Supplementary Material

The Association and Clinical Significance of CDKN2A Promoter Methylation in Head and Neck Squamous Cell Carcinoma: a Meta-Analysis

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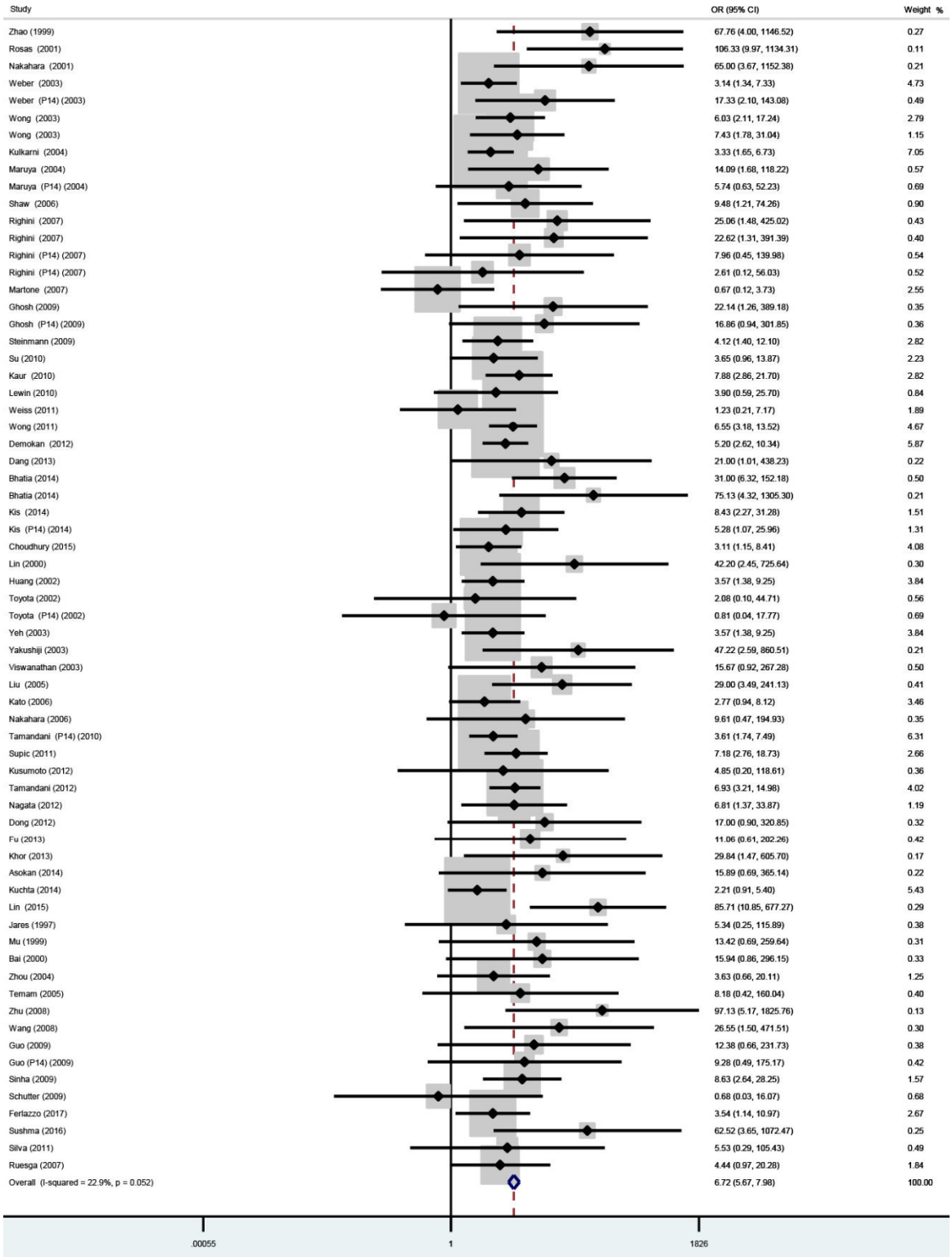
