

Meta-analysis reveals no correlation of caveolin-1 G14713A (G>A) gene polymorphism with increased cancer risk in Taiwanese population

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ABSTRACT

Objectives: The role of caveolin-1 (CAV1)(G>A, rs3807987) polymorphism is still dubious in cancer causation in Taiwanese population. The present study is an effort to assess the above relation for precise conclusion.

Methods: EMBASE and PubMed (MEDLINE) databases were explored for the pertinent case-control studies reporting the connection of CAV1 G14713A polymorphism to the vulnerability to cancer. A cumulative analysis using meta-analytic approach was accomplished and pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated for all the polymorphs.

Results: Overall, 2549 subjects and 3161 controls were analyzed from six selected studies. Our study showed no confirmation of noteworthy risk between CAV1 G14713A polymorphism and susceptibility to cancer in any of the polymorph, for instance, allele (A vs. G: $P = 0.165$; OR = 1.252, 95% CI = 0.911–1.721), homozygous (AA vs. GG: $P = 0.252$; OR = 1.328, 95% CI = 0.817–2.157), heterozygous (AG vs. GG: $P = 0.091$; OR = 1.356, 95% CI = 0.952–1.930), dominant (AA vs. GG + AG: $P = 0.345$; OR = 1.191, 95% CI = 0.829–1.709), and recessive (AA + AG vs. GG: $P = 0.125$; OR = 1.344, 95% CI = 0.921–1.961).

Conclusions: We conclude that CAV1 G14713A polymorphism does not contribute as an independent predisposing risk factor for developing cancer in Taiwanese population.

Keywords: Cancer, caveolin-1, genetic models, meta-analysis, polymorphism

Introduction

These days cancer has been identified as one of the leading causes of death worldwide. It is proving to be a serious socioeconomic burden on the health-care system of different countries and is deteriorating the quality of life of the victims.^[1] Despite advances in treatment, the prognosis still remains unexposed fully. The cancer is a multifactorial disease and the various studies suggest that environmental factors interplay with certain polymorphs may play an important role in the carcinogenesis.^[2] Thus, it proves the importance of early

detection genetic methods to take the adequate measures for the prevention of the disease.

Caveolin-1 (CAV1) gene mapped on 7q31.1 consists of three exons. At the outset, it was identified as tumor suppressor gene.^[3] The gene is crucial in molecular transport, a number of metabolic pathways, as well as proliferation and differentiation processes. The increased expression of CAV1 gene has also been found to be linked with metastasis of cancers which negatively affects the survival of cancer patients.^[4,5] The reports also suggest that CAV1 can undergo abnormal methylation

in preclinical stages of cancer, leading to its silencing during developmental stages of cancer.^[6] The reported studies indicate the multifaceted role of CAV1 proposed as an oncogene.^[7]

There are several SNPs in the CAV1 gene, and very lately various studies published on the same matter has been investigated that establishes the role of rs3807987 G14713A (G>A) polymorphism on the risk of various cancer including bladder, breast, nasopharyngeal, prostate, and urothelial tract cancer.^[8-13] However, the findings of previous studies are still controversial. It is possible that variations in findings result from differential effects of CAV1 gene polymorphisms in different tumor. Sample size is a foremost constraint in all the individual genetic case-control studies evaluating the association of gene polymorphisms with the disease susceptibility. Hence, individual studies largely fail to accomplish accurate and enough statistical power to appraise a significant association and such underpowered studies usually show false-positive genetic associations and misinterpretations of the outcomes.^[14] To clarify the discrepancies from the past studies, we did a meta-analysis using the information available from the previously published case-control studies for the precise assessment of the relation between G14713A (G>A)(rs3807987) polymorphism and cancer vulnerability in Taiwanese population. A meta-analysis is a strong statistical instrument for examining collective data from the independent research findings, where discrete population sizes are insufficient and bear low statistical significance.^[15]

Materials and Methods

Identification and eligibility of relevant studies

The EMBASE and PubMed (Medline) web databases were explored for the research articles of interest. The combinations of words used were like: “CAV1 gene AND (polymorphism OR variant OR mutation) AND Carcinoma or Cancer or Malignancy” (updated on July 2016). Studies showing possible significance for genetic connection were evaluated by examining them methodically. The published studies corresponding to the stated eligible standards were retrieved and encompassed in the present study.

