

Supplementary Material

Salivary DNA methylation as an epigenetic biomarker for head and neck cancer. Part II: A cancer risk meta-analysis

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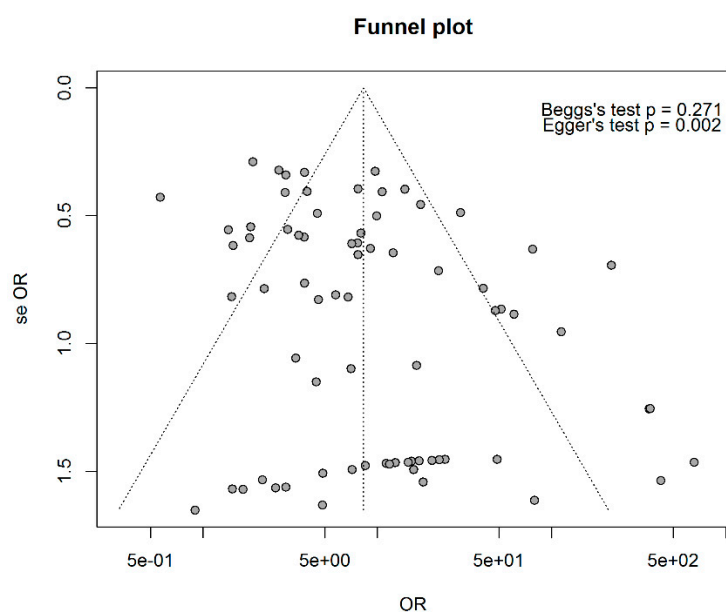


Figure S1. Funnel plot for studies (of 18 studies) on the association between salivary DNA hypermethylation and HNC. *Abbreviations:* HNC = head and neck cancer.

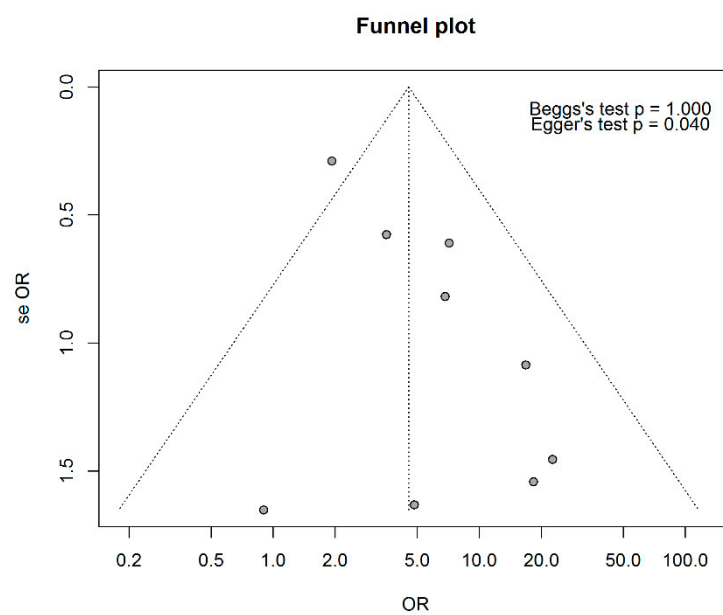


Figure S2. Funnel plot for studies (of 9 studies) on the association between salivary hypermethylation of *p16* gene promoter and HNC. *Abbreviations:* HNC = head and neck cancer.

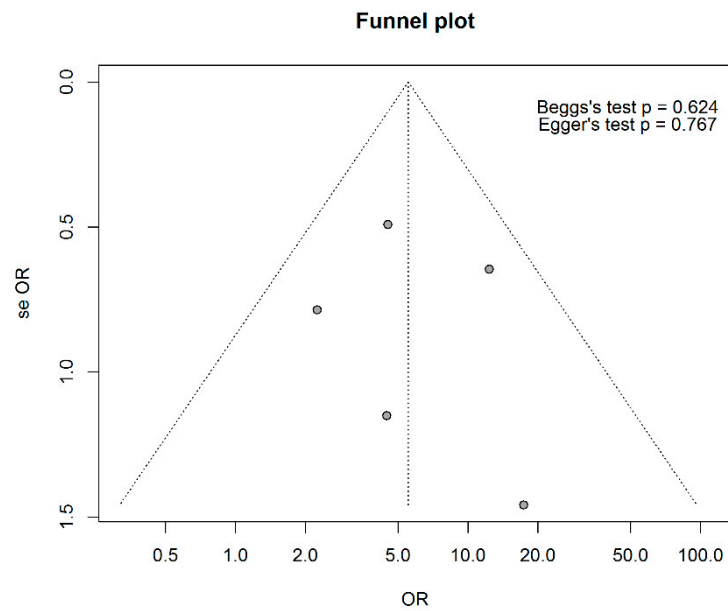


Figure S3. Funnel plot for studies (of 5 studies) on the association between salivary hypermethylation of *MGMT* gene promoter and HNC. Abbreviations: HNC = head and neck cancer.

