

Supplementary Table S1: Characteristics of NPC patients and healthy controls included in the study.

Characteristics		Bax -248 G>A Case/Control: 70/70		Bcl2 -938 C>A Case/Control: 92/68	
		Case (%) [†]	Control (%)	Case (%)	Control (%)
Gender	Male	48 (68.6)	51 (72.9)	62 (67.4)	44 (64.7)
	Female	22 (31.4)	19 (27.1)	30 (32.6)	24 (35.29)
Age (Year)	<28	6 (8.6)	5 (7.1)	12 (13.4)	4 (5.9)
	28-50	41 (58.6)	41 (58.6)	57 (61.9)	24 (35.3)
	>50	23 (32.9)	24 (34.3)	23 (25.0)	25 (36.8)
Addiction	Tobacco	22 (31.4)	4 (5.7)	31 (33.7)	4 (5.9)
	Areca Nut	16 (22.9)	0	13 (14.1)	0
	Betel Nut	15 (21.4)	2 (2.9)	27 (29.3)	1 (1.5)
	Alcohol	17 (24.3)	5 (7.1)	19 (20.7)	5 (7.4)
Specific Clinical symptoms	Ear Ache	24 (34.3)	1 (1.4)	38 (41.3)	1 (1.5)
	Deafness	18 (25.7)	2 (2.9)	32 (34.8)	3 (4.4)
	Infection	9 (12.9)	0	10 (10.9)	0
	Tinnitus	11 (15.7)	1 (1.4)	11 (11.9)	1 (1.5)
	Obstruction	19 (27.1)	2 (2.9)	27 (29.3)	2 (3.0)
	Bleeding	22 (31.4)	2 (2.9)	22 (23.9)	2 (3.0)
	Congestion	18 (25.7)	3 (4.3)	29 (31.5)	3 (4.4)
	Headache	26 (37.1)	4 (5.7)	39 (42.4)	3 (4.4)
Clinical Examination [‡]	Cranial nerve palsy	17 (24.3)	1 (1.4)	24 (26.1)	1 (1.5)
	Lymphadenopathy	33 (47.1)	2 (2.9)	46 (50.0)	3 (4.4)
	Keratinizing squamous cell carcinoma	38 (54.3)	NE	47 (51.1)	NE
	Nonkeratinizing differentiated carcinoma	14 (20.0)	NE	25 (27.2)	NE
	Undifferentiated carcinoma	18 (25.7)	NE	20 (21.7)	NE
TNM staging [§]	stage 0: T _{is} , N ₀ , M ₀	0	NE	1 (1.1)	NE
	stage I: T ₁ , N ₀ , M ₀	3 (4.3)	NE	6 (6.5)	NE
	stage II: T ₂ , N ₀ , M ₀ (or T ₁ /T ₂ , N ₁ , M ₀)	28 (40.0)	NE	33 (35.9)	NE
	stage III: T ₃ , N ₀ to N ₂ , M ₀ (or T ₁ /T ₂ , N ₂ , M ₀)	15 (21.4)	NE	19 (20.7)	NE
	stage IVA: T ₄ , N ₀ , N ₁ /N ₂ , M ₀	22 (31.4)	NE	26 (28.3)	NE
	stage IVB: any T, N ₃ , M ₀	2 (2.9)	NE	5 (5.4)	NE
	stage IVC: any T, any N, M ₁	0	NE	2 (2.2)	NE

T: tumor; N: lymph node; M: metastasis; NE, Not Examined. The subjects are marked and the Data are the number of participants unless otherwise specified.

[†]Frequency distribution is denoted by %.

[‡]According to the WHO histopathological grading system and

[§]According to AJCC classification system.

Supplementary Table S2: Survival analysis by Kaplan-Meier log-rank test.

BAX -248 G>A	Estimate Survival Mean \pm SE	Estimated Proportion Surviving at 5 years	Chi-squared	DF	P-value
GG	47.346 \pm 1.043	54.00	26.6436	2	< 0.0001
GA	35.900 \pm 1.035	52.63			
AA	32.000 \pm 0.000	0.00			
GA+AA	35.692 \pm 1.001	50.00	18.1428	1	< 0.0001
GG	47.346 \pm 1.043	54.00			
BCL2 -938 C>A					
CC	55.111 \pm 1.135	82.35	23.2897	2	<0.0001
CA	46.926 \pm 2.460	60.71			
AA	38.423 \pm 1.808	30.77			
CA+AA	45.114 \pm 1.969	51.22	17.0379	1	< 0.0001
CC	55.218 \pm 1.109	82.35			
GA+CA dual positive	41.657 \pm 1.563	28.57	14.5348	1	0.0001
Others	51.799 \pm 1.035	87.30			

Abbreviation: SE: standard error, DF: Degrees of freedom.

