Association between Phosphatidylinositol 3-Kinase Regulatory Subunit p85α *Met326Ile* Genetic Polymorphism and Colon Cancer Risk

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Abstract

Purpose: The phosphatidylinositol 3-kinase signaling pathway is frequently activated in cancer. Emerging evidence supports the p85α regulatory subunit gene, *PIK3R1*, as a novel oncogene.

Experimental Design: We examined the association of a functional missense polymorphism (*Met326Ile*) of *PIK3R1* with colon cancer risk in a population-based case-control study of 421 incident cases and 483 controls.

Results: In our base unconditional logistic regression model controlling for age, gender, and race, we observed a 47% increase in risk among those carrying one or two copies of the 326*Ile* variant ($P = 0.01$). Further adjustment for family history of colorectal cancer, body mass index, nonsteroidal anti-inflammatory drugs, smoking, alcohol consumption, and physical activity strengthened the association [odds ratio (OR), 1.73; 95% confidence interval (CI), 1.24-2.42, $P = 0.001$]. The association was more pronounced among those older than 64 years (OR, 2.10; 95% CI, 1.19-3.70, $P = 0.01$). Evaluation of the genotypes assuming an additive mode of inheritance showed a significant trend for gene-dose response, where compared with *Met*/*Met*, the OR estimates for *Ile*/*Met* and *Ile*/*Ile* were 1.68 (95% CI, 1.19-2.37) and 2.27 (95% CI, 0.98-5.29), respectively (P for trend = 0.001).

Conclusions: This study is the first to describe a significant association between a germ line functional variant in *PIK3R1* and cancer, providing new evidence supporting a role for *PIK3R1* in the development of colon cancer.

Phosphatidylinositol 3-kinases (PI3K) are members of a family of lipid kinases that catalyze the phosphorylation of phosphatidylinositols and phosphoinositides (1). These phosphorylated lipids activate a variety of downstream targets, including Akt, that regulates a wide range of important cellular processes, including cell proliferation, transformation, adhesion, apoptosis, survival and motility, and intracellular trafficking of proteins (2). Loss of function of the tumor suppressor PTEN, which dephosphorylates the PI3K substrates and negatively regulates the PI3K/Akt-dependent cellular survival pathway, has been reported in primary colon cancers (3, 4). Numerous growth factors signal through the PI3K/Akt pathway, including insulin-like growth factors. The activation of PI3K by a growth factor–bound receptor tyrosine kinase and subsequent production of the second messenger phosphatidylinositol 3,4,5-trisphosphate drives the various downstream pathways that regulate a number of cellular functions involved in tumor development and progression (1, 5). High levels of circulating insulin-like growth factor-I have been associated with increased risks of colon cancer in several epidemiologic studies (6).

A number of genetic and functional studies have established an important role for the PI3K signaling pathway in the development of cancer (5, 7). It has been shown that activation of the PI3K pathway occurs in most tumor types through a variety of mechanisms (8). The heterodimeric PI3Ks are composed of catalytic and regulatory subunit variants encoded by separate genes and alternative splicing. Genomic amplification, deletions, and more recently, somatic missense mutations in the *PIK3CA* gene, which code for the p110α catalytic subunit of PI3K, have been reported in a number of different tumor types (9–12), including a large series of colorectal cancers which revealed a high frequency (31.6%) of somatic mutations in *PIK3CA* (13).

Somatic mutations in the *PIK3R1* gene, which encodes the p85α regulatory subunit, have also been reported in primary colon tumors (14). Expression of one of these mutant proteins led to constitutive activation of the PI3K complex, providing the first evidence that *PIK3R1* could act as an oncogene in colon tumor cells (14). Mouse models containing a heterozygous deletion of the PTEN gene show a near doubling of the incidence of intestinal polyps when at least one allele of the *PIK3R1* gene is also deleted (15).

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A single nucleotide missense polymorphism in codon 326 of *PIK3R1* results in the substitution of methionine (*Met*) by isoleucine (*Ile*) near the NH_2-terminal SH2 domain coding region that is crucial for the binding of receptor tyrosine kinases. Functional studies show that the *PIK3R1 Met326Ile* polymorphism results in reduced p85α protein expression and increased binding to IRS-1 (16). The regulatory subunit p85α is an important component of the PI3K pathway, and it has been proposed that a reduction of p85α protein would lead to reduced negative regulation of PI3K and hyperactivation of the PI3K pathway (17). The only epidemiologic study of human cancer reported thus far found no association of the *PIK3R1 Met326Ile* polymorphism and risk of prostate cancer (18). The potential role of this genetic variant in the development of colon cancer remains unexplored.

