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Original Article

Association between *E-cadherin (CDH1)* polymorphisms and pancreatic cancer risk in Han Chinese population

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Abstract: This study was designed to investigate the associations between *E-cadherin (CDH1)* gene polymorphisms and pancreatic cancer (PC) risk predisposition. We undertook a case-control study to analyze three *E-cadherin* polymorphisms (+54T>C, -160C>A and -347G→GA) in an Han Chinese population, by extraction of genomic DNA from the peripheral blood of 368 patients with PC and 376 control participants and performed *E-cadherin* genotyping using DNA sequencing. Overall, no statistically significant association was observed in +54T>C. Nevertheless, -347G→GA genotype was at increased risk of PC (*P*=0.022; odds ratio (OR) =1.128, CI 95%: 1.017-1.251). Furthermore, -347GA/GA genotype pancreatic cancers were more significantly common in cases of advanced T stage, lymph node metastasis and clinical pathological stage than G or G/GA genotypes PC. However, -160C>A genotype demonstrated a protective effect in PCs (*P*=0.017; OR=0.883, CI 95%: 0.798-0.977). In conclusion, polymorphism in -347G→GA was observed to be associated with susceptibility of PC. However, -160C>A polymorphism indicated to play a protective role in susceptibility to PC. Nevertheless, further investigation with a larger sample size is needed to support our results.

Keywords: Pancreatic cancer, E-cadherin, allele, polymorphism

Introduction

Pancreatic cancer (PC) takes up 3% of all reported cases of cancer and it is the eighth most common cause of cancer-related deaths in the world [1, 2]. There were 44,000 new cases diagnosed and 37,000 deaths from PC in 2012 [3, 4]. Despite ongoing research in the treatment of PC, the prognosis for patient long-term survival remains poor and the 5-year survival rate is less than 5% [5]. The situation has not significantly changed over the past several decades [6]. It is extremely important for us to find more effective methods to treat PC. Therefore, enhancing our knowledge of the molecular basis of PC is necessary [7, 8]. Previous studies indicated that possible risk factors for PC include advanced age, smoking status, alcohol consumption, overweight, body mass index, diabetes mellitus, and family history of PC [9-13]. However, not all people exposed to those risk factors develop PC, suggesting a genetic contribution to the development of PC [14, 15].

E-cadherin is a 97-kDa transmembrane glycoprotein encoded by the *E-cadherin* gene (*CDH1*) located on chromosome 16q22.1, and is one of the major constituents of cell adhesion complexes in epithelial cells [16, 17]. It plays central roles in the establishment of adherent type junctions by mediating calcium-dependent cellular interactions, and is thought to be a tumor suppressor protein [18]. Loss of cell adhesion may contribute to loss of growth contact inhibition, which is an early step in the neoplastic process [19]. Besides its role in physical cell-cell adhesions, E-cadherin is also thought to be involved in intracellular signaling in normal epithelial cells, since downregulation of this molecule in epithelial cells is frequently associated with tumor formation and differentiation [20].

Previous studies have reported that the loss of E-cadherin expression has been associated with poor clinical outcome in several types of cancers [21-23], including pancreatic cancer [24, 25]. Rarely, this decrease in expression is attributable to mutation of the *CDH1* gene, loss of heterozygosity [26], or hypermethylation of the *CDH1* promoter [27]. In most tumors the mechanism of CDH1 down-regulation is, however, unknown. In a recent study, the promoter region of *CDH1* was reported to be highly polymorphic [28]. One of the polymorphisms is the -347G→GA (rs5030625) single nucleotide polymorphism (SNP) upstream from the transcriptional start site [29]. Just as nucleotide variations in the coding region of a gene can alter protein expression, the -347G→GA polymorphism within the promoter region may change the transcriptional efficiency of CDH1 [30]. Moreover, several other SNPs, including +54T>C, -3159T>C, -160C>A, -2076C>T and -616G>C, were studied in Japanese and Italian populations, which resulted in the identification of haplotypes associated with increased risk of carcinoma [30, 31].

