**Tumour suppressor gene methylation and renal cell carcinoma risk: a comprehensively systematic review and meta-analysis**

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**Supplementary Information**

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**SUPPLEMENTARY METHODS**

**Search strategy in details**

***PubMed database*:**

**#1**. (((((((((((((((((kidney neoplasms[MeSH Terms]) OR kidney neoplasm[Title/Abstract]) OR kidney cancer[Title/Abstract]) OR renal cancer[Title/Abstract]) OR nephric cancer[Title/Abstract]) OR cancer of kidney[Title/Abstract]) OR kidney tumour[Title/Abstract]) OR renal tumour[Title/Abstract]) OR nephric tumour[Title/Abstract]) OR tumour of kidney[Title/Abstract]) OR kidney carcinoma[Title/Abstract]) OR renal carcinoma[Title/Abstract]) OR nephric carcinoma[Title/Abstract]) OR carcinoma of kidney[Title/Abstract]) OR renal neoplasm[Title/Abstract]) OR nephric neoplasm[Title/Abstract]))

**#2**. (((DNA methylation[MeSH Terms]) OR DNA methylation[Title/Abstract]) OR DNA methylations[Title/Abstract])

**#3**.#1 AND #2

***EMBASE database*:**

**#1**. 'kidney neoplasm':ti,ab,kw OR 'kidney cancer':ti,ab,kw OR 'kidney tumor':ti,ab,kw OR 'kidney tumour':ti,ab,kw OR 'kidney carcinoma':ti,ab,kw OR 'renal neoplasm':ti,ab,kw OR 'renal cancer':ti,ab,kw OR 'renal tumor':ti,ab,kw OR 'renal tumour':ti,ab,kw OR 'renal carcinoma':ti,ab,kw OR 'renal cell cancer':ti,ab,kw OR 'renal cell tumor':ti,ab,kw OR 'renal cell carcinoma':ti,ab,kw

**#2**. 'dna methylation':ti,ab,kw OR 'dna methylations':ti,ab,kw

**#3**. #1 AND #2

***CNKI database*:**

**#1**. kidney neoplasm[Subject] OR kidney cancer[Subject] OR kidney tumor[Subject] OR kidney tumour[Subject] OR kidney carcinoma[Subject] OR renal neoplasm[Subject] OR renal cancer[Subject] OR renal tumor[Subject] OR renal tumour[Subject] OR renal carcinoma[Subject] OR renal cell cancer[Subject] OR renal cell tumor[Subject] OR renal cell carcinoma[Subject]

**#2**. DNA methylation[Subject] OR DNA methylations[Subject]

**#3**. #1 AND #2

**SUPPLEMENTARY TABLE**

**Table S1.** Detailed quality scores of individual studies assessed with the Newcastle-Ottawa Quality Assessment Scale (NOS).

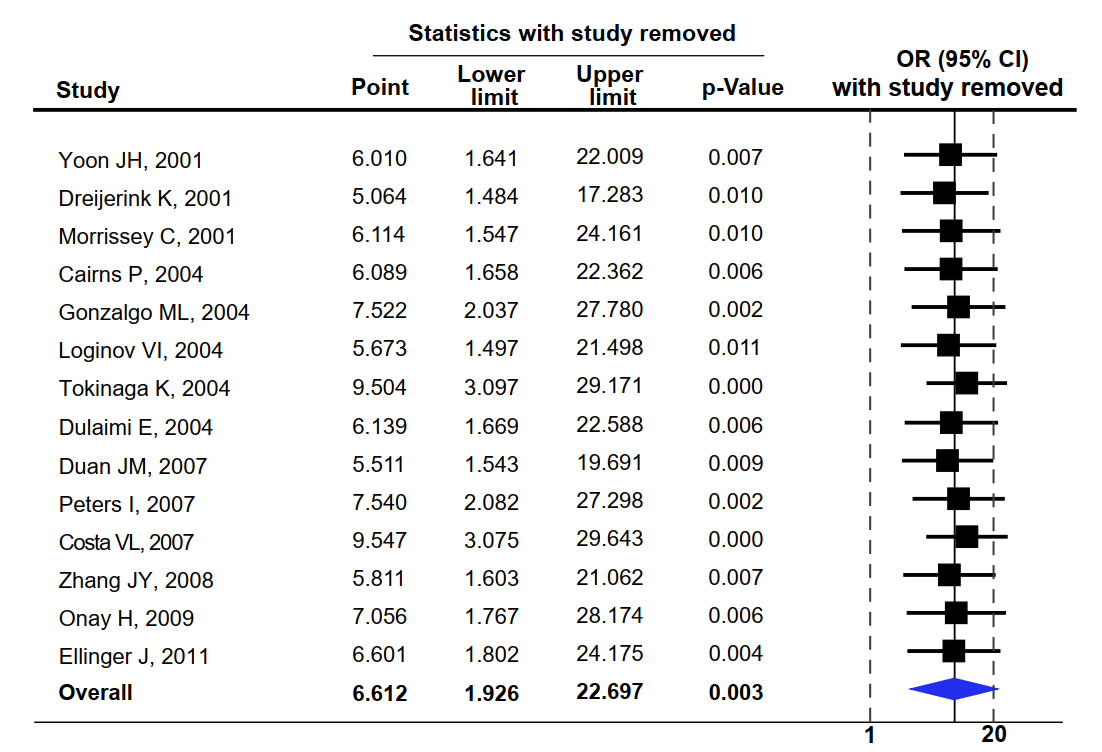
|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | **Selection** | | | | **Comparability** | | **Exposure** | | | **Total Score** |
| **Is the case definition adequate?** | **Representativeness of the cases** | **Selection of controls** | **Definition of controls** | **Study controls for the most important factor** | **Study controls for any additional factor** | **Ascertainment of exposure** | **Same method of ascertainment for cases and controls** | **Non-Response rate** |
| Jung-Hoon Yoon,2001 | \* | \* |  |  |  | \* | \* | \* | \* | 6 |
| Koen Dreijerink,2001 |  |  | \* | \* |  |  | \* | \* | \* | 5 |
| Catherine Morrisey,2001 | \* | \* |  |  | \* | \* | \* | \* | \* | 7 |
| Paul Cairrns,2003 |  |  | \* |  |  |  | \* | \* | \* | 4 |
| Mark L. Gonzalgo,2004 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Loginov VI,2004 | \* | \* | \* |  |  | \* | \* | \* | \* | 7 |
| KenJi Tokinaga,2004 | \* | \* | \* |  |  | \* | \* | \* | \* | 7 |
| Essel Dulaimi,2004 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Duan jianmin,2007 | \* | \* | \* | \* |  |  | \* | \* | \* | 7 |
| Inga Peters,2007 | \* | \* | \* |  |  |  | \* | \* | \* | 6 |
| Vera L Costa,2007 | \* | \* | \* |  |  | \* | \* | \* | \* | 7 |
| Michelle L. Gumz, 2007 | \* | \* | \* |  |  |  | \* | \* | \* | 6 |
| Yasuo Awakura, 2008 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Zhang Jian-Ying,2008 | \* | \* | \* |  |  |  | \* | \* | \* | 6 |
| Huseyin Onay,2008 | \* | \* | \* | \* |  | \* | \* | \* | \* | 8 |
| Jorg Ellinger,2010 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Liu bin,2010 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Yin fengchao, 2010 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9 |
| Zheng fufu,2011 | \* | \* | \* | \* |  |  | \* | \* | \* | 7 |
| Faranaz Atschekzei, 2012 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Yin fengchao, 2018 | \* | \* | \* | \* |  | \* | \* | \* | \* | 8 |

