**Supplementary Methods**

**Gene expression analysis.** Gene expression data existed for 61 breast tumors with metabolome data in the discovery set, as described (1). Briefly, mRNA was converted into cDNA using the Ambion WT Expression Kit. After fragmentation and labeling using the GeneChip WT Terminal Labeling Kit from Affymetrix, ssDNA was hybridized onto Gene Chip Human Gene 1.0 ST Arrays (representing 28,869 genes) according to Affymetrix standard protocols (Affymetrix, Santa Clara, CA). For the gene expression profiling in breast tumors, probeset intensity data were processed by RMA algorithm of the *Oligo* package, and further analyzed with the Bioconductor *limma* R package for comparison.

We performed RNA sequencing to obtain additional gene expression data from bile acid-treated cell lines.Cells were seeded in 12-well Corning cell culture plates and treated in triplicates with 20 µM and 50 µM deoxycholate for 24 hours. RNA extraction was performed according to the RNeasy miniKit protocol from Qiagen. RNA integrity for each sample was confirmed with the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). One µg of RNA was sent to the Center for Cancer Research Sequencing Facility at the NCI for library preparation with the TruSeq PolyA kit (Illumina, San Diego, CA) and sequencing with the HiSeq 2500 system using 126 bp paired-end reads. About 300 million paired end reads in total were generated with a base call quality of Q30 and above. Reads were trimmed using the Trimmomatic software and about 90% of them were uniquely aligned to the human genome (hg19) using TopHat v2.0.8. RNA mapping statistics were calculated using Picard with more than 90% of the reads being mapped to the transcriptome. Read count per gene was calculated by HTSeq under the annotation of Gencode v19 and normalized by size factor implemented in the *DESeq2* package. Regularized-logarithm transformation (rlog) values of gene expression were used to perform hierarchical clustering and principle component analysis. To assess differential gene expression between different treatment conditions (e.g., deoxycholate vs. mock) or to investigate a treatment dosage effect, we used a generalized linear model within *DESeq2* that incorporates information from counts and uses negative binomial distribution with fitted mean and a gene-specific dispersion parameter. *DESeq2* used Wald statistics for significance testing and the Benjamini-Hochberg adjustment for multiple corrections.

**Proteomics data.** The mass spectrometry (MS)-based analysis of the proteome was performed as previously described (2). Briefly, frozen tissue samples were pulverized for protein isolation. Extracted proteins were digested with trypsin and analyzed using an untargeted MS analysis approach. MS data were searched against the UniProt *Homo sapiens* database downloaded from the European Bioinformatics Institute website (<http://www.ebi.ac.uk/integr8>). For selection of proteins based on FDR cutoffs, the MS data were also processed using the Proteome Discoverer 2.0 software (Thermo Fisher Scientific) interfaced with the SEQUEST HT algorithm and filtered with protein percolator to yield peptide and protein lists at 1% FDR cutoffs. We applied the “Strict Maximum Parsimony Principle” option when data were compiled to ensure that only one peptide-spectrum match per spectrum was used for protein identification and grouping. To further reduce false discovery, only proteins identified by at least two peptides in a tissue sample were considered as a legitimate identification and kept in the analysis. Lastly, we eliminated all proteins from further downstream computational analysis if they were not present in at least 15% of the tissues, which reduces possible false discovery associated with spectral count-based protein quantification of low-abundant proteins. Using these criteria, we identified ~4,000 proteins with confidence for further analysis.

**LASSO feature selection.** Metabolites were pre-selected from our dataset using univariable Cox Proportional-Hazards Regression models followed by a likelihood ratio test. Selected top-ranked metabolites (*P* < 0.01 cutoff) were taken forward for the multivariable Cox modeling with LASSO (abbreviation for least absolute shrinkage and selection operator) feature selection [L1 penalized as described (3)] in a 10-fold cross-validation setting. The model with the smallest mean cross-validation error was selected (1000 iterations) and then further tested in the validation cohort. The predicted response scores and risk were then evaluated for association with survival in the validation set using the concordance index (C-index) (4). The described survival modelling was performed using the R packages *survival, glmnet, glmpath, survcomp*. Kaplan-Meier plots were used to graph survival curves. The integrated models included as variables the 398 metabolites and the following demographic/clinical data: age at enrollment, self-reported race/ethnicity, disease stage and grade, node status, menopausal status (pre-/post-menopausal disease), neoadjuvant, hormone, or chemotherapy. In the survival analysis, metabolite tissue levels were median-dichotomized to define high-abundance and low-abundance groups, except for glycochenodeoxycholate where the cutoff was set at the detection limit. In the multivariable analysis, our dataset was randomly split into training and validation sets at a 2:1 ratio.

**References**

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