Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Meta-analysis

The effects of CDKN2A rs3731249, rs11515, and rs3088440 polymorphisms on cancer risk

Y. Dong[1], X. Wang[2], Y-W. Yang[3], Y-J. Liu[4*]

[1] The Third Department of Radiotherapy, Jilin Provincial Tumor Hospital, Changchun 130012, Jilin, China
[2] Department of Anesthesiology, The First Hospital of Jilin University, Changchun 130000, Jilin, China
[3] Department of Internal Medicine, Jilin Provincial Tumor Hospital, Changchun 130012, Jilin, China
[4] Department of Orthopaedics, The First Hospital of Jilin University, Changchun 130000, Jilin, China

Correspondence to: hanhaisuquepin@sohu.com

Received January 9, 2017; **Accepted** March 25, 2017; **Published** March 31, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.3.8

Abstract: Many studies have been carried out to examine whether there is an association between CDKN2A polymorphisms and cancer risk, but the results from these studies were controversial. In the present study, we performed a meta-analysis to clarify whether there is an association of CDKN2A polymorphisms and cancer risk. Published reports were searched in PubMed and Google Scholar. ORs with 95% CIs were calculated in the dominant models. Twenty six case-control studies that met the inclusion criteria were included in the final meta-analysis. Overall, we found that rs3731249, rs11515, and rs3088440 polymorphisms were not associated with cancer risk (OR=1.27, 95%CI: 0.79-2.03; OR=0.91, 95%CI: 0.79-1.03; OR=1.02, 95%CI: 0.95-1.09). However, CDKN2A rs3731249 polymorphism was significantly associated with ovarian cancer risk (OR=0.78, 95%CI: 0.65-0.95). A significant association was observed in Asian with rs11515 polymorphism (OR=0.48, 95%CI: 0.28-0.83). This meta-analysis shows that CDKN2A rs3731249 polymorphism was significantly associated with ovarian cancer risk. In addition, CDKN2A rs11515 polymorphism might associate with cancer risk in Asians.

Key words: Cancer; CDKN2A; Meta-analysis.

Introduction

Cancer is a disease resulting from complex interactions between environmental and genetic factors (1). Genetic factors, including the sequence alterations and organization aberrations of the cellular genome that range from single-nucleotide substitutions to gross chromosome, could modulate several important biological progress and alert susceptibility to cancer consequently.

Cyclin-dependent kinase inhibitor 2A (CDKN2A) gene is located on chromosome 9p21 and, what is very interesting, encodes two different proteins: p16 and p14ARF, which are involved in cell cycle regulation(2). It is one of the crucial defenses against cancer development in number of human cancers (3). During the past decade, various studies have been carried out to examine whether there is an association between CDKN2A polymorphisms and cancer risk, but the results from these studies were controversial (4-29). In the present study, we performed a meta-analysis to clarify whether there is an association of CDKN2A polymorphisms and cancer risk.

Materials and Methods

Search strategy

Published reports were searched in PubMed and Google Scholar, with the following key words: “CDKN2A”, “Cyclin-dependent kinase inhibitor 2A”, “polymorphism” and “cancer”. Publication language and time of publication were not restricted in this search. Reference lists of articles retained for review were examined manually to further identify potentially relevant reports. Unpublished studies were not considered.

Inclusion and exclusion criteria

Abstracts of all retrieved studies were reviewed. Studies that meet the following criteria were included: (1) Addressing the association between CDKN2A polymorphisms and cancer risk; (2) Having a case-control design; (3) Providing with sufficient data for calculating odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following facts existed: (1)Books and other literatures that were not case-control studies; (2) Studies of which the primary goal is not the investigation of the association between CDKN2A polymorphisms and cancer risk; (3) Articles without control group information or without the retrievable original data. When the studies that were covered in different articles overlapped, only the ones showing the most extensive results were included in this study.