**Table S2.** Publication bias analysis.

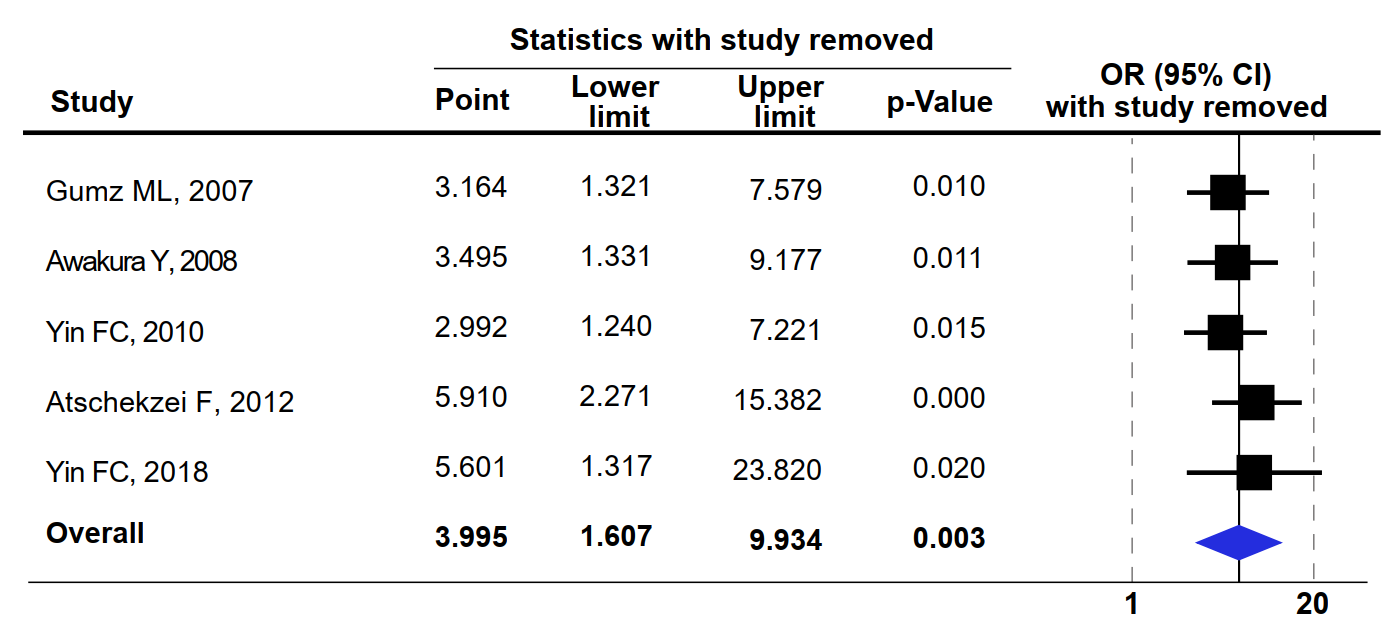
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | P-value | | Pooled ORs (95% CIs)Trim and fill method | |
| Begg’s test | Egger’s test | Unadjusted | Adjusted with  the Trim and fill method |
| RASSF1A (n=14) | 0.743 | 0.691 | 6.612 (1.926-22.697) | 5.156 (1.480-17.966) |
| SFRP1 (n=5) | 0.221 | 0.006 | 3.995 (1.607-9.934) | 1.478 (0.631-3.462) |
| TIMP3 (n=5) | 0.806 | 0.037 | 2.895 (0.684-12.240) | 0.802 (0.201-3.196) |
| APC (n=4) | 0.734 | 0.547 | 2.052 (0.837-5.031) | 1.954 (0.829-4.602) |
| CDH1 (n=4) | 0.734 | 0.854 | 2.745 (0.303-24.874) | 0.584 (0.047-7.164) |
| GSTP1 (n=3) | 1.000 | 0.823 | 4.508 (1.004-20.239) | 4.508 (1.004-20.239) |
| MGMT (n=3) | 1.000 | 0.828 | 0.679 (0.099-4.650) | 0.679 (0.099-4.650) |
| RARβ2 (n=3) | 1.000 | 0.188 | 1.232 (0.296-5.126) | 0.632 (0.192-2.074) |
| P16 (n=3) | 1.000 | 0.599 | 1.968 (0.669-5.787) | 1.968 (0.669-5.787) |

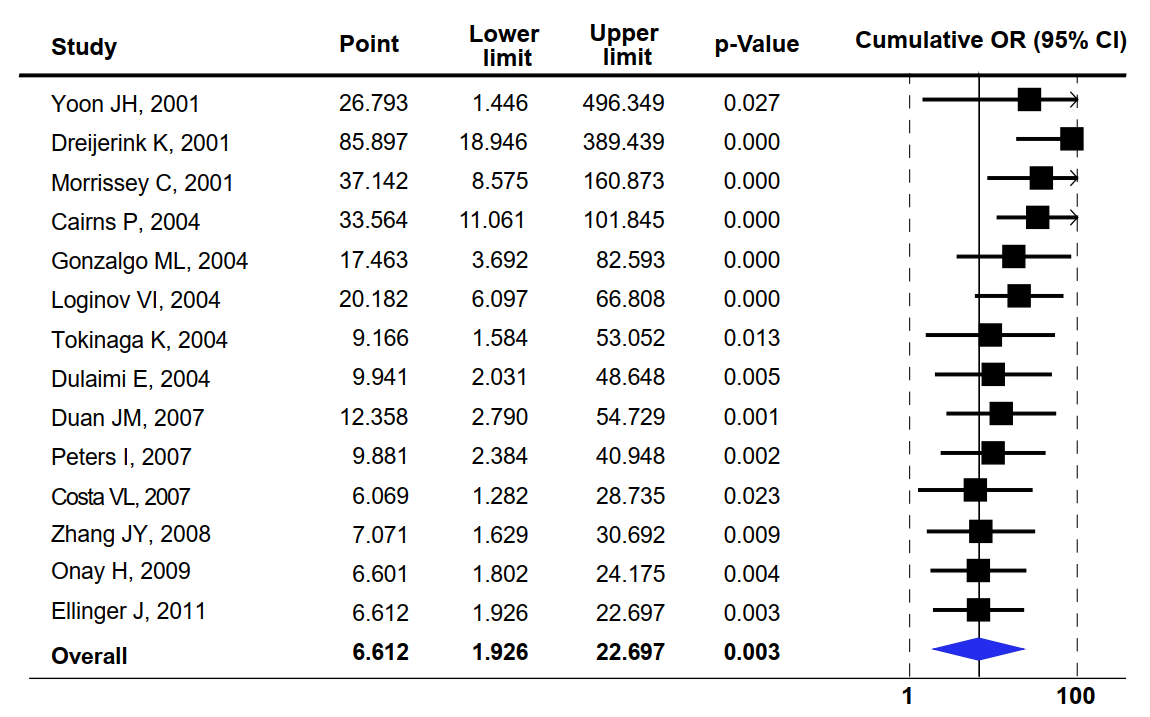
**SUPPLEMENTARY FIGURES**

**Figure S1** Sensitivity analyses for the association of *RASSF1A* methylation and RCC risk by omitting each individual study

