Supplementary Figure 1: Waterfall plots showing the methylation change in significant genes between normal and tumor samples involved in neurogenesis and epidermis development (GO terms). Positive values indicate hypermethylation in cancer, while negative values indicate hypomethylation in cancer.

A. Neurogenesis

**Neurogenesis (GO)**

- **Breast**: N = 231 genes
- **LungSCC**: N = 141 genes
- **Colorectal**: N = 189 genes
- **Myeloma**: N = 5 genes
- **Glioblastoma**: N = 30 genes
- **Ovarian**: N = 135 genes
- **Kidney**: N = 252 genes
- **Prostate**: N = 188 genes
- **LungAC**: N = 202 genes
- **Stomach**: N = 211 genes
B. Epidermis Development

Epidermis Development (GO)

Breast
N = 34 genes

LungSCC
N = 52 genes

Colorectal
N = 64 genes

Myeloma
N = 53 genes

Glioblastoma
N = 33 genes

Ovarian
N = 45 genes

Kidney
N = 52 genes

Prostate
N = 49 genes

LungAC
N = 54 genes

Stomach
N = 60 genes

Change in Methylation
(average Tumor - average Normal)
Supplementary Figure 2: Change in average percent methylation of HOX gene family, PAX gene family, and WT1 involved in Transcription Factor Activity
Supplementary Figure 3: Unsupervised clustering of probes involved in Sequence-specific Transcription Factor Activity

[Diagram showing unsupervised clustering with heat map and change in average % Methylation, with color bars indicating Hypo to Hyper and labels for tissues and PRC2 targets vs. Non-targets]
Supplementary Figure 4: The status of PRC2 targets and CpG islands for those probes involved in the specified GO terms
Supplementary Figure 5: The proportion of differentially methylated genes among the PRC2 targets and non-PRC2 targets (those probes with the p-value<0.05 and the minimum difference between the average methylation percentage of tumor vs. normal greater than 5% are graphed)
Supplementary Figure 6: Clustering of metabolite, drug target, and transcription factor concepts. Hypomethylated concepts are shown in red and hypermethylated concepts are shown in green. A. Metabolite concepts. B. Drug concepts. C. Transcription Factor concepts.
Supplementary Figure 7: Change in average percent methylation of the probes for TP73, CDKN1A, 1B, 1C, 2A and 2B, 2C, 2D, and APC.
**Supplementary Figure 8:** Cancer-specific enriched concepts in LRpath directional analysis

Biological concepts enriched with a significant p-value < 1e-4 in one tumor type are listed in the table below. In myeloma, kinase activities are enriched among hypermethylated genes, and muscle-related processes and components are enriched among hypomethylated genes. In breast cancer, several circadian processes are shown up to be enriched among hypomethylated genes.
Supplementary Figure 9: Bar graphs showing the methylation change in genes involved in circadian rhythm process in breast cancer. In tumor samples, the increase in the level of methylation in DRD1, PTGDS, CASP1, and PGLYRP1 genes are observed.