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Bile Acids Contribute to the Gender-Biased Incidence of HCC

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Hepatocellular carcinoma (HCC) is a male-predominant cancer. Despite many implicated pathways, the mechanism underlying female protection is not fully understood. Utilizing Farnesoid X Receptor (*Fxr*) and Small Heterodimer Partner (*Shp*) double-knockout (DKO) mice, we showed that excess bile acids (BAs) caused spontaneous HCC only in males. In contrast, DKO females had 50% lower serum BAs and were resistant to HCC. Consistently, reducing serum BAs with cholestyramine reduced tumor burden in DKO males, highlighting the role of circulating BA levels in promoting HCC. To elucidate the processes responsible for lower serum BA levels in DKO females, we tested BA synthetic, transport, and metabolic capacity. Basal expression of BA synthetic and transport genes was similar between genders. Despite deletion of negative feedback, DKO female livers were still able to suppress BA synthesis, indicating that females may be equipped with additional mechanisms to regulate BA homeostasis.

Global transcriptional analysis revealed upregulation of cholesterol, glutamate, and amino acid metabolism only in female mice. Transcription motif analysis showed enrichment of estrogen receptor-alpha (ERα), forkhead box protein A2 (FOXA2), and nuclear factor-kappa B (NF-kB) in females. Ovariectomized females displayed reduced ability to handle BA overload and negatively regulate BA synthesis indicating the importance of the estrogen axis in biliary homeostasis. In addition, we found that estrogen signaling programs female livers to recycle and reduce nitrogen availability. In fact, increasing BA levels reduced ERα, induced *Hippo* targets and caused liver cancer in DKO females. Overall, these data implicate a role for estrogen-BA crosstalk in female resistance to HCC.