

The big C's

Bile acids as carcinogens in colon cancer

- Western countries with high-fat diets have the greatest incidence of colon cancer.
- In a recent review, Dr Carol Bernstein, a retired professor from the University of Arizona in the USA, brings together years of epidemiological, experimental, and cell culture research that collectively implicates increased bile acids due to a high-fat diet as a significant cause of colon cancer.
- DNA damage, mutations, and evading cell death are at the heart of this pathology.
- This improved understanding of the mechanisms involved helps reveal prevention strategies and provides insight into the carcinogenic role of bile acids in other gastrointestinal cancers.

We know eating a high-fat diet is not good for our health or waistline, but are you aware of the significantly heightened risk of colon cancer? When thinking of cancer-causing agents, well-known carcinogens such as tobacco smoke, UV radiation, or alcohol come to mind. But for our gastrointestinal tract, excessive bile acids are emerging as common culprits.

Bile acids play a crucial role in digesting fat and have biological functions. Still, excessive fat intake requires more primary bile acids for digestion. Elevated primary bile acids are acted upon by some bacteria to increase the levels of more toxic bile acids (secondary bile acids) that enhance intracellular reactive oxygen species (ROS), causing DNA damage and cancer.

In her latest publication, Dr Carol Bernstein, a retired professor from the University of Arizona in the USA, adopts an integrative approach to evaluate the mounting evidence from diverse studies. Her work shows that bile acids cause gastrointestinal cancers through underlying mechanisms of DNA damage and signalling pathways.

Fatty diets

In the last few years, figures reveal a global death toll of almost one million from colon cancer, with the prevalence of the disease a staggering twenty-five times greater in Western countries with high saturated fat diets. Native Alaskans with the greatest incidence have a diet much higher in fat content and lower in fibre compared to rural African populations with the lowest case rates. Red meat, processed meats, and dairy contain a lot of saturated fat – these are fatty acid chains that have no C=C double bonds but have chains of C-C single bonds.

The more fat you eat, the more bile acid is needed to digest it. The problem is that certain bacteria favour such high-fat environments. These species begin to dominate the gut, leading to an imbalance known as dysbiosis. Some gut bacteria convert primary bile acids into secondary bile acids such as deoxycholic acid (DOC), which are more toxic to cells. Evidence is growing that disruption to the gut microbiome elevates these secondary bile acids and leads to DNA damage and a predisposition to colon cancer.

Initially, epidemiological studies revealed a link between a high-fat diet and colon cancer. Subsequent observational studies suggested this is

because of elevated bile acids, with a recent study showing that blood levels of secondary bile acids like DOC predict colon cancer risk in women years before diagnosis. Now, experimental and in vitro studies dig deeper to reveal the underlying cellular and molecular mechanisms.

