EBacteria and Cancer

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We live with trillions of microbes in our gut, a rich community of bacteria and other microorganisms that metabolize foods and support our health. A new animal study published in Science now suggests that gut inflammation alters this microbial community—the microbiota—fostering the growth of a toxic form of bacteria that may then cause colorectal cancer.

The research also linked this toxic bacterium—a strain of E. coli—to human cancer: People with colorectal cancer had relatively higher proportions of this E. coli strain than healthy people.

The study, partially supported by AICR, suggests a novel and complex interaction in which our microbiota and an inflammatory microenvironment act in concert with one another to promote colon cancer.

The work identified the toxic bacterium as a form of E. coli carrying genes called pks (polyketide synthase).

“It’s long been a dogma in cancer research that inflammation promotes cancer, but the mechanism by which inflammation increases colon cancer risk isn’t known,” said James C. Fleet, PhD, a professor in food and nutrition at Purdue University and an expert on colon cancer prevention who was not involved in this study. “This work is so important because it provides a unique perspective…It says we have to consider the impact of the gut microbiome on cancer risk and it suggests that we could reduce colon cancer risk if we could reduce the number of microbes in the gut that have the pks gene.”

Aggressive and Pathogenic

Researchers already knew that people with inflammatory bowel diseases are at increased risk of developing colorectal cancer. And there are microbes recognized to cause cancer, such as the bacterium Helicobacter pylori for stomach cancer. But there are numerous strains of harmless E. coli and many are living in our gut.

“These bugs are just sitting there, being quiet until an opportunity comes.”

“This is not the classic, invasive pathogenic bacteria; this is a commensal E. coli. It does not cause disease in a regular mouse, it acquires traits when the host is susceptible or when exposed to different stressors, such as inflammation,” says Christian Jobin, PhD, the lead author of the paper and an AICR grantee. “Then these E. coli may become more virulent and become your worst enemy.”

Jobin, an associate professor at the University of North Carolina School of Medicine, and his colleagues first started with mice susceptible to inflammation and housed them in a germ-free environment. After five months, all the mice had developed colitis and 60 to 80 percent of the mice had colon tumors. When comparing these groups against controls, the researchers saw that inflammation led to a microbiota with far fewer kinds of microbes and a 100-fold increase of one form of E. coli.

They identified this strain of E. coli as an aggressive form already linked to damaging DNA. Later they found it carried pks genes and produces a toxin called colibactin.

When the researchers placed E. coli with and without pks in mice prone to inflammation, the E. coli pks promoted tumor formation. The E. coli without the pks gene decreased the ability of tumors to invade and multiply.

Then the scientists looked at tissues from 80 people. One group was from colon cancer patients and another group of people had inflammatory bowel disease, conditions that involve inflammation. The third group was the comparison, without inflammation or cancer. Two-thirds of the colorectal cancer patients and about a third of the patients with inflammation had E. coli that carried the pks gene. Only one-fifth of the comparison group had the pks bacteria.

Still, having this E. coli pks, by itself, was not enough to promote cancer in mice. In the absence of inflammation, mice given the bacteria did not develop inflammation or cancer.

Inflammation sets up the perfect environment for E. coli pks to cause cancer, says Jobin. It shifts the gut’s microbial strains and also allows the toxic bacteria to adhere to the epithelial cells that line our colon and where colon cancer begins, the work purports.

“You may have this E. coli and it may not come into close contact with your epithelium because we have a lot of defense mechanisms in place that keep them from invading,” says Jobin. “These bugs are just sitting there, being quiet until an opportunity comes…The inflammation allows them to expand, they have the opportunity and the numbers to then interact with the host—everything together is like the perfect storm.”

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Diet Blocking Bacteria
More research is needed to understand how inflammation-related changes affect the microbiota and colon cancer risk, researchers note, but it is recognized that diet can alter the microbiome. And AICR/WCRF’s expert report and its updates show that a high fiber diet reduces the risk of colon cancer.

Studies by the team of University of Liverpool scientists who were co-authors of the Science paper now suggest that dietary fiber may affect E. coli, which plays a role in our gut health. Dietary fiber may prevent the movement of E. coli through cells in our gut, says Barry Campbell, PhD, co-author of the Science paper and an associate professor of gastroenterology.

