LIST OF SUPPLEMENTARY MATERIALS

Methods

Supplementary Text

Fig. S1. Comparison of transcriptional strand bias between *in vitro* exposure to benzo[*a*]pyrene and signature 4 extracted from all tobacco-associated cancer types.

Fig. S2. Extracting the pattern of signature 4 from different cancer types.

Fig. S3. Similarity between extraction of signature 4 across different cancer types and other known mutational signatures.

Fig. S4. Sensitivity for detecting signature 4 in cervix, bladder and renal cancer.

Fig. S5. Strong transcriptional strand bias of signature 16.

Fig. S6. Comparison between lifelong non-smokers and smokers based on overall CpG methylation profiles.

Fig. S7. CpG islands and differentially methylated CpGs in smokers compared to non-smokers.

Fig. S8. Cancer tissue methylation of individual CpGs near genes differentially methylated in blood or buccal cells of smokers.

Fig. S9. Interquartile range of methylation levels in tobacco-associated cancer types.

Fig. S10. Mutation rate variation across normal cells can lead to complex relationships between cancer mutation burden and cancer risk.

References and notes (*32* – *54*)

Author Contributions

Table S1: Detailed information about each examined tobacco-associated cancer sample.

Table S2: Comparison of features of tobacco smokers to the ones of lifelong non-smokers.

Table S3: Relationships between mutational signatures and pack years smoked.

Table S4: Individual CpGs with differential methylation in lung adenocarcinoma.

Table S5: Individual CpGs with differential methylation in oral cancer.

Table S6: Numerical patterns of mutational signatures associated with tobacco smoking.