Cyclin D1 G870A polymorphism and risk of colorectal cancer: A case control study

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Abstract. The present study aimed to analyse the role of *cyclin D1* A870G polymorphism in modulating the susceptibility to colorectal cancer (CRC) in the Kashmiri population. The genotype distribution of the *cyclin D1* gene in 130 CRC cases in comparison with 160 healthy controls was investigated. No direct significant association between *cyclin D1* genotypes and CRC was observed; however, the AG and AA genotypes were found to be associated with an increased risk of CRC compared to the GG genotype, with an almost 2-fold increase in OR. This study suggests that the *cyclin D1* polymorphism is associated with an increased risk of CRC in the Kashmiri population.

Introduction

Cyclin D1 (*CCND1*) is a key regulatory protein that plays a vital role in cell cycle control, particularly in the transition from G1 to S phase, which is regulated by cyclin-dependent kinases (1). It results in the release of E2F transcription factors and allows cells to enter the S phase (2).

Located on chromosome 11q13 (3), the *cyclin D1* gene activation (due to amplification or chromosomal rearrangement), as well as its protein overexpression have been described in a wide variety of tumour types, including colon (4-6), breast (7,8), head and neck (9,10) and lung (11,12) cancer, as its abnormal expression disrupts normal cell cycle control, hence possibly promoting the development and progression of cancer (13).

Single nucleotide polymorphism (SNP) of *cyclin D1* at G870A has been studied in various cancers (14-20), demonstrating its role in modulating the risk of cancers in different populations.

This common G to A polymorphism in the splice donor region of exon 4 in the *cyclin D1* gene located at codon 242 (nucleotide 870) is implicated on the splicing of the *cyclin D1* transcript (14,21). The dominant allele A preferentially transcribes the truncated transcript (transcript b), encoding a *cyclin* D1 protein with a longer half-life. The transcript b results in deregulated cell proliferation since it lacks a PEST sequence postulated to target for rapid degradation (22). The higher levels of this protein may be associated with proliferation and a great risk of developing adenomas and cancer. The allele A, particularly in the homozygous state (AA genotype), has been associated with an increased risk of colorectal cancer (CRC) and adenomas, mostly in younger patients and in patients with family history of the illness (23,24). However, no association was found between the AG or GG genotypes (25,26) and others (27,28). The role of *cyclin D1* SNP in CRC risk remains controversial.

In the present case-control study we evaluated the potential impact of *cyclin D1* (G870A) gene polymorphism on the risk of CRC in the Kashmiri population. We also investigated whether or not there was a link between the clinicopathological variables of the *cyclin D1* variant genotype (AA), as well as its role in modulating the risk of CRC.

Materials and methods

Population study. This study comprised 130 CRC cases. All the participants were patients of the Department of General Surgery of the Sher-I-Kashmir Institute of Medical Sciences in Kashmir. Blood samples were collected from 160 age- and gender-matched individuals, with no signs of any malignancy, serving as external controls. The mean age of both the patients and the control group was 53 years (Table I).

Data on all CRC patients were obtained from personal interviews with patients and/or their guardian, as well as from their medical records. All patients and/or guardians were informed of the study and they provided written consent in the form of a pre-designed questionnaire (available on request). The collection and use of blood samples (from patients and

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Table I. Demographic and clinical characteristics of study subjects.

Variable	CRC cases (n=130)	Healthy controls (n=160)	P-value
Age group			
≤50	48 (36.9%)	56 (35.0%)	0.80
>50	82 (63.1%)	104 (65.0%)	
Gender			
Female	54 (41.54%)	72 (45.0%)	0.63
Male	76 (58.46%)	88 (55.0%)	
Dwelling			
Rural	91 (70.0%)	104 (65.0%)	0.38
Urban	39 (30.0%)	56 (35.0%)	
Smoking status			
Ever	81 (62.3%)	90 (56.3%)	0.33
Never	49 (37.7%)	70 (43.7%)	
Tumour location			
Colon	52 (40.0%)		
Rectum	78 (60.0%)		
Tumour grade			
Well-differentiated	98 (75.4%)		
Moderately/poorly differentiated	32 (24.6%)		