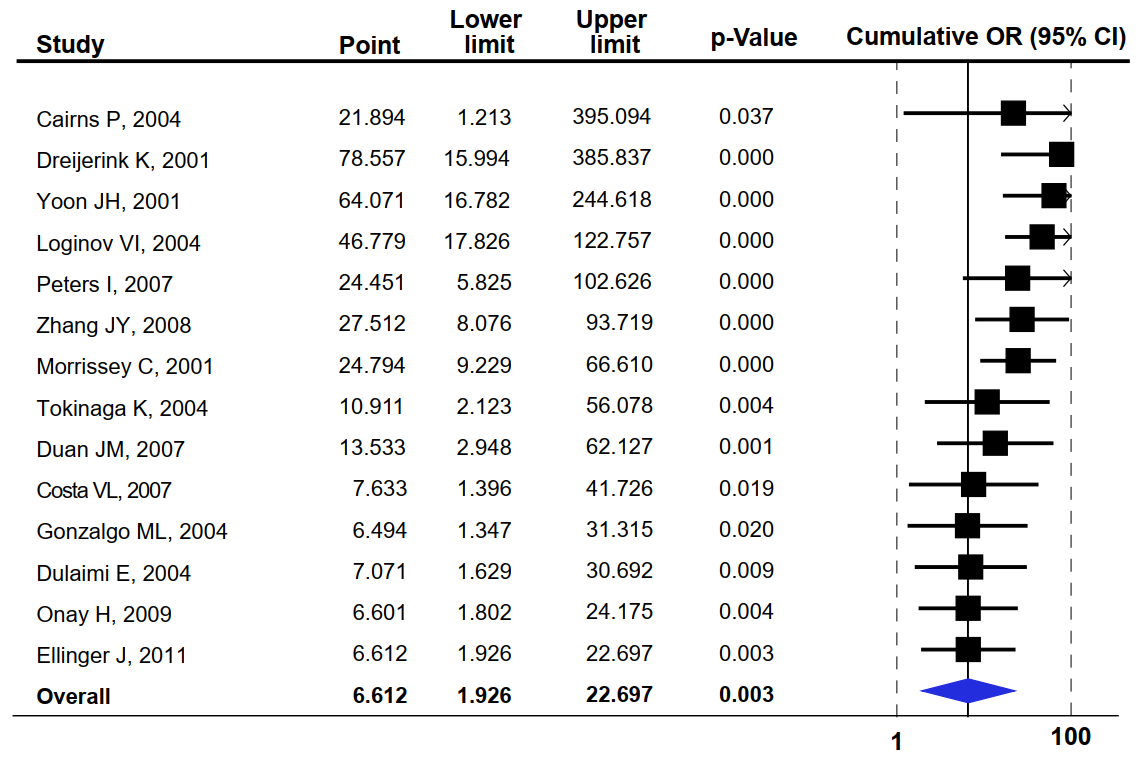


**Figure S2** Sensitivity analyses for the association of *SFRP1* methylation and RCC risk by omitting each individual study

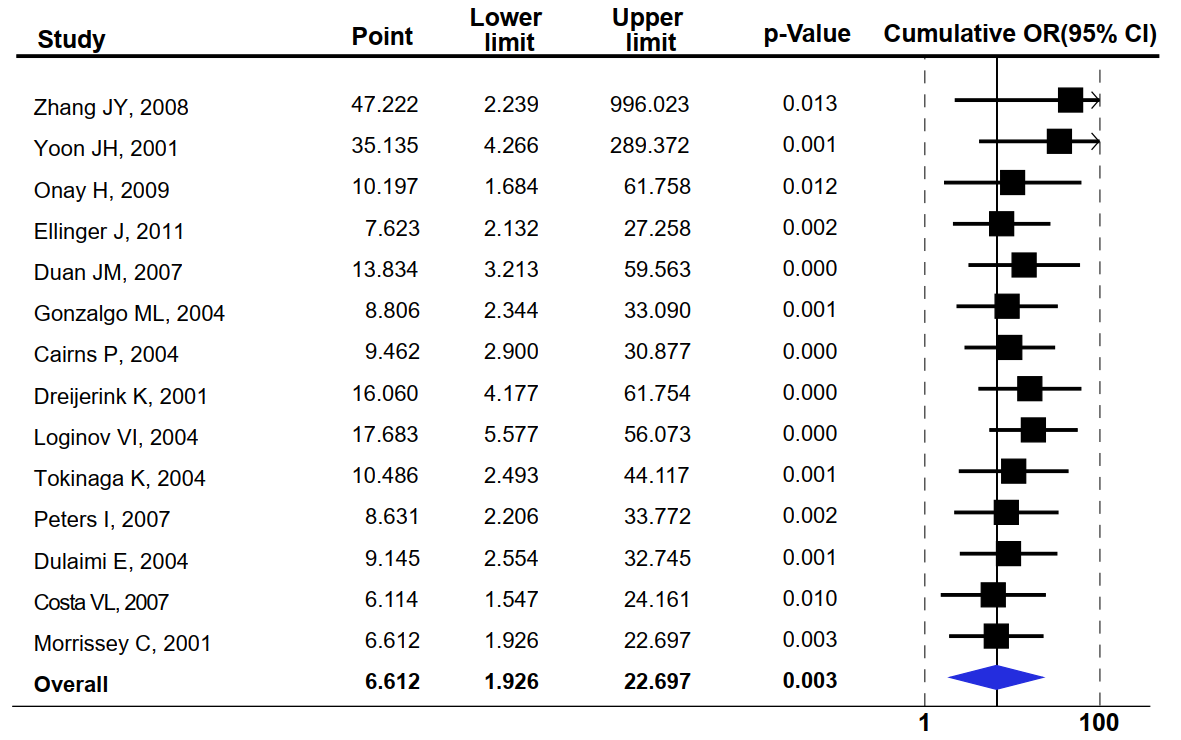


**Figure S3** Cumulative meta-analysis by publication year of original studies for the association between *RASSF1A* methylation and RCC risk.

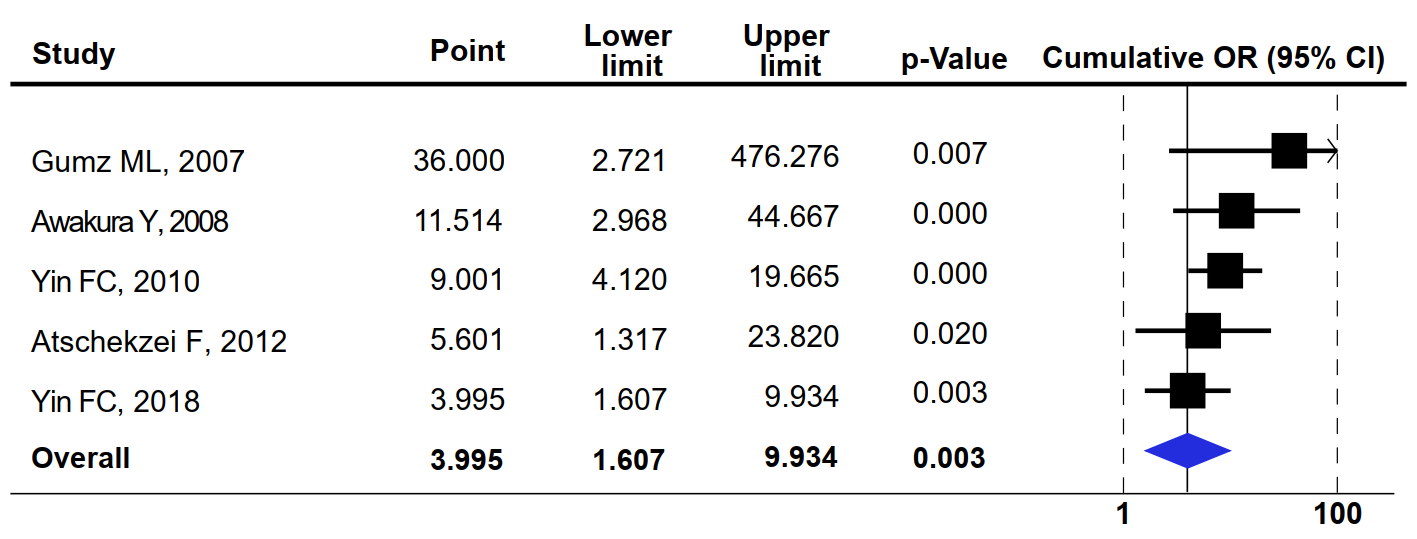
**Figure S4** Cumulative meta-analysis by quality assessment score of original studies for the association between *RASSF1A* methylation and RCC risk.

