RESEARCH ARTICLE

RPSA Gene Mutants Associated with Risk of Colorectal Cancer among the Chinese Population

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Abstract

The primary aim of this study was to evaluate the relationship of single nucleotide polymorphisms (SNPs) in ribosomal protein SA (RPSA) gene with colorectal cancer (CRC). A case-control study including 388 controls and 387 patients with CRC was conducted in a Chinese population. Information about socio-demography and living behavior factors was collected by a structured questionnaire. Three SNPs (rs2133579, rs2269349, rs7641291) in RPSA gene were genotyped by Illumina SnapShot method. Multiple logistic regression models were used for assessing the joint effects between tea consumption and SNPs on CRC. The subjects with rs2269349 CC genotype had a decreased risk for CRC (OR=0.60; 95%CI = 0.37-0.99), compared with TT/CT genotype after adjustment for covariates. A similar association of rs2269349 with rectal cancer was observed (OR=0.49; 95%CI=0.24-1.00). Further analyses indicated that this SNP could modify the protective effect of tea drinking on CRC. Among the subjects with rs2269349 TT/CT or rs2133579 AA/GA, there was a marginal significantly lower risk of CRC (OR and 95%CI: 0.63 and 0.39-1.01 for rs2269349; 0.64 and 0.40-1.02 for rs2133579) in tea-drinking subjects in comparison to non-tea-drinking subjects. Mutants in the RPSA gene might be associated with genetic susceptibility to CRC and influence the protective effect of tea consumption in the Chinese population.

Keywords: RPSA - association - single nucleotide polymorphism (SNP) - colorectal cancer

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the leading cause of cancer mortality in western countries (Siegel et al., 2012). During the past several decades, the incidence of colorectal cancer was changed remarkably in Asian countries. China, Japan, and South Korea have experienced an increase of two to four times in the incidence of CRC (Sung et al., 2005). From 2000 to 2005, the total number of CRC cases increased by 19.1% and 17.7% in Chinese males and females, respectively (Yang et al., 2005). Numerous studies have indicated that both genetic and environmental factors are involved in the etiology of CRC. However, the accurate genetic and environmental risk factors of CRC remain to be elucidated.

Tea drinking has been one of these factors as a living behavior, as a common daily beverage, teas was consumed by over two-thirds of the population worldwide. In China, tea drinking is a conventional lifestyle among adults, including green tea and black tea. Green tea contains a high level of polyphenols known as catechins, such as epigallocatechin-3gallate, epigallocatechin, and epicatechin-3 gallate (-)- Epigallocatechin-3- O- gallate (EGCG), and EGCG is the main catechin containing in the leaves, and it is the most significant compound which attributes to the health benefit. EGCG was also reported to have anti-oxidative (Sang et al., 2005), anti-mutagenic (Wang et al., 1989), anti-inflammatory (Lin and JK Lin, 1997), and anti-carcinogenic activities (Qiao et al., 2009). However, the effects of tea consumption on CRC are inconsistent in previous epidemiologic studies. A case–control study reported that the risk of colon cancer was significantly higher in subjects with the highest levels of tea intake than those with the lowest levels of tea consumption (Kato et al., 1990). Recently, a meta-analysis indicated that tea consumption was associated with a modest increased risk of colon cancer in 13 prospective cohort studies conducted in North America and Europe (Zhang et al., 2010). Observed from some case–control and cohort studies, the risk of CRC was reduced by 30%–40% for people who drink green tea (Kato et al., 1990; Ji et al., 1997; Yang et al., 2007), but there's no association between tea drinking and CRC risk in other studies (Nagano et al., 2001; Lee et al., 2007; Sun et al., 2007). Therefore, the association between tea consumption and the CRC risk is still vague.