Inclusion and exclusion criteria

Below mentioned study, selection criteria were used to include the past studies in the current analysis to reduce heterogeneity and assist the proper explanation: (i) Assessment of the CAV1 G14713A (G>A) and cancer risk in Taiwanese population, (ii) application of case-control design, (iii) recruitment of cancer-free controls and pathologically confirmed cancer cases, (iv) encompassed the all polymorphs frequency both in cases and controls, and (v) the language of publication was English. Furthermore, the articles where same case pool was used the study with the largest population size were used. Likewise, following exclusion criteria were fixed for the elimination of

inappropriate studies (i) case-only studies, (ii) studies with overlapping of the data, and (iii) review articles.

Data extraction and quality assessment

A standard protocol was used by two sovereign investigators for the data extraction and procedural quality assessment in duplicate. Data accurateness was validated using the data collection form as per inclusion/exclusion standards stated above. The incongruent items were fully debated to reach a conclusion. The characteristics summarized from the selected studies were the name of the first author, the year of publication, the country of origin, the sources of cases and controls, the number of cases and controls, types of study, and polymorph frequencies.

Statistical analysis

The analysis was accomplished by calculating the pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) for all the polymorphs to evaluate the association between the CAV1 G14713A (G>A) polymorphism and cancer susceptibility. Heterogeneity suppositions were examined by the Chi-square based Q-test.^[16] The significance level (P value) <0.05 for the Q-test denoted an absence of heterogeneity among the selected data set. The fixed effects model^[17] and/or the random effects model^[18] were used to calculate the pooled ORs. The I^2 statistics was also utilized to measure interstudy variability, which ranged between 0 and 100%. A value of 0% specifies no observed heterogeneity, whereas larger values specify higher levels of heterogeneity.^[19] In the control group, the Chi-square test was used to calculate the Hardy-Weinberg equilibrium (HWE). The funnel plot asymmetry on the natural logarithmic scale of the OR was calculated by the Egger's linear regression test. The t-test ($P < 0.05$ was considered as a representation of statistically significant publication bias) was used to test the significance of the intercept.^[20] The meta-analysis discussed here was completed by the comprehensive meta-analysis (CMA) V2 software (Biostat, USA). The CMA V2 is more advantageous over other programs being used for meta-analysis studies. A comparison of these programs can be retrieved through <http://meta-analysis.com/pages/comparisons.html>.

Results

Characteristics of the published studies

A total of six articles comprising 2549 cancer cases and 3161 controls were recovered from the PubMed (Medline) and the EMBASE database. The recovered literature was scrutinized by the titles, their abstracts, and the full texts analysis for the strong relevance. Published articles were further analyzed for their relativity for the meta-analysis under consideration. To find any further relevant article, the reference lists of all the retrieved articles were also investigated. The studies that comprise the CAV1 polymorphism to estimate the indicators of the survival and as for the prognosis were excluded.

A strict principle was followed in article searches, only those case–controls or cohort studies which included all the three polymorphs were considered for the present analysis. Following the thorough selection and strict inclusion and exclusion criteria, six original articles were considered relevant and were added in the present analysis [Table 1].

The prescribed PRISMA flow diagram or describing the selection of the studies is not given here as all the studies were from Taiwan and restricted to CAV1 G14713A (G>A) gene polymorphism, and during the study selection, we obtained only six reports which were included in this study. Frequency of genotypes, HWE *P* values in the controls, and susceptibility to cancer has been tabulated in Table 2.

Publication bias

The Begg's funnel plot and Egger's test were implemented to examine the publication bias among the included studies [Table 3]. No evidence of publication bias was encountered as apparent by the outcomes of Egger's test and the shape of

funnel plots for all the comparison sets (A vs. G, AA vs. GG, AG vs. GG, AA+AG vs. GG, and AA vs. GG+AG).