Laboratory studies by Barry Campbell and his colleagues showed that soluble fiber from plantain and broccoli can prevent pathogenic bacteria from adhering to the gut’s epithelium. In one cell study published last year, the scientists found that dietary plantain can block toxic E. coli from adhering to epithelial cells. The plantain fiber also blocked Shigella, Salmonella, and other pathogens that cause diarrhea. The more plantain fiber applied to the cells, the stronger the effect. Dietary fiber from other foods, including leeks and apples, did not show the same effects, although they clearly have many health benefits, Campbell adds.

“This might be a very important mechanism underlying some of the beneficial associations between fruit/vegetable intake and gut health, including the reduced risk of bowel cancer,” said Campbell.

Understanding the ecosystem in our gut and how inflammation and diet affect it is a work in progress, researchers agree. “We know these bugs talk to us and vice versa,” says Jobin. It’s possible that some foods are linked to cancer risk because of how the foods affect the microbiome. “Looking at the microbiome and cancer … it’s a wide open field.”

Interplay between inflammation, microbiome and cancer

Inflammation induces expansion of carcinogen-associated microbes. These bacteria, such as E. coli producing pks-derived colibactin, could promote tumorigenesis.

Source: Dr. Christian Jobin and Dr. Janelle Arthur, UNC.

Science Shorts: Physical Activity and Cancer Prevention

Exercise Reduces Fatigue for Survivors
Both during and after treatment, walking and other exercise may help survivors reduce the fatigue that is one of the most reported side effects of treatment, suggests a major systematic review of the evidence published in The Cochrane Library.

A 2008 Cochrane review found that moderate exercise could combat fatigue. This updated review includes double the number of studies – 56 in total; half of the studies focused on breast cancer survivors.

Review authors included only randomized controlled trials (RCTs) that examined the effect of exercise on cancer-related fatigue in adults. The majority of RCTs included an aerobic exercise regimen, such as walking or biking.

Aerobic exercise both during and after cancer therapy reduced fatigue more effectively when compared to those who did not exercise. The beneficial effects of exercise were seen specifically for survivors of breast and prostate cancers. More research is needed to determine the exercise type, intensity and timing that best helps reduce cancer-related fatigue, note the authors.


Minutes of Activity to Improve Metabolic Markers
Twenty minutes of daily aerobic exercise are good, 40 minutes are even better, to help overweight children lose weight and reduce a handful of risk factors shared between both diabetes and cancer, finds a study published in the Journal of the American Medical Association.

The study was conducted among 222 sedentary children; most were obese and a quarter had prediabetes. The 7- to 11-year olds were randomly divided into one of three groups: One group was aerobically active 40 minutes every day after school; a second group for 20 minutes after school, and the third group continued their non-active lifestyle, acting as the control. The activities were all designed to keep the heart rate up, including running games, jumping rope and playing soccer.

After 13 weeks, the children who were active 40 minutes a day showed the greatest reductions in insulin resistance, body fat and visceral fat compared to the control group. Those who exercised 20 minutes a day also showed marked improvement in each category compared to the control. Both the 20-minute and 40-minute exercisers showed similar benefits in fitness.


Activity Lowers Adults’ Leukemia Risk
In one of the largest studies of its kind, research now suggests that adults who are regularly physically active have a lower risk of developing leukemia and other cancers that affect the blood and lymph system. The study was published in the Annals of Oncology.

Non-Hodgkin lymphoma, leukemia and blood-related cancers are called hematologic malignancies. This study pulled data from approximately 65,300 participants of the large Vitamins and Lifestyle (VITAL) study. When the participants entered the study, at ages 50 to 76, they gave information about their physical activity habits over the last ten years. Participants reported activities they participated in more than once a week for over one year.

After an average of seven years, the study found that those who were the most physically active had a lower risk of all hematologic cancers combined when compared to those who did no activity. The more activity people did, the lower their risk.

When separated by type of hematologic cancer, the greatest risk reduction – over 50 percent – linked regular moderate to high intensity activity to fewer myeloid neoplasms, cancers that develop inside the bone marrow.

Carotenoids and Breast Cancer Prevention: The Latest Research

AICR/WCRF’s expert report and its Continuous Update Project (CUP) show that foods high in carotenoids protect against cancers of the mouth, pharynx, larynx and lung.