[†]P value <0.05 was considered significant

Supplementary Table S3: Computational analysis for the Transcription factors binding affinity changes.

SNP	TFs	Weight Score SNP (p)	Weight Score Ref (p)	Absolute log(p) difference	Predicted binding region
Bax (-248) G>A	HIF1	1.856 (0.547)	5.748 (0.066)	-0.914	TGGACGGGCGGC
	SP1	0.764 (0.726)	2.726 (0.687)	-0.024	TTGGACGGGC
BCL2 (-938) C>A	PAX3	6.308 (0.006)	2.502 (0.089)	1.143	TCGTCCCCTCTCC
	CREB	3.697(0.082)	0.652 (0.465)	0.750	TCGTCCCATCTCCCC
	PAX9	2.927 (0.338)	5.760 (0.063)	-0.724	ATCGTCCCATCTCCCC TGTCTCTCTCCT

Abbreviation: SNP: Single Nucleotide Polymorphism, TFs: Transcription Factors.

Supplementary Table S4: Meta-analysis results of the BAX -248 G>A association with tissue-specific cancer in the overall and stratified study.

Study comparison	Forest plot analysis			Heterogeneity			
	OR	95% CI	P-value	Q-value [†]	P _Q [‡]	I ² (%) [§]	Model
Overall studies							
A vs G	1.23	0.98, 1.55	0.06	54.24	<0.05	74.19	Random
AA vs GG	1.79	1.31, 2.43	0.00	20.24	>0.05	40.73	Fixed
GA vs GG	1.13	0.92, 1.38	0.22	29.55	<0.05	52.63	Random
AA+GA vs GG	1.21	0.97, 1.52	0.09	40.99	<0.05	65.84	Random
AA vs GG+GA	1.73	1.28, 2.33	0.00	18.93	>0.05	36.62	Fixed
Carcinomas							
A vs G	1.60	1.09, 2.34	0.01	19.41	<0.05	74.24	Random
AA vs GG	2.61	1.68, 4.06	0.00	3.57	>0.05	0.00	Fixed
GA vs GG	1.31	0.93, 1.86	0.12	10.42	>0.05	52.03	Random
AA+GA vs GG	1.53	1.04, 2.25	0.02	14.10	<0.05	64.54	Random
AA vs GG+GA	2.53	1.65, 3.87	0.00	3.21	>0.05	0.00	Fixed
Other Malignancies							
A vs G	1.05	0.78, 1.41	0.73	29.89	<0.05	73.24	Random
AA vs GG	1.25	0.81, 1.91	0.30	11.07	>0.05	36.78	Fixed
GA vs GG	1.05	0.79, 1.38	0.72	18.76	<0.05	57.37	Random
AA+GA vs GG	1.06	0.78, 1.44	0.69	24.91	<0.05	67.88	Random
AA vs GG+GA	1.21	0.80, 1.83	0.36	9.79	>0.05	28.55	Fixed

Abbreviation: OR: Odd Ratio, 95% CI: Confidence Intervals, Q: Cochran's Q test, P_Q: P-value of the Cochran's Q test, Random: Random-effect model, Fixed: Fixed-effect model.

[†]Q is distributed as a chi-square statistic with number of studies minus 1 degree of freedom

[‡]P with <0.05 was considered significant

[§]I² statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance

Supplementary Table S5: Distribution of Bax (-248) G>A genotypes of NPC cases and controls of different cancers included in the meta-analysis.