Pathways to cancer

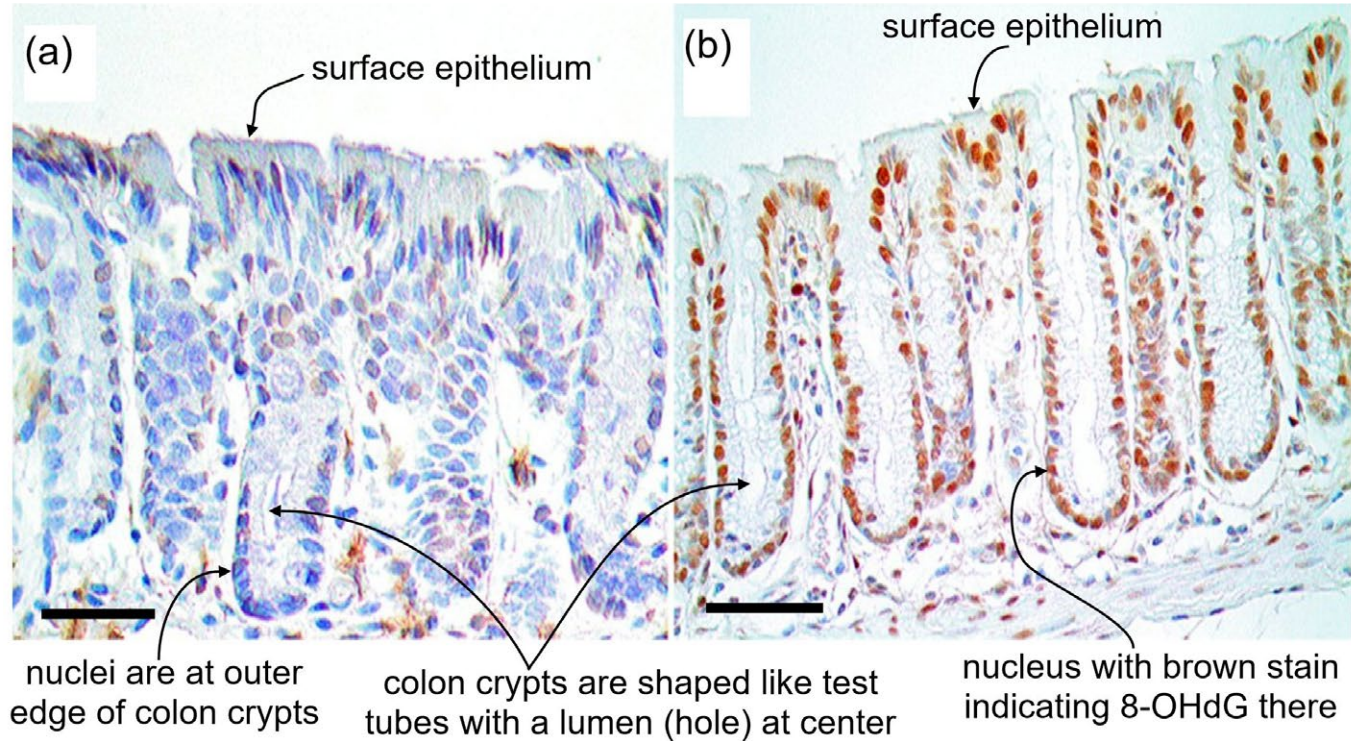
Mistakes happen! Damages in our DNA are common. Thankfully, we are equipped with repair mechanisms and have checkpoints in place to halt cell division so repairs can be done. If the damage is beyond repair, cell death is triggered so the damaged cell is not replicated. However, if these protective pathways are overwhelmed or compromised, damages may remain and mutations may occur when DNA is replicated past these damages. Mutated cells can multiply, and this may result in cancer.

In mice, DOC increases reactive oxygen species which can directly alter DNA, leading to mutations or indirectly causing epimutations. During DNA repair, epigenetic alterations are needed to silence genes. However, sometimes these silenced genes are not turned back on, resulting in epimutations. Such mutations or epimutations can give

Elevated bile acids, including the more toxic secondary bile acids, enhance intracellular reactive oxygen species, causing DNA damage and cancer.

cells a reproductive advantage, meaning these mutated cells outgrow and outcompete their healthy neighbours. This growth advantage may be because a mutated cell is evading its inherent protective mechanism of programmed cell death (apoptosis). In fact, studies show cells exposed to DOC developed apoptosis resistance, allowing them to escape the mechanism that would otherwise ensure their termination when DNA damages are present.

These mutated or epimutated cells may rapidly duplicate and form field defects or patches that appear normal under the microscope because the eye cannot see mutations or epigenetic alterations. In addition to



Colonic crypts in epithelium from two mice. (a) Photomicrograph of tissue from a mouse fed a standard diet. (b) Photomicrograph of tissue from a mouse fed a diet supplemented with deoxycholate. Mice fed a standard diet were stained blue in their nuclei, indicating normal DNA. Mice fed a diet supplemented with deoxycholate were stained brown in their nuclei, indicating 8-OHdG (oxidised guanine) in their DNA. 8-OHdG is mutagenic and triggers epigenetic alterations. Deoxycholate added to the mouse diet gave a concentration of deoxycholate in the mouse colon similar to the concentration in the colon of humans on a high-fat diet.

Research now implicates bile acids in the carcinogenesis of colon, stomach, pancreas, liver, and even oesophagus cancers.

escaping apoptosis, studies suggest cells in these field defects have epigenetically repressed DNA repair genes meaning they are less able to repair damaged DNA and can replicate DNA without slowing down to repair DNA damages. Equipped with