Ribosomal protein SA (RPSA), which is also called 37

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kDa laminin receptor precursor/67 kDa laminin receptor, is a protein with 295 amino acids coded by RPSA gene and the amino acid sequence of RPSA shares high homology in mammals (Qiao et al., 2009). RPSA has been notably identified as a cell-surface EGCG receptor capable of mediating the anti-tumor effects of EGCG in vivo (Tachibana et al., 2004; Umeda et al., 2008; Tsukamoto et al., 2012). Recently, Fujimura (Fujimura et al., 2012) identified that the RPSA extracellular domain was corresponding to the 161–170 region as the EGCG binding site. RPSA is a non-integrin laminin receptor and known to be over expressed on the cell surface of various tumor cells. The expression of RPSA confers EGCG responsiveness to tumor cells, and the expression level of this protein strongly correlates with the risk of tumor invasion and metastasis (Menard et al., 1997). Thus, it was assumed that RPSA plays a significant role in the tumor progression (Martignone et al., 1993; Menard et al., 1997). Previous studies reported that RPSA interacted with many ligands, but the underlying interaction mechanism had not been elucidated yet (Gauczynski et al., 2001; Thepparit and Smith, 2004; Kim et al., 2005; Akache et al., 2006; Gauczynski et al., 2006). In addition, the crystal structure of the partial domain of human RPSA was discovered and it might suggest the function of RPSA and facilitate the design of novel therapeutics targeting RPSA (Jamieson et al., 2008). Also, EGCG-RPSA interaction and RPSA-mediated functions of EGCG has been found, and mimicking the EGCG-RPSA interaction could help the development of potential anti-cancer compounds for chemoprevention or therapeutic (Tachibana et al., 2004). However, the effect of the interaction of EGCG with RPSA in CRC remains unclear and there's no specific report of population study focused on the associations between RPSA gene polymorphisms and CRC.

There were two aims of the present study, one is to assess whether tea consumption, RPSA gene polymorphisms were individually associated with the risk of CRC; and the other is to study whether tea consumption induced the protective effect of RPSA gene polymorphisms against CRC in a Chinese community-based population.

Materials and Methods

Study Population

The detailed population information of this case–control study had been described in our previous publication (Zhang et al., 2009). The registry information of this population was initially collected for a cohort study on colorectal cancer in 1989 in Jiashan County, Zhejiang Province, China. In addition, a cancer surveillance and registry system covering the whole county was established for reporting new cancer patients of colorectal cancer and all other kinds of cancers. All the participants were ethnic Han Chinese, although there were no restrictions on patients' age, gender or tumor stage, only those patients who were free of metastases or other cancers were included in our study, whereas subjects with other malignant diseases were excluded from this study. In total, a number of 387 eligible CRC cases based on the surveillance and registry system, were recruited in this study. Cancer-free controls (388) were randomly selected from the same population during the same period, matched by age (±5years), gender and residential location with cases. The study protocol was approved by the Medical Ethical Committee of Zhejiang University School of Medicine.

There were several qualitative methods applied to collect the data. A face-to-face interview was conducted by well-trained interviewers using a structured questionnaire involving socio-demographic characteristics (e.g., age, sex, occupation, marital status and education level), lifestyle (e.g., cigarette smoking habits, alcohol drinking and tea drinking), dietary history (e.g., intake frequencies of red meat, salted meat, vegetable and milk) , medical history, and family history of cancer, after the written informed consent was obtained from the study subjects. The definition of a smoker was a person who had smoked at least once per day for more than 1 year, and an alcohol drinker was defined as an individual who consumed alcohol at least once per day for over 3 months, and a tea drinker was defined as an individual who consumed tea no less than once per day for at least 3 months.

Venous blood specimen was also collected, by using a vacuum tube containing Ethylene Diamine Tetraacetic Acid (EDTA) anticoagulation, 5 ml for each subject. All the samples were transferred in a cooling box within 30 min, and stored at –80°C until DNA extraction.

SNP Selection and Genotyping

Genomic DNA was isolated from peripheral blood samples using the modified salting-out procedure (Nasiri et al., 2005), and stored at -80 °Cfor genotyping. Candidate single nucleotide polymorphisms (SNPs) were selected by the following criteria: a) minor allele frequency (MAF) was more than 0.1 based on HapMap Chinese dataset of SNP; b) Tag SNP were chosen from HapMap dataset; c) pairwise r^2 >0.8. We employed Haploview software to implement Paul de Bakker's Tagger tag SNP selection algorithm and then three SNPs in RPSA (rs2133579, rs2269349 and rs7641291) were selected. Genotypes for RPSA polymorphisms were detected by Illumina SnapShot method. In addition, 5% of the samples were randomly selected and genotyped repeatedly, and a concordance rate reached 100%.