Data extraction

Two investigators independently extracted the data from each eligible paper. Disagreements were resolved by discussion and a consensus was reached on all items between the two investigators. The following data were collected from each study: first author, year of publication, site of cancer, ethnicity, source of controls, and genotype numbers of cases and controls.

Statistical analysis

The statistical analysis was conducted using STATA 12.0 (Stata Corp LP, College Station, TX, USA). P-value< 0.05 was considered as statistically significant. In addition to the overall database, two ethnic subgroups were created that covered all studies with Caucasian and Asian. ORs with 95% CIs were calculated in the dominant models. For each study, numbers of three genotypes in case and control groups were used as pooled data. The heterogeneity between studies was tested using I2 index (I2< 25%, no heterogeneity; I2 = 25-50%, moderate heterogeneity; I2> 50%, large or extreme heterogeneity). Publication bias was evaluated with Begg's funnel plots based on the analysis results and database size. Moreover, Egger's test was also completed for each dataset to get a better analysis on the publication bias.

Results

Studies characteristics

A total of 3110 papers were retrieved after the first search, and 3083 of them were excluded (Figure 1). As a result, 26 case-control studies that met the inclusion criteria were included in the final meta-analysis. The characteristics of all studies were included in Tables 1-3. Three polymorphisms, such as rs3731249, rs11515, and rs3088440, were investigated in this meta-analysis.

Quantitative synthesis

Overall, we found that rs3731249 polymorphism was not associated with cancer risk (OR=1.27, 95%CI: 0.79-2.03). In the subgroup analysis of site of cancer, CDKN2A rs3731249 polymorphism was significantly associated with ovarian cancer risk (OR=0.78, 95%CI: 0.65-0.95). However, no significant association was observed in melanoma (OR=1.43, 95%CI: 0.82-2.50). In the subgroup analysis of race and source of control, we did not find significant association between CDKN2A rs3731249 polymorphism and cancer risk (Table 4).

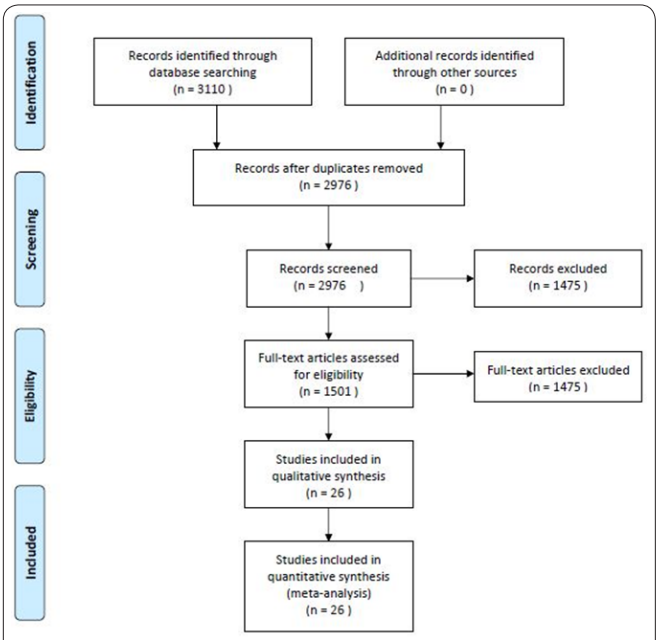

Figure 1. Flow chart of study selection.

In addition, we found that rs11515 polymorphism was not associated with cancer risk (OR=0.91, 95%CI: 0.79-1.03). In the subgroup analysis of site of cancer, CDKN2A rs11515 polymorphism was not associated with ovarian cancer (OR=0.98, 95%CI: 0.87-1.09), melanoma risk (OR=1.12, 95%CI: 0.97-1.30), and colon cancer risk (OR=0.74, 95%CI: 0.45-1.22). However, a significant association was observed in Asian population (OR=0.48, 95%CI: 0.28-0.83). In the subgroup analysis of source of control, we did not find significant association between CDKN2A rs11515 polymorphism

Table 1. characteristics of the included studies with rs3731249.