Study	Control/ Case	Genotype (Control)			Genotype (Case)			MAF (control/ Case)	HWE	
		GG	GA	AA	GG	GA	AA		χ^2	P value [†]
Chen K et al, 2007	934/814	723	200	11	627	170	17	0.11/0.12	0.46	0.49
Cingeetham A et al, 2015	305/218	253	48	4	193	25	0	0.09/0.05	0.96	0.32
Dholariya et al 2016	70/70	47	19	4	34	24	12	0.19/0.34	1.14	0.28
Edathara PM et al, 2016	509/477	429	74	6	42	54	2	0.08/0.06	1.84	0.17
Javid J et al, 2015	160/160	90	51	19	70	43	47	0.27/0.42	6.80	0.009
Mirmajidi H. et al, 2015	89/100	67	21	1	69	31	0	0.12/0.15	0.20	0.64
Mozhagan Moazami, 2016	62/62	24	25	13	23	24	15	0.41/0.43	1.73	0.18
Nuckel H et. Al, 2006	95/112	79	15	1	87	21	4	0.08/0.12	0.09	0.76
Oliveira C et al, 2014	215/200	167	43	5	163	35	2	0.12/0.09	1.42	0.23
Present study, 2018	70/70	66	4	0	52	17	1	0.02/0.13	0.06	0.80
Saxena A et al, 2002	25/34	24	1	0	22	12	0	0.02/0.17	0.01	0.91
Skogsberg A et al, 2006	207/463	163	40	4	373	84	6	0.11/0.10	0.68	0.40
Starczynski J et al, 2005	135/203	115	19	1	157	44	2	0.07/0.11	0.04	0.84
Wang WL et al, 2014	446/424	340	90	16	287	108	29	0.13/0.19	9.43	0.002
Yildiz Y et al, 2013	82/53	63	19	0	40	13	0	0.11/0.12	1.40	0.23

Abbreviation: MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium

[†]P-value >0.05 was considered significant

Supplementary Table S6: Meta-analysis results of the BCL2 -398 C>A association with tissue-specific cancer in the overall and stratified study.

Study comparison	Forest plot analysis			Heterogeneity			
	OR	95% CI	P-value	Q-value [†]	P _Q [‡]	I ² (%) [§]	Model
Overall studies							
A vs C	0.98	0.81, 1.17	0.83	133.22	<0.05	88.74	Random
AA vs CC	0.93	0.64, 1.37	0.74	127.83	<0.05	88.26	Random
CA vs CC	0.96	0.79, 1.17	0.74	61.63	<0.05	75.66	Random
AA+CA vs CC	0.95	0.76, 1.19	0.70	95.08	<0.05	84.22	Random
AA vs CC+CA	0.97	0.71, 1.33	0.88	103.80	<0.05	85.55	Random
Carcinomas							
A vs C	0.88	0.74, 1.06	0.18	81.36	<0.05	85.25	Random
AA vs CC	0.75	0.51, 1.09	0.14	76.07	<0.05	84.22	Random
CA vs CC	0.87	0.71, 1.07	0.29	40.66	<0.05	70.49	Random
AA+CA vs CC	0.85	0.68, 1.07	0.18	61.61	<0.05	80.52	Random
AA vs CC+CA	0.81	0.60, 1.10	0.19	62.40	<0.05	80.77	Random
Other Malignancies							
A vs C	1.45	1.26, 1.66	0.00	0.52	>0.05	0.00	Fixed
AA vs CC	2.07	1.15, 3.72	0.01	7.39	<0.05	72.94	Random
CA vs CC	1.33	0.97, 1.82	0.07	4.30	>0.05	53.84	Random
AA+CA vs CC	1.42	1.18, 1.72	0.00	0.60	>0.05	0.00	Fixed
AA vs CC+CA	1.89	1.02, 3.50	0.04	8.87	<0.05	77.46	Random

Abbreviation: OR: Odd Ratio, 95% CI: Confidence Intervals, Q: Cochran's Q test, P_Q: P-value of the Cochran's Q test, Random: Random-effect model, Fixed: Fixed-effect model.

[†]Q is distributed as a chi-square statistic with number of studies minus 1 degree of freedom