The above studies have highlighted the ethnic variation in frequency and risk predisposition of these SNPs [32]. However, association of E-cadherin (CDH1) gene polymorphisms and pancreatic cancer susceptibility has not been reported. Thus, in this study, in order to clarify association between three CDH1 gene polymorphisms (+54T>C, -160C>A and -347G→GA) and PC risk, we have performed a hospital-based case-control study on Han Chinese population.

Materials and methods

Subjects

A total of 368 cases of patients with PC and 376 healthy controls were qualified for this study. All samples were collected before any kind of therapeutic measures between March 2009 and May 2014 at Department of Hepatobiliary Surgery, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University and Department of Radiation Oncology, Sun Yat-Sen University Cancer Center. The patient samples were collected after the diagnosis was confirmed by pathologically exam. Written informed consent was obtained from all participants. The study protocol was approved by the Ethics Com¬mittee of Sun Yat-Sen University in accordance with the Declaration of Helsinki (2000). The PCs were staged according to the American Joint Committee on Cancer/International Union Against Cancer tumor-node-metastasis (TNM) staging system [33].

DNA extraction

Genomic DNA from whole blood cells was extracted using a QIAamp Blood kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. DNA concentration and purity of each sample were measured by ultraviolet spectrophotometer (Eppendorf, Hamburg, Germany). DNA samples were routinely stored at -20°C.

Genotyping

Analysis of the CDH1 SNPs, +54T>C, -160C>A and -347G→GA, was performed using multiplex polymerase chain reaction (PCR) with an ABI premix. Genomic DNA from whole blood was used as a PCR template in a total reaction volume of 10 μL that contained 10 pmol designed primers: +54T>C (rs3743674): 5'-CCCCTGGTCTCATCATTTC-3' (forward) and 5'-AATTCCTCCAAGAATCCCCAG-3' (reverse); -160C>A (rs16260): 5'-TGATCCCAGGTCTTAGTGAG-3' (forward) and 5'-GCTCCTCAGGACCCGAAC-3' (reverse); -347G→GA (rs5030625): 5'-GCCCCGACTTGTCTCTCTAC-3' (forward) and 5'-GGCCACAGCCAATCAGCA-3' (reverse). PCR was performed as follows: one cycle at 94°C for 10 min, 35 cycles at 94°C for 30 s, 59°C for 30 s, and 72°C for 30 s, followed by 72°C for 5 min. The final extension was at 72°C for 10 min. PCR products were analyzed on a 3% ethidium bromide added agarose gel, photographs were taken under ultraviolet light transilluminator. Subsequently, PCR product was sequenced in an ABI PRISM 3100 sequencer using BigDye Terminator v3.1 Cycle Sequencing method (Applied Biosystems, USA) as recommended by the manufacturer. Candidate SNP regions were detected and typed with the aid of DNA Star Software (DNASTAR, Madison, WI, USA).

Statistical analysis

Statistical calculations were performed using the SPSS Statistics 13.0 for Windows software package (SPSS Inc., Chicago, Ill). Frequency and susceptibilities of mutations were compared with the χ^2 test. The *P* values obtained were 2-tailed, and the association of signifi-

Table 1. General characteristics for the PC cases (n=368) and control population (n=376)

Characteristics	Cases, n (%) (n=368)	Controls, n (%) (n=376)	χ^2 value	*P* value[c]
Gender				
Male	247 (33.2)	259 (34.8)	0.266	0.606
Female	121 (16.3)	117 (15.7)		
Age[a,b]				
<55	174 (23.4)	181 (24.3)	0.055	0.815
≥55	194 (26.1)	195 (26.2)		
Smoking habits				
Never	187 (25.2)	201 (27.0)	0.520	0.471
Ever	181 (24.3)	175 (23.5)		
Alcohol consumption				
Never	194 (26.1)	201 (27.0)	0.041	0.840
Ever	174 (23.4)	175 (23.5)		
Body mass index				
<23	180 (24.2)	183 (24.6)	0.004	0.947
≥23	188 (25.3)	193 (25.9)		
Diabetes mellitus				
Yes	112 (15.1)	121 (16.3)	0.264	0.608
No	256 (34.4)	255 (34.3)		
Family history of PC				
Yes	54 (7.3)	50 (6.7)	0.293	0.588
No	314 (42.2)	326 (43.8)		