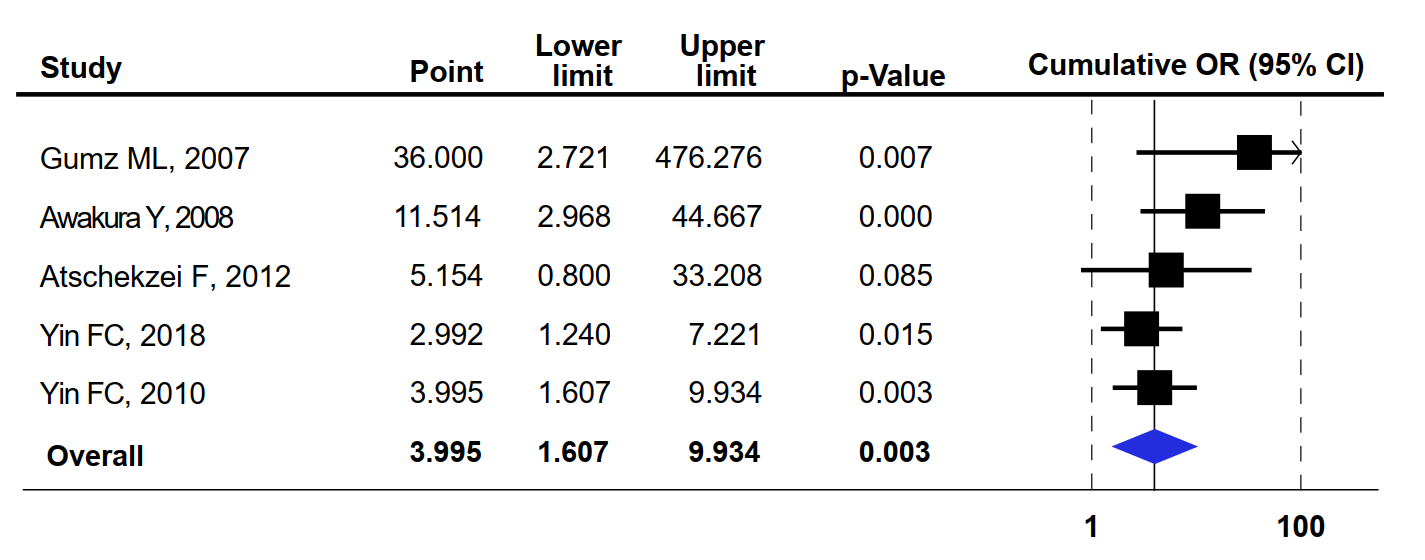


**Figure S5** Cumulative meta-analysis by sample size of original studies for the association between *RASSF1A* methylation and RCC risk.

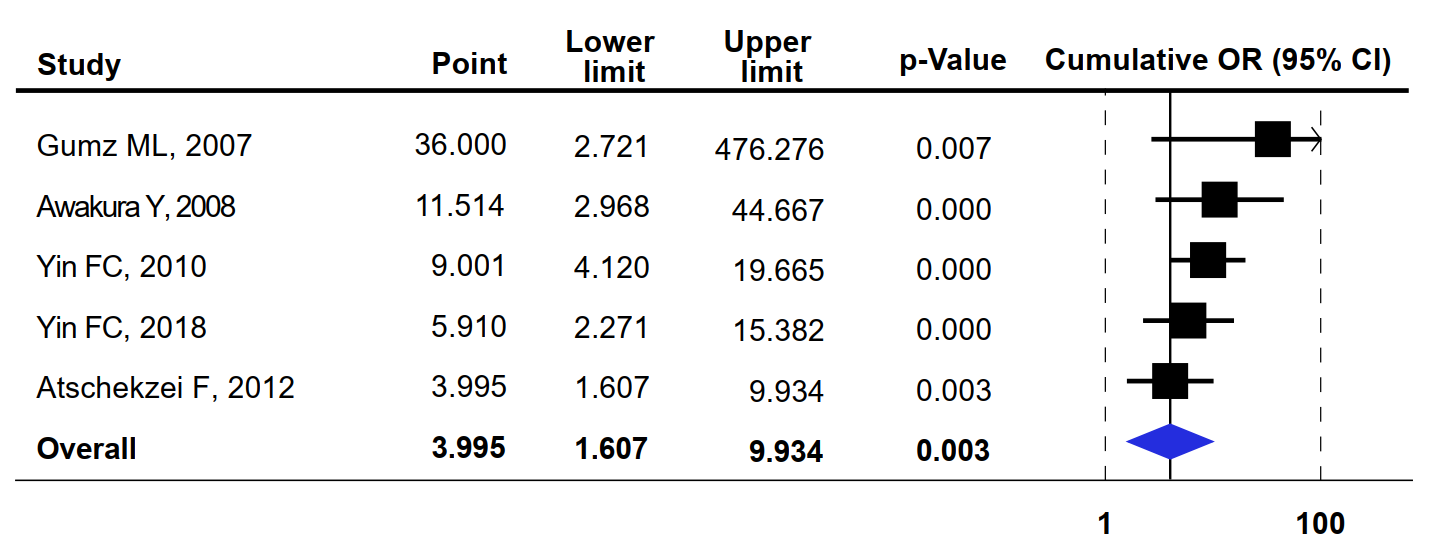


**Figure S6** Cumulative meta-analysis by publication year of original studies for the association between *SFRP1* methylation and RCC risk