[‡]P with <0.05 was considered significant

[§]I² statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance

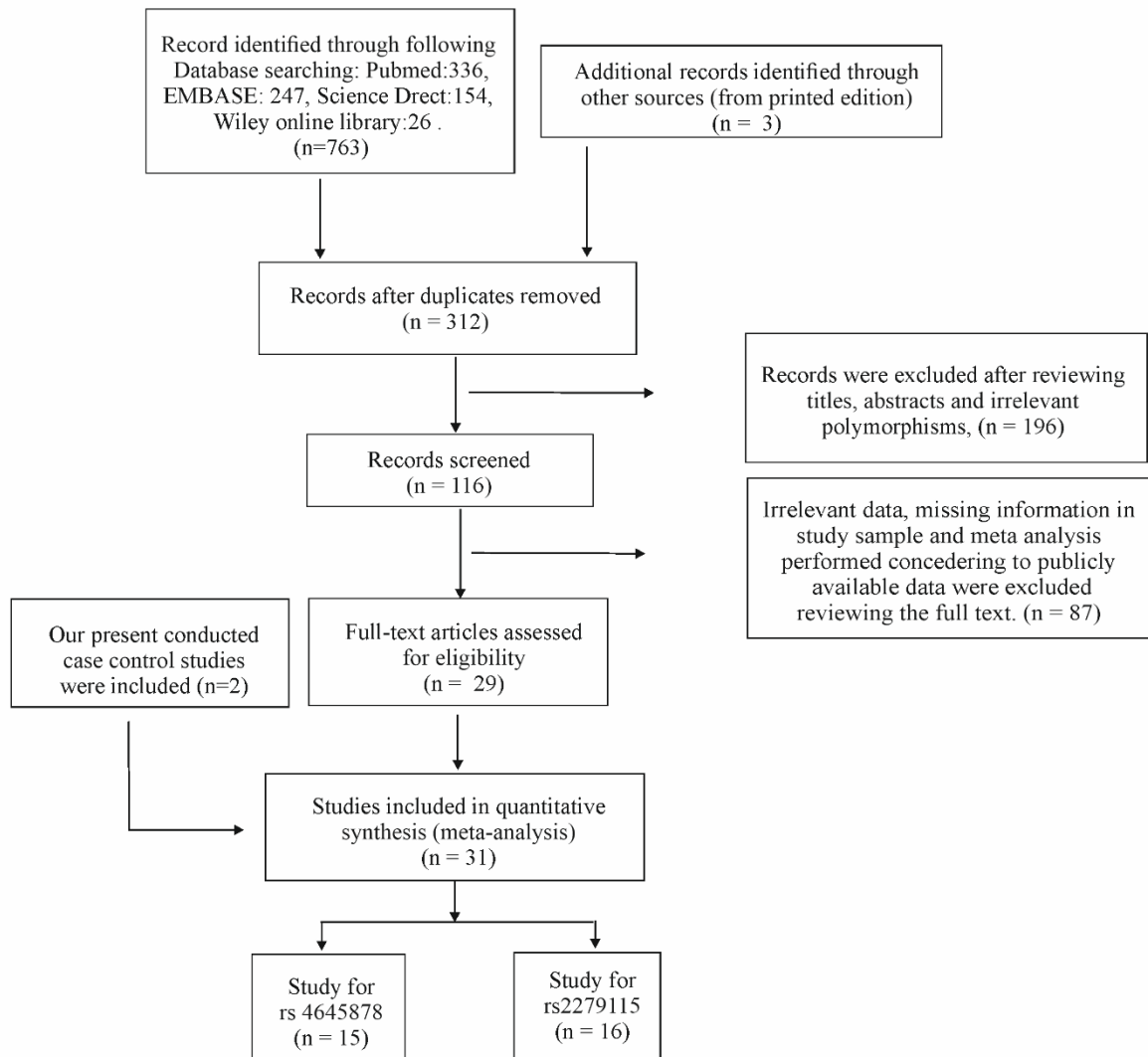
Supplementary Table S7: Distribution of BCL2 -938 C>A genotypes in cases and controls of different cancers included in the meta-analysis.