PC pancreatic cancer. [a]Age of diagnosis for cases. [b]Age of control population at the time of diagnosis for the matched case. [c]*P* value obtained by χ^2 (cases vs. control group).

cance was assumed to be less than 0.05. The Hardy-Weinberg equilibrium (HWE) was verified for the different polymorphisms studies, *P* value >0.05 was considered not deviate from the equilibrium. The crude and adjusted odds ratio (OR) and the corresponding 95% confidence intervals (CI) were calculated using unconditional multiple logistic regression.

Results

Characteristics of subjects

This study comprised 368 patients and 376 controls. All the cases and controls were randomly selected from the general Han Chinese population of China. **Table 1** shows the main characteristics of case-control populations. The gender, age distribution, smoking habits, alcohol consumption, body mass index, diabetes mellitus and family history of PC in case and control population group are not statistically different. The frequency of males was significantly higher, being in accordance with a worldwide estimation for PC.

E-cadherin (CDH1) +54T>C, -160C>A and -347G→GA polymorphisms in PC

The gene polymorphisms of E-cadherin (CDH1) +54T>C, -160C>A and -347G→GA were successfully amplified in all of PCs and control cases, as shown in **Table 2**. The number of patients with E-cadherin polymorphisms of +54T>C, -160C>A and -347G→GA were 167/368 cases, 211/368 cases and 252/368 cases, respectively. The genotypic distributions of all the three gene polymorphisms in cases and controls were in Hardy-Weinberg equilibrium (all P>0.05). Overall, no statistically significant association was observed in +54T>C. Individuals with -347G→GA genotype were more susceptible to PC (P=0.022, OR= 1.128). Moreover, the variant allele frequency AA of -160C>A was higher in controls as compared with cases (15.7% versus 9.5%, P=0.008). In case of alleles, association was observed with A allele of -160C>A with statistically significant reduced risk of PC (P=0.017, OR=0.883).

Relationship between E-cadherin (CDH1) +54T>C, -160C>A and -347G→GA polymorphisms and known clinicopathological variables

Table 3 listed the association of +54T>C, -160C>A and -347G→GA polymorphism with clinicopathological characteristics, including gender, age at diagnosis, body mass index, diabetes mellitus, lymph node metastasis and pathological stage of the cancer. The *CHD1* -160AA genotype was observed to be significantly associated with reduced risk with T stage, lymph node metastasis and pathological stage (*P*=0.008, *P*=0.024 and *P*=0.027, respectively).

Table 2. Association between *E-cadherin (CDH1)* +54T>C, -160C>A and -347G→GA polymorphisms T and PC