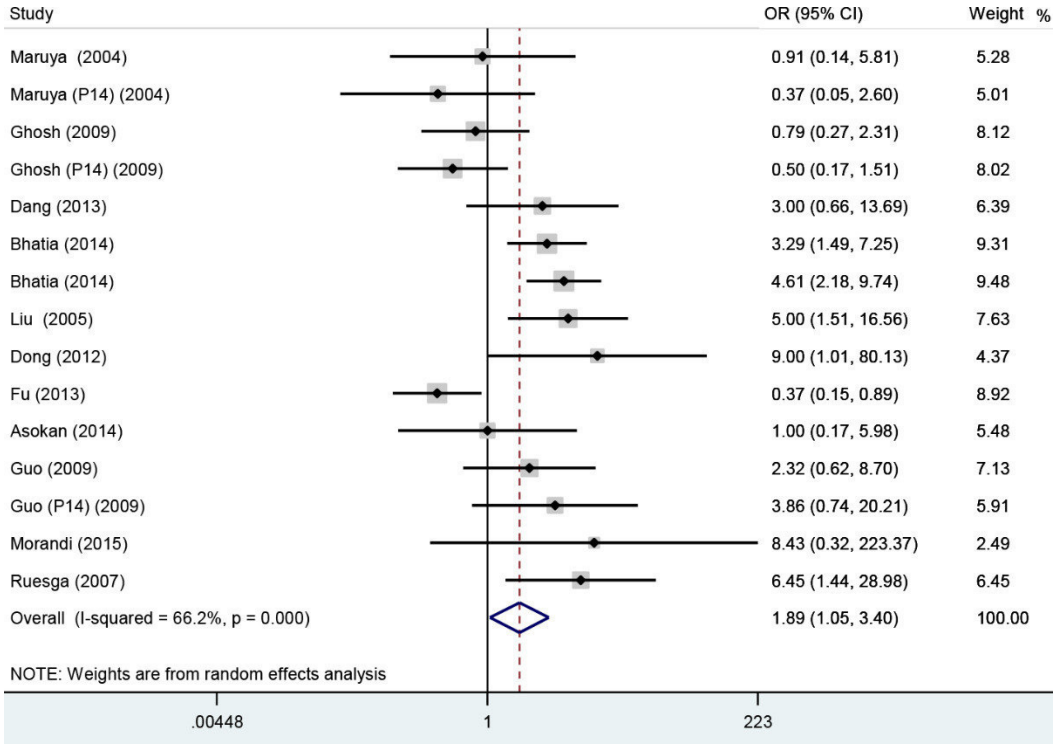
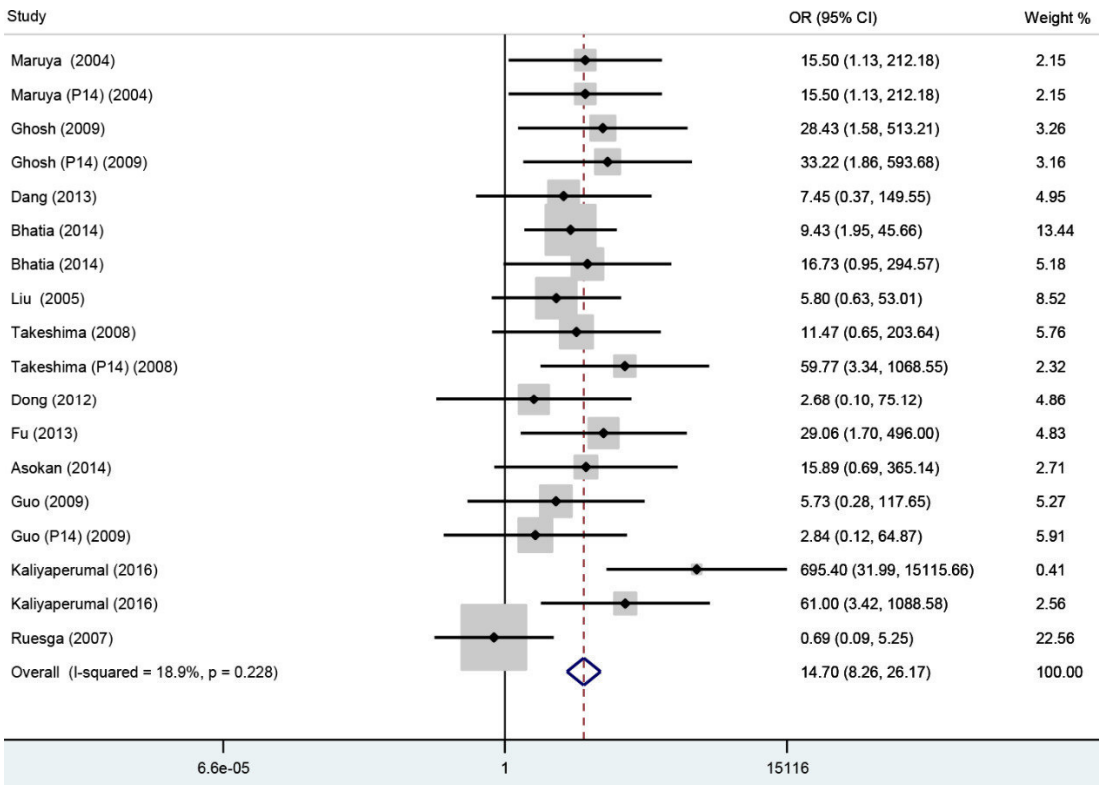
Supplement Figure 1：Forest plot for evaluating the association of *CDKN2A* promoter methylation with HNSCC.