Study	Control/ Case	Genotype (Control)			Genotype (Case)			MAF (control/ Case)	HWE	
		CC	CA	AA	CC	CA	AA		χ^2	P value [†]
Bachmann HS et al, 2007	120/274	21	63	36	58	140	76	0.56/0.53	0.53	0.46
Christian DF et al, 2010	40/40	12	18	10	14	21	5	0.47/0.38	0.38	0.53
Cingeetham A et al, 2015	305/221	229	37	39	144	47	30	0.18/0.24	111.08	0.00
Hirata H et al, 2008	209/216	101	72	36	92	83	41	0.34/0.38	11.34	0.0006
Javid J et al, 2014	155/155	31	68	56	56	71	28	0.58/0.40	1.52	0.21
Lehnerdt GF et al, 2009	150/133	26	80	44	38	59	36	0.56/0.49	1.01	0.31
Li W et al, 2014	252/248	128	105	19	109	103	36	0.28/0.35	0.15	0.69
Meka PB et al, 2015	204/110	116	81	7	58	38	14	0.23/0.30	2.53	0.11
Moghaddam E et al,2017	130/120	29	65	36	34	74	12	0.52/0.40	0.001	0.97
Mou X et al, 2015	129/200	52	50	27	90	95	15	0.40/0.31	3.20	0.07
Pan W et al, 2015	1600/1587	510	828	262	658	718	211	0.42/0.35	5.82	0.01
Present study, 2018	68/92	54	11	3	51	28	13	0.12/0.29	4.61	0.03
Wang WL et al, 2014	446/424	191	223	32	147	198	79	0.32/0.41	1.59	0.20
Xu P et al, 2013	1017/1017	393	479	145	378	483	156	0.37/0.39	0.002	0.96
Yang X et al, 2016	1040/520	306	544	190	228	238	54	0.44/0.33	3.66	0.05
Zhang N et al, 2011	107/114	46	53	8	42	53	19	0.32/0.39	1.91	0.16

Abbreviation: MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium

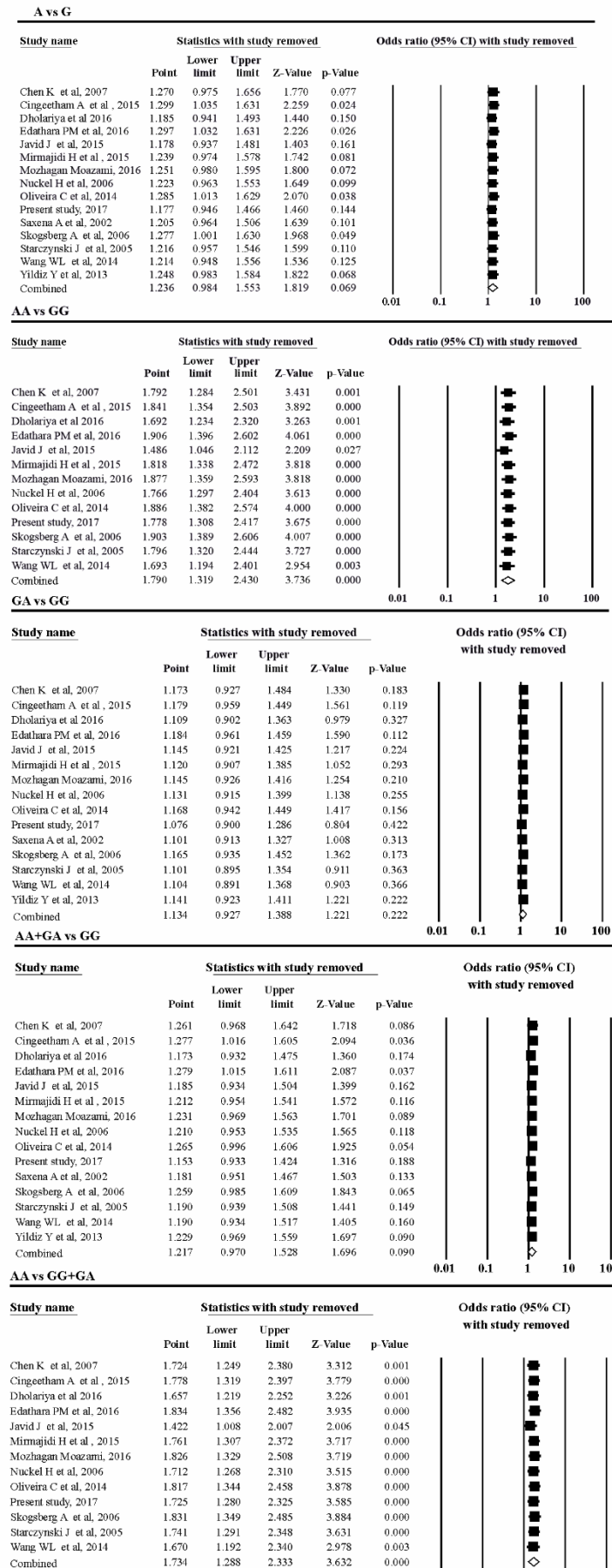
[†]P-value >0.05 was considered significant

Supplementary Figure S1: Identification and selection of the study for Meta-analysis.