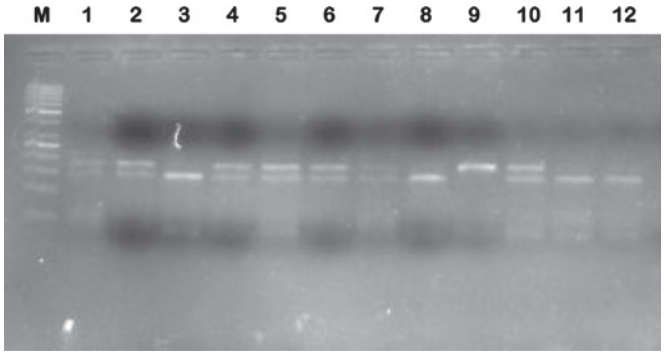

Figure 1. Representative gel of *cyclin D1* A870G polymorphism, representing amplicon digest with MspI (ClCGG), where variant (AA) is cleaved to generate a visible 175-bp band and wild-type (GG) is cleaved to generate a visible 141-bp band. Lanes: M, 50-bp ladder; 3, 8, 11 and 12, homozygous wild-type (GG) form; 1, 2, 4, 5, 6, 7 and 10, heterozygous (AG) form; 9, homozygous (AA) variant form.

controls) for this study was approved by the appropriate institutional ethics committee.

DNA extraction and polymerase chain reaction (PCR). DNA extraction was performed using the ammonium precipitation method. Genotyping for the *cyclin D1* A870G polymorphism was determined by the method described previously by Satinder *et al* (3). The oligonucleotide primers used for the amplification of the target region were: forward 5'-AGT TCATTTCCAATCCGCCC-3' and reverse 5'-TTTCCGTGGCACTAGGTGTC-3'. PCR was carried out in a final volume of 20 μl, containing 50 ng genomic DNA template, 1X PCR buffer (Fermentas, MD, USA), with 2 mM $MgCl_2$, 0.5 μM of each primer (Sigma-Aldrich, Bangalore, India), 50 μM deoxynucleotide triphosphates (dNTPs) (Cinnagen, Tehran, Iran) and 0.25 units of Taq DNA polymerase (Invitrogen, Bangalore, India). For PCR amplification, the standard program was used as follows: one initial denaturation step at 94˚C for 7 min, followed by 40 denaturation cycles of 30 sec at 94˚C, 30 sec of annealing at 60˚C and 30 sec of extension at 72˚C for 40 cycles, followed by a final elongation cycle at 72˚C for 7 min.

The PCR product of *cyclin D1* was 212 bp in length and was then digested with 2 units of *MspI* in a reaction mixture of 20 μl for 3 h at 37˚C. The digestion resulted in the generation of 3 bands of 141, 37 and 34 bp for the wild genotype (GG), whereas for the homozygous variant genotype (AA) 2 bands of 175 and 37 bp were produced (Fig. 1).

DNA amplicons, as well as the digestion products, were electrophoresed through a 2-3% agarose gel (Genie, Bangalore, India) for resolution. The genotypes of >20% of the samples were reassessed in a double-blind manner by 2 independent researchers to confirm the results. A positive control for each polymorphism was used for 50% of the samples.

Statistical analysis. The observed frequencies of genotypes in CRC patients were compared with controls using Chi-square or Fisher's exact (FET) tests, when the expected frequencies were small. The Chi-square test was used to verify whether or not the genotype distributions were in Hardy-Weinberg equilibrium. P≤0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using PASW version 18 software.

Results

The present study comprised 130 CRC cases and 160 control subjects. The patients comprised 76 males and 54 females

Table II. Genotype frequencies of *cyclin D1* gene polymorphism in CRC cases and controls.