Test of heterogeneity

The Q-test and *I*² statistics were utilized to determine the heterogeneity of the selected literature. As there was no heterogeneity in all genetic models, the random model was engaged for calculating the combined OR and 95% CI for all comparisons [Table 3].

Meta-analysis of CAV1 G14713A (G>A) polymorphism and cancer susceptibility

All the six literatures were considered, which accumulated as 3161 controls and 2549 cancer cases. The overall relationship between the G14713A (G>A) polymorphism and proneness to carcinogenesis was assessed using the random effects models (based on heterogeneity). As a result, none of the genetic model [Figure 1], allele (A vs. G: *P* = 0.165; OR = 1.252, 95% CI = 0.911–1.721), homozygous (AA vs. GG: *P* = 0.252;

Table 1: The characteristics of the selected studies included in the present study

First authors	Year	Country of origin	Cancer	Genotyping method	Cases	Controls	Source of genotyping
Bau <i>et al.</i> ^[8]	2011	Taiwan	Bladder	PCR-RFLP	375	375	Blood
Liu <i>et al.</i> ^[9]	2011	Taiwan	Breast	PCR-RFLP	1232	1232	Blood
Tsou <i>et al.</i> ^[10]	2011	Taiwan	Nasopharyngeal	PCR-RFLP	176	176	Blood
Wu <i>et al.</i> ^[11]	2011	Taiwan	Prostate	PCR-RFLP	250	500	Blood
Hsu <i>et al.</i> ^[12]	2013	Taiwan	Hepatocellular	PCR-RFLP	298	298	Blood
Chang <i>et al.</i> ^[13]	2013	Taiwan	Urothelial tract	PCR-RFLP	218	580	Blood

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism

Table 2: Distribution of CAV1 rs3807987 G14713A (G>A) polymorphism literature included in the present study

Authors and year	Controls				Cases				HWE
	Genotype			Minor allele	Genotype			Minor allele	<i>P</i> value
	GG	AG	AA	MAF	GG	AG	AA	MAF	
Bau <i>et al.</i> 2011	245	96	34	0.21	144	160	71	0.40	<0.001
Liu <i>et al.</i> 2011	801	311	120	0.22	704	409	119	0.26	<0.001
Tsou <i>et al.</i> 2011	116	45	15	0.21	113	47	16	0.22	0.001
Wu <i>et al.</i> 2011	330	129	41	0.21	151	72	27	0.25	<0.001
Hsu <i>et al.</i> 2013	162	96	40	0.29	196	77	25	0.21	<0.001
Chang <i>et al.</i> 2013	377	146	57	0.22	118	72	28	0.29	<0.001

CAV1: Caveolin-1

Table 3: Publication bias and heterogeneity and their statistics

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% confidence interval	<i>P</i> value	Q-value	<i>P</i> _{heterogeneity}	<i>I</i> ² (%)	
A versus G	-0.94	-14.18–12.30	0.85	57.90	<0.001	91.36	Random
AA versus GG	0.24	-9.79–10.29	0.94	31.59	<0.001	84.17	Random
AG versus GG	-1.87	-11.98–8.23	0.63	36.66	<0.001	86.36	Random
AA+AG versus GG	-1.25	-13.53–11.02	0.79	51.30	<0.001	90.25	Random
AA versus GG+AG	0.62	-6.99–8.25	0.82	18.33	0.003	72.73	Random

