Common Genetic Variants of PSCA, MUC1 and PLCE1 Genes are not Associated with Colorectal Cancer

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Abstract

**Background:** Polymorphisms of genes encoding PSCA, PLCE1 and MUC1 have been associated with the risk of different cancers in genome wide association studies (GWAS). Up to date there are limited data on the role of these genetic alterations in colorectal cancer (CRC) development. The aim of this study was to evaluate potential associations between single nucleotide polymorphisms (SNPs) of genes encoding PSCA, PLCE1 and MUC1 and the presence of CRC in European populations. **Materials and Methods:** Gene polymorphisms were analyzed in 574 European subjects (controls: n=382; CRC: n=192). PSCA C>T (rs2294008), PSCA G>A (rs2976392), MUC1 A>G (rs4072037) and PLCE1 A>G (rs2274223) SNPs were genotyped by RT-PCR. **Results:** The distribution of genotypes for all four SNPs was in line with the Hardy-Weinberg equilibrium (rs2294008, P=0.153; rs2976392, P=0.269; rs4072037, P=0.609; rs2274223, P=0.858). The distribution of genotypes and alleles of PSCA C>T, PSCA G>A, MUC1 A>G and PLCE1 A>G SNPs was similar among controls and CRC patient groups (P>0.05). GG genotype of MUC1 SNP was more frequent in CRC patients (24.0%) than in controls (20.2%); however, this association failed to reach significance (OR-1.45, P=0.15). Overall, in the present study SNPs of PSCA (rs2294008, rs2976392), MUC1 (rs4072037) and PLCE1 (rs2274223) genes were not associated with the presence of CRC. **Conclusions:** Gene polymorphisms of PSCA, PLCE1 and MUC1 genes are not associated with the presence of CRC in European subjects.

Keywords: Colorectal cancer - gene polymorphism - PSCA - PLCE1 - MUC1
Potential carcinogenic role of the SNPs of the genes described above was identified in several genome wide association studies (GWAS). The most recent GWAS analysis performed by Tanikawa and colleagues in Japanese population revealed correlation between C allele of rs2294008 in PSCA gene and rs4072037 in MUC1 (Shi et al., 2011; Li et al., 2012a; Tanikawa et al., 2012). Other two GWAS in Chinese population identified rs2274223 variant of PLCE1 gene as the risk factor for esophageal squamous cell carcinoma and gastric adenocarcinoma (Abnet et al., 2010; Wang et al., 2010). Currently, there are very few studies analyzing the association between these SNPs and CRC risks. Rs2274223 of PLCE1 gene was found to have protective effect against CRC development in Chinese population (Li et al., 2012c; Wang et al., 2014), but no significant associations were reported for rs4072037 and rs2294008 variants (Li et al., 2012c; Smith et al., 2012). Recent meta-analysis have confirmed the role of these SNPs for the development of different cancers (Hao et al., 2013; Umar et al., 2013; Zheng et al., 2013), outlining the need of studies on CRC patients.

As discussed above, PSCA, MUC1 and PLCE1 genes have an established role in carcinogenesis. SNPs of these genes have been related to gastric and other gastrointestinal diseases in different GWAS studies and meta-analysis. It is well known that mechanisms of developing different cancers may share common triggers and pathways (Bunney and Katan, 2006). Therefore, we conducted a case-control genotyping study evaluating the association between rs2294008, rs2976392 in PSCA, rs4072037 in MUC1 and rs2274223 in PLCE1 gene and rs4072037 and rs2294008 variants (Li et al., 2012c; Smith et al., 2012). After initial genotyping, 5% of all samples in each group were manually confirmed by visual inspection with the SDS 2.0.5 software compatible with the TaqMan® system. DNA samples were extracted using phenol-chloroform extraction method from peripheral blood mononuclear cells. DNA samples were stored at −20°C until analysis. PSCA C>T (rs2294008), PSCA G>A (rs2976392), MUC1 A>G (rs4072037) and PLCE1 A>G (rs2274223) SNPs were genotyped by using predesigned TaqMan® assays with a 7500TM real-time cycler, in accordance with the manufacturer’s instructions (Life Technologies, CA, USA). Genotype assignments were manually confirmed by visual inspection with the SDS 2.0.5 software compatible with the TaqMan® system. After initial genotyping, 5% of all samples in each group were included in repetitive analysis, which showed 100% concordance rate. Dubious samples had triplet repetitive analysis. Samples that failed to genotype were recorded as undetermined.