First author/Year	Ethnicity	Site of cancer	Source of control	AA in case	AT in case	TT in case	AA in control	AT in control	TT in control	HWE in control
Bertram/2002	Caucasian	Melanoma	Population	464	24	0	568	31	0	0.52
Debniak/2005	Caucasian	Melanoma	Mixed	438	33	0	1175	35	0	0.61
Wang/2006	Caucasian	Lymphoma	Population	700	49	1	601	36	1	0.55
Spica A/2006	Caucasian	Melanoma	Hospital	104	14	1	107	13	1	0.4
Spica B/2006	Caucasian	Melanoma	Hospital	467	32	1	131	12	0	0.6
Hung/2006	Caucasian	Lung	Mixed	1993	129		2086	135		NA
Debniak A/2006	Caucasian	Bladder	Population	216	7	0	2895	105	0	0.33
Debniak B/2006	Caucasian	Colon	Population	687	37	0	2895	105	0	0.33
Debniak C/2006	Caucasian	Stomach	Population	238	8	0	2895	105	0	0.33
Debniak D/2006	Caucasian	Larynx	Population	379	17	0	2895	105	0	0.33
Debniak E/2006	Caucasian	Ovary	Population	328	12	0	2895	105	0	0.33
Debniak F/2006	Caucasian	Lung	Population	463	34	0	2895	105	0	0.33
Debniak G/2006	Caucasian	Prostate	Population	335	13	0	2895	105	0	0.33
Debniak H/2006	Caucasian	Kidney	Population	258	6	0	2895	105	0	0.33
Debniak I/2006	Caucasian	Thyroid	Population	170	3	0	2895	105	0	0.33
Debniak J/2006	Caucasian	Lymphoma	Population	156	6	0	2895	105	0	0.33
Debniak K/2006	Caucasian	Pancreas	Population	202	8	0	2895	105	0	0.33
Landi/2006	Caucasian	Lung	Hospital	240	15	1	253	10	0	0.75
Gayther/2007	Caucasian	Ovary	Mixed	1405	70	3	2295	153	4	0.39
Driver/2008	Caucasian	Breast	Population	2053	121	2	2140	132	2	0.98
Quaye/2009	Caucasian	Ovary	Hospital	1391	70	3	2295	153	4	0.39
Polakova/2009	Caucasian	Colon	Hospital	565	40	2	579	29	0	0.05
Bakos/2011	Mixed	Melanoma	Hospital	111	14	2	123	5	0	0.82

Table 2. characteristics of the included studies with rs11515.

First author/ Year	Ethnicity	Site of cancer	Source of control	CC in case	CG in case	GG in case	CC in control	CG in control	GG in control	HWE in control
Kumar/2001	Caucasian	Melanoma	Population	164	61	4	186	43	6	0.08
Zheng/2002	Caucasian	Head and neck	Population	160	46	2	172	49	3	0.82
McCloud/2004	Caucasian	Colon	Hospital	153	43	12	119	48	5	0.95
Debniak/2005	Caucasian	Melanoma	Mixed	360	103	8	966	229	15	0.73
Geddert/2005	Caucasian	Gastrointestinal	Hospital	273	42	0	190	40	0	0.15
Wang/2006	Caucasian	Lymphoma	Population	547	188	14	469	158	14	0.87
Landi/2006	Caucasian	Lung	Hospital	219	69	3	238	70	6	0.75
Gayther/2007	Caucasian	Ovary	Mixed	781	243	29	940	318	18	0.12
Driver/2008	Caucasian	Breast	Population	1600	538	52	1688	553	38	0.34
Yan/2008	Asian	Ovary	Mixed	193	11	1	244	22	2	0.07
Quaye/2009	Caucasian	Ovary	Hospital	1075	366	38	1810	639	43	0.12
Polakova/2009	Caucasian	Colon	Hospital	431	159	18	457	138	13	0.5
Tuna/2012	Asian	Colon	Population	58	27	2	26	36	13	0.93
Thakur/2012	Asian	Cervix	Hospital	132	18	0	104	44	2	0.26
Azimzadeh/2012	Asian	Colon	Hospital	172	65	12	257	122	15	0.91
Chansaenroj/2013	Asian	Cervix	Hospital	52	4	0	28	4	0	0.71
Maccioni/2013	Caucasian	Melanoma	Population	538	214	20	796	316	31	0.96
Pinheiro/2014	Mixed	Head and neck	Population	74	15	7	67	26	7	0.06
Barbieri/2012	Mixed	Thyroid	Population	38	7	0	66	30	2	0.5