Genotype	Cases[a], n (%)	Controls[a], n (%)	*P* value	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
+54T>C					
TT	201 (54.6)	218 (58.0)		1 (Reference)	1 (Reference)
TC	133 (36.1)	125 (33.2)	0.366	1.074 (0.919-1.255)	1.061 (0.827-1.218)
CC	34 (9.3)	33 (8.8)	0.673	1.056 (0.815-1.370)	1.035 (0.742-1.275)
T allele	535 (36.0)	561 (37.7)			
C allele	201 (13.5)	191 (12.8)	0.403	1.051 (0.935-1.181)	
-160C>A					
CC	157 (42.7)	139 (37.0)		1 (Reference)	1 (Reference)
CA	176 (47.8)	178 (47.3)	0.399	0.934 (0.796-1.095)	0.914 (0.765-1.106)
AA	35 (9.5)	59 (15.7)	0.008	0.748 (0.614-0.911)	0.735 (0.609-0.914)
C allele	490 (32.9)	456 (30.6)			
A allele	246 (16.6)	296 (19.9)	0.017	0.883 (0.798-0.977)	
-347G→GA					
GG	116 (31.5)	145 (38.6)		1 (Reference)	1 (Reference)
G/GA	164 (44.6)	159 (42.3)	0.128	1.129 (0.966-1.318)	1.057 (0.857-1.219)
GA/GA	88 (23.9)	72 (19.1)	0.035	1.235 (1.008-1.512)	1.215 (1.004-1.355)
G allele	396 (26.6)	449 (30.2)			
GA allele	340 (22.8)	303 (20.4)	0.022	1.128 (1.017-1.251)	

[a]The χ^2 for HWE of *E-cadherin (CDH1)* +54T>C, -160C>A and -347G→GA polymorphisms in case and control group is 2.96 and 5.66, 2.05 and 0.03, and 3.94 and 5.52, respectively (all *P*>0.05). [b]ORs were adjusted for gender, age (<55 and ≥55 years) , smoking status, alcohol consumption (never and current smokers) and body mass index (<23 and ≥23).

Table 3. Clinicopathological relevance of *E-cadherin (CDH1)* +54T>C, -160C>A and -347G→GA polymorphisms in PC

Parameters	+54T>C		*P* value	-160C>A		*P* value	-347G→GA		*P* value
	TT+TC (%)	CC (%)		CC+CA (%)	AA (%)		GG+G/GA (%)	GA/GA (%)	
Gender									
Male	226 (61.4)	21 (5.7)	0.485	221 (60.1)	26 (7.1)	0.343	194 (52.7)	53 (14.4)	0.115
Female	108 (29.3)	13 (3.6)		112 (30.4)	9 (2.4)		86 (23.4)	35 (9.5)	
Age									
<55 years	159 (43.2)	15 (4.1)	0.698	161 (43.8)	13 (3.5)	0.207	131 (35.6)	43 (11.7)	0.733
≥55 years	175 (47.6)	19 (5.2)		172 (46.7)	22 (6.0)		149 (40.5)	45 (12.2)	
Body mass index									
<23	162 (44.0)	18 (4.9)	0.622	168 (45.7)	12 (3.3)	0.069	132 (35.9)	48 (13.0)	0.226
≥23	172 (46.7)	16 (4.4)		165 (44.8)	23 (6.3)		148 (40.2)	40 (10.9)	
Diabetes mellitus									
Present	101 (27.4)	11 (3.0)	0.799	97 (26.4)	15 (4.1)	0.093	82 (22.3)	30 (8.2)	0.393
Absent	233 (63.3)	23 (6.3)		236 (64.1)	20 (5.4)		198 (53.7)	58 (15.8)	
T stage									
1+2	121 (32.9)	14 (3.8)	0.568	115 (31.3)	20 (5.4)	0.008	112 (30.4)	23 (6.3)	0.019
3+4	213 (57.9)	20 (5.4)		218 (59.2)	15 (4.1)		168 (45.6)	65 (17.7)	
Lymph node metastasis									
Present	89 (24.2)	13 (3.5)	0.150	98 (26.6)	4 (1.1)	0.024	67 (18.2)	35 (9.5)	0.004
Absent	245 (66.6)	21 (5.7)		235 (63.9)	31 (8.4)		213 (57.9)	53 (14.4)	
TNM pathological stage									
Stage I and II	143 (38.9)	13 (3.5)	0.607	135 (36.7)	21 (5.7)	0.027	130 (35.3)	26 (7.1)	0.005
Stage III and IV	191 (51.9)	21 (5.7)		198 (53.8)	14 (3.8)		33 (40.8)	62 (16.8)	

For *CHD1* -347G→GA, the GA/GA genotype pancreatic cancers were significantly more common in cancers of higher lymph node metastasis (Present *versus* Absent, *P*=0.004)

and pathological stages (stages 3&4 *versus* 1&2, *P*=0.005). The polymorphism of +54T>C was not related to the age and gender of the patients and pathological features (body mass index, diabetes mellitus, lymph node metastasis and pathological stage) of the cancer.