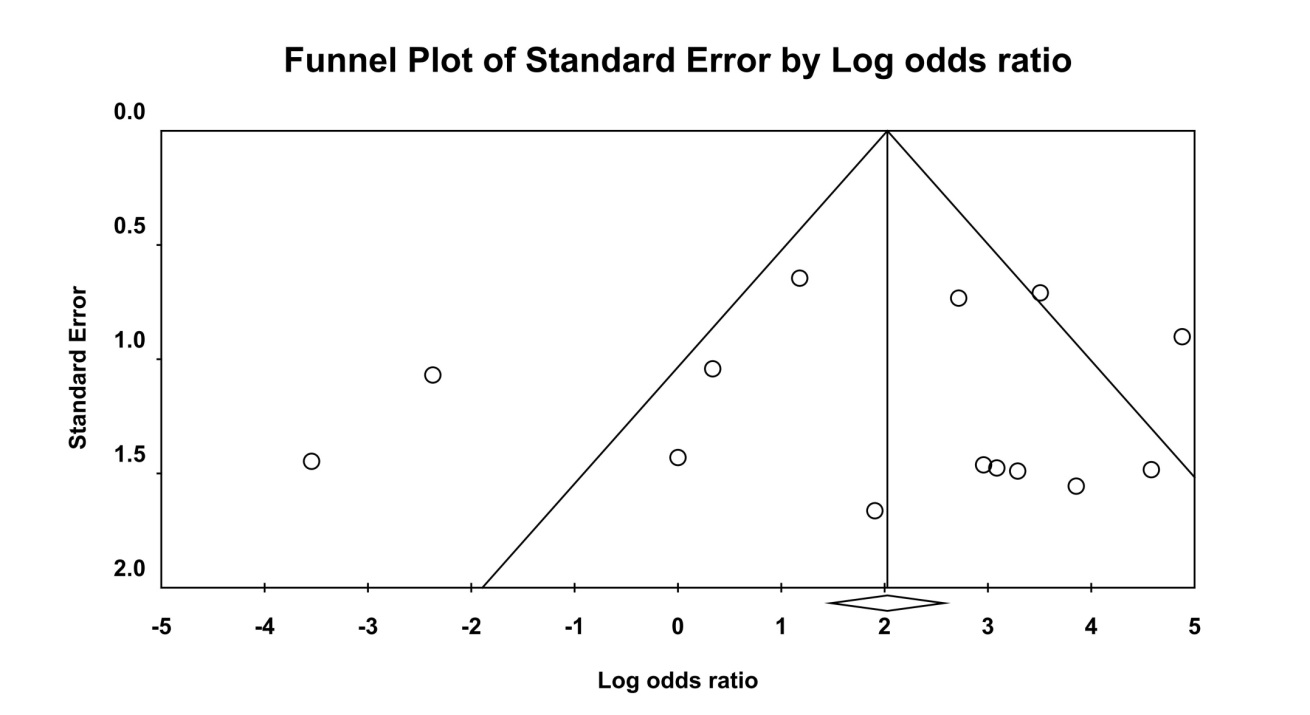


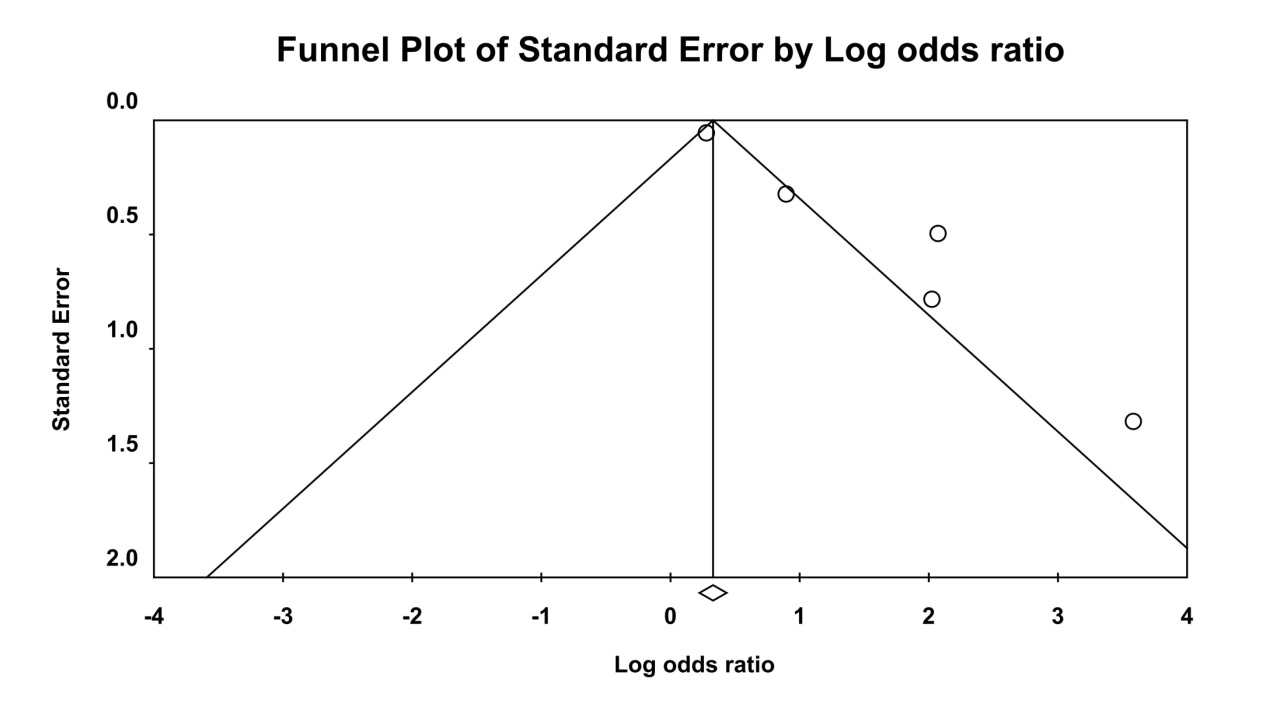
**Figure S7** Cumulative meta-analysis by quality assessment score of original studies for the association between *SFRP1* methylation and RCC risk

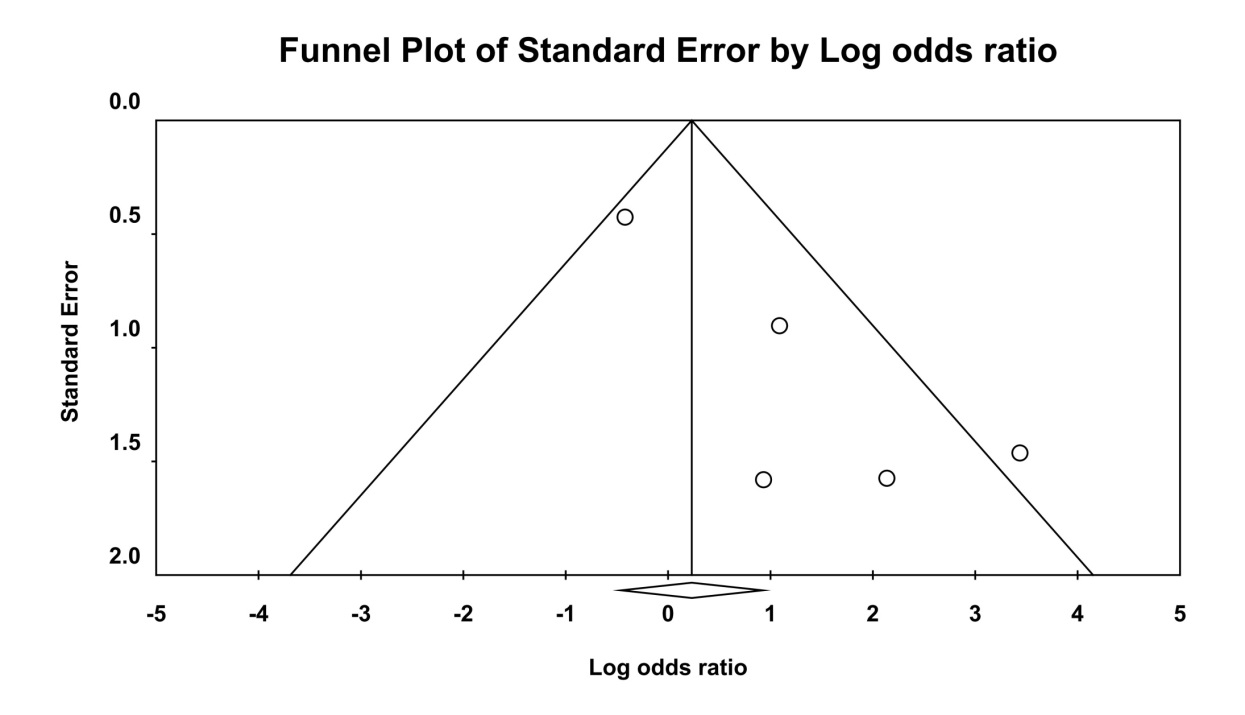
**Figure S8** Cumulative meta-analysis by sample size of original studies for the association between *SFRP1* methylation and RCC risk