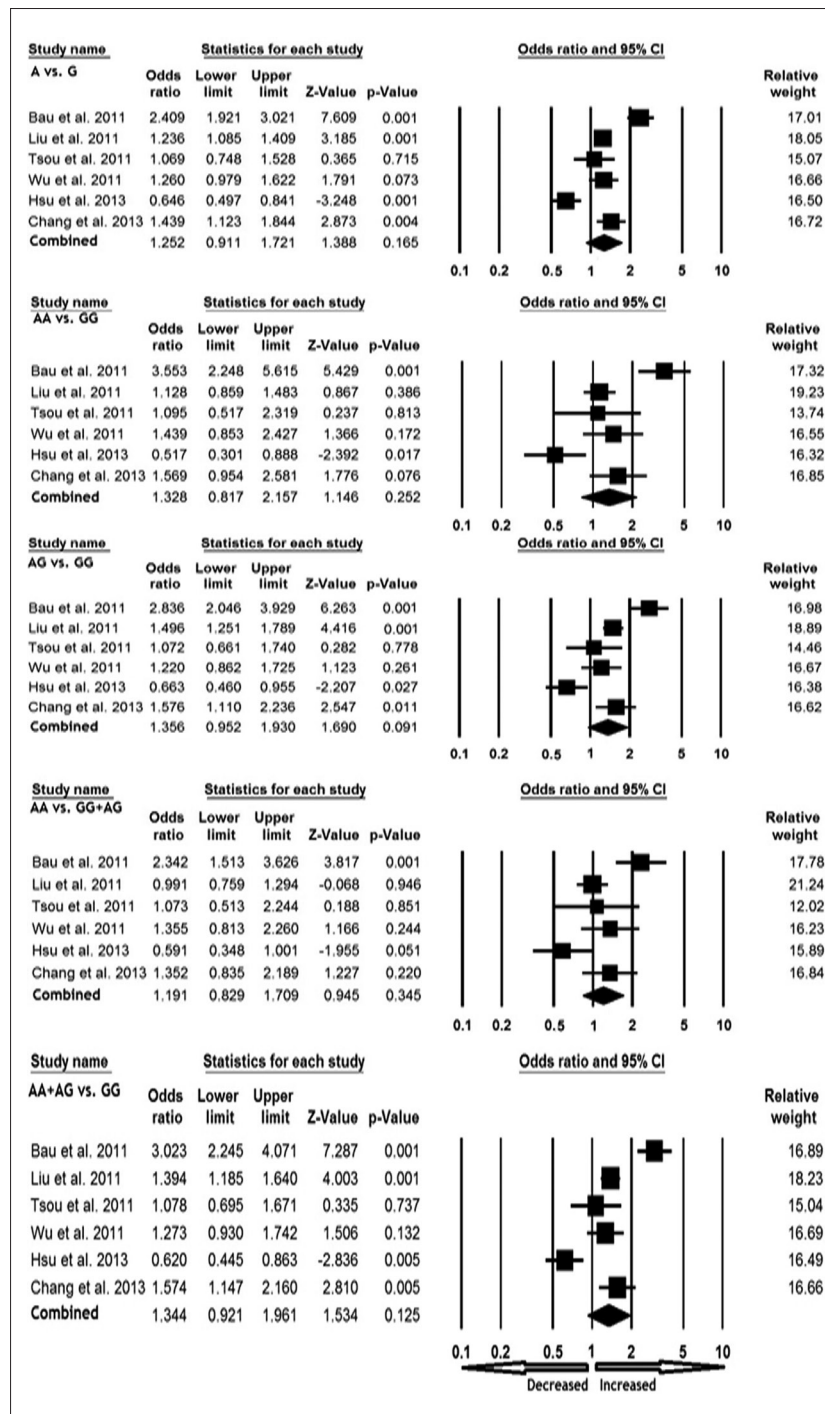


Figure 1: Forest plot of odds ratios (OR) with 95% confidence interval (CI) using random effect model for the risk assessment of cancer associated with caveolin-1 G14713A (G>A) polymorphism in Taiwanese population. Black square denotes the value of OR and the square size denotes the inverse proportion relative to its variance. Horizontal line shows 95% CI of OR. None of the genetic models, i.e., allele (A vs. G), homozygous (AA vs. GG), heterozygous (AG vs. GG), dominant (AA vs. GG + AG), and recessive (AA + AG vs. GG) depicted any association with cancer risk

OR = 1.328, 95% CI = 0.817–2.157), heterozygous (AG vs. GG: $P = 0.091$; OR = 1.356, 95% CI = 0.952–1.930), dominant (AA vs. GG+AG: $P = 0.345$; OR = 1.191, 95% CI = 0.829–1.709), and recessive (AA + AG vs. GG: $P = 0.125$; OR = 1.344, 95% CI = 0.921–1.961) were found associated with any risk of developing cancer.