Our data indicated that *CHD1* -160AA polymorphism may be protective genotype for PC development and may decrease the risk of PC among Han Chinese population. However, the -347G→GA promoter polymorphism in *CDH1* gene may be a susceptibility factor of PC.

Discussion

PC is one of the leading causes of cancer death resulting from complex interactions between environmental and genetic factors, and the genetic factors have the key functions in the pathogenesis of PC [34-36]. Recently, genetic variants of the *E-cadherin* gene in the etiology of several cancers have drawn increasing attention [28-30, 37]; however, studies on PC risk have been sparse. In this study, we evaluated the association of *E-cadherin (CHD1)* gene polymorphisms with PC susceptibility in Han Chinese population.

E-cadherin -160C/A polymorphism has been identified in the promoter region related to the transcriptional start site [38], and the -160AA SNP has also been reported to have a direct effect on its transcriptional regulation and therefore may influence susceptibility to cancers, such as prostate cancer, urothelial cancer, and gastric cancer [39]. Li *et al* first reported that the -160C/A polymorphism directly affects the *E-cadherin* gene transcriptional regulation [30]. However, findings related to the influence of the -160C/A promoter polymorphism and haplotypes of the *E-cadherin (CDH1)* gene have not been consistent in previous studies regarding the risk for sporadic gastric cancer [40-43]. Conversely, two studies in Asian populations reported that the -160A allele decreased the risk of gastric cancer [40, 41]. In another study, Lei *et al* genotyped the -160C/A SNP among 576 cases and 348 controls, and also found no association with breast cancer risk [44]. Interestingly, in our work, -160AA genotype showed a negative role in susceptibility to PCs (OR=0.883, *P*=0.017). And also, it seems to be association with lower T stage, lymph node metastasis rate and pathological stage. However, further investigation with a larger sample size is needed to support our results.

In a previous study, Zhang and his colleagues have found an association between *E-cadherin (CDH1)* +54T>C and esophageal and gastric cancer [45]. Moreover, another study has also shown that the haplotypes analysis of +54T>C genotype revealed the OR of gastric cancer 1.5, but did not reach statistical significance [46]. However, the present study shows that there is no association between *E-cadherin (CDH1)* gene +54T>C SNPs and PCs development. Similarly, in our previous study, we also reported this polymorphism with no risk in papillary thyroid carcinoma in Chinese population [21]. These differences can be attributed to discrepancy in polymorphisms studied, genetic background and local environmental factors, and highlights the need for comparative studies between different ethnic groups.

In several molecular epidemiological studies, *E-cadherin (CDH1)* -347G→GA SNP has been demonstrated to be association with the risk of cancers, including gastric, esophageal and colorectal carcinoma [47]. These studies suggested that GA-allele could result in transcriptional downregulation of *E-cadherin* (*CDH1)* and low expression of E-cadherin compared with the G-allele, thereby increasing the risk of cancer. However, one recent study has indicated that some functional polymorphisms may play more important roles in the prognosis of cancer than in its formation [48]. To further investigate the association between *E-cadherin* (*CDH1)* -347G→GA polymorphism and PCs, we conducted the present case-control study in a Chinese population. We found that the GA-allele increased the risk of PC compared with the G-allele in this Chinese population (OR=1.128, *P*=0.022). Meanwhile, our result showed that the GA/GA genotype pancreatic cancers were significantly more common in cancers of higher lymph node metastasis and pathological stages. However, further investigation with a larger sample size is needed to support our results.