Table 3. characteristics of the included studies with rs3088440.

First author/ Year	Ethnicity	Site of cancer	Source of control	CC in case	CT in case	TT in case	CC in control	CT in control	TT in control	HWE in control
Zheng/2002	Caucasian	Head and neck	Population	174	33	1	185	37	2	0.92
McCloud/2004	Caucasian	Colon	Hospital	154	15	9	125	32	2	0.98
Debniak/2005	Caucasian	Melanoma	Mixed	404	64	3	1058	145	7	0.41
Wang/2006	Caucasian	Lymphoma	Population	600	144	5	509	119	9	0.5
Landi/2006	Caucasian	Lung	Hospital	245	42	1	270	42	0	0.2
Gayther/2007	Caucasian	Ovary	Mixed	1207	267	15	2048	425	17	0.32
Driver/2008	Caucasian	Breast	Population	1834	334	15	1872	365	22	0.37
Yan/2008	Asian	Ovary	Hospital	161	44	0	204	61	3	0.51
Quaye/2009	Caucasian	Ovary	Hospital	1195	265	15	2048	425	17	0.32
Canova/2009	Caucasian	Gastrointestinal	Mixed	1310	186	12	1229	205	9	0.89
Polakova/2009	Caucasian	Colon	Hospital	528	80	3	526	76	6	0.09
Tuna/2012	Asian	Colon	Population	64	19	4	54	18	3	0.35
Jin/2012	Asian	Salivary Gland	Population	125	26	5	402	98	11	0.09
Chansaenroj/2013	Asian	Cervix	Hospital	46	10	0	25	7	0	0.49
Zhang/2013	Asian	Thyroid	Hospital	241	62		402	109		NA
Maccioni/2013	Caucasian	Melanoma	Population	660	108	5	1020	108	5	0.25

and cancer risk (Table 4).

Furthermore, we did not find that rs3088440 polymorphism was associated with cancer risk (OR=1.02, 95%CI: 0.95-1.09). In the subgroup analysis of site of cancer, race, and source of control, we also did not find significant association between CDKN2A rs11515 polymorphism and cancer risk (Table 4).

To test the publication bias of overall dataset, both Begg's and Egger's test were performed. The result of Begg's test did not suggest a publication bias (P>0.05). Funnel plots were also generated, which didn't show any significant publication bias in all three SNPs (data not shown).

Discussion

Recently, many studies have investigated the association between CDKN2A polymorphisms and the risk of cancer, but the results were not consistent. Thus this meta-analysis is aimed to get a better insight on the association between CDKN2A polymorphisms and cancer risk. After a comprehensive search and a careful selection, 26 studies were critically reviewed and included in this study. The result of this meta-analysis shows that CDKN2A rs3731249 polymorphism was significantly associated with ovarian cancer risk. Additionally, Asians with CDKN2A rs11515 polymorphism might have decreased cancer risk.

CDKN2A gene functions as an important tumour suppressor in various human malignancies including colorectal cancer, and its activation prevents carcinogenesis via induction of cell growth arrest and senescence (30). Promoter silencing of CDKN2A through methylation lead to loss of control of the restriction point in the G1 phase of the cell cycle and favor cellular transformation (31). Abnormal CDKN2A promoter hypermethylation has been found in several types of tumor (32). It results in uncontrolled cell proliferation and tumour

Table 4. Results of the meta-analysis.

