Obesity-dependent changes in lipid handling in cells may explain why overweight people are more prone to developing cancer than those of normal weights. The study, published in *Nature Communications* (14 January 2022), identifies higher levels of palmitic acid as the prime culprit, setting in chain a series of negative chemical reactions in obese people. This could be the missing link in explaining clear epidemiological data.

“Our findings suggest that obese patients with cancer would benefit from personalised medicine taking into consideration their obesity,” says Nils Halberg, the corresponding author, from University of Bergen, Norway.

Obesity is estimated to be the cause of approximately 500,000 new cancer cases worldwide each year, a number expected to rise as obesity levels continue to grow. Extensive epidemiological evidence suggests that obesity is a driving factor for cancer development and spread in 13 different cancers, including breast, endometrial and colon cancer. In breast cancer, postmenopausal obesity is an independent risk factor accounting for up to 20% higher risk of developing breast cancer. Furthermore, every five-unit increase in BMI has been associated with a 12% increase in breast cancer risk. In addition to breast cancer risk, meta-analyses suggest obesity is associated with worse overall survival and metastasis free survival that is independent of menopause or hormone receptor status.

“So, it appears obese people are both more likely to develop cancer and if they do tumours appear to be more aggressive,” says Halberg. “But despite such clear connections, no unbiased in-depth mechanistic studies have been undertaken to establish how tumour cells take advantage of the altered energy state present in obese individuals. Without this mechanistic insight we are unable to develop effective therapeutic strategies.”

Utilizing both in vitro and in vivo experimental breast cancer systems, combined with molecular biology and clinical bioinformatics, Halberg and colleagues set out to systemically address the question. First, the team undertook animal studies mimicking both obese and non-obese environments, where six-week-old female mice were randomly assigned to standard diets (7.5% kcals were obtained from fat) or high fat containing diets (60% kcals were obtained from fat) prior to tumour implantation in the mammary pads at 10 weeks.

To validate mice findings the team had access to an historical cohort of 223 patients with primary stage III breast cancer who had been enrolled between November 1997 and December 2003, of whom 115 were postmenopausal (defined age >50 years), together with the relevant tumour blocks. “For the historical period what’s unusual for this cohort was that BMI was documented at the time of diagnosis, along with age and hormone status,” says Halberg, adding overall survival and disease specific survival were recorded at a later date.

In both mouse models and human tumour blocks, the team stained for CD133 and Axl, two proteins known to be biomarkers of ‘cancer stemness’ (a term describing the ability of cancer cells to differentiate into different cell types, reflecting ability to form tumours).

Mouse and in vitro studies show:

- In the mouse models, investigators demonstrated high fat environments consistently promoted tumour formation, with 6- to 10-fold enrichment in cancer stem cell frequencies compared to low fat environments.
- To assess how breast cancer cells adapt to palmitic acid exposure, the team exposed cultured hormone receptor-negative breast cancer cell lines to increasing palmitic acid concentrations over two months. Cellular subpopulations exposed to higher levels of palmitic acid were

characterised by increased expression of cancer stem cell markers CD44, CD133, and Axl. “Such work suggested that palmitic acid adapted cells have greater tumour initiation capacity in obese settings,” says Halberg.
- The team went on to identify that epigenetic activation of the CCAAT/ enhancer-binding protein beta (C/EBPB), through increased chromatin occupancy, was required as a regulator of cancer stem-like properties, ‘stemness’, through modulation of key downstream regulators including *CLDN1* and *LCN2*.

Human studies show:

- Overweight and obese patients with hormone receptor negative breast cancers (BMI >25) had significantly reduced disease specific survival compared to non-obese patients (HR 2.94; P=0.0241). No such effect was observed in patients with hormone receptor positive cancers.
- Tumour tissue microarrays from patients with oestrogen and progesterone receptor negative cancers showed that patients with BMI >25 displayed higher stemness markers (CD133+ and Axl) compared with normal BMI patients. Again, such results suggest adaptation to obese environments leads to an enrichment in cancer ‘stemness’.

“Taking these findings together, we believe when people have elevated levels of palmitic acid, as occurs with obesity, cancer cells adapt to the environment and change towards a tumour stem cell-like phenotype that’s more efficient at forming new tumours,” explains Halberg.

In the context of personalised medicine, he adds, the study suggests obese cancer patients might benefit from specific targeted therapies rather than generic treatment regimens. “While C/EBPB is specific to the obese setting, it’s a really hard protein to target. It might therefore make more sense to think about blocking key downstream regulators, such as *CLDN1* or *LCN2*,” suggests Halberg.

Ultimately, the goal would be to use knowledge of the palmitic acid connection in population-based cancer prevention strategies. “But at present, apart from encouraging people to lose weight, we have no clear idea how to reduce levels of palmitic acid in the blood,” says Halberg. The team, he adds, are currently exploring whether a similar relationship with obesity occurs in pancreatic cancer.