Supplement Figure 2：Forest plot for evaluating the association between methylation of *CDKN2A* in HNSCCs and precancerous lesions.



Supplement Figure 3：Forest plot for evaluating the association of *CDKN2A* promoter methylation with HNSCC precancerous lesions.



Supplement Table 1: The basic characteristics of all eligible studies. M+: positive for *CDKN2A* methylation test; QMSP: quantitative methylation-specific polymerase chain reaction; MSP: methylation-specific polymerase chain reaction; MSRE: methylation-sensitive restriction endonuclease; MS-HRM: methylation-sensitive high-resolution melting analyses; A: autologous (control samples from the same patients); H: heterogeneous (control samples from other individuals).

First author	Year	Country	Ethnicity	Method	Case	Case		Control		control	Premalignancy	
					Sample	M+	total	M+	total	type	M+	total
Zhao	1999	China	Asian	MSP	Tissue	22	65	0	65	A		
Rosas	2001	USA	Caucasian	MSP	Saliva	11	14	1	30	H		
Nakahara	2001	Japan	Asian	MSP	Tissue	16	32	0	32	A		
Weber	2003	Germany	Caucasian	MSP	Tissue	16	50	0	50	A		
								12	42	H		
Weber (*P14*)	2003	Germany	Caucasian	MSP	Tissue	8	50	0	50	A		
								1	42	H		
Wong	2003	China	Asian	MSP	Tissue	36	73	5	29	A		

								0	7	H		
Wong	2003	China	Asian	QMSP	Blood	13	20	4	20	H		
Kulkarni	2004	India	African	MSP	Tissue	40	60	30	60	A		
								0	20	H		
Maruya	2004	USA	Caucasian	MSP	Tissue	10	32	1	32	A	2	6
Maruya (*P14*)	2004	USA	Caucasian	MSP	Tissue	5	32	1	32	A	2	6
Shaw	2006	UK	Caucasian	Pyro	Tissue	22	80	1	26	A		
Righini	2007	France	Caucasian	MSP	Tissue	26	90	0	30	A		
Righini	2007	France	Caucasian	MSP	Saliva	16	60	0	30	H		
Righini (*P14*)	2007	France	Caucasian	MSP	Tissue	10	90	0	30	A		
Righini (*P14*)	2007	France	Caucasian	MSP	Saliva	2	60	0	30	H		
Martone	2007	Italy	Caucasian	MSP	Tissue	4	20	3	11	A		
Ghosh	2009	India	African	MSRA	Tissue	9	63	0	63	A	7	40
Ghosh (*P14*)	2009	India	African	MSRA	Tissue	7	63	0	63	A	8	40
Steinmann	2009	Germany	Caucasian	MSP	Tissue	32	54	6	23	A		
Su	2010	China	Asian	QMSP	Tissue	15	52	3	30	A		
Kaur	2010	India	African	QMSP	Tissue	44	92	5	48	A		
Lewin	2010	Sweden	Caucasian	MSP	Tissue	39	41	15	18	A		
Weiss	2011	Germany	Caucasian	MSP	Tissue	4	51	2	31	H		
Wong	2011	China	Asian	MSP	Tissue	43	64	20	64	A		
								0	20	H		
Demokan	2012	Turkey	Caucasian	MSP	Tissue	52	77	22	77	A		
Dang	2013	China	Asian	MSP	Tissue	6	12	0	10	H	5	20
Bhatia	2014	India	African	MSP	Tissue	62	76	2	16	H	31	54
Bhatia	2014	India	African	MSP	Blood	53	76	0	16	H	18	54
Kis	2014	Hungary	Caucasian	MSP	Tissue	14	50	3	68	H		
Kis (*P14*)	2014	Hungary	Caucasian	MSP	Tissue	8	58	2	68	H		
Choudhury	2015	India	African	MSP	Tissue	23	71	6	45	A		
Lin	2000	China	Asian	MSRE	Tissue	15	56	0	56	A		
Huang	2002	China	Asian	MSP	Tissue	20	48	8	48	A		
Toyota	2002	Japan	Asian	MSP	Tissue	28	96	0	2	A		
Toyota (*P14*)	2002	Japan	Asian	MSP	Tissue	13	96	0	2	A		
Yeh	2003	China	Asian	MSP	Tissue	20	48	8	48	A		
Yakushiji	2003	Japan	Asian	MSP	Tissue	12	25	0	25	A		
Viswanathan	2003	India	African	MSRE	Tissue	23	99	0	25	A		
Liu	2005	China	Asian	MSP	Tissue	15	30	1	30	H	5	30
Kato	2006	Japan	Asian	MSP	Tissue	28	55	6	22	A		
Nakahara	2006	Japan	Asian	MSP	Blood	6	17	0	8	H		
Tamandani (*P14*)	2010	Iran	Caucasian	MSP	Tissue	46	76	17	57	H		
Supic	2011	Serbia	Caucasian	MSP	Tissue	28	47	8	47	A		
Kusumoto	2012	Japan	Asian	MSP	Saliva	4	10	0	3	H		
Tamandani	2012	Iran	Caucasian	MSP	Tissue	56	75	17	57	H		
Nagata	2012	Japan	Asian	MSP	Saliva	13	34	2	24	H		