In this population-based case-control study, we seek to investigate the relationship between this functional genetic polymorphism and colon cancer. We hypothesize that the *PIK3R1 326Ile* variant is associated with an increased risk of colon cancer.

Materials and Methods

Study population. The study population was comprised of 421 incident colon cancer cases and 483 population controls. All subjects were recruited between July 2003 and April 2006. Eligible cases were identified through the population-based Surveillance, Epidemiology, and End Results Kentucky Cancer Registry, covering all residents living in the State of Kentucky at the time of diagnosis. We queried the cancer registry database every 3 months and identified all histopathologically confirmed incident primary colon cancer cases reported within 6 months of diagnosis preceding the recruitment.

We first sent an introductory letter explaining the study to potentially eligible cases. After 3 weeks, or when the subject initiated contact, we phoned each case subject for a screening interview to determine eligibility and their willingness to participate in the study. We collected information on demographics, family history of colorectal cancer, and personal history of cancer at the recruitment phone call. We then used a two-step approach to collect blood samples and lifestyle questionnaire data. First, we sent a prepacked phlebotomy kit with detailed written instructions for blood sample collection and written consent forms to each consenting case subject. The subjects were instructed to go to their physician's offices or adjacent medical facilities for blood draw after overnight fasting. The samples were collected in Purple Top (K_3EDTA) blood collection tubes and shipped overnight on frozen ice packs. Upon receipt, the blood tubes were spun for 15 min at 600 × *g* and aliquots of plasma and concentrated buffy coat were prepared and frozen at -80°C. We then sent each subject a self-administered lifestyle risk factor questionnaire developed by the National Cancer Institute Colon Cancer Family Cancer Registry[5] to collect detailed information on family history of colorectal cancer, lifestyle, and behavioral risk factors.

We used random digit dialing to recruit population controls following a protocol similar to that described above for cases. As a proxy for frequency matching, the residential locations between the cases and the controls, the area codes and exchanges of the phone numbers of potential cases were used, along with randomly generated four-digit numbers, to produce the list of phone numbers for control recruitment. Recruitment was not conducted when a business was reached. We included as controls subjects who were 40 years or older and free of personal history of cancer other than skin cancer. We excluded those with known inflammatory bowel diseases, family history of familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer. As with case subjects, each control first donated a sample of blood after fasting overnight and then was asked to complete the self-administered risk factor questionnaire.

The participation rates were 72.2% for case subjects. Due to the nature of random digit dialing, the response rate for controls cannot be precisely assessed as we could not determine the eligibility of those subjects that were reached, but refused to disclose personal information. Nevertheless, among those individuals that allowed us to explain the study and were determined to be eligible, the participation rate was 62.5%. The overall participation rate among potential controls reached by random digit dialing, regardless of their eligibility, was 33.3%. The completion proportions—i.e., the percentage of participants that returned blood samples and completed the risk factor questionnaire—were 86.5% for cases and 91.3% for control subjects, respectively. All participants provided written informed consent. The study was approved by the Institutional Review Boards of the University of Kentucky (Lexington, KY), and Case Western Reserve University/University Hospitals of Cleveland (Cleveland, OH).

Genotypes. The *PIK3R1 Met326Ile* variant (rs3730089) was genotyped using the TaqMan allelic discrimination assay with a predesigned primer/probe set (C_25474527_10; Applied Biosystems). Assays were done on 2.5 ng of genomic DNA extracted from buffy coat fractions (Biorobot EZ1; Qiagen) which were quantitated with Quant-It picogreen reagent (Invitrogen). Assays were read and genotypes assigned using a 7900HT Sequence Detection System with SDS 2.2 software (Applied Biosystems). The genotyping failure rate was <0.1%. Two percent of the replicate samples were sequenced for quality control, and had a concordance rate of 100%. Laboratory personnel were blinded to case-control status.