Sensitivity analysis

Sensitivity analysis was executed to weigh the effect of each study on the collective OR by eliminating each study individually each time. Sensitivity analysis depicted that no individual research study affected the collective OR

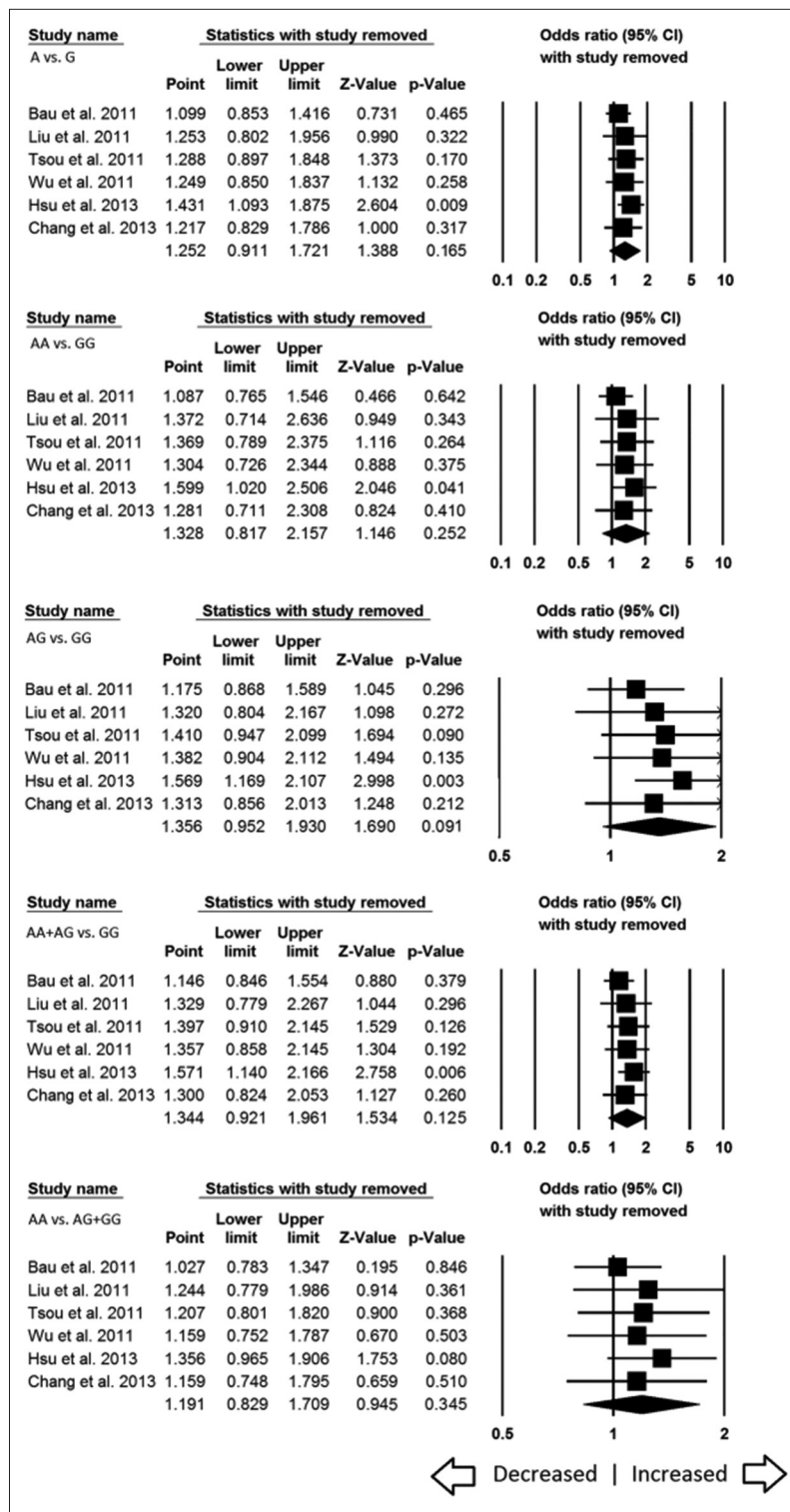


Figure 2: Sensitivity analysis of the studies encompassed in the current meta-analysis