	OR (95% CI)	I^2 (%)
rs3731249		
Overall	1.27 (0.79-2.03)	95.4
Site of cancer		
Melanoma	1.43 (0.82-2.50)	71.2
Ovarian	0.78 (0.65-0.95)	0.0
Ethnicity		
Caucasian	1.21 (0.75-1.97)	95.6
Source of control		
Population	1.23 (0.61-2.44)	96.5
Hospital	1.20 (0.80-1.82)	63.7
rs11515		
Overall	0.91 (0.79-1.03)	65.7
Site of cancer		
Melanoma	1.12 (0.97-1.30)	44.2
Ovarian	0.98 (0.87-1.09)	0.0
Colon	0.74 (0.45-1.22)	85
Ethnicity		
Caucasian	1.04 (0.97-1.10)	0.0
Asian	0.48 (0.28-0.83)	72.2
Source of control		
Population	0.88 (0.70-1.10)	73.9
Hospital	0.85 (0.68-2.07)	66.8
rs3088440		
Overall	1.02 (0.95-1.09)	28
Site of cancer		
Ovarian	1.06 (0.94-1.19)	0.0
Colon	0.73 (0.39-1.37)	72.5
Ethnicity		
Caucasian	1.02 (0.97-1.15)	54.8
Asian	0.87 (0.66-1.17)	0
Source of control		
Population	1.02 (0.91-1.15)	50.4
Hospital	1.00 (0.87-1.14)	47.4

development and progression (33).

Bihl et al. suggested that CDKN2A methylation positivity was associated with microsatellite instability, BRAF mutation, higher tumor grade, and mucinous histology in colorectal cancer (34). Zhang et al. found that CDKN2A methylation is associated with OS and DFS in NSCLC patients (35). Xing et al. indicated that CDKN2A hypermethylation might be a predictive factor for unfavourable prognosis of colorectal cancer patients (36).

To our knowledge, this is the first meta-analysis using case-control studies to examine the association of CDKN2A polymorphisms with the susceptibility of cancer. Our meta-analysis augment statistical power via pooling data from studies satisfies our inclusion criteria. However, there remains several limitations should be noted. First, we adopted unadjusted ORs for we could not get sufficient information to calculate adjusted ORs with refer to potential confounders (*e.g.* age and sex). Second, all studies we included were published in English and no African group was involved. Besides, modest to high heterogeneity was found in major comparison. Finally, our study did not analyze gene-gene and gene-environment interactions because of insufficient data in the studies we enrolled.

This meta-analysis shows that CDKN2A rs3731249 polymorphism was significantly associated with ovarian cancer risk. In addition, CDKN2A rs11515 polymorphism might associate with cancer risk in Asians.