Cyclin D1 genotype	CRC cases (n= 130)	Controls (n=160)	OR (95% CI) P[a],F[b]	P-value (overall)
Co-dominant inheritance				
GG (wild)	19 (14.6%)	41 (25.6%)	1.0 (Ref)	5.31;0.07
AG (heterozygous)	70 (53.9%)	76 (47.5%)	1.99 (1.05-3.74); **0.03; 0.04**	
AA (variant)	41 (31.5%)	43 (26.9%)	2.05 (1.03-4.10); **0.03; 0.05**	
Dominant inheritance				
GG	19 (14.6%)	41 (25.6%)	1.0 (Ref)	
AG + AA	111 (85.4%)	119 (52.5%)	2.01 (1.10-3.68); **0.02; 0.03**	
Recessive inheritance				
GG + AG	89 (68.5%)	117 (73.1%)	1.0 (Ref)	
AA	41 (31.5%)	43 (26.9%)	1.25 (0.75-2.08); 0.38; 0.44	

[a]Pearson's p-value; [b]Fisher's exact p-value; statistically significant p-values in bold. CRC, colorectal cancer.

(M/F ratio=1.41), while the control subjects were 88 males and 72 females (M/F ratio=1.2). The mean age in the patient and control groups was 52 years. No significant gender- or age-related differences were observed between the groups (p>0.05). Furthermore, out of 130 confirmed cases of CRC, 125 cases were sporadic, 4 were familial adenomatous polyposis and one case was hereditary non-polyposis (Lynch Syndrome) CRC. All but one case had adenocarcinoma, one had squamous cell carcinoma of the basal cell type, and 52 had carcinoma in the colon, while 78 had carcinoma in the rectum. A total of 78 resided in rural areas, while 39 resided in urban areas; 81 were smokers and 49 non-smokers (Table I).

Among the CRC cases, we found the frequency of the *cyclin D1* genotype to be 14.61% (19/130) for GG, 53.85% (70/130) for AG and 31.54% (41/130) for AA, while the frequency in the general control population was 25.62% (41/160) for GG, 47.50% (76/160) for AG and 26.88% (43/160) for AA. The overall association between the *cyclin D1* polymorphism and the CRC cases was found to be non-significant (p>0.05; Table II). However, a separate analysis for the AG and AA genotypes revealed a marked association with the risk of CRC (p<0.05). The overall hazard ratio of the *cyclin D1* A allele in CRC was 2.01 (95% CI=1.10-3.68).

The correlation between the *cyclin D1* polymorphic status and the clinicopathological characteristics was also carefully analysed. A marked association (p<0.05) was observed among the A allele, age and dwelling (p<0.05; Table III), while the remaining parameters were not found to be markedly associated with the variant A allele of the *cyclin D1* gene.

Discussion

The Kashmiri population is exposed to a special set of environmental and dietary risks, such as exposure to nitroso compounds or amines and nitrates reported to be present in local foodstuffs, most of which have been shown to contain important irritants and carcinogens (29-32).

CRC is the third most common cancer in males and the second in females worldwide (33). In the Kashmir valley, it represents the third most common gastrointestinal tract (GIT) cancer, following oesophageal and gastric cancer (30,31,34).

The *cyclin D1* A870G polymorphism has 3 distinct genotypes: GG (wild-type), AG and AA (variants). All 3 forms synthesise similar proteins due to their identical biological functionality. However, the difference among the genotypes is the capability of A allele to cause the truncation of the transcript, which in turn increases the half-life of the resulting protein (1,28).

In the present study, we investigated the association between the *cyclin D1* A870G polymorphism and CRC in the Kashmiri population. Although no association was found between this polymorphism and the risk of CRC, our results demonstrated a statistically significant (p<0.05) 1.99-fold increase in the OR for the AG genotype and a 2.05-fold increase in the OR for the AA genotype (Table II), when compared to the GG genotype. Furthermore, there was a statistically significant (p<0.05) 2.01-fold increase in the OR for the A allele in a dominant model of inheritance, although only a 1.25-fold increase in the OR for the A allele in a recessive model of inheritance. These results are quite different from those of Jian *et al* (25), who reported a recessive model of inheritance for this polymorphism in the Indian population on the basis of high fold increase in OR (1.56). The frequency of the different genotypes of *cyclin D1* polymorphism in our Kashmiri CRC cases was 14.61% (19/130) for the GG, 53.85% (70/130) for the AG and 31.54% (41/130) for the AA genotype. The frequencies for the rest of Indian population reported by Jian *et al* were 5.28% (46/301) for the GG, 43.19% (130/301) for the AG and 41.52% (125/301) for the AA genotype. The differences between the Kashmiri and the Indian populations may be due to the fact that the former belongs to the Persian genotypic pool, having descended from Persian migrants settled in the Kashmir valley during the 15th century. However, the present study was consistent with a Brazilian study regarding the frequencies of the 3 genotypes of *cyclin D1* A870G polymorphism (28). Moreover, consistent with our findings, results supporting the dominant model of inheritance have been reported by Tan *et al* (35).