Lifestyle risk factors. Body mass index (BMI) was calculated based on self-reported current weight (kg) divided by height in meters squared (kg/m^2). A positive family history of colorectal cancer was defined as reporting colorectal cancer in one or more first-degree relatives. Regular nonsteroidal anti-inflammatory drug (NSAID) use was defined as reporting usage at least twice a week for 6 or more months. Recreational physical activity, as assessed by metabolic equivalents of energy expenditure units (METS) for different life periods (in their 20s, 30s and 40s, and since turning 50) were grouped into three categories as "light" (METS < 3.0), "moderate" (METS = 3-6), and "vigorous" (METS > 6). We chose to use recreational physical activity in the 20s in the regression analysis as this is the variable that showed the strongest association with risk of colon cancer in our study population, and seemed to be closely correlated with overall adult physical activity. Smoking and alcohol were both grouped into "never" and "ever" based on self-reported usage. Ever smoking was defined as smoking at least one cigarette a day for 3 months or longer. Ever use of alcohol was defined as consuming any alcoholic beverages at least once a week for 6 months or longer.

Statistical analysis. We first examined the Hardy-Weinberg equilibrium of allelic distribution separately for the cases and controls, and compared the allele frequencies between cases and controls. We then evaluated the association of *PIK3R1 Met326Ile* genotypes with colon cancer in multivariate unconditional logistic regression models assuming dominant (*Ile/Ile* and *Met/Ile* versus *Met/Met*), additive (*Ile/Ile*, *Met/Ile*, versus *Met/Met)* or recessive (*Ile/Ile* versus *Met/Met* and *Met/Ile*) modes of inheritance, respectively. In our base models, we adjusted for age (at diagnosis for the cases and at recruitment for the controls), gender, and race. In our full model, we further controlled for family history of colorectal cancer, BMI, NSAIDs, alcohol use, smoking, and recreational physical activity in the 20s. We further explored potential effect modification by age in analyses stratified by the cases' median age (≤64 or >64 years) at diagnosis, and tested multiplicative interactions with BMI (centered at the mean), NSAIDs, and family

[5] http://epi.grants.cancer.gov/CFR/about_questionnaires.html

history of colorectal cancer by including the main effects and cross-product terms in a logistic regression model. Statistical significance was assessed via both Wald test and likelihood ratio test, comparing full and reduced models (i.e., with and without the cross-product term). All *P* values were two-sided, and all analyses were undertaken with SAS software (version 9.1; SAS Institute, Inc.).

Results

The majority (93.4%) of the participants were Caucasians (Table 1), consistent with the general population in Kentucky. Cases were older at diagnosis than the controls at recruitment, were more likely to have a positive family history of colorectal cancer, had higher BMI, and reported less regular NSAID use. The *Ile* variant allele was more prevalent among cases (20.1%) than among controls (14.3%). The allele frequency distribution in our control population is comparable with reports by others (18), and conforms to Hardy-Weinberg proportions in both case and control groups ($P > 0.1$).

Table 1. Descriptive characteristics and *PIK3R1 Met326Ile* polymorphism variant frequency of the Kentucky Colon Cancer Genetic Epidemiology Study

	Cases (*n* = 421)	Controls (*n* = 483)
Age (y)*	62.7 ± 10.6	57.6 ± 11.6
Gender (%)		
Female	216 (51.3)	306 (63.2)
Male	205 (48.7)	178 (36.8)
Race (%)		
Caucasian	394 (93.6)	450 (93.2)
African-American	22 (5.28)	21 (4.4)
Other	5 (1.20)	12 (2.5)
BMI †,‡ (kg/m^2)	29.16 ± 6.21	28.10 ± 6.05
Family history †,§ (%)		
Yes	94 (24.0)	72 (15.4)
No	297 (76.0)	395 (84.6)
NSAID use †,‖ (%)		
Regular	235 (64.2)	306 (68.9)
Smoking † (%)		
Ever	207 (54.2)	248 (54.2)
Never	175 (45.8)	210 (45.9)
Alcohol use † (%)		
Ever	134 (35.1)	191 (41.7)
Never	248 (64.9)	267 (58.3)
Physical activity † (%)		
Vigorous	165 (42.7)	247 (53.8)
Moderate	106 (27.5)	98 (21.4)
Light	115 (29.8)	114 (24.8)
PIK3R1 allele frequency (%)		
Met	681 (79.9)	828 (85.7)
Ile	161 (20.1)	138 (14.3)
PIK3R1 genotype frequency (%)		
Met/Met	277 (65.8)	358 (74.1)
Ile/Met	127 (30.2)	112 (23.2)
Ile/Ile	17 (4.0)	13 (2.7)

*Age (mean ± SD) at diagnosis for cases, and age at recruitment for controls.
†Calculations based on 364 cases and 441 controls with available information.
‡BMI (mean ± SD).
§Family history of first-degree relatives with colorectal cancer.
‖NSAIDs: regular = at least twice a week for 6 or more months.