### Statistical analysis

All subjects were classified into two study groups: Controls (n=382) CRC (n=192)  P value

| Age Mean ± SD | Controls (n=382) | CRC (n=192) | P value |
|---------------|-----------------|-------------|---------|
| Gender Male, n (%) | 102 (26.7%) | 109 (56.8%) | <0.001 |
| Female, n (%) | 280 (73.3%) | 83 (43.2%) |         |
| TNM staging | | | |
| I, n (%) | - | 9 (5%) | |
| II, n (%) | - | 86 (45%) | |
| III, n (%) | - | 61 (32%) | |
| IV, n (%) | - | 18 (9%) | |
| Unknown, n (%) | - | 18 (9%) | |
| T 1/2 | - | 27 (14%) | |
| 3 | - | 85 (44%) | |
| 4 | - | 61 (32%) | |
| Unknown | - | 19 (10%) | |
| N 0 | - | 96 (50%) | |
| 1 | - | 53 (28%) | |
| 2 | - | 23 (12%) | |
| Unknown | - | 20 (10%) | |
| M 0 | - | 153 (80%) | |
| 1 | - | 23 (12%) | |
| Unknown | - | 16 (8%) | |

CRC - colorectal cancer

### Statistical analysis

All subjects were classified into two study groups:

### Materials and Methods

**Study population**

Patients and controls were recruited during the years 2006-2013 at two university hospitals in Lithuania (Department of Gastroenterology and Department of Surgery; Lithuanian University of Health Sciences, Kaunas) and Latvia (Riga East University Hospital and Digestive Diseases Centre GASTRO, Riga). All CRC cases and control subjects were genetically unrelated. Control subjects were healthy individuals included from the out-patient departments who were referred to gastroenterologists due to dyspeptic symptoms; the inclusion criteria for controls was no history of previous malignancy. Diagnosis and staging of CRC was confirmed by standard laboratory, endoscopic and radiological methods. All CRC patients had histological verification of colorectal adenocarcinoma and were recruited from the out-patient and stationary departments. In total 574 (382 controls, 192 CRC) individuals were included in the study. All patients were of Caucasian origin in a case-control study. There were 223 subjects in Latvian group (160 controls, 63 CRC) and 351 subjects in Lithuanian group (229 controls, 129 CRC). Detailed clinical characteristics of CRC and control study groups are provided in Table 1.

### DNA extraction and genotyping

DNA extraction and genotyping methods are outlined in detail in our previous genotyping studies (Kupcinskas et al., 2011, 2014). In short, genomic DNA from samples was extracted using phenol-chloroform extraction method from peripheral blood mononuclear cells. DNA samples were stored at −20°C until analysis. PSCA C>T (rs2294008), PSCA G>A (rs2976392), MUC1 A>G (rs4072037) and PLCE1 A>G (rs2274223) SNPs were genotyped by using predesigned TaqMan® assays with a 7500TM real-time cycler, in accordance with the manufacturer’s instructions (Life Technologies, CA, USA). Genotype assignments were manually confirmed by visual inspection with the SDS 2.0.5 software compatible with the TaqMan® system. After initial genotyping, 5% of all samples in each group were included in repetitive analysis, which showed 100% concordance rate. Dubious samples had triplet repetitive analysis. Samples that failed to genotype were recorded as undetermined.
controls (n=382) and CRC (n=192). Age was compared using unpaired Student’s t-test and is presented as mean and standard deviations. Quality and statistical analysis of the genotyping data were performed using PLINK software version 1.07 (Purcell et al., 2007). Hardy-Weinberg equilibrium (HWE) was assessed for each of the four SNPs. Differences in allele frequencies between cases and controls were calculated in the combined Lithuanian and Latvian study sample. Association between control and CRC groups with gene polymorphisms was calculated using logistic regression analysis with adjustment for age, gender, country of birth and presented as odds ratios (OR) with 95% confidence intervals (CI). The relative risks for SNPs were studied using allelic, genotypic, dominant and recessive models. Adjusted significance threshold α=0.0125 (0.05/4) was used to eliminate the potential influence of multiple comparisons.