References

1. Bredberg A. Cancer: more of polygenic disease and less of multiple mutations? A quantitative viewpoint.Cancer. 2011;117(3):440-5.
2. Nelson AA, Tsao H. Melanoma and genetics. ClinDermatol. 2009;27(1):46-52.
3. Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K, Carson DA. Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple human cancers.Nature. 1994;368(6473):753-6.
4. Kumar R, Smeds J, Berggren P, Straume O, Rozell BL, Akslen LA, et al. A single nucleotide polymorphism in the 3'untranslated region of the CDKN2A gene is common in sporadic primary melanomas but mutations in the CDKN2B, CDKN2C, CDK4 and p53 genes are rare. Int J Cancer, 2001;95: 388-393
5. McCloud JM, Sivakumar R, Greenhough A, Elder J, Jones PW, Deakin M, et al. p16INK4a polymorphism: associations with tumour progression in patients with sporadic colorectal cancer. Int J Oncol, 2004;25: 1447-52
6. Bertram CG, Gaut RM, Barrett JH, Pinney E, Whitaker L, Turner F, et al. An assessment of the CDKN2A variant Ala148Thr as a nevus/melanoma susceptibility allele. J Invest Dermatol, 2002;119: 961-5
7. Geddert H, Kiel S, Zotz RB, Zhang J, Willers R, Gabbert HE, et al. Polymorphism of p16 INK4A and cyclin D1 in adenocarcinomas of the upper gastrointestinal tract. J Cancer Res ClinOncol, 2005;131: 803-8
8. Hung RJ, Boffetta P, Canzian F, Moullan N, Szeszenia-Dabrowska N, Zaridze D, et al. Sequence variants in cell cycle control pathway, X-ray exposure, and lung cancer risk: a multicenter case-control study in Central Europe. Cancer Res, 2006;66: 8280-6
9. Spica T, Portela M, Gérard B, Formicone F, Descamps V, Crickx B, et al. The A148T variant of the CDKN2A gene is not associated with melanoma risk in the French and Italian populations. J Invest Dermatol, 2006;126: 1657-60
10. Debniak T, Scott RJ, Huzarski T, Byrski T, Rozmiarek A, Debniak B, et al. CDKN2A common variant and multi-organ cancer risk--a population-based study. Int J Cancer, 2006;118: 3180-2
11. Canova C, Hashibe M, Simonato L, Nelis M, Metspalu A, Lagiou P, et al. Genetic associations of 115 polymorphisms with cancers of the upper aerodigestive tract across 10 European countries: the ARCAGE project. Cancer Res, 2009;69: 2956-65
12. Bakos RM, Besch R, Zoratto GG, Godinho JM, Mazzotti NG, Ruzicka T, et al. The CDKN2A p.A148T variant is associated with cutaneous melanoma in Southern Brazil. ExpDermatol, 2011;20: 890-3
13. Thakur N1, Hussain S, Nasare V, Das BC, Basir SF, Bharadwaj M. Association analysis of p16 (CDKN2A) and RB1 polymorphisms with susceptibility to cervical cancer in Indian population. MolBiol Rep, 2012;39: 407-414
14. Azimzadeh P, Romani S, Mohebbi SR,Mahmoudi T, Vahedi M, Fatemi SR, et al. Association of polymorphisms in microRNA-binding sites and colorectal cancer in an Iranian population. Cancer Genet, 2012;205: 501-7
15. Jin L, Xu L, Song X,Wei Q, Sturgis EM, Li G. Genetic variation in MDM2 and p14ARF and susceptibility to salivary gland carcinoma. PLoS One, 2012;7: e49361
16. Pinheiro UB, de CarvalhoFraga CA, Mendes DC, Marques-Silva L, Farias LC, de Souza MG, et al: p16 (CDKN2A) SNP rs11515 was not associated with head and neck carcinoma. TumourBiol, 2014;35: 6113-8
17. Barbieri RB, Bufalo NE, Secolin R, Assumpção LV, Maciel RM, Cerutti JM, et al. Polymorphisms of cell cycle control genes influence the development of sporadic medullary thyroid carcinoma.