In conclusion, our findings imply that continued research into *E-cadherin* (*CDH1)* polymorphisms will be an important source of information on the pathogenesis and prediction of clinical behavior of pancreatic cancers. In particular, to explore the predictive value of this SNP, an

adequately powered, prospective randomized trial should be carried out.

Disclosure of conflict of Interest

None.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] Ghaneh P, Costello E and Neoptolemos JP. Biology and management of pancreatic cancer. Gut 2007; 56: 1134-52.

[3] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[4] Hariharan D, Saied A and Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford) 2008; 10: 58-62.

[5] Tanaka M, Okazaki T, Suzuki H, Abbruzzese JL and Li D. Association of multi-drug resistance gene polymorphisms with pancreatic cancer outcome. Cancer 2011; 117: 744-51.

[6] Bednar F and Simeone DM. Pancreatic cancer stem cell biology and its therapeutic implications. J Gastroenterol 2011; 46: 1345-52.

[7] Gutierrez ML, Munoz-Bellvis L, Abad Mdel M, Bengoechea O, Gonzalez-Gonzalez M, Orfao A and Sayagues JM. Association between genetic subgroups of pancreatic ductal adenocarcinoma defined by high density 500 K SNP-arrays and tumor histopathology. PLoS One 2011; 6: e22315.

[8] Rizzato C, Campa D, Giese N, Werner J, Rachakonda PS, Kumar R, Schanne M, Greenhalf W, Costello E, Khaw KT, Key TJ, Siddiq A, Lorenzo-Bermejo J, Burwinkel B, Neoptolemos JP, Buchler MW, Hoheisel JD, Bauer A and Canzian F. Pancreatic cancer susceptibility loci and their role in survival. PLoS One 2011; 6: e27921.

[9] Nakao M, Hosono S, Ito H, Watanabe M, Mizuno N, Sato S, Yatabe Y, Yamao K, Ueda R, Tajima K, Tanaka H and Matsuo K. Selected polymorphisms of base excision repair genes and pancreatic cancer risk in Japanese. J Epidemiol 2012; 22: 477-83.

[10] Li D, Frazier M, Evans DB, Hess KR, Crane CH, Jiao L and Abbruzzese JL. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. J Clin Oncol 2006; 24: 1720-1728.

[11] Lowenfels AB and Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol 2006; 20: 197-209.

[12] Larsson SC, Orsini N and Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer 2007; 120: 1993-8.

[13] Luo J, Iwasaki M, Inoue M, Sasazuki S, Otani T, Ye W and Tsugane S. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan--the JPHC study. Cancer Causes Control 2007; 18: 603-12.

[14] Li G, Chen Q, Wang L, Ke D and Yuan Z. Association between FTO gene polymorphism and cancer risk: evidence from 16,277 cases and 31,153 controls. Tumour Biol 2012; 33: 1237-43.

[15] Dong LM, Potter JD, White E, Ulrich CM, Cardon LR and Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. JAMA 2008; 299: 2423-36.

[16] Martinez-Rico C, Pincet F, Thiery JP and Dufour S. Integrins stimulate E-cadherin-mediated intercellular adhesion by regulating Src-kinase activation and actomyosin contractility. J Cell Sci 2010; 123: 712-22.

[17] Kucharczak J, Charrasse S, Comunale F, Zappulla J, Robert B, Teulon-Navarro I, Pelegrin A and Gauthier-Rouviere C. R-Cadherin expression inhibits myogenesis and induces myoblast transformation via Rac1 GTPase. Cancer Res 2008; 68: 6559-68.

[18] Suzuki SC and Takeichi M. Cadherins in neuronal morphogenesis and function. Dev Growth Differ 2008; 50 Suppl 1: S119-30.

[19] Chen HC, Chu RY, Hsu PN, Hsu PI, Lu JY, Lai KH, Tseng HH, Chou NH, Huang MS, Tseng CJ and Hsiao M. Loss of E-cadherin expression correlates with poor differentiation and invasion into adjacent organs in gastric adenocarcinomas. Cancer Lett 2003; 201: 97-106.