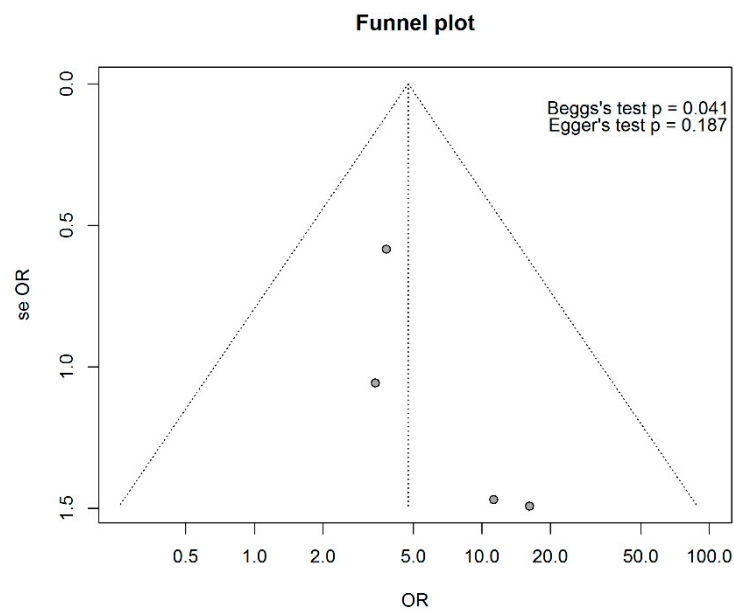


Figure S4. Funnel plot for studies (of 4 studies) on the association between salivary hypermethylation of *DAPK* gene promoter and HNC. Abbreviations: HNC = head and neck cancer.

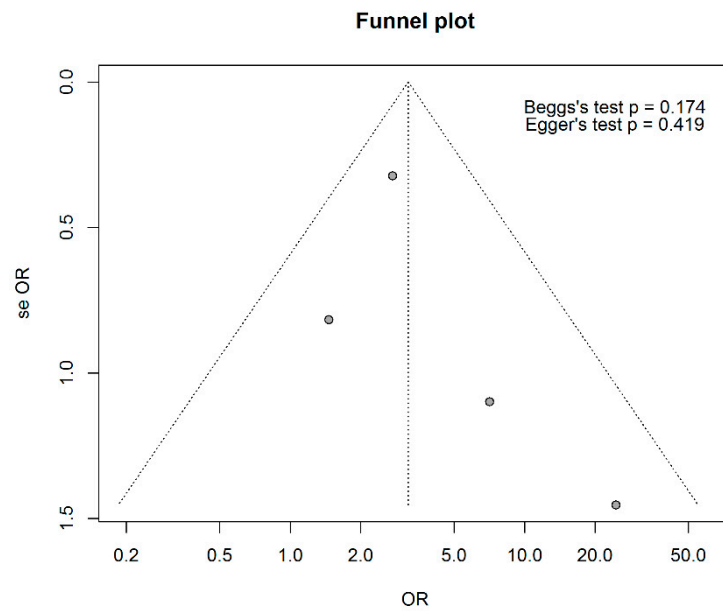


Figure S5. Funnel plot for studies (of 4 studies) on the association between salivary hypermethylation of *TIMP3* gene promoter and HNC. Abbreviations: HNC = head and neck cancer.

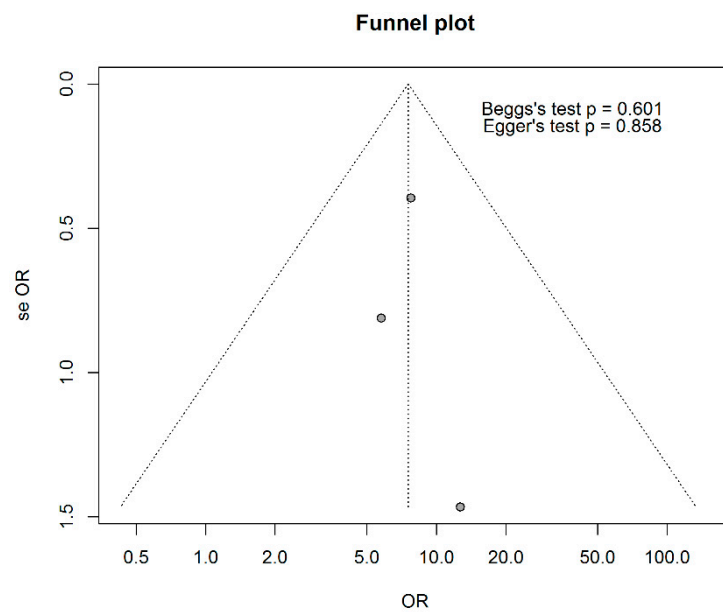


Figure S6. Funnel plot for studies (of 3 studies) on the association between salivary hypermethylation of *RASSF1A* gene promoter and HNC. *Abbreviations:* HNC = head and neck cancer.