Statistical Analyses

Category and continuous variables of socio-demographic characteristics between the cases and controls were tested by χ^2 test and Student's t-test, respectively. Hardy–Weinberg equilibrium was tested for all SNPs among the control group. The associations of the risk of CRC, colon and rectal cancer with each SNP and tea consumption (yes/no) were performed respectively. The joint association of SNP in RPSA gene and tea consumption on CRC were also evaluated, using multivariate unconditional logistic regression models with adjustment for potential confounding factors, including age (continuous), gender (male/female), BMI (<median,>median), education (illiterate, primary school, middle school or above), occupation (farmers/

Table 1. The Distribution of Demographic Characters among Cases and Controls

Variables	Cases	Controls	*P*
N	387	388	
Age, year (Mean ± SD)	63.3 ± 11.5	62.9 ± 11.1	0.613
BMI, kg/m2 (Mean ± SD)	22.1±3. 5	22.4±3.1	0.262
Gender, n(%)			
Male	203(52.5)	203(52.3)	0.969
Female	184(47.6)	185(47.7)	
Education, n(%)			
Illiterate	217(56.1)	197(50.8)	0.287
Primary school	125(32.3)	134(34.5)	
Middle school or above	45(11.6)	57(14.7)	
Occupation, n(%)			
Farmers	354(91.5)	361(93.0)	0.396
Non-farmers	33(8.5)	27(7.0)	
Marital status, n(%)			
Married	322(83.2)	328(84.5)	0.625
Unmarried	65(16.8)	60(15.5)	
Current smoking, n(%)			
No	254(65.5)	247(63.5)	0.547
Yes	133(34.5)	141(36.5)	
Alcohol consumption, n(%)			
No	289(74.7)	295(76.0)	0.692
Yes	98(25.3)	93(24.0)	
Tea drinking, n(%)			
No	242(62.5)	222(57.2)	0.122
Yes	145(37.5)	166(42.8)	
Physical activity, n(%)			
No	355(91.7)	349(89.9)	0.416
Yes	32(8.3)	39(10.1)	

non-farmers), marital status (married/unmarried), current smoking (yes/no), tea drinking (yes/no), alcohol drinking (yes/no), the intake frequencies of red meat, salted meat, vegetable, milk and physical activity. The analyses were conducted using Statistical Analysis System software version 9.2 (SAS Institute Inc, Cary, North Carolina) and the Statistic significant threshold was *P* value less than 0.05.

Results

Table 1 showed the distributions of socio-demographic characteristics among CRC patients and control group. 387 patients with CRC and 388 well-matched controls were finally included in the analyses. There was no significant difference of the average age between CRC group and control group. The frequencies of gender, occupation, marital status, current smoking and alcohol drinking were comparable between cases and controls. Nevertheless, CRC patients had lower BMI, lower education level and lower experience of drinking tea and physical activity than control while there was no significant difference. All SNPs met Hardy-Weinberg equilibrium.

The associations of RPSA gene polymorphisms with CRC were presented in Table 2. In comparison with subjects with TT/CT of rs2269349 in RPSA, the subjects with rs2269349 CC genotype had a significantly lower risk of CRC (OR=0.60; 95%CI: 0.37-0.99), after adjustment for covariates. The similar association of rs2269349 with rectal cancer was also observed (OR=0.49, 95%CI=0.24-1.00) (Table 3). However, there were no significant