**Results**

**Characteristics of the subjects**

In total 574 individuals were included in the study - 382 controls and 192 CRC patients. There were 223 subjects in Latvian group (160 controls, 63 CRC) and 351 subjects in Lithuanian group (229 controls, 129 CRC). There were no significant differences in terms of gender, age or genotype distribution between Lithuanian and Latvian groups (data not shown); therefore, respective CRC patients and controls were merged in common groups for further analyses. The percentage of males was 56.8% in CRC group, while in control group males accounted only for 26.7% (P<0.001). Control subjects were significantly younger (63.7 ± 10.1) than CRC patients (67.2 ± 10.3) by approximately 3.5 years (P<0.001). Since the distribution of subjects in control and CRC groups differed significantly according to the age and gender, these covariates covariates were included in all further calculations of statistical analysis to eliminate the potential bias.

**Associations of PSCA, MUC1 and PLCE1 SNPs and the risk of CRC**

The observed genotype frequencies for all 4 SNPs were concordant with Hardy-Weinberg equilibrium (rs2294008 P=0.153; rs2976392 P=0.269; rs4072037 P=0.609; rs2274223 P=0.858). The frequencies of genotypes and alleles among controls and CRC patients are presented in Table 2. Overall distribution of genotypes and alleles of the investigated SNPs was similar between the two groups. The distribution of genotypes of PSCA (CC, CT, TT) was 26.5%, 50.1%, 23.3% and 31.4%, 40.3%, 28.3% in control and CRC groups, respectively. PSCA G>A SNP genotype

| SNP | Genotypes/Alleles | Controls (n=382) | CRC (n=192) | aOR | 95% CI | P value |
|-----|-------------------|----------------|------------|-----|-------|---------|
| PSCA C>T a | rs2294008 | CC | 100 | 26.5 | 60 | 31.4 | 1 |
| | | CT | 189 | 50.1 | 77 | 40.3 | 0.74 (0.49-1.18) | 0.173 |
| | | TT | 88 | 23.3 | 54 | 28.3 | 1.09 (0.68-1.75) | 0.710 |
| | | CC vs CT + TT | | | | 0.85 (0.58-1.26) | 0.441 |
| | | CC + CT vs TT | | | | 1.31 (0.87-1.95) | 0.189 |
| | Allele C | 389 | 51.6 | 197 | 51.6 | 1.00 (0.78-1.28) | 0.995 |
| | Allele T | 365 | 48.4 | 185 | 48.4 | |
| PSCA G>A b | rs2976392 | GG | 99 | 27.2 | 56 | 29.3 | 1 |
| | | GT | 180 | 49.5 | 84 | 44.0 | 0.91 (0.59-1.39) | 0.666 |
| | | TT | 85 | 23.4 | 51 | 26.7 | 1.13 (0.69-1.84) | 0.610 |
| | | GG vs GT + TT | | | | 0.98 (0.66-1.46) | 0.936 |
| | | GG + GT vs TT | | | | 1.20 (0.80-1.81) | 0.375 |
| | Allele G | 378 | 51.9 | 196 | 51.3 | | |
| | Allele T | 350 | 48.1 | 186 | 48.7 | 1.02 (0.80-1.33) | 0.845 |
| MUC1 A>G c | rs4072037 | AA | 105 | 29.0 | 47 | 24.5 | 1 |
| | | AG | 184 | 50.8 | 99 | 51.6 | 1.22 (0.79-1.87) | 0.360 |
| | | GG | 73 | 20.2 | 46 | 24.0 | 1.45 (0.87-2.43) | 0.152 |
| | | AA vs AG + GG | | | | 1.29 (0.86-1.93) | 0.223 |
| | | AA + AG vs GG | | | | 1.28 (0.83-1.95) | 0.264 |
| | Allele A | 394 | 54.4 | 193 | 50.3 | 1.18 (0.92-1.51) | 0.187 |
| | Allele G | 330 | 45.6 | 191 | 49.7 | |
| PLCE1 A>G d | rs2274223 | AA | 147 | 39.1 | 77 | 40.1 | 1 |
| | | AG | 173 | 46.0 | 91 | 47.4 | 0.98 (0.67-1.44) | 0.930 |
| | | GG | 56 | 14.9 | 24 | 12.5 | 0.86 (0.49-1.51) | 0.601 |
| | | AA vs AG + GG | | | | 0.95 (0.66-1.37) | 0.799 |
| | | AA + AG vs GG | | | | 0.87 (0.52-1.46) | 0.597 |
| | Allele A | 467 | 62.1 | 245 | 63.8 | | |
| | Allele G | 285 | 37.9 | 139 | 36.2 | 0.93 (0.72-1.20) | 0.575 |

CRC, colorectal cancer; aOR, adjusted OR (age, sex, country); CI, confidence interval; n, sample size; a 6 individuals failed to be genotyped for rs2294008; b 19 individuals failed to be genotyped for rs2976392; c 20 individuals failed to be genotyped for rs4072037; d 6 individuals failed to be genotyped for rs2274223.
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rs2294008 and the risk of CRC (Smith et al., 2012). Our data controls and found no associations of this polymorphism in Asian individuals (Fu et al., 2012). In vitro experiments revealed the importance of rs2294008 on transcriptional activity, which may even have clinical implications in the future (Kohaar et al., 2013). To date, there was only one attempt to associate rs2294008 polymorphisms of PSCA gene with CRC in European subjects. Smith and colleagues performed a study in 388 CRC patients and 496 controls and found no associations of this polymorphism and the risk of CRC (Smith et al., 2012). Our data support the findings of the later study, as rs2294008 and rs2976392 were not related with CRC development. Based on the currently available data, these SNPs are unlikely to have a role in a CRC development in Caucasians, but larger studies including patients from different ethnic backgrounds are desirable.

MUC1 A>G SNP (rs4072037) was associated with gastric cancer development in GWAS analysis. MUC1 gene polymorphism increased diffuse-type gastric cancer risk with an OR of 1.66 and genotypes of this SNP affected promoter activity (Suiki et al., 2011). A recent large meta-analysis study of 6,580 gastric cancer cases and 10,324 controls including both Asian and European populations showed that G allele of rs4072037 polymorphism was associated with decreased risk of gastric cancer (OR = 0.72) (Zheng et al., 2013). Recent publications showed that genetic variation of MUC1 may be associated with ovarian cancer (Williams et al., 2014) and esophageal cancer (Palmer et al., 2012). In the only case-control study including CRC patients (Li et al., 2012c) rs4072037 showed a marginal association in Chinese population (OR 0.69, P=0.06). The findings of our work show that MUC1 SNP is not related to CRC development in European population; however, currently no comparison of our results to the other Caucasian populations can be made and further studies are warranted.

The studies conducted in Chinese population found that rs2274223 of PLCE1 gene was associated with CRC development (Li et al., 2012b; Wang et al., 2014). A case-control research including 417 CRC patients and 416 controls reported that carriers of AG and GG genotypes had an increased risk for CRC. This study also showed that lower levels of PLCE1 mRNA were observed both in carriers of AG and GG genotypes (Wang et al., 2014). Similar results were obtained in a study by Li and colleagues which reported a significant association between rs2274223 and CRC (Li et al., 2012b). The results of our study do not support these findings as the distribution differences of genotypes and alleles between CRC and control groups were not present. Inconsistent findings between previous studies and our results might be related to ethnical differences as this is a common phenomenon in genetic associations studies (Dura et al., 2013). Unfortunately, due to the lack of studies, no comparison for our results can be made in terms of other Caucasian populations. GWAS conducted on gastric and esophageal cancer patients have shown an evident role of rs2274223 gene polymorphism (Abnet et al., 2010; Wang et al., 2010); these findings were confirmed in subsequent replication studies (Palmer et al., 2012) and recent meta-analysis (Hao et al., 2013; Umar et al., 2013). Nevertheless, the ultimate role of this SNP in CRC development needs further investigation in large scale studies.

The results of this study suggest that none of the four investigated polymorphisms in PSCA, MUC1 and PLCE1 genes are associated with the risk of CRC. Rs2294008, rs2976392, rs4072037 and rs2274223 variants do not appear as potential diagnostic markers for CRC. Our results are discordant with the results presented by Li and colleagues which associated rs2274223 with CRC risks, but the different outcomes of the studies could be related...
to different ethnic backgrounds (Li et al., 2012b).

We admit that our case-control genotyping study has some limitations. First of all, the size of the population is not large and may be underpowered to detect subtle associations. Although there were gender and age differences between CRC and control groups, these factors were included as covariates in the statistical logistic regression analysis, thus minimizing the potential bias. Due to a relatively small number of individuals we were not able to carry out a subanalysis stratifying CRC patients according to TNM stage, tumor localization in the colon, differentiation grade etc. Survival data were available only for a small part of subjects; therefore, we did not perform SNP-survival association analysis. Our study was not designed to evaluate the potential gene expression changes in relation to the SNPs and this might be aimed in further research projects. The results of our study did not reveal significant associations; nevertheless, this data may contribute to the future meta-analysis of case-control studies in the field.

In conclusion, gene polymorphisms of PSCA, PLCE1 and MUC1 genes are not associated with the presence of CRC in European subjects.

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