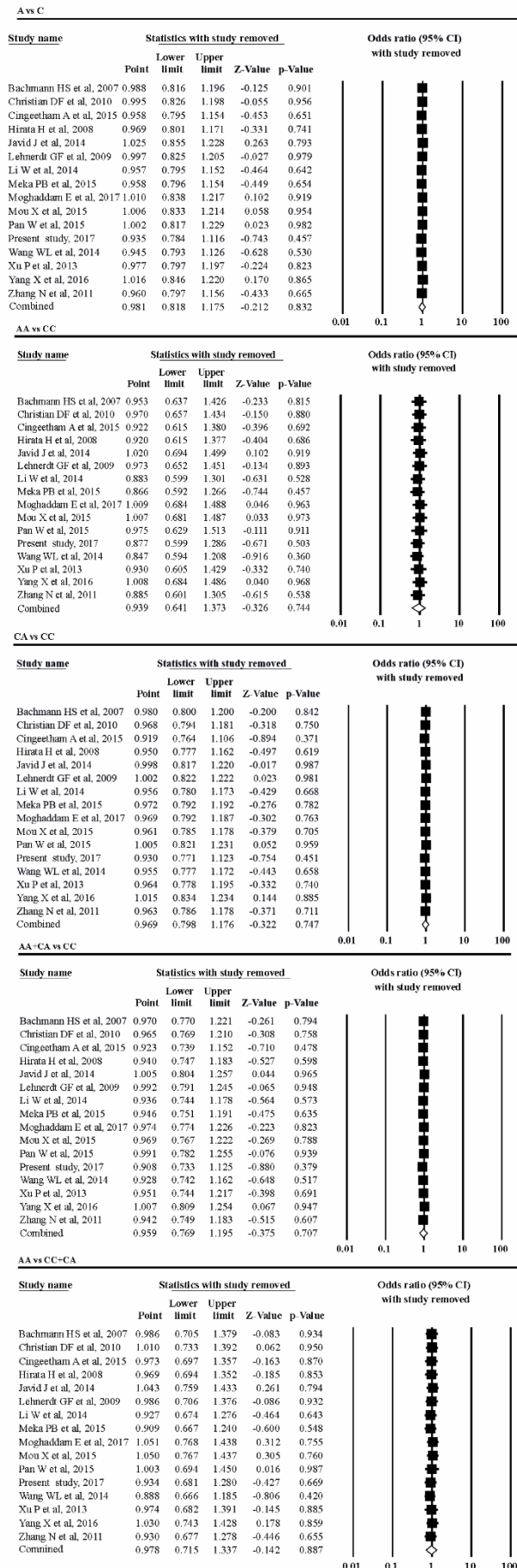


Supplementary Figure S1

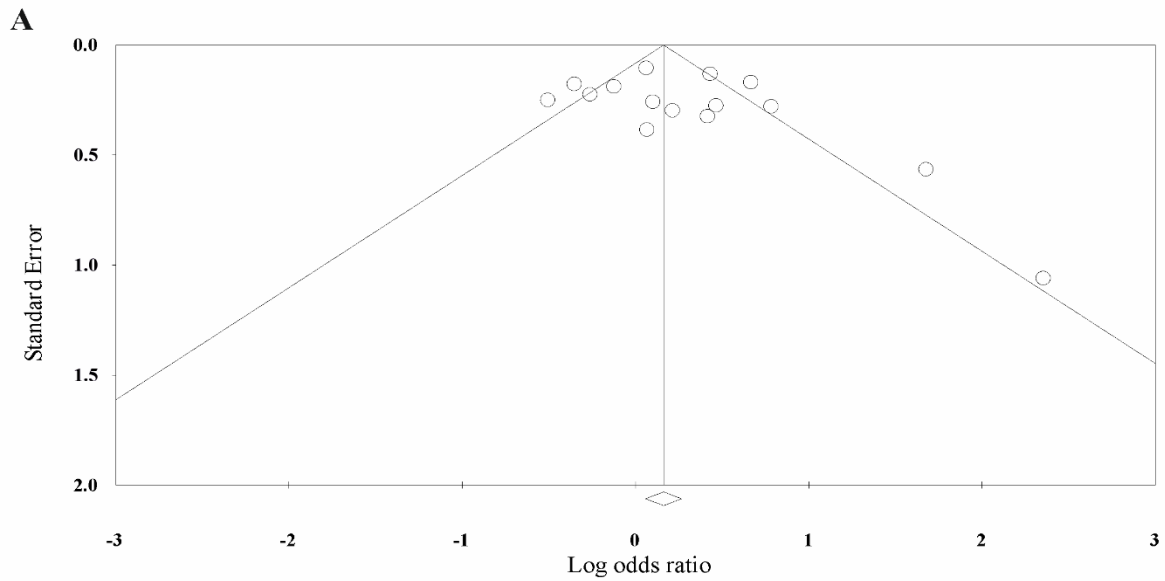
Supplementary Figure S2: Sensitivity analysis of BAX -248 G>A polymorphism with overall cancer. The odds ratios (OR) are represented by the square, the 95% CIs are denoted by horizontal lines and the diamond signifies the pooled OR for each allelic and genetic combination