Two recent reviews of the research that looked at blood levels now point to the possibility that sweet potatoes, tomatoes and the many other colorful fruits and vegetables high in carotenoids may also reduce women’s risk of breast cancer.

Carotenoids are a large group of phytochemicals that include beta-carotene, alpha-carotene and beta-cryptoxanthin. The phytochemicals are well recognized by their red, orange and yellow hues, but many dark green vegetables, such as kale and spinach, are also rich sources. Beta-carotene, lycopene, zeaxanthin and lutein are a handful of the well-studied carotenoids for their role in cancer prevention – and other health benefits, such as eye health.

Earlier population studies on dietary carotenoids and breast cancer have had mixed findings.

It’s possible measurement errors by dietary questionnaires may be obscuring the link between carotenoids and reduced breast cancer risk, says Dagfinn Aune, an epidemiologist at Imperial College London and lead author of an analysis that assessed carotenoids and breast cancer risk, says Dagfinn Aune, an epidemiologist at Imperial College London and lead author of an analysis that assessed carotenoid intake by both dietary recall and blood concentrations.

Diet and Blood

Published in the August issue of The American Journal of Clinical Nutrition, the study was funded by the World Cancer Research Fund as part of AICR/WCRF’s CUP.

Aune and his colleagues reviewed 24 publications on breast cancer risk and six carotenoids. Some of the studies used dietary recall to estimate carotenoid intake and others measured carotenoid blood levels. The carotenoids studied include beta-carotene, alpha-carotene, lycopene and lutein. For the dietary studies, no link was found between five of the dietary carotenoids and breast cancer risk. Estimates of high beta-carotene intake showed a slightly reduced risk.

Yet the studies measuring blood concentration showed a strong link between carotenoids and reduced breast cancer risk. The reduced risk was seen for total carotenoids and the individual phytochemicals.

“In our study, we saw about a 20 to 30 percent decreased risk of breast cancer when comparing the highest blood concentration of carotenoids to the lowest, but not for diet,” said Aune.

The analysis suggests that dietary studies add blood measures when possible to better determine carotenoid intake.

The second analysis, published in the Journal of the National Cancer Institute, also focused on blood levels of carotenoids in order to overcome potential problems with dietary recall. The study was a pooled analysis of eight population studies. Each of the studies collected blood samples from women who were initially healthy, and then tracked their health over time. At the time their blood was drawn, most of the women were postmenopausal.

Together, the studies made up over 80 percent of all the published literature on the topic, note the authors, including approximately 3,000 women who were diagnosed with breast cancer and 4,000 women who were not.

When comparing the women who measured the highest versus the lowest blood levels, those with the highest levels of total carotenoids linked to almost 20 percent lower breast cancer risk. Lower risk was also associated with higher levels of many individual carotenoids, including lycopene, alpha-carotene and beta-carotene.

The link was generally strongest for tumors that were estrogen-receptor (ER) negative, a tumor less common and more difficult to treat than ER-positive tumors. There was also a stronger link to carotenoid levels and reduced risk among current smokers.

The Whole Package

Carotenoids may influence carcinogenesis directly or through metabolism to retinol, a form of vitamin A. Lab studies show that many carotenoids have antioxidant properties and improve immune function.

There are several alternative explanations for the observed risk reduction, researchers add. For example, women with higher blood concentrations of carotenoids are also more likely to have healthy lifestyle habits, such as being more physically active and a healthy weight, and it’s possible these factors played a role, although many studies adjusted for these.

Carotenoid-packed plant foods are also rich in a variety of phytochemicals that could interact with the carotenoids. “Most of the published studies are small, and we need bigger studies on the subject with biomarkers,” said Aune. “We know that carotenoids are biomarkers of fruits and vegetables … it could be specific benefits of carotenoids, but it could also be the whole package of antioxidants and other beneficial things you find in fruits and vegetables.”

Foods That Fight Cancer

The Latest Research

CAROTENOID

<table>
<thead>
<tr>
<th>ALPHACAROTENE</th>
<th>BETA-CAROTENE</th>
<th>BETA-CRYPTOXANTHIN</th>
<th>LