	1.00 (ref)	1.90 (1.28,2.83)	***0.0004***	***0.0005***
			High deep-yellow vegetables	17.20/15.20	32.64/18.00	1.07 (0.65,1.76)	0.66 (0.42,1.05)		

Table 5

Additional top metabolism/antioxidant gene SNP – fruit, vegetable, fiber, and grain intake category interactions that are associated with pancreatic adenocarcinoma. These interactions are significant based on a $P \leq 0.008$.

				(Control %/Case %)		Odds Ratio (95% CI)		
Gene	**Possible Influence**	**RS number**	**Nutrient**	**0**	**≥ 1**	**0**	**≥ 1**	**Interaction *P***
UGT2B4	intron	rs17671289	Low dry beans and peas	29.11/28.69	20.84/29.48	1.00 (ref)	1.43 (0.965,2.106)	***0.0078***
			High dry beans and peas	28.56/27.89	21.50/13.94	1.02 (0.690,1.492)	0.634 (0.403,1.008)	
CAT	intron	rs11032703	Low total grains	38.52/32.80	11.37/14.80	1.00 (ref)	1.48 (0.932,2.356)	***0.0018***
			High total grains	37.97/45.20	12.14/7.20	1.62 (1.147,2.283)	0.75 (0.424,1.338)	
	3′downstream	rs475043	Low total grains	17.31/9.96	32.64/37.85	1.00 (ref)	1.90 (1.155,3.136)	***0.0033***
			High total grains	16.65/20.72	33.41/31.47	2.45 (1.418,4.227)	1.77 (1.065,2.929)	
GSTP1	missense	rs1138272	Low total grains	41.46/42.63	8.49/5.18	1.00 (ref)	0.49 (0.253,0.964)	***0.003***
			High total grains	42.45/40.24	7.61/11.95	1.03 (0.742,1.429)	1.80 (1.086,2.975)	
			Low non-whole grains	41.46/39.04	8.49/4.38	1.00 (ref)	0.49 (0.240,1.002)	***0.0072***
			High non-whole grains	42.45/43.82	7.61/12.75	1.28 (0.918,1.783)	2.05 (1.241,3.391)	
MT1E	5′upstream	rs7403881	Low total fruits	13.02/22.31	37.09/38.25	1.00 (ref)	0.63 (0.419,0.946)	***0.0011***
			High total fruits	13.47/5.18	36.42/34.26	0.24 (0.124,0.475)	0.53 (0.349,0.809)	
			Low other fruits	11.48/21.12	38.63/41.83	1.00 (ref)	0.61 (0.403,0.920)	***0.0018***
			High other fruits	15.01/6.37	34.88/30.68	0.27 (0.142,0.505)	0.51 (0.329,0.787)	
GAA	5′upstream	rs3816257	Low other starches	19.51/15.20	30.54/43.20	1.00 (ref)	1.88 (1.222,2.883)	***0.0022***
			High other starches	18.63/18.40	31.31/23.20	1.40 (0.854,2.286)	1.00 (0.630,1.593)	
	synonymous	rs1042396	Low orange/grapefruit juice	25.91/29.48	23.93/25.50	1.00 (ref)	0.97 (0.654,1.446)	***0.0036***
			High orange/grapefruit juice	26.57/14.34	23.59/30.68	0.43 (0.275,0.678)	1.02 (0.697,1.506)	
	3′UTR	rs2304851	Low orange/grapefruit juice	22.38/20.72	27.45/34.26	1.00 (ref)	1.43 (0.954,2.146)	***0.0043***
			High orange/grapefruit juice	21.17/24.30	29.00/20.72	1.15 (0.742,1.786)	0.70 (0.446,1.088)	