Zheng *et al* (17) previously reported the frequency of the AA genotype to be higher in patients with squamous cell

Table III. Association between *cyclin D1* polymorphism and clinicopathological characteristics.

Variables	Cases[a] All cases n=130	GG 19 (14.6%)	AG 70 (53.9%)	AA 41 (31.5%)	P-value
Age group					
≤50	48 (36.9%)	6	33	9	7.32; 0.035
>50	82 (63.1%)	13	37	32	
Gender					
Female	54 (41.54%)	8	27	19	0.65; 0.720
Male	76 (58.46%)	11	43	22	
Dwelling					
Rural	91 (70.0%)	11	57	23	**9.45; 0.008**
Urban	39 (30.0%)	8	13	18	
Smoking status					
Ever	81 (62.3%)	10	48	23	2.6; 0.272
Never	49 (37.7%)	9	22	18	
Tumour location					
Colon	52 (40.0%)	7	31	14	1.2; 0.548
Rectum	78 (60.0%)	12	39	27	
Nodal status					
Involved	88 (67.7%)	14	49	25	1.33; 0.514
Not involved	42 (32.3%)	5	21	16	
Tumour grade					
Well-differentiated	98 (75.4%)	15	54	29	0.72; 0.697
Moderately/poorly differentiated	32 (24.6%)	4	16	12	

[a]One was squamous cell carcinoma; Statistically significant p-values in bold.

carcinoma of the head and neck (SCCHN) (23.6%) compared to controls (16.5%) in a non-hispanic white population, and concluded beyond doubt that the subjects with the AA genotype had a higher probability of developing SCCHN at an earlier stage than those with the GG genotype. However, in the present study we found quite the reverse. Subsequent to statistical analysis of the data using clinicopathological parameters (Table III), a significant association of the AA genotype with the older age group (>50 years) was observed ($p<0.05$), demonstrating that older patients were at a higher risk of developing CRC, compared to younger ones. These results are also contradictory to those reported by Huang *et al* in the Taiwanese population (36). The AA genotype was also found to be markedly associated with dwelling, suggesting that rural dwellers were at increased risk of CRC.

In a recent meta-analysis by Zhang *et al* (37) it was determined that the A allele significantly elevated the risk of CRC in co-dominant and dominant models. This supports our own observations from the present study. Furthermore, on the basis of ethnic stratification, significant associations were found in Caucasian populations, although not in Asians, thereby suggesting a possible role of ethnic differences in genetic background in addition to environmental factors (38,39).

Pabalan *et al* reported in a meta-analysis on all cancers that the *cyclin D1* G870A polymorphism confers susceptibility to cancer development, irrespective of the population studied (40). Its interaction with other genetic variants and environmental factors was also observed to have resulted in an elevated risk of cancer (OR, 1.6-7.1).

Furthermore, the interaction between polymorphism and various environmental factors induces and increases the overall susceptibility to CRC in any population (37-39). Therefore, we also suggest that since the Kashmiri population is exposed to a special set of environmental and dietary risks, which include the consumption of sun-dried and smoked fish and meat, dried and pickled vegetables, red chilli, hakh (a leafy vegetable of the Brassica family), hot noon chai (salted tea) and hukka (water pipe) smoke (30-32), this may play a significant role in modulating the effect of polymorphism on the dominant model of inheritance. The etiology and incidence of various GIT cancers in the Kashmiri population has been previously reported to be attributed to probable exposure to nitroso compounds, amines and nitrates that are present in local foodstuffs, most of which have been proven to contain notable irritants and carcinogens (29).

In conclusion, we found a clear association between the *cyclin D1* A870G polymorphism and the risk of CRC in the ethnic Kashmiri population. Nevertheless, these correlations need to be verified in a large-scale study, in order to discern racial differences and determine the aggressiveness of CRC.

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