Eur J Endocrinol, 2014;171: 761-7
18. Zheng Y, Shen H, Sturgis EM, Wang LE, Shete S, Spitz MR, et al. Haplotypes of two variants in p16 (CDKN2/MTS-1/INK4a) exon 3 and risk of squamous cell carcinoma of the head and neck: a case-control study. Cancer Epidemiol Biomarkers Prev, 2002;11: 640-5
19. Yan L, Na W, Shan K, Xiao-Wei M, Wei G, Shu-Cheng C. p16(CDKN2) gene polymorphism: association with histologic subtypes of epithelial ovarian cancer in China. Int J Gynecol Cancer, 2008;18: 30-5
20. Tuna G, Küçükhüseyin O, Arıkan S, KaytanSağlam E, Güler E, Cacına C, et al: Do CDKN2 p16 540 C>G, CDKN2 p16 580 C>T, and MDM2 SNP309 T>G gene variants act on colorectal cancer development or progression? DNA Cell Biol, 2013;32: 400-8
21. Chansaenroj J, Theamboonlers A, Junyangdikul P, Swangvaree S, Karalak A, Chinchai T, et al. Polymorphisms in TP53 (rs1042522), p16 (rs11515 and rs3088440) and NQO1 (rs1800566) genes in Thai cervical cancer patients with HPV 16 infection. Asian Pac J Cancer Prev, 2013;14: 341-6
22. Maccioni L, Rachakonda PS, Bermejo JL, Planelles D, Requena C, Hemminki K, et al. Variants at the 9p21 locus and melanoma risk. BMC Cancer, 2013;13: 325
23. Debniak T, Scott RJ, Huzarski T, Byrski T, Rozmiarek A, Debniak B, et al. CDKN2A common variants and their association with melanoma risk: a population-based study. Cancer Res, 2005;65: 835-9
24. Wang SS, Cozen W, Severson RK, Hartge P, Cerhan JR, Davis S, et al. Cyclin D1 splice variant and risk for non-Hodgkin lymphoma. Hum Genet, 2006;120: 297-300
25. Landi S, Gemignani F, Canzian F, Gaborieau V, Barale R, Landi D, et al. DNA repair and cell cycle control genes and the risk of young-onset lung cancer. Cancer Res, 2006;66: 11062-9
26. Gayther SA, Song H, Ramus SJ, Kjaer SK, Whittemore AS, Quaye L, et al. Tagging single nucleotide polymorphisms in cell cycle control genes and susceptibility to invasive epithelial ovarian cancer. Cancer Res, 2007;67: 3027-35
27. Driver KE, Song H, Lesueur F, Ahmed S, Barbosa-Morais NL, Tyrer JP, et al. Association of single-nucleotide polymorphisms in the cell cycle genes with breast cancer in the British population. Carcinogenesis, 2008;29: 333-41
28. Polakova V, Pardini B, Naccarati A, Landi S, Slyskova J, Novotny J, et al. Genotype and haplotype analysis of cell cycle genes in sporadic colorectal cancer in the Czech Republic.Hum Mutat, 2009;30: 661-8
29. Quaye L, Tyrer J, Ramus SJ, Song H, Wozniak E, DiCioccio RA, et al. Association between common germline genetic variation in 94 candidate genes or regions and risks of invasive epithelial ovarian cancer.PLoS One, 2009;4: e5983
30. Collado M, Blasco MA, Serrano M. Cellular senescence in cancer and aging. Cell. 2007;130(2):223-33.
31. Voorhoeve PM, Agami R. The tumor-suppressive functions of the human INK4A locus.Cancer Cell. 2003;4(4):311-9.
32. Merlo A, Herman JG, Mao L, Lee DJ, Gabrielson E, Burger PC, et al. 5' CpG island methylation is associated with transcriptional silencing of the tumour suppressor p16/CDKN2/MTS1 in human cancers. Nat Med. 1995;1(7):686-92.
33. Samowitz WS, Albertsen H, Herrick J, Levin TR, Sweeney C, Murtaugh MA, et al. Evaluation of a large, population-based sample supports a CpG island methylator phenotype in colon cancer. Gastroenterology. 2005;129(3):837-45.
34. Bihl MP, Foerster A, Lugli A, Zlobec I. Characterization of CDKN2A(p16) methylation and impact in colorectal cancer: systematic analysis using pyrosequencing. J Transl Med. 2012;10:173.
35. Lou-Qian Z, Rong Y, Ming L, Xin Y, Feng J, Lin X. The prognostic value of epigenetic silencing of p16 gene in NSCLC patients: a systematic review and meta-analysis. PLoS One. 2013;8(1):e54970.
36. Jiang W, Wang PG, Zhan Y, Zhang D. Prognostic value of p16 promoter hypermethylation in colorectal cancer: a meta-analysis. Cancer Invest. 2014;32(2):43-52.