Table 2. The Association of SNPs in RPSA with CRC Risk, Respectively

Genotype	Cases, n(%)	Controls, n(%)	Adjusted	
			OR(95%CI)	*P*
rs2133579				
AA/GA	360(94.2)	351(91.9)	1	--
GG	22(5.8)	31(8.1)	0.75(0.41,1.36)	0.339
rs2269349				
TT/CT	348(91.1)	328(85.9)	1	--
CC	34(8.9)	54(14.1)	0.60(0.37,0.99)	0.046
rs7641291				
AA	331(86.7)	317(83.0)	1	--
GA/GG	51(13.3)	65(17.0)	0.76 (0.49,1.18)	0.223
Tea Drinking				
No	237(62.0)	216(56.5)	1	
Yes	145(38.0)	166(43.5)	0.69(0.45,1.00)	0.053

Adjusted for age, sex, BMI, tea drinking, alcohol drinking, smoking, education, occupation, marital status, physical activity, intake frequency of red meat, salted meat, vegetable, garlic and milk; **P*<0.05 (statistic significance)

Table 3. The Association of SNPs in RPSA (rs2133579, rs2269349 and rs7641291) with Risk of Colon Cancer and Rectal Cancer, Respectively

Genotype	Cases, n(%)	Controls, n(%)	Adjusted	
			OR(95%CI)	*P*
Colon cancer				
rs2133579				
AA/GA	177(93.2)	173(91.1)	1	--
GG	13(6.8)	17(8.9)	0.73(0.32,1.69)	0.463
rs2269349				
TT/CT	171(90.0)	164(86.3)	1	--
CC	19(10.0)	26(13.7)	0.62(0.30,1.29)	0.202
rs7641291				
AA	169(88.9)	160(84.2)	1	--
GA/GG	21(11.1)	30(15.8)	0.64(0.33,1.24)	0.188
Rectal cancer				
rs2133579				
AA/GA	187(94.9)	184(92.9)	1	--
GG	10(5.1)	14(7.1)	0.73(0.30,1.80)	0.496
rs2269349				
TT/CT	181(91.9)	170(85.9)	1	--
CC	16(8.1)	28(14.1)	0.49(0.24,1.00)	0.051
rs7641291				
AA	167(84.8)	163(82.3)	1	--
GA/GG	30(17.7)	35(17.7)	0.81(0.45,1.46)	0.488

Adjusted for age, sex, BMI, tea drinking, alcohol drinking, smoking, education, occupation, marital status, physical activity, intake frequency of red meat, salted meat, vegetable, garlic and milk

associations between CRC risk and the other two SNPs (rs2133579 and rs7641291).

The modified effects of RPSA gene SNPs on the protective effect of tea drinking for CRC susceptibility were shown in Table 4. 382 cases and 382 controls had been analyzed except 5 cases and 6 controls had no information on tea drinking.. Among the subjects with rs2269349 TT/CT genotype, after adjustment for covariates, a lower risk of CRC (OR=0.63, 95%CI= 0.39-1.01) was found in tea-drinking subjects in comparison to non-tea-drinking subjects, but this protective effect of

Table 4. The Joint Effects Between Tea Drinking and RPSA Gene Polymorphisms on CRC, Respectively

Genotype	Tea drinking	Cases, n(%)	Controls, n(%)	Adjusted OR(95%CI)	*P*
rs2133579					
AA/GA	No	224(62.2)	198(56.4)	1	--
	Yes	136(37.8)	153(43.6)	0.64(0.40,1.02)	0.058
GG	No	13(59.1)	18(58.1)	1	--
	Yes	9(40.9)	13(41.9)	1.49(0.18,12.79)	0.714
rs2269349					
TT/CT	No	221(63.5)	187(57.0)	1	--
	Yes	127(36.5)	141(43.0)	0.63(0.39,1.01)	0.055
CC	No	16(47.1)	29(53.7)	1	--
	Yes	18(52.9)	25(46.3)	1.20(0.23,6.15)	0.826
rs7641291					
AA	No	208(62.8)	182(57.4)	1	--
	Yes	123(37.2)	135(42.6)	0.69(0.42,1.13)	0.137
GA/GG	No	29(56.9)	34(51.5)	1	--
	Yes	22(43.1)	31(48.5)	0.83(0.26,2.67)	0.759

Adjusted for age, sex, BMI, tea drinking, alcohol drinking, smoking, education, occupation, marital status, physical activity, intake frequency of red meat, salted meat, vegetable, garlic and milk

tea-drinking was not observed among subjects with CC genotype. The similar results were also observed in SNP rs2133579, tea-drinking subjects with AA/GA genotype had a decreased risk of CRC than non-tea-drinking subjects with AA/GA genotype (OR=0.64; 95%CI: 0.40-1.02), but this effect was not found among subjects with GG genotype.