Dong	2012	China	Asian	MSP	Tissue	15	30	0	8	H	1	10
Fu	2013	China	Asian	MSRE	Tissue	8	39	0	20	H	36	87
Khor	2013	Malaysia	Asian	MSP	Tissue	31	40	0	4	H		
Asokan	2014	India	African	MSP	Tissue	6	10	0	5	H	6	10
Kuchta	2014	Poland	Caucasian	MSP	Tissue	18	53	10	53	A		
Lin	2015	China	Asian	QMSP	Tissue	31	48	1	48	H		
Jares	1997	Spain	Caucasian	MSRE	Tissue	2	31	0	31	A		
Mu	1999	China	Asian	MSRE	Tissue	4	30	0	39	A		
Bai	2000	China	Asian	MSRE	Tissue	6	32	0	32	A		
Zhou	2004	China	Asian	MSRE	Tissue	6	25	2	25	H		
Temam	2005	France	Caucasian	MSP	Tissue	14	33	0	5	H		
Zhu	2008	China	Asian	MSP	Tissue	23	30	0	15	A		
Wang	2008	China	Asian	MSRE	Tissue	8	52	0	69	A		
Guo	2009	China	Asian	MSP	Tissue	11	30	0	10	A	4	20
Guo (*P14*)	2009	China	Asian	MSP	Tissue	9	30	0	10	A	2	20
Sinha	2009	India	Caucasian	MSP	Tissue	33	38	13	30	A		
Schutter	2009	Belgium	Caucasian	MSP	Tissue	2	42	0	5	H		
Ferlazzo	2017	Italy	Caucasian	MSP	Tissue	10	58	5	90	H		
Sushma	2016	India	African	MSP	Tissue	19	50	0	50	A		
Silva	2011	Brazil	Caucasian	MSP	Tissue	4	71	0	41	H		
Ruesga	2007	Spain	Caucasian	MSP	Tissue	25	87	2	24	H	2	34
Morandi	2015	Italy	Caucasian	BNGS	Tissue	1	11				0	29
Cespedes	2000	USA	Caucasian	MSP	Tissue	23	83					
Taioli	2009	USA	Caucasian	QMSP	Tissue	7	61					
Supic	2009	Serbia	Caucasian	MSP	Tissue	45	77					
Silva	2012	Brazil	Caucasian	MSP	Tissue	11	45					
Regan	2008	Ireland	Caucasian	MSP	Tissue	4	24					
Dikshit	2007	France	Caucasian	MSP	Tissue	55	126					
Kraunz	2006	USA	Caucasian	MSP	Tissue	52	169					
Calmon	2007	Brazil	Caucasian	MSP	Tissue	27	43					
Calmon (*P14*)	2007	Brazil	Caucasian	MSP	Tissue	13	43					
Misawa	2016	Japan	Asian	QMSP	Tissue	59	133					
Pierini	2013	Bulgaria	Caucasian	MS-HRM	Tissue	46	97					
Shiga	2012	Japan	Asian	MSP	Tissue	97	121					
Farias	2010	Brazil	Caucasian	MSP	Tissue	59	75					
Nakahara	2006	Japan	Asian	MSP	Tissue	11	17					
Virani	2015	USA	Caucasian	Pyro	Tissue		343					
Roh	2014	Korea	Asian	QMSP	Tissue		353					
Sun	2012	USA	Caucasian	QMSP	Tissue		197					
Lim	2014	Australia	Caucasian	MS-HRM	Tissue	20	113					
Sailasree	2008	India	African	MSP	Tissue		116					
Takeshima	2008	Japan	Asian	MSP	Tissue			0	10		26	74

