Figure S1. Sanger sequencing traces of *IDH2* and *PIK3CA* hotspot mutations identified in SPCRPs. Mutations are highlighted with a black arrow.

Figure S2. DNA methylation profile of *IDH2*/*TET2*-mutant SPCRPs.

Scatter plot of methylation difference between *IDH2*/*TET2*-mutant SPCRPs and *IDH2*/*TET2* wild-type IDCs. Red dots indicate statistically significant differentially methylated genes between *IDH2*/*TET2*-mutant SPCRPs and *IDH2*/*TET2* wild-type IDCs (FDR adjusted p-value <0.05).

Figure S3. IDH2 expression in non-malignant breast epithelial cells.

(A) Forced expression of wild-type IDH2 ($IDH2^{WT}$) and R172S-mutant IDH2 ($IDH2^{R172S}$) leads to an increase in IDH2 mRNA in parental MCF10A ($MCF10A^{P}$) and *PIK3CA* H1047R-mutant MCF10A ($MCF10A^{H1047R}$) cells. Error bars represent standard deviation of mean. (B) Forced expression of $IDH2^{WT}$ and $IDH2^{R172S}$ in $MCF10A^{P}$ and $MCF10A^{H1047R}$ cells leads to IDH2 protein mitochondrial localization. Blue, DAPI; green, $IDH2^{WT}$ and $IDH2^{R172S}$; red, Mito-tracker (scale bar, 7.5μm).

Figure S4. Downstream effects of IDH2 expression in non-malignant breast epithelial cells. Whole cell lysates of $MCF10A^{P}$ and $MCF10A^{H1047R}$ cells were analyzed for H3K9me3, H3K27me3 and total H3 protein expression by western blotting (left), and quantified using near-infrared detection (LI-COR; Odyssey) (right); error bars represent standard deviation of mean.

Figure S5. Representative micrographs obtained from *PIK3CA* H1047R-mutant MCF10A cells transiently expressing R172S-mutant IDH2.

$IDH2^{R172S}$ expression in $MCF10A^{H1047R}$ cells led to the formation of anastomosing solid cell nests/ cell nodules.