In our base regression model assuming a dominant mode of inheritance, we observed a 47% increase of cancer risk among those carrying at least one copy of the *Ile* variant compared with those homozygous for the *Met* variant ($P = 0.01$; Table 2). Further adjustment for family history of colorectal cancer, BMI, NSAIDs, smoking, alcohol use, and physical activity among the 364 cases and 441 controls with available information strengthened the association [odds ratio (OR), 1.73; 95% confidence interval (CI), 1.24-2.42]. Evaluation of the genotype in the additive mode of inheritance revealed evidence of a significant gene-dose response: compared with those homozygous for *Met/Met*, the OR estimates for those heterozygous (*Met/Ile*) and those homozygous for *Ile/Ile* were 1.68 (95% CI, 1.19-2.37) and 2.27 (95% CI, 0.98-5.29), respectively (P for trend = 0.001). Analysis assuming recessive mode of inheritance was not statistically significant.

Age seems to be an effect modifier, with an estimated OR of 2.10 (95% CI, 1.19-3.70) among those older than 64 years assuming a dominant mode of inheritance, whereas the estimated risk for those 64 years or younger was reduced to nonsignificance (OR, 1.52; 95% CI, 0.99-2.34). Because of the important role of PI3K signaling in insulin sensitivity and inflammation, we also explored the association with BMI and potential multiplicative interactions with BMI and NSAIDs as well as with family history of colorectal cancer, and found no evidence for effect modification or association with BMI (data not shown). Finally, restricting our analyses to Caucasians only revealed very similar results (data not shown).

Discussion

In this population-based case-control study, we found a statistically significant association between the *PIK3Rl Met326Ile* polymorphism and risk of colon cancer. Those carrying two copies of the *Ile* variant had a >2-fold increase of risk, and there was a linear trend for gene-dose response relationship. The risk associated with the *Ile* variant was more pronounced among those older than 64 years. To our knowledge, this is the first study to show a significant association of this functional genetic variant with colon or any type of cancers.

One previous report from the Physician's Health Study found no overall association for the *PIK3R1 Met326Ile* polymorphism with risk of prostate cancer, although stratified analyses were suggestive of a weak protective effect against high grade/stage diseases for carriers of two copies of the 326*Ile* variant (OR, 0.61; 95% CI, 0.17-2.17; ref. 18). To this end, it is noteworthy that although somatic mutations of *PI3KCA*, the gene coding for the catalytic unit of PI3K, have been detected in a number of solid tumors, with the highest frequency in colorectal cancer, there is a lack of evidence of somatic mutations of *PI3KCA* in prostate cancer (19).

Recent studies provide insight into the mechanisms by which the p85α subunit can negatively regulate PI3K signaling (17). The p85α regulatory subunit of PI3K is necessary for the stability and membrane recruitment of the p110 catalytic subunit. However, in its unbound, monomeric form, p85α can limit the extent of PI3K signaling by competing with the p85-p110 dimer for binding to IRS-1 leading to its sequestration in the cytosol.

Table 2. Multivariate unconditional logistic regression estimates of OR and 95% CI for colon cancer

PIK3R1 genotype	Cases/controls*	OR (95% CI)	*P*
Base model †			
Met/Met	277/358	1.0 (referent)	—
Ile/Met or *Ile/Ile*	144/125	1.47 (1.09-2.00)	0.012
Full model/dominant ‡			
Met/Met	277/358	1.0 (referent)	—
Full model/additive ‡			
Met/Met	277/358	1.0 (referent)	
Ile/Met	127/112	1.68 (1.19-2.37)	
Ile/Ile	17/13	2.27 (0.98-5.29)	0.001§
Full model/recessive ‡			
Met/Met and *Ile/Met*	404/470	1.0 (referent)	
Ile/Ile	17/13	1.89 (0.82-4.33)	0.14
Age ≤ 64 (y)‖			
Met/Met	148/249	1.0 (referent)	—
Ile/Met or *Ile/Ile*	78/93	1.52 (0.99-2.34)	0.054
Age > 64 (y)			
Met/Met	129/109	1.0 (referent)	—
Ile/Met or *Ile/Ile*	66/32	2.10 (1.19-3.70)	0.010

*Number of cases and controls.
† Base model adjusted for age, gender, and race.
‡ Full model further adjusted for BMI, family history of colorectal cancer, NSAID use, smoking, alcohol use, and physical activity based on 364 cases and 441 controls with available information.
§ *P* for trend.
‖ Median age at diagnosis for cases; full model with dominant mode.