Discussion

The findings of the present study suggested that a tag SNP (rs2269349) of RPSA gene was significantly associated with CRC susceptibility. Additionally, the single nucleotide polymorphisms (rs2269349, rs2133579) of RPSA gene might influence the protective effect of tea drinking on CRC risk.

The human Ribosomal Protein SA belongs to the ribosome, which is a membrane receptor for laminin, growth factors, prion, pathogens and EGCG. The expression level of RPSA strongly correlates with the risk of tumor invasion and metastasis (Menard et al., 1997). RPSA was up-regulated in the progression of human colorectal carcinomas and might play a role in the local and metastatic progression of this tumor, and our results further indicated a protective effect of SNP rs2269349 of RPSA gene against CRC risk. SNP rs2269349 is located in the 3'UTR region of RPSA gene, and the 3'UTR region of functional gene is an important region for gene expression or stability. The function of the SNP rs2269349 is unclear, and no previous study has reported that the SNP of RPSA gene was involved in the genetic susceptibility of CRC. But, as a 3'UTR region SNP, the rs2269349 itself may be a potential functional SNP to influence the genetic susceptibility of CRC, or it is just as a surrogate biomarker for other functional SNP to associated with the CRC risk.

A number of studies (Kuzuhara et al., 2007; Hakim et al., 2008; Kawai et al., 2008) had demonstrated that tea drinking was a protective factor for CRC risk. The most active constituents of green tea were EGCG, which accounted for almost 50% of the total catechin content in green tea extract, and it had very potent antioxidant effects. These green tea catechins (particularly EGCG) were reported to induce apoptosis and cell cycle arrest in cancer cells (Sang et al., 2005). However, some epidemiological studies have reported the null association between green tea drinking and CRC risk (Nagano et al., 2001; Sun et al., 2007; Umeda et al., 2008; Tsukamoto et al., 2012). The inconsistent results from studies based on different populations indicated that the genetic factors may involve in the protective effect of tea drinking on CRC susceptibility. SNP rs2133579 is located in 5'near gene region of RPSA, and the 5'near gene region of functional gene is important for regulating gene expression. There was no previous study focused on the function of SNP rs2133579, and RPSA has been notably identified as a cell-surface EGCG receptor capable of mediating the anti-tumor effects of EGCG in vivo, so our data suggested that the two tag SNPs (rs2269349 and rs2133579) from the EGCG receptor gene (i.e. RPSA gene) might be the potential modifying factors for the protective effect of tea consumption on CRC. Tachibana (H Tachibana et al., 2004) had maintained that there is co-regulation of EGCG and RPSA, and there's potential sensing motif on the extracellular domain of RPSA contributed to the inhibitory effect of EGCG on cancer cell proliferation. The findings of the present study provide potential epidemiological evidence for modified effect of the RPSA gene polymorphisms on the anti-cancer action of tea-drinking mediated by EGCG.

There are several limitations in this study. Firstly, due to the relatively small sample size, the statistical power may not be adequate to detect the weak gene-disease association. Secondly, the quantity and duration information of tea consumption were not considered in the analysis. It may distort the association of tea drinking and CRC. Thirdly, the functions of the selected polymorphisms in RPSA gene have not been explored, and we cannot assure whether the genotyped mutants in RPSA gene could affect the expression level or function of RPSA protein.

In conclusion, the present study explored the associations of CRC risk with three SNPs in RPSA gene, and the potential modifying effect of these SNPs on the protective action of tea consumption on CRC risk in a community-based Chinese population. The data showed that SNP rs2269349 in RPSA gene was associated with the risk of CRC. Additionally, the result also suggests that two SNPs of RPSA gene might modify the protective effect of tea consumption against CRC in human population. Therefore, further research should be implemented to confirm this potential relationship in future.

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