meaningfully, hence, results of our study were relatively stable [Figure 2].

Discussion

The genetic variants are capable of enhancing cancer development and could be helpful for the early diagnosis, and help in design

of targeted treatment and prevention strategies. Lately, lots of scientists have devoted their efforts and research to elucidate the relationship between the genetic variants and susceptibility to cancer. A number of low-penetrance genes have been explored to have the possible influence on the susceptibility to cancer in Taiwanese population. Several studies have been conducted to figure out the relation between CAV1 G14713A (G>A)

gene polymorphism and susceptibility to cancer in Taiwanese population, although the results from studies published so far were inconsistent. This is the first meta-analysis conducted to increase the statistical strength and to obtain more detailed and dependable inference from six studies of CAV1 G14713A (G>A)(rs3807987) polymorphism and cancer susceptibility in Taiwanese population. Combining the data from many studies reduces the chance of random error.^[17] The CAV1 protein performs various functions in different situations in different cells.^[21] Various studies have revealed that caveolins play a major role in various human diseases in caveolin deficient animal models.^[22] The expression of CAV1 gene prevents the lamellipodia formation induced by epidermal growth factor, and thus reduces MTLn3 cells migration and invasiveness.^[23] Alteration of a single nucleotide in CAV1 may alter its differential expression and individual's risk to carcinogenesis.

With the best possible efforts made, we claim that the present meta-analytic study is the first report exploring the association between CAV1 G14713A (G>A)(rs3807987) polymorphism and risk of developing cancer in Taiwanese population. The collective outcomes of this meta-analysis present that G14713A (G>A) polymorphism does not influence the susceptibility to carcinogenesis in all polymorphisms. This points out that the G14713A (G>A) polymorphism cannot be used as potential biomarker for the risk assessment of cancer in the Taiwanese population. The investigated variants possibly do not play a role as a direct susceptibility polymorphism and probably interacts with some other causative gene polymorphisms from the linkage disequilibrium. The susceptibility of cancer is largely polygenic which means that multiple loci may be responsible, contributing small effects to cancer proneness.^[24] Therefore, single gene polymorphism is normally inadequate to determine the susceptibility to this deadly disease.

While interpreting the results of the current meta-analysis, we acknowledged the few limitations and included only those studies that were published in the English language. Further to this, we have included only those data cited by the designated databases (PubMed, EMBASE). A possibility exists that we might have missed some pertinent studies which have been published in languages other than English and sited elsewhere. Owing to the lack of original data, we restricted our results to a single-factor and could not correlate to other factors such as age, sex, and socioeconomic conditions, and other risk factors such as smoking and drinking habits of the patients.

The present study has a number of fortes as well. First, since the current study is free from publication bias, it could be considered statistically robust. Second, the application of the stringent data extraction strategy based on manual searches as well as computer assistance, make it a dependable deduction.

Conclusion

The current study indicates that CAV1 G14713A (G>A) gene polymorphism is not related to the overall susceptibility to

cancer in Taiwanese population. Furthermore, there is a need to conduct more studies with large sample size considering other CAV1 polymorphisms, gene-gene, and gene-environment interaction to explore this relationship. Furthermore, the additional functional analyses of the G14713A (G>A) polymorphism would help in understanding the mechanisms by which CAV1 gene regulates the cancer risk.