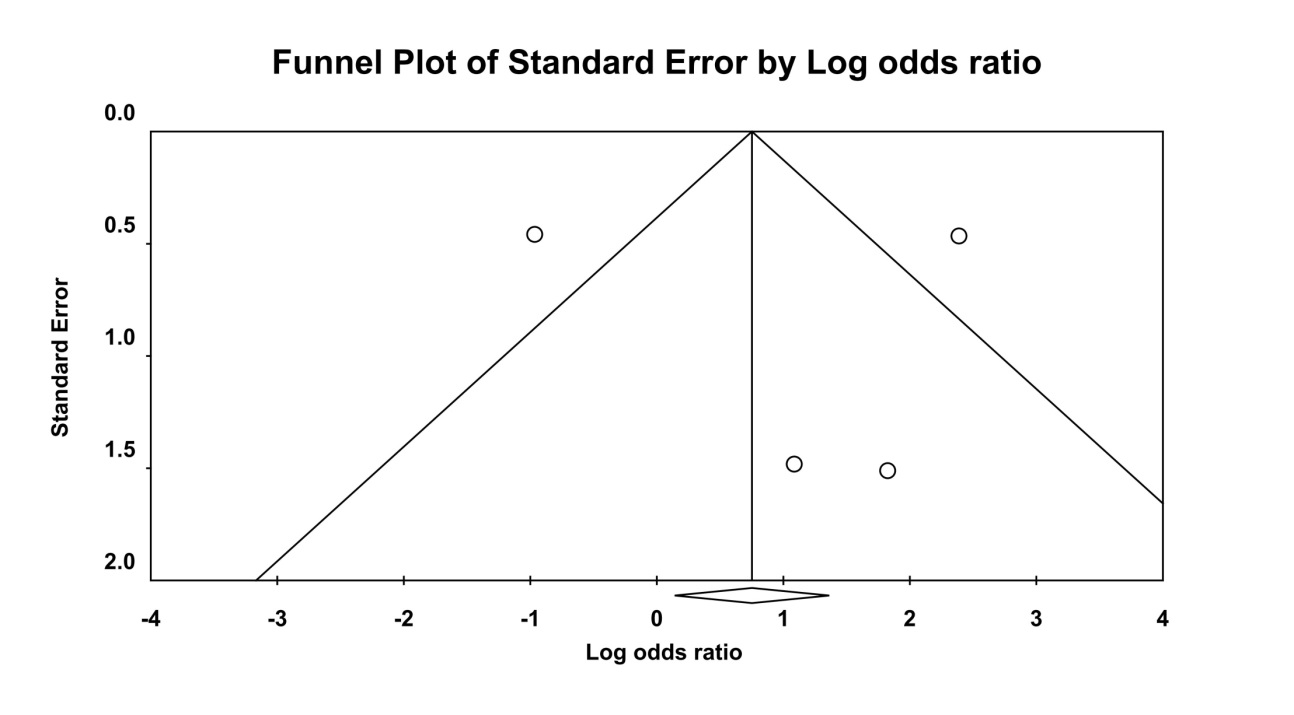
**Figure S4.** Funnel plots of potential publication bias for meta-analyses of (**A**) *RASSF1A*, (**B**) *SFRP1*, (**C**) *TIMP3*, (**D**) *APC*, (**E**) *CDH1*, (**F**) *GSTP1*, (**G**) *MGMT*, (H) *RARβ2*, (I) *p16*.