Takeshima (*P14*)	2008	Japan	Asian	MSP	Tissue	0	10	55	74
Kaliyaperumal	2016	India	African	QMSP	Tissue	0	30	28	30
Kaliyaperumal	2016	India	African	QMSP	Saliva	0	30	15	30

Supplement Table 2: Sensitivity analysis of pooled odds ratio (OR) for *CDKN2A* promoter methylation and head and neck squamous cell carcinoma (HNSCC) under the random-effects model. LL: Low limited; HL: High limited.

Study omitted	OR	LL	HL
Zhao (1999)	6.559	5.523	7.788
Rosas (2001)	6.613	5.568	7.853
Nakahara (2001)	6.605	5.562	7.842
Weber (2003)	6.902	5.793	8.224
Weber (P14) (2003)	6.673	5.62	7.923
Wong (2003)	6.744	5.671	8.022
Wong (2003)	6.716	5.653	7.979
Kulkarni (2004)	6.982	5.849	8.334
Maruya (2004)	6.683	5.628	7.934
Maruya (P14) (2004)	6.731	5.67	7.992
Shaw (2006)	6.67	5.643	7.954
Righini (2007)	6.645	5.598	7.887
Righini (2007)	6.662	5.612	7.907
Righini (P14) (2007)	6.718	5.66	7.973
Righini (P14) (2007)	6.746	5.684	8.007
Martone (2007)	6.883	5.793	8.178
Ghosh (2009)	6.67	5.619	7.918
Ghosh (P14) (2009)	6.688	5.634	7.938
Steinmann (2009)	6.8	5.717	8.088
Su (2010)	6.795	5.718	8.074
Kaur (2010)	6.691	5.625	7.959
Lewin (2010)	6.748	5.683	8.014
Weiss (2011)	6.83	5.75	8.113
Wong (2011)	6.733	5.647	8.028
Demokan (2012)	6.82	5.715	8.138
Dang (2013)	6.693	5.638	7.944
Bhatia (2014)	6.602	5.558	7.844
Bhatia (2014)	6.584	5.544	7.818

Kis (2014)	6.699	5.637	7.96
Kis (P14) (2014)	6.744	5.677	8.01
Choudhury (2015)	6.878	5.781	8.184
Lin (2000)	6.618	5.574	7.857
Huang (2002)	6.85	5.755	8.154
Toyota (2002)	6.751	5.688	8.013
Toyota (P14) (2002)	6.765	5.7	8.03
Yeh (2003)	6.85	5.755	8.154
Yakushiji (2003)	6.638	5.591	7.881
Viswanathan (2003)	6.68	5.628	7.928
Liu (2005)	6.633	5.585	7.876
Kato (2006)	6.866	5.772	8.168
Nakahara (2006)	6.714	5.657	7.97
Tamandani (P14) (2010)	6.934	5.813	8.272
Supic (2011)	6.712	5.641	7.986
Kusumoto (2012)	6.731	5.671	7.989
Tamandani (2012)	6.716	5.634	8.003
Nagata (2012)	6.724	5.661	7.986
Dong (2012)	6.692	5.638	7.943
Fu (2013)	6.706	5.65	7.91
Khor (2013)	6.685	5.632	7.936
Asokan (2014)	6.705	5.649	7.958
Kuchta (2014)	6.984	5.862	8.319
Lin (2015)	6.494	5.465	7.716
Jares (1997)	6.73	5.67	7.988
Mu (1999)	6.704	5.648	7.957
Bai (2000)	6.694	5.64	7.946
Zhou (2004)	6.764	5.695	8.033
Temam (2005)	6.719	5.661	7.975
Zhu (2008)	6.606	5.563	7.844
Wang (2008)	6.665	5.615	7.912
Guo (2009)	6.703	5.647	7.956
Guo (P14) (2009)	6.714	5.656	7.969
Sinha (2009)	6.694	5.632	7.957
Schutter (2009)	6.766	5.701	8.03
Ferlazzo (2017)	6.812	5.728	8.1
Sushma (2016)	6.583	5.544	7.816
Silva (2011)	6.73	5.671	7.988
Ruesga (2007)	6.767	5.698	8.038