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References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
2. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al.* Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from sweden, denmark, and finland. *N Engl J Med* 2000;343:78-85.
3. Glenney JR Jr. Tyrosine phosphorylation of a 22-kDa protein is correlated with transformation by rous sarcoma virus. *J Biol Chem* 1989;264:20163-6.
4. Kato K, Hida Y, Miyamoto M, Hashida H, Shinohara T, Itoh T, *et al.* Overexpression of caveolin-1 in esophageal squamous cell carcinoma correlates with lymph node metastasis and pathologic stage. *Cancer* 2002;94:929-33.
5. Yang G, Truong LD, Wheeler TM, Thompson TC. Caveolin-1 expression in clinically confined human prostate cancer: A novel prognostic marker. *Cancer Res* 1999;59:5719-23.
6. Lin SY, Yeh KT, Chen WT, Chen HC, Chen ST, Chang JG, *et al.* Promoter CPG methylation of caveolin-1 in sporadic colorectal cancer. *Anticancer Res* 2004;24:1645-50.
7. Patlolla JM, Swamy MV, Raju J, Rao CV. Overexpression of caveolin-1 in experimental colon adenocarcinomas and human colon cancer cell lines. *Oncol Rep* 2004;11:957-63.
8. Bau DT, Chang CH, Tsai RY, Wang HC, Wang RF, Tsai CW, *et al.* Significant association of caveolin-1 genotypes with bladder cancer susceptibility in taiwan. *Chin J Physiol* 2011;54:153-60.
9. Liu LC, Su CH, Wang HC, Tsai CW, Chang WS, Ho CY, *et al.* Significant association of caveolin-1 (CAV1) genotypes with breast cancer in taiwan. *Anticancer Res* 2011;31:3511-5.
10. Tsou YA, Tsai CW, Tsai MH, Chang WS, Li FJ, Liu YF, *et al.* Association of caveolin-1 genotypes with nasopharyngeal carcinoma susceptibility in taiwan. *Anticancer Res* 2011;31:3629-32.
11. Wu HC, Chang CH, Tsou YA, Tsai CW, Lin CC, Bau DT, *et al.* Significant association of caveolin-1 (CAV1) genotypes with prostate cancer susceptibility in taiwan. *Anticancer Res* 2011;31:745-9.
12. Hsu CM, Yang MD, Tsai CW, Ho CY, Chang WS, Chang SC, *et al.* The contribution of caveolin-1 genotype and phenotype to hepatocellular carcinoma. *Anticancer Res* 2013;33:671-7.
13. Chang WS, Lin SS, Li FJ, Tsai CW, Li LY, Lien CS, *et al.* Significant association of caveolin-1 (CAV1) genotypes with upper urothelial tract cancer. *Anticancer Res* 2013;33:4907-12.
14. Hattersley AT, McCarthy MI. What makes a good genetic association study? *Lancet* 2005;366:1315-23.

15. Cohn LD, Becker BJ. How meta-analysis increases statistical power. *Psychol Methods* 2003;8:243-53.
16. Wu R, Li B. A multiplicative-epistatic model for analyzing interspecific differences in outcrossing species. *Biometrics* 1999;55:355-365.
17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
21. Li WP, Liu P, Pilcher BK, Anderson RG. Cell-specific targeting of caveolin-1 to caveolae, secretory vesicles, cytoplasm or mitochondria. *J Cell Sci* 2001;114:1397-408.
22. Cohen AW, Hnasko R, Schubert W, Lisanti MP. Role of caveolae and caveolins in health and disease. *Physiol Rev* 2004;84:1341-79.
23. Zhang W, Razani B, Altschuler Y, Bouzahzah B, Mostov KE, Pestell RG, *et al.* Caveolin-1 inhibits epidermal growth factor-stimulated lamellipod extension and cell migration in metastatic mammary adenocarcinoma cells (MTLn3). Transformation suppressor effects of adenovirus-mediated gene delivery of caveolin-1. *J Biol Chem* 2000;275:20717-25.
24. Dragani TA, Canzian F, Pierotti MA. A polygenic model of inherited predisposition to cancer. *FASEB J* 1996;10:865-70.