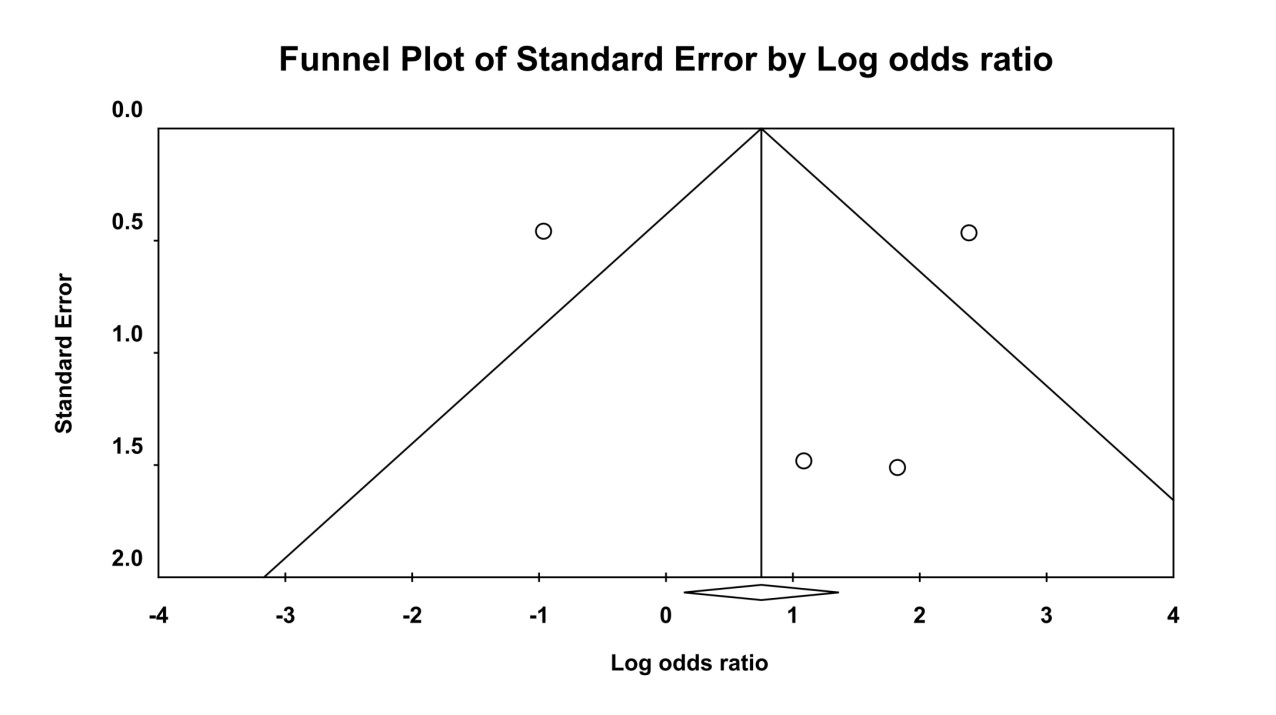
**Figure S4A.** *RASSF1A*

**Figure S4B.** *SFRP1*

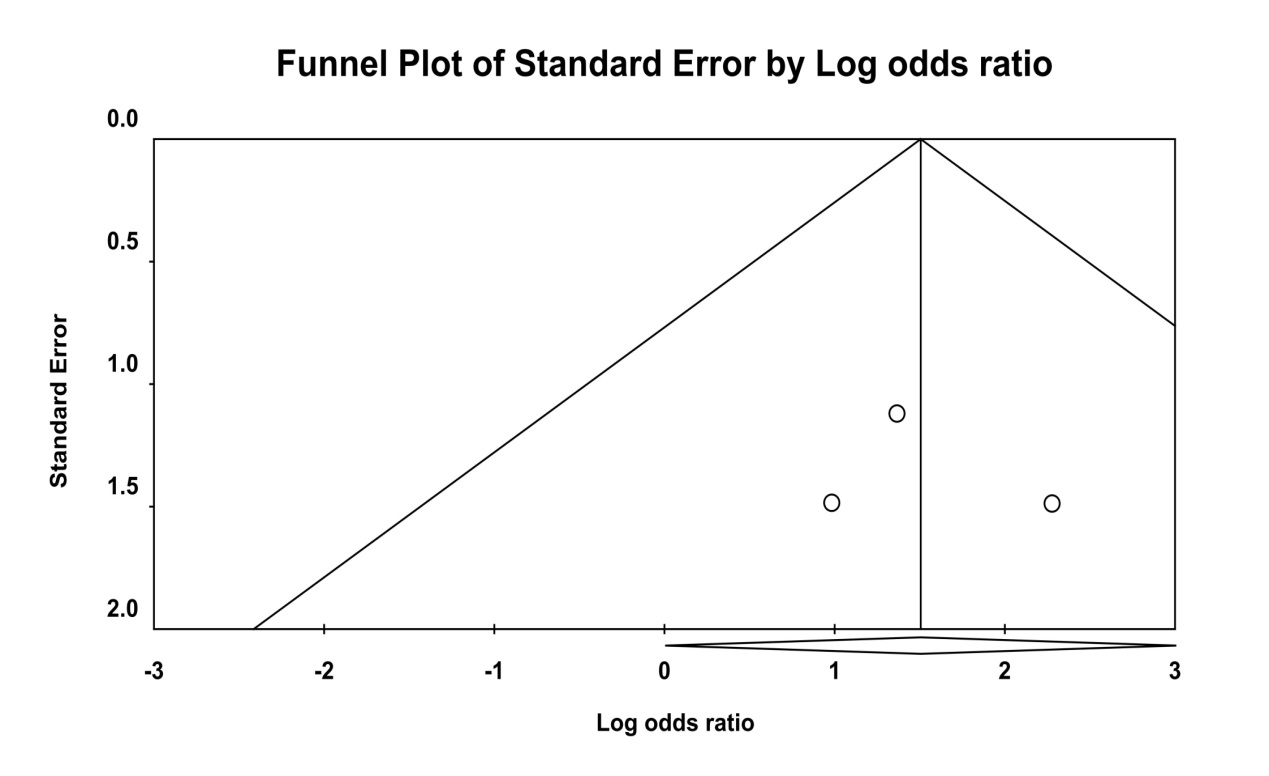
**Figure S4C.** *TIMP3*

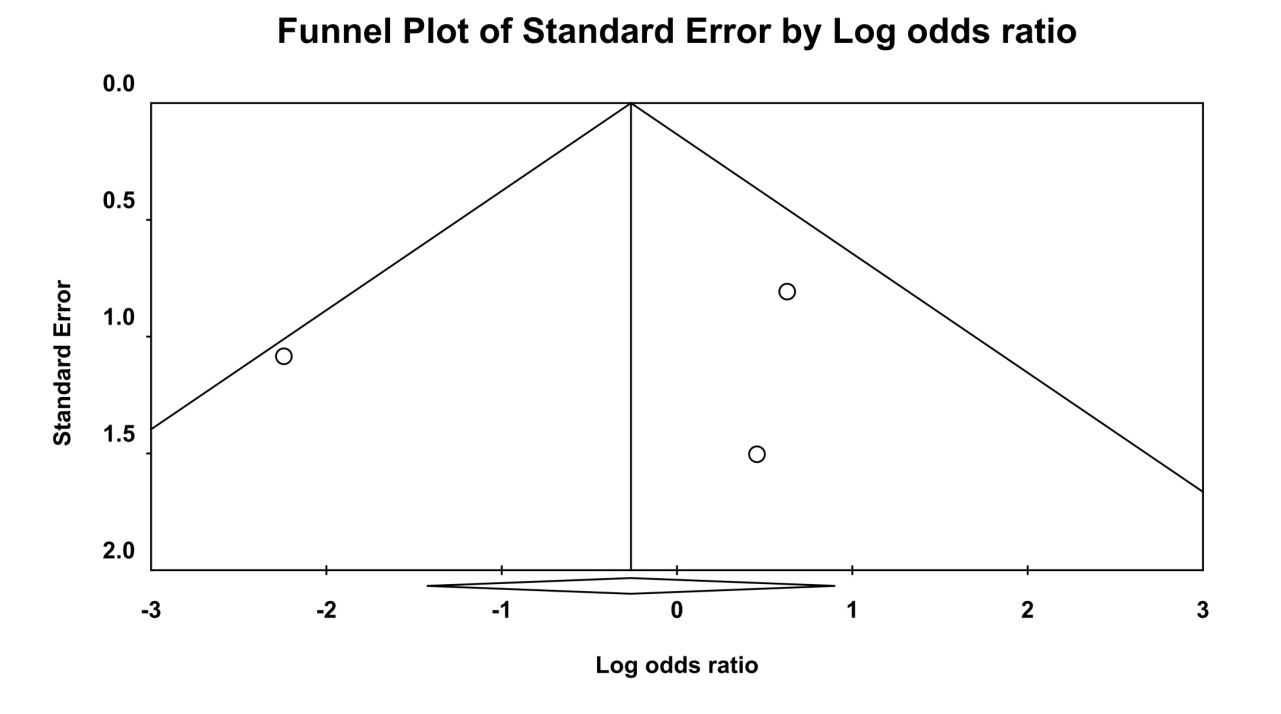
**Figure S4D.** *APC*

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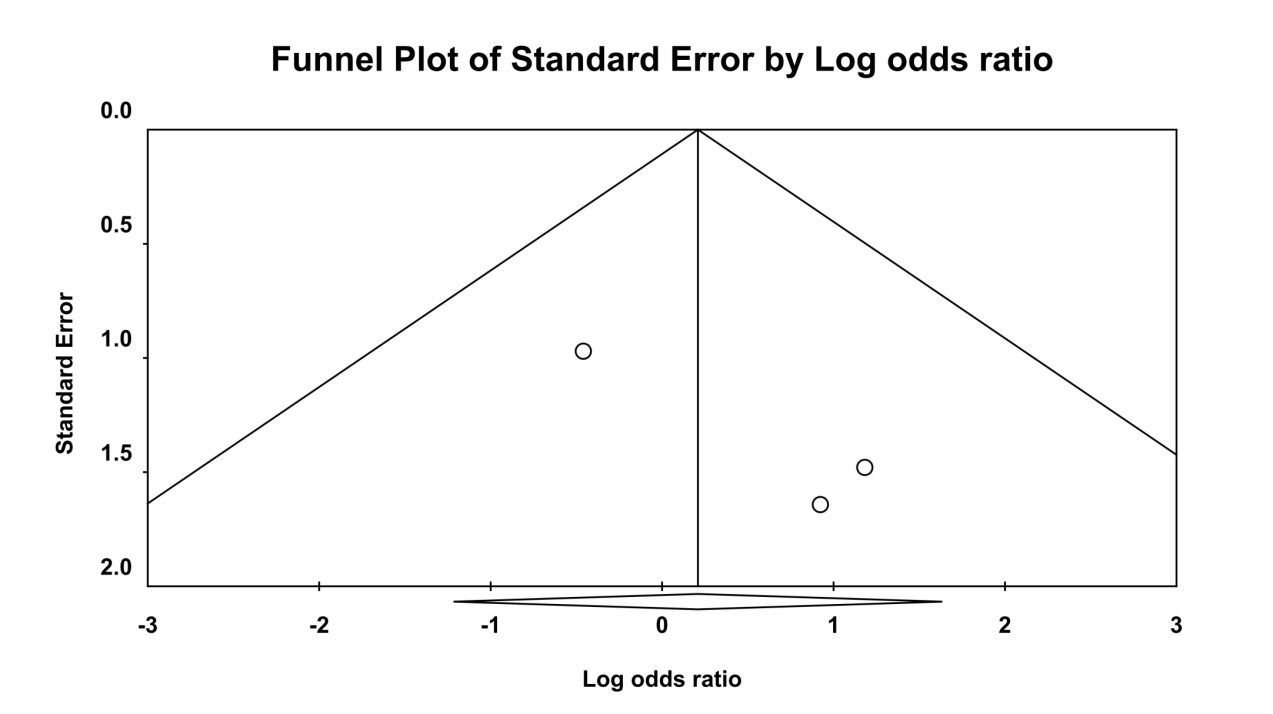
** Figure S4E.** *CDH1*