[20] Cavallaro U and Christofori G. Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. Nat Rev Cancer 2004; 4: 118-32.

[21] Wang YX, Zhao L, Wang XY, Liu CM and Yu SG. Association between E-cadherin (CDH1) polymorphisms and papillary thyroid carcinoma risk in Han Chinese population. Endocrine 2012; 41: 526-31.

[22] Katagiri A, Watanabe R and Tomita Y. E-cadherin expression in renal cell cancer and its significance in metastasis and survival. Br J Cancer 1995; 71: 376-9.

[23] Jawhari A, Jordan S, Poole S, Browne P, Pignatelli M and Farthing MJ. Abnormal immunoreactivity of the E-cadherin-catenin complex in gastric carcinoma: relationship with patient survival. Gastroenterology 1997; 112: 46-54.
[24] Shimamura T, Sakamoto M, Ino Y, Sato Y, Shimada K, Kosuge T, Sekihara H and Hirohashi S. Dysadherin overexpression in pancreatic ductal adenocarcinoma reflects tumor aggressiveness: relationship to e-cadherin expression. J Clin Oncol 2003; 21: 659-67.
[25] Hong SM, Li A, Olino K, Wolfgang CL, Herman JM, Schulick RD, Iacobuzio-Donahue C, Hruban RH and Goggins M. Loss of E-cadherin expression and outcome among patients with resectable pancreatic adenocarcinomas. Mod Pathol 2011; 24: 1237-47.
[26] Soares P, Berx G, van Roy F and Sobrinho-Simoes M. E-cadherin gene alterations are rare events in thyroid tumors. Int J Cancer 1997; 70: 32-8.
[27] Rocha AS, Soares P, Seruca R, Maximo V, Matias-Guiu X, Cameselle-Teijeiro J and Sobrinho-Simoes M. Abnormalities of the E-cadherin/catenin adhesion complex in classical papillary thyroid carcinoma and in its diffuse sclerosing variant. J Pathol 2001; 194: 358-66.
[28] Nakamura A, Shimazaki T, Kaneko K, Shibata M, Matsumura T, Nagai M, Makino R and Mitamura K. Characterization of DNA polymorphisms in the E-cadherin gene (CDH1) promoter region. Mutat Res 2002; 502: 19-24.
[29] Shin Y, Kim IJ, Kang HC, Park JH, Park HR, Park HW, Park MA, Lee JS, Yoon KA, Ku JL and Park JG. The E-cadherin -347G->GA promoter polymorphism and its effect on transcriptional regulation. Carcinogenesis 2004; 25: 895-9.
[30] Li LC, Chui RM, Sasaki M, Nakajima K, Perinchery G, Au HC, Nojima D, Carroll P and Dahiya R. A single nucleotide polymorphism in the E-cadherin gene promoter alters transcriptional activities. Cancer Res 2000; 60: 873-6.
[31] Yamada H, Shinmura K, Ikeda S, Tao H, Otani T, Hanaoka T, Tsuneyoshi T, Tsugane S and Sugimura H. Association between CDH1 haplotypes and gastric cancer risk in a Japanese population. Scand J Gastroenterol 2007; 42: 1479-85.
[32] Gao L, Nieters A and Brenner H. Meta-analysis: tumour invasion-related genetic polymorphisms and gastric cancer susceptibility. Aliment Pharmacol Ther 2008; 28: 565-73.
[33] Edge SB and American Joint Committee on Cancer. AJCC Cancer Staging Manual. New York: Springer; 2010: 1471-4.
[34] Lowenfels AB and Maisonneuve P. Environmental factors and risk of pancreatic cancer. Pancreatology 2003; 3: 1-7.
[35] Landi S. Genetic predisposition and environmental risk factors to pancreatic cancer: A review of the literature. Mutat Res 2009; 681: 299-307.
