*Supplementary Materials*

**Table S1: Characteristics of the patients included in the study.**

**Figure S1: Patient overall survival according to tumor site.** Kaplan-Meier survival curve according to tumor site, with follow-up duration of five years after diagnosis. Censored values (+) indicate the last known follow-up time for the corresponding individuals. The numbers indicate the median overall survival for each tumor site. ESCC, esophageal squamous cell carcinoma; LSCC, laryngeal squamous cell carcinoma; ND, not determined, OSCC, oral squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma.

**Figure S2: Study workflow.**

**Figure S3: Stromal and immune cell contribution in ESCC and HNSCC.** Methylation beta-values from stromal and immune cells built-in the R package MethylCIBERSORT (v0.2.0) were used to determine the relative abundance of non-tumor cells within tumor samples. Each graph represents a tumor type, and each column represents a tumor sample. ESCC, esophageal squamous cell carcinoma; LSCC, laryngeal squamous cell carcinoma; OSCC, oral squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma.

**Table S2: Differentially methylated probes stratified by their gene position in ESCC, LSCC, OSCC and OPSCC.**

**Table S3: Differentially methylated probes stratified by their relation to CpG island in ESCC, LSCC, OSCC and OPSCC.**

**Figure S4: DMP delta beta differences reflect non-tumor and tumor differences.** (A) Boxplot showing the mean delta betas of all hypo- and hypermethylated DMPs in each tumor subsite. (B) Boxplot showing the mean delta betas of all hypo- and hypermethylated common DMPs by tumor subsite. (C) Heatmap showing the methylation profile of all common DMPs among tumor

subsites in non-tumor and tumor tissues. Blue and red represent lower and higher methylation levels, respectively.

**Table S4: Differentially methylated probes stratified by chromosomes in ESCC, LSCC, OSCC and OPSCC.**

**Table S5: Over-representation (ORA) analysis of genes carrying DMRs in ESCC, LSCC, OSCC and OPSCC.**

**Table S6: DMR description and correlation with the expression of the associated gene in ESCC, LSCC, OSCC and OPSCC.**

**Figure S5: Gene expression profile of WNT genes carrying DMRs in ESCC.** Box plots showing the expression levels of each gene involved in the WNT signaling pathway for which at least one DMR was detected in ESCC relative to non-tumor surrounding tissue. Genes are organized according to their function. Ligands: *WNT1*, *WNT3A*, *WNT4*, *WNT5A*, *WNT5B*, *WNT6*, *WNT7A*, *WNT9A*. Receptors: *FZD1*, *FZD7*. Activators: *CSNK2B*, *PORCN*, *PRKACA*, *SMAD3*, *TCF7*, *DVL3*. Inhibitors: *CTBP1*, *CTBP2*, *CTNNBIP1*, *DKK4*, *FBXW11*, *MAP3K7*, *NKD2*, *SFRP1*, *SFRP2*, *SFRP5*, *SOX17*. Targets: *CCND1*, *FOSL1*, *JUN*, *MYC*. WNT/$Ca^{2+}$ signaling: *CAMK2B*, *NFATC1*, *NFATC2*, *PLCB2*, *PPP2R5C*, *PRKCA*. Planar cell polarity pathway: *PRICKLE2*, *ROCK1*, *VANGL2*.

**Figure S6: Gene expression profile of WNT genes carrying DMRs in LSCC.** Box plots showing the expression levels of each gene involved in the WNT signaling pathway for which at least one DMR was detected in LSCC relative to non-tumor surrounding tissue. Genes are organized according to their function. Receptors: *FZD2*, *FZD6*, *FZD10*. Activators: *CSNK2B*. Inhibitors: *CSNK1A1L*, *CTBP1*, *SOX17*. WNT/$Ca^{2+}$ signaling: *CAMK2B*. Planar cell polarity pathway: *ROCK1*.

**Figure S7: WNT target genes are upregulated in ESCC, LSCC and OSCC.** Heatmaps showing the expression profile of significantly altered (BH adjusted p-value < 0.05) WNT target genes in esophageal (ESCC), laryngeal (LSCC) and oral cavity squamous cell carcinomas (OSCC) and

corresponding non-tumor surrounding tissues (NTST). On the right side of the heatmaps de mean log2 fold-change between tumors and NTST (T_log2FC) is represented in pink for upregulated and in blue for downregulated genes.