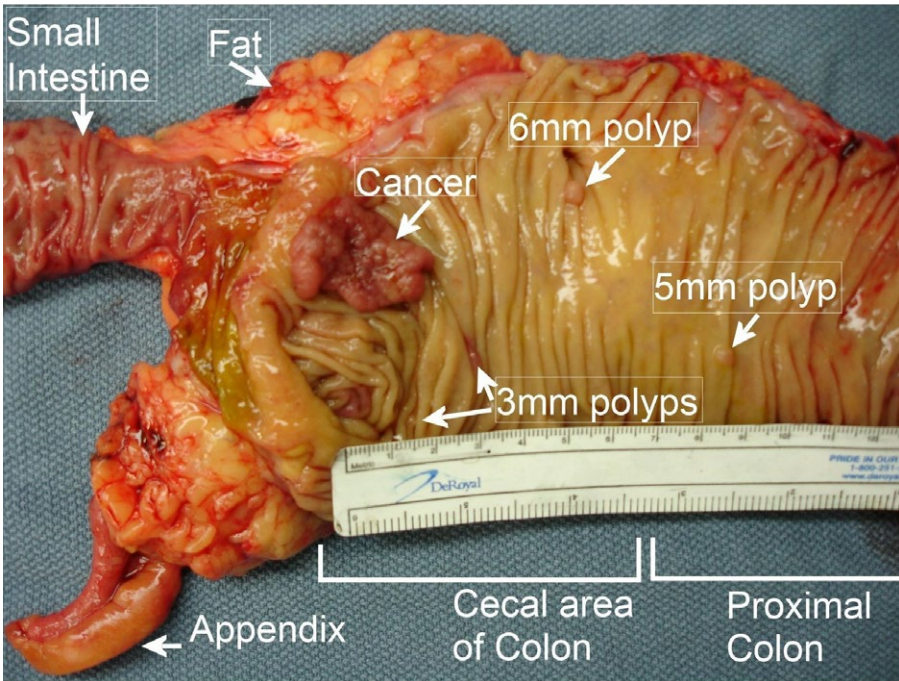
such replication advantages, they can now dominate the local tissue and grow to form a cancer. Colonic polyps can grow in such precancerous field defects, with one study finding the reoccurrence of polyps in a quarter of patients undergoing

colonoscopies after having small colon cancers removed.

Another way bile acids can contribute to causing cancer is through their role as signalling molecules that orchestrate the expression of genes. For example, bile acids increase the level of the protein nuclear factor kappa B in the nucleus which, in turn, controls the expression of hundreds of genes with far-reaching functions such as inflammation, apoptosis, and cell proliferation. Thus, bile acids may act in at least two ways – through ROS-induced mutations and epimutations – and signalling pathways to induce colon cancer.

After breaking down fat for absorption, bile acids, including the more toxic secondary bile acids, are reabsorbed by the gut and return to the liver and then the gall bladder to be used again when needed. Recirculation around the gastrointestinal tract can occur up to twelve times a day. This means that other organs in the system are exposed to carcinogenic secondary bile acids, increasing the risk of other types of cancer. Research now implicates bile acids in the carcinogenesis of colon, stomach, pancreas, liver, and even oesophagus cancers, among others.

Bernstein hopes that by integrating the evidence from studies worldwide implicating bile acids as carcinogens in the colon and gastrointestinal system, dietary changes will be promoted. Dietary changes could save thousands of lives a year, worldwide.



Resection from a human colon shows a colon cancer within a field defect in which four precancerous polyps are also arising. This was a patient with sporadic colon cancer.



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Collaborators

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Bio

Carol Bernstein was a Research Associate Professor at the University of Arizona College of Medicine for 44 years. She now contributes to Wikipedia in her areas of expertise. Bernstein's main research areas are cancer, ageing, sexual reproduction, epigenetics, DNA repair, and the molecular basis of memory.

Further reading

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- Marchand, V, et al, (2010) [Trans fats: What physicians should know](#), *Paediatrics & Child Health*, 15(6), 373–375.

Personal response

After decades of research, what advice would you give a young researcher interested in getting started in your field?

Major advances in controlling cancer could be accomplished by further understanding the lifestyle factors that contribute to causing cancer and how these factors could be modified. Cancer prevention is a promising field of study that would be worthwhile for a young researcher.

What are the next steps needed to take this area of research forward?

Studies of diet and exercise need to be expanded to determine which specific elements of diet and exercise affect the levels of carcinogenic secondary bile acids in the blood and in the faeces of humans.

What could your findings one day mean for patients with gastrointestinal cancers?

After a gastrointestinal cancer is removed, patients should be advised to alter their diet and exercise patterns to reduce the chance of a subsequent gastrointestinal cancer.