Maternal obesity may promote liver cancer

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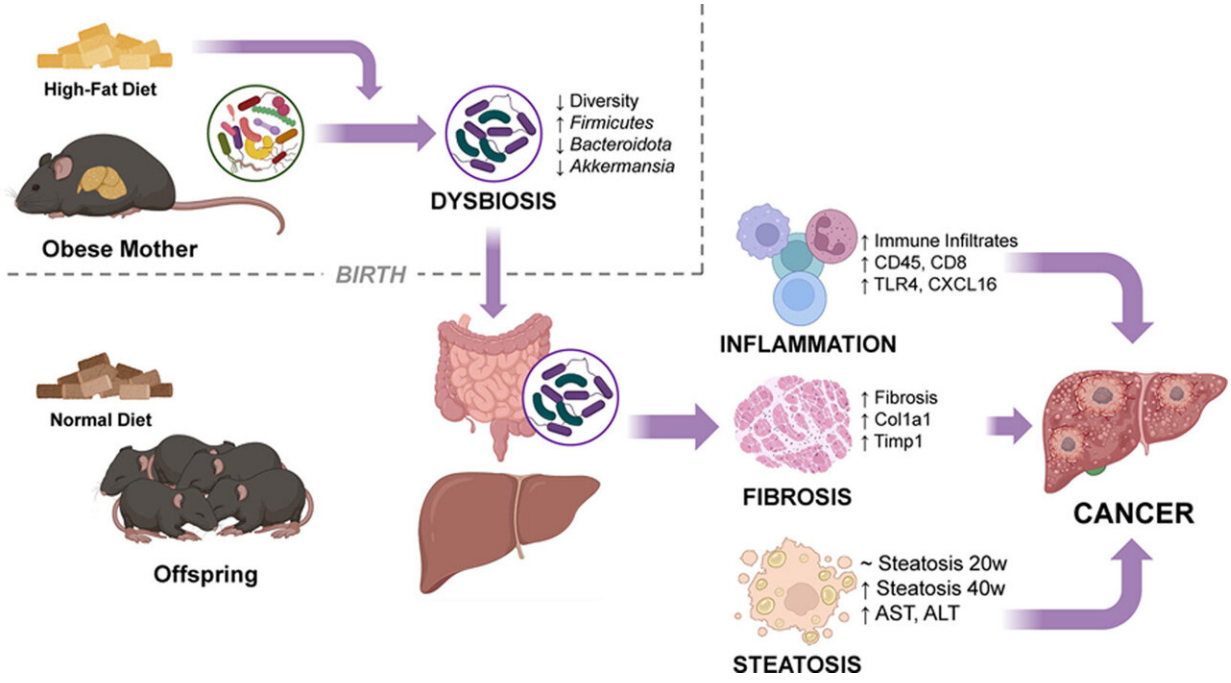

Credit: *JHEP Reports* (2024). DOI: 10.1016/j.jhepr.2024.101056

Obesity, which could reach 50% of the population in certain developed countries by 2030, is a major public health concern. It not only affects the health of those who suffer from it, but could also have serious consequences for their offspring. Scientists at the University of Geneva (UNIGE) and the Geneva University Hospitals (HUG) have studied the impact of maternal obesity on the risk of developing liver disease and liver cancer.

Using an animal model, the team discovered that this risk was indeed much higher in the offspring of mothers suffering from obesity. One of the main causes was the transmission of a disturbed intestinal microbiota from the mother, resulting in a chronic liver disease whose effects became apparent in adulthood.

These results, which have yet to be confirmed in humans, are a warning signal and a call for action to limit the deleterious effect of obesity on children. This research is published in the journal *JHEP Reports*.

The scientific community suspects that maternal obesity disrupts the metabolic balance of the unborn child, and even increases the risk of childhood cancer and colorectal cancer. But to what extent?

"We wanted to understand whether the children of mothers suffering from obesity were at greater risk of developing liver diseases, and by what biological mechanisms," explains Christian Toso, full professor at the UNIGE Faculty of Medicine and director of the Division of digestive surgery at the HUG, who led this research. "Indeed, while the risk of liver cancer due to a hepatic virus is decreasing, obesity-related liver diseases are constantly on the rise."

The scientists studied two groups of female mice: the first fed with a diet rich in fat and sugar—similar to junk food—which rapidly became obese. The second—the control group—was fed normally. All their offspring were fed with a normal diet and were not overweight. The only difference was therefore the maternal obesity of the first group.

"At 20 weeks, which corresponds to adulthood in humans, we could not detect any notable differences," explains Beat Moeckli, junior staff surgeon and researcher in professor Toso's team, the first author of this work.

"However, at 40 weeks, a senior age in mice, the liver health of the first group began to deteriorate. All the parameters of liver disease—fat deposits, fibrosis, and inflammation—were significantly higher in the offspring of mothers suffering from obesity. And these are the main risk factors for liver cancer in humans."

From disease to cancer: The role of microbiota

To confirm whether these mice had a higher risk of developing liver cancer, the team injected two groups of these mice with an oncogenic product just after weaning. And indeed, the offspring of obese mothers had an 80% risk of developing cancer, compared with 20% for the control group.

"The mother's obesity thus has an impact long after the birth of its offspring, which seem to inherit a dysfunctional microbiota despite their own living conditions," says Moeckli. "Obesity alters the composition and diversity of the mother's microbiota, which is passed on to the next generation and persists throughout life."

However, by placing mice from both groups in the same cage, the scientists observed a normalization of the microbiota. As mice are coprophagous (they eat their feces), they quickly share the same microbiotic strains. Bacterial diversity then increased, favoring the good bacteria.

As a result, the healthy microbiota naturally regains the upper hand, and the marker of liver disease dramatically decreased. "We see a clear effect of the microbiota on the risk of developing liver cancer, indicating its central role in transmitting the risk of disease from mother to child."

The junk food diet encourages the proliferation of bad bacteria and reduces bacterial diversity. This altered microbiota, transmitted at birth,

then leads to greater inflammation in the liver and, over time, generates fibrosis and steatosis (an excessive presence of fat), which in turn increase the risk of developing liver cancer. Normalizing the microbiota also normalizes the risk of cancer.

And in humans?

These data come from a study on an animal model, in a highly controlled environment. To be applied in a clinical context, they need to be confirmed in humans under real-life conditions. The first stage will consist of an epidemiological study based on large bodies of data obtained from following mothers and their children over several decades.

"However, we already know that it is possible to modify the microbiota, for instance by using probiotics. Having highlighted the importance of the microbiome represents a first step towards new therapies," the scientists conclude.

More information: Beat Moeckli et al, Maternal obesity increases the risk of hepatocellular carcinoma through the transmission of an altered gut microbiome, *JHEP Reports* (2024). DOI: 10.1016/j.jhepr.2024.101056

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