The team tackling the serious side effects of cancer treatment in an aging population

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By 2066, it's predicted that around a quarter of the total UK population will be over 65 years old. A number approximately equivalent to the population of London.

This is in part due to increasing life expectancy, a result of progress made through medical research. But as life expectancy increases, an aging population brings up a whole host of new challenges for healthcare, as we've blogged about before.

One of these problems is considering the side effects of cancer treatments, which can often be experienced more intensely by older patients.

We can see this with radiosensitisation, where additional treatment, such as small doses of chemotherapy, can be added to enhance the sensitivity of a tumor to radiotherapy.

But this comes at the cost of harmful side effects.

We caught up with Professor Anne Kiltie and Ph.D. student, Chee Then, who are part of a team looking into the relationship between the gut microbiome and radiosensitisation in bladder cancer.

What is radiosensitisation?

A radiosensitiser can be thought of as an enhancer, an additional agent that increases the sensitivity of tumor cells to radiotherapy.

"So classically, radiotherapy was given on its own for any sort of tumor. And then people discovered that if you add a little bit of chemo at the same time as giving radiotherapy, it acts locally to enhance the effects of the radiotherapy," explains Kiltie.

This is often the case for patients who are being treated for pelvic tumors including cervical, rectal and bladder cancers. The problem, Kiltie explains, is that the radiosensitising chemotherapy frequently results in increased toxicity in local organs and tissues, causing negative side effects.

And these negative side effects may be too much for older people to cope with. Kiltie has witnessed this first-hand in her clinics. "The median age of my radiotherapy patients is about 81 to 82," Kiltie explains, "and patients older than this end up having radiotherapy alone."

So Kiltie and Then set out on the hunt for a radiosensitiser with reduced side effects, which led them to the gut.

Fiber consumption and the microbiome

The gut is one of the most widely researched parts of the body, but scientists are finding out eye-opening information about the gut and its unusual inhabitants every day.

More specifically, the trillions of bacteria, fungi and viruses that call the human body home, often called the microbiome.

The vibrant community of bugs can help protect us from harm, programming our immune system as well as providing nutrients for our cells. And it's a real area of interest for cancer research.

Scientists, including our OPTIMISTICC Cancer Grand Challenges team,

are interested in a whole host of possible links between the gut and cancer, from looking for cancer clues in poo, to discovering unique strains of bacteria that could act as a genetic marker for bowel cancer.

So far, changes to the gut microbiome enhancing anti-cancer treatment have only been explored in the context of chemotherapy and immunotherapy, "but there is not any study about radiotherapy and the gut microbiome," says Then.

Because of its effect on the microbiome, scientists are also interested in the role that diet—particularly high fiber foods—can play in cancer. Previous studies have looked at how a high fiber diet has the capacity to reduce tumor growth, but haven't looked explicitly at the mechanism behind how a high fiber diet could change the bacterial composition in the gut.

Kiltie and her team wanted to explore this gap in the research by further examining the connection between the microbiome and radiotherapy.

Back to bacteria

The lab focussed their work on mice with a compromised immune system and bladder cancer, who were fed a variety of fiber diets. "We treated the mice with either a low fiber diet, or a high soluble fiber or insoluble fiber diet or a mix of the two," Then explains.

The team went on to analyze the composition of the gut microbiome of the different groups of mice, and how they responded to radiotherapy.

The team found that the mice fed with the high soluble fiber diet on average had the slowest tumor growth rate following small doses of radiotherapy.

Changes to fiber consumption can be seen almost immediately in the mice's poo. With an indication of an increased amount of a short chain fatty acid known to confer anti-cancer effects, called butyrate.

Interestingly, and more unexpectedly, of the mice administered the high soluble fiber diet, those who responded to radiotherapy were enriched with a strain of bacterium known as Bacteroides acidifaciens. "A relatively newly-discovered bacterium, I suppose isolated in 2000," Then comments.

The team believe the increase in the Bacteroides acidifaciens could be the missing link between the change in fiber consumption, short chain fatty acids and radiosensitisation. And that this bacterial strain plays a crucial role in the production of short chain fatty acids.

"So, the gut microbiota needs the fiber to produce short chain fatty acids and we think that this might be a potential radiosensitiser," Then explains.

Like Kiltie and Chee, Our Cancer Grand Challenges OPTIMISTICC team are also investigating correlations between the microbiome and treatment response. Some of their latest work has identified a bacterial strain which is associated with a higher chance of relapse of patients with rectal cancer who have been treated with chemotherapy.

From the lab to the clinic

Kiltie and her team believe the proof is in the fiber. And it won't take any expensive medicine to get this into practice, but repurposing of an existing treatment.

The team are looking into different types of fiber, including ispaghula husk. This is currently administered as a standard treatment for

radiotherapy patients, but as a way to reduce diarrhea.

Currently, patients "only start taking it halfway through their radiotherapy to help the side effects," explains Kiltie. "But the argument is that the fiber can actually increase the short chain fatty acid production."

The idea would be to get patients to take the fiber supplement before and during their radiotherapy to act as a radiosensitiser, whilst also reducing side effects. And most importantly, this would be something easily administered to older patients.

"The beauty of ispaghula husk, or whatever fiber supplement we end up giving, is it's a medicine and old people take lots medicines and they're generally pretty compliant," says Kiltie. "To try and modify somebody's diet is unlikely to work in a 78-year old, they're probably going to say 'no way.'"

It's early days, and the team have lots planned before they can trial it in humans, but the latest results are promising. "The idea has been kind of boiling, bubbling along for two or three years," says Kiltie, "but to actually show something in the mice is really exciting."

More information: Chee Kin Then et al. Association of Bacteroides acidifaciens relative abundance with high-fiber diet-associated radiosensitisation, *BMC Biology* (2020). DOI: 10.1186/s12915-020-00836-x

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