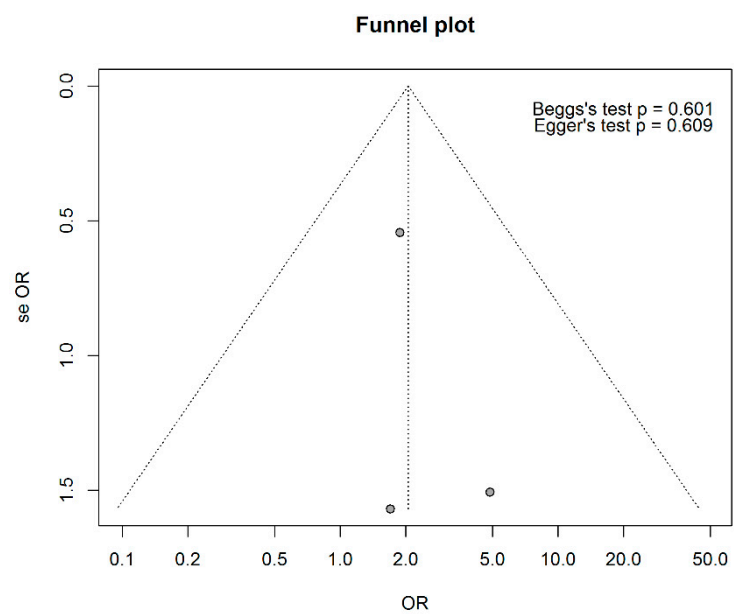


Figure S7. Funnel plot for studies (of 3 studies) on the association between salivary hypermethylation of *APC* gene promoter and HNC. *Abbreviations:* HNC = head and neck cancer.

Table S1. The Newcastle-Ottawa Scale (NOS) for assessing the quality of included studies.

Study	Subject Selection (Max. 4★)	Study Comparability (Max. 2★)	Ascertainment of exposure (Max. 3★)	Final quality assessment
Rosas et al.; 2001	★★★★	0	★★★	7
Righini et al.; 2007	★★★★	0	★★★	7
Franzmann et al.; 2007	★★	★★	★★★	7
Guerrero-Preston et al.; 2011	★★★★	0	★★★	7
Nagata et al.; 2012	★★★★	0	★★★	7
Ovchinnikov et al.; 2012	★★★★	0	★★★	7
Ksumoto et al.; 2012	★★★★	0	★★★	7
Rettori et al.; 2012	★★★★	0	★★★	7
Ovchinnikov et al.; 2014	★★★★	0	★★★	7
Gaykalova et al.; 2015	★★★★	0	★★★	7
Lim et al.; 2016	★★★★	0	★★★	7
Ferlazzo et al.; 2017	★★★★	★★	★★★	9
Cheng et al.; 2017	★★★★	0	★★★	7
Puttipanyalears et al.; 2018	★★★★	0	★★★	7
Liyanage et al.; 2020	★★★★	★★	★★★	9
Srisutte et al.; 2020	★★★★	★	★★★	8
Shen et al.; 2020	★★★★	0	★★★	7
González-Pérez et al.; 2020	★★★★	★	★★★	8

Note: “★” means one point

Table S2. Subgroup analysis of salivary DNA methylation for HNC detection based on different covariates.

Abbreviations: HNC = head and neck cancer; OC = oral cancer; OPC = oropharyngeal cancer; MSP = methylation-specific polymerase chain reaction; qMSP = quantitative-MSP.

Subgroups	No of study units	Sample size (cases/controls)	Heterogeneity		Mode I	Effect size	
			I ² (%)	P-Q-test		OR (95% CI)	P-value
Sample type							
Saliva	16		79	<0.01	R	6.33 (3.90–10.27)	<0.01
Oral Rinse	58		68	<0.01		9.42 (6.30–14.08)	<0.01
Samples size							
N>100	25		84	<0.01	R	8.34 (6.10–11.39)	<0.01
N<100	49		53	<0.01		9.58 (6.44–14.27)	<0.01
Tumor Location							
HNC	43		70	<0.01	R	5.78 (3.86–8.67)	<0.01
OC	33		73	<0.01		13.07 (8.19–20.88)	<0.01
OPC	8		80	<0.01		13.26 (3.17–5.42)	<0.01
Technique							
MSP	48		70	<0.01	R	9.06 (6.30–13.03)	<0.01
qMSP	26		75	<0.01		6.81 (3.70–12.54)	<0.01
Gene profiling							
Single gene	62		63	<0.01	R	6.02 (4.46–8.13)	<0.01
Combination gene	12		74	<0.01		36.79 (16.81–81.32)	<0.01