IRS-1 is a major adaptor molecule that mediates PI3K activation downstream of insulin and insulin-like growth factor-I receptors. A reduction in the gene dosage of p85α is postulated to compromise this dominant negative regulation of IRS-1/PI3K signaling and therefore lead to the hyperactivation of this pathway. The tumor suppressor PTEN, functions through inactivation of the PI3K pathway, and p85α has been shown to regulate PTEN activity directly (20). Furthermore, in the PTEN+/- mouse model, p85α heterozygosity leads to a 2-fold increase in the incidence of intestinal polyps (15). It is therefore consistent that a functional genetic polymorphism of *PIK3R1* that results in reduced p85α protein expression and increased IRS-1 binding would lead to enhanced PI3K signaling and hence cancer development.

Although more than 40 tagging single nucleotide polymorphisms have been reported for the *PIK3R1* gene,[6] in this study, we carried out a focused investigation of the *Met326Ile* variant as that is the only known nonsynonymous coding single nucleotide polymorphism that has been shown to be functional. Others have attempted to evaluate gene-wide association with insulin resistance–related phenotypes or biomarkers using selected sets of tagging single nucleotide polymorphisms, and reported inconsistent results (21–24). In a large female twin study of eight selected tagging single nucleotide polymorphisms, Jamshidi et al. found associations between other single nucleotide polymorphisms in *PIK3R1* with serum leptin levels, body fat, and other measures of insulin resistance, but reported no association for the *Met326Ile* variant (21). An earlier Danish study of 380 young healthy subjects reported a significant association of this variant with insulin sensitivity (22), but the same research group failed to replicate that association in a subsequent study (23). We did not find an association of the *Met326Ile* variant with BMI in our sample.

There are some potential limitations to our study. Controls were randomly recruited regardless of their colon screening status, and it is possible that we included some unscreened controls with asymptomatic adenomatous polyps, a precursor for colon cancer. However, it is important to bear in mind that excluding these participants from the analysis would bias the risk estimate away from the unity. As in all case-control studies, we cannot exclude the possibility of bias in recalling questionnaire-based lifestyle risk factors. Another limitation is the relatively modest participation rate among the controls recruited in our study by random digit dialing. However, it is not conceivable that the controls in our study would have been disproportionately enriched with one allele or another. It is also possible that the sickest individuals with colon cancer were less likely to participate in the study. We attempted to minimize this bias by recruiting incident cases within 3 to 6 months of their diagnosis and by allowing the patients to have blood drawn at scheduled follow-up visits to their personal physicians. Also, we found no difference in stage distribution across the three genotypes among the cases (data not shown). It is thus unlikely that selection bias could have potentially accounted for our observed associations. Moreover, our findings of a protective effect of NSAID use (OR, 0.69; 95% CI, 0.50-0.96, $P = 0.02$) and a positive association with family history of colorectal cancer (OR, 2.13; 95% CI, 1.46-3.11, $P < 0.001$) are in agreement with their well-documented associations with colon cancer (25), lending credibility to our data. In any study of genetic factors, investigators must be concerned

[6] http://www.HapMap.org

about potential bias due to population stratification. We addressed this issue first by adjusting for ethnicity in our analyses. In addition, when restricting our analysis to Caucasians only, we observed results very similar to those presented here. This suggests that our findings were unlikely to be due to population stratification bias.

In summary, we found that the functional *PIK3R1 Met326Ile* polymorphism is associated with an increased risk of colon cancer. This observation is consistent with the dominant negative regulation of PI3K signaling by the p85α subunit, providing important new evidence supporting *PIK3R1* as a novel susceptibility gene in colon cancer.

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Correction: Article on PI3K p85α Genetic Polymorphism and Colon Cancer Risk

In the article by Li et al. entitled "Association between phosphatidylinositol 3-kinase regulatory subunit p85α *Met326Ile* genetic polymorphism and colon cancer risk," published in the February 1, 2008, issue of *Clinical Cancer Research*, a row of data was inadvertently omitted from Table 2. The *Ile*/*Met* or *Ile*/*Ile* data have been restored in the "Full model/dominant" heading, and the corrected table is reproduced below.

Table 2. Multivariate unconditional logistic regression estimates of OR and 95% CI for colon cancer

PIK3R1 genotype	Cases/controls*	OR (95% CI)	*P*
Base model †			
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