[36] Chu D, Kohlmann W and Adler DG. Identification and screening of individuals at increased risk for pancreatic cancer with emphasis on known environmental and genetic factors and hereditary syndromes. JOP 2010; 11: 203-12.
[37] Cattaneo F, Venesio T, Molatore S, Russo A, Fiocca R, Frattini M, Scovassi AI, Ottini L, Bertario L and Ranzani GN. Functional analysis and case-control study of -160C/A polymorphism in the E-cadherin gene promoter: association with cancer risk. Anticancer Res 2006; 26: 4627-32.
[38] Jonsson BA, Adami HO, Hagglund M, Bergh A, Goransson I, Stattin P, Wiklund F and Gronberg H. -160C/A polymorphism in the E-cadherin gene promoter and risk of hereditary, familial and sporadic prostate cancer. Int J Cancer 2004; 109: 348-52.
[39] Tsukino H, Kuroda Y, Nakao H, Imai H, Inatomi H, Kohshi K, Osada Y and Katoh T. E-cadherin gene polymorphism and risk of urothelial cancer. Cancer Lett 2003; 195: 53-8.
[40] Kuraoka K, Oue N, Yokozaki H, Kitadai Y, Ito R, Nakayama H and Yasui W. Correlation of a single nucleotide polymorphism in the E-cadherin gene promoter with tumorigenesis and progression of gastric carcinoma in Japan. Int J Oncol 2003; 23: 421-7.
[41] Wu MS, Huang SP, Chang YT, Lin MT, Shun CT, Chang MC, Wang HP, Chen CJ and Lin JT. Association of the -160 C --> a promoter polymorphism of E-cadherin gene with gastric carcinoma risk. Cancer 2002; 94: 1443-8.
[42] Lu Y, Xu YC, Shen J, Yu RB, Niu JY, Guo JT, Hu X and Shen HB. E-cadherin gene C-160A promoter polymorphism and risk of non-cardia gastric cancer in a Chinese population. World J Gastroenterol 2005; 11: 56-60.
[43] Corso G, Berardi A, Marrelli D, Pedrazzani C, Garosi L, Pinto E and Roviello F. CDH1 C-160A promoter polymorphism and gastric cancer risk. Eur J Cancer Prev 2009; 18: 46-9.
[44] Lei H, Sjoberg-Margolin S, Salahshor S, Werelius B, Jandakova E, Hemminki K, Lindblom A and Vorechovsky I. CDH1 mutations are present in both ductal and lobular breast cancer, but promoter allelic variants show no detectable breast cancer risk. Int J Cancer 2002; 98: 199-204.
[45] Zhang XF, Wang YM, Ge H, Cao YY, Chen ZF, Wen DG, Guo W, Wang N, Li Y and Zhang JH. Association of CDH1 single nucleotide polymorphisms with susceptibility to esophageal squamous cell carcinomas and gastric cardia carcinomas. Dis Esophagus 2008; 21: 21-29.

[46] Al-Moundhri MS, Al-Khanbashi M, Al-Kindi M, Al-Nabhani M, Burney IA, Al-Farsi A and Al-Bahrani B. Association of E-cadherin (CDH1) gene polymorphisms and gastric cancer risk. World J Gastroenterol 2010; 16: 3432-6.

[47] Zhang B, Pan K, Liu Z, Zhou J, Gu L, Ji J, Ma J, You WC and Deng D. Genetic polymorphisms of the E-cadherin promoter and risk of sporadic gastric carcinoma in Chinese populations. Cancer Epidemiol Biomarkers Prev 2008; 17: 2402-8.

[48] Kim JG, Chae YS, Sohn SK, Cho YY, Moon JH, Park JY, Jeon SW, Lee IT, Choi GS and Jun SH. Vascular endothelial growth factor gene polymorphisms associated with prognosis for patients with colorectal cancer. Clin Cancer Res 2008; 14: 62-6.