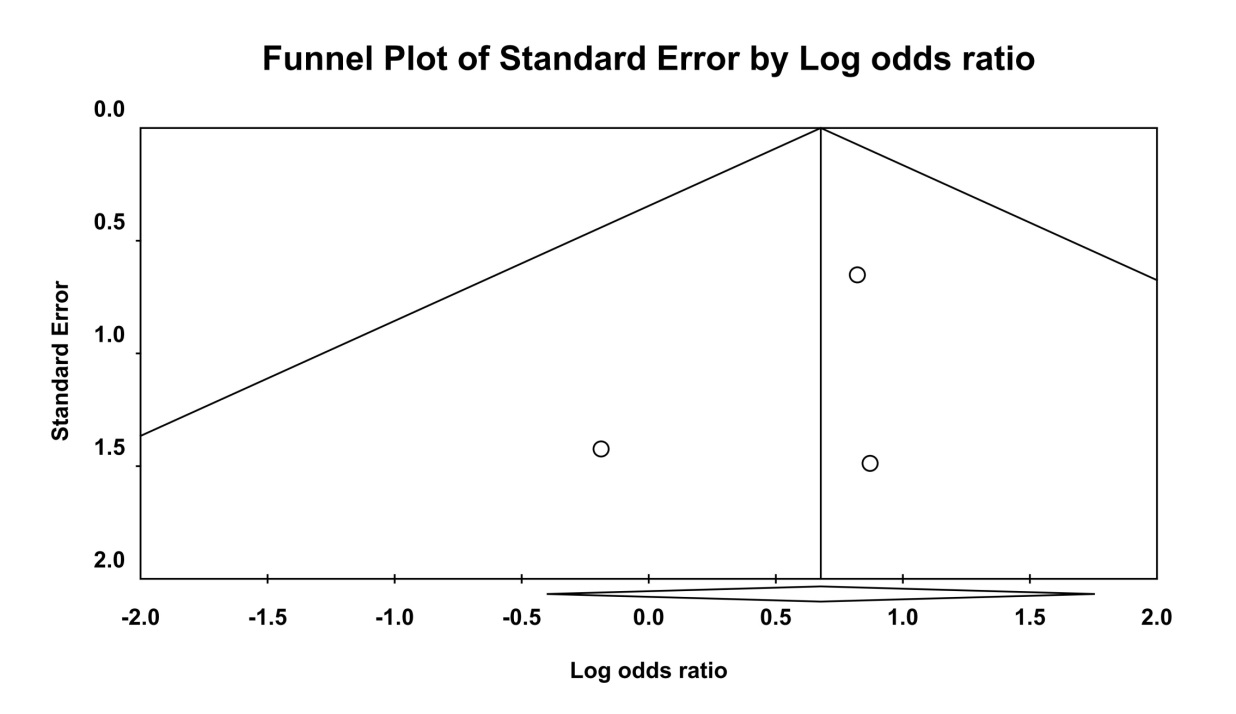
**Figure S4F.** *GSTP1*

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**Figure S4G.** *MGMT*

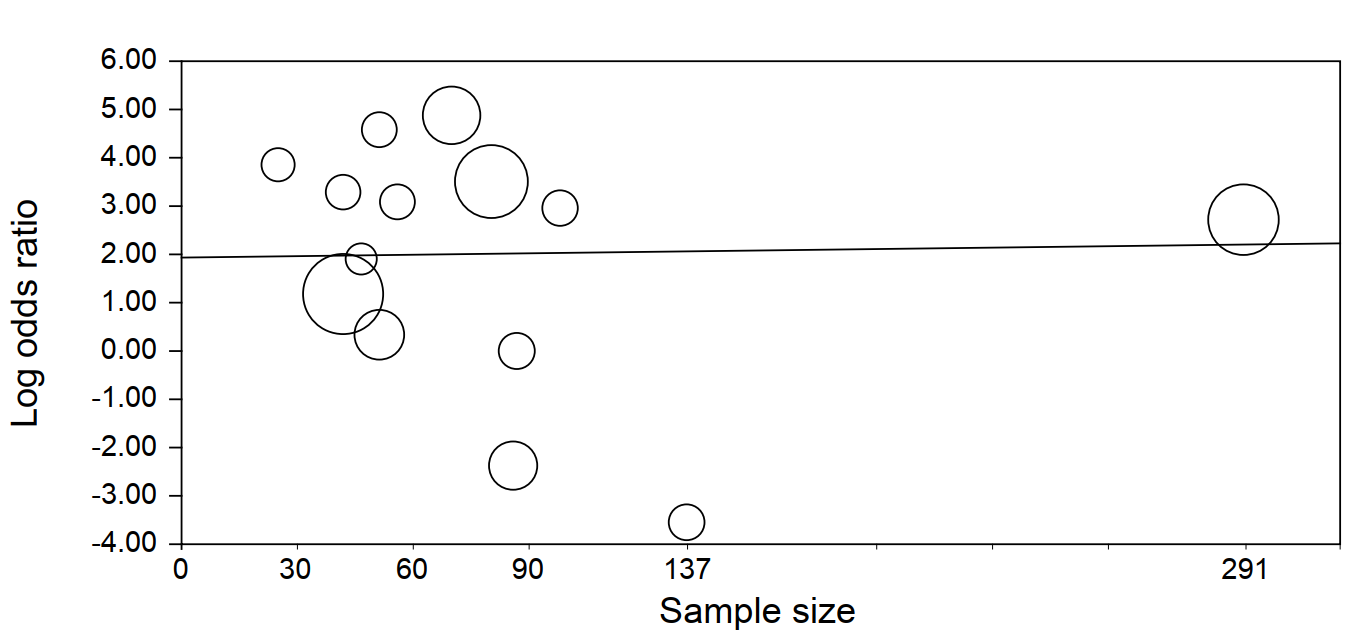
**Figure S4H.** *RARβ2*

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**Figure S4I.** *p16*

**Figure S5.** Meta-regression analyses by sample size of original studies for the associations of RCC risk with (**A**) *RASSF1A* or (**B**) *SFRP1*.

**Figure S5A.** *RASSF1A*



**Figure S5B.** *SFRP1*