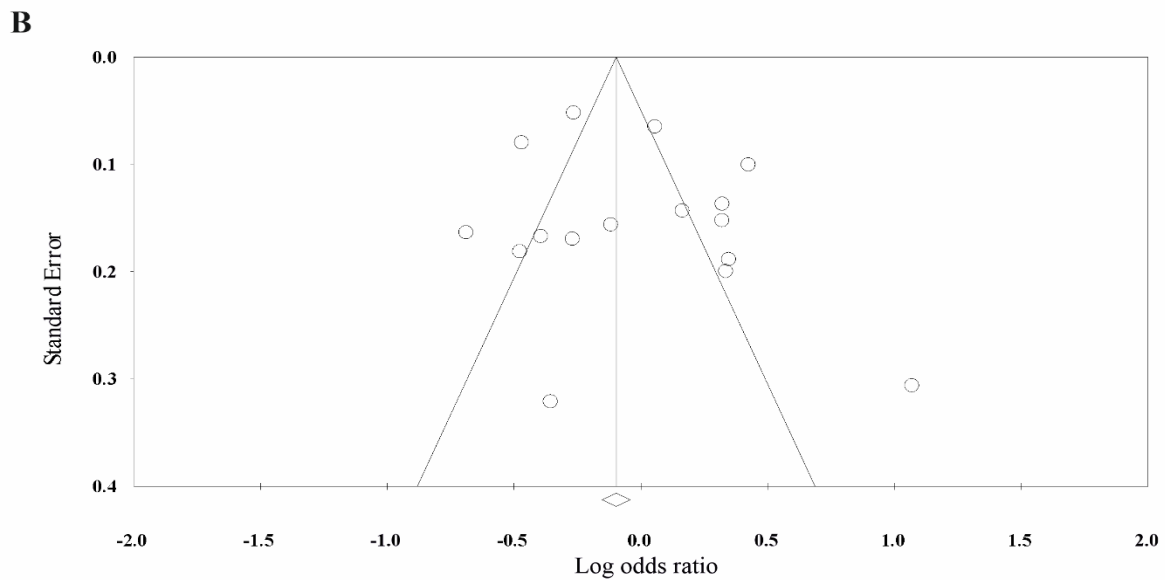
Supplementary Figure S3: Sensitivity analysis of BCL2 (-938) C>A polymorphism with overall cancer. The odds ratios (OR) are represented by the square, the 95% CIs are denoted by horizontal lines and the diamond signifies the pooled OR for each allelic and genetic combination



Supplementary Figure S3



Eggr's Regression: Intercept= 1.20, 95%CI= -1.26 to 3.68, P= 0.31
Begg & Mazumder test: Tau= 0.22, Tau_z=1.18, p=0.23



Eggr's Regression: Intercept= 1.60, 95%CI= -1.69 to 4.90, P= 0.31
Begg & Mazumder test: Tau= 0.02, Tau_z=0.13, p=0.89

Supplementary Figure S4

Supplementary Figure S4: Funnel Plot analysis. Panel A. represents the funnel plot analysis of A vs G of BAX -248 G>A. panel B represents the funnel plot analysis of A vs C of BCL2 (-938) C>A. Y-axis represents the Standard error and the X-axis represents the Odds Ratio. Each dot indicates the individual study. Dotted lines signify the 95% Confidence Interval. A solid line at the middle indicates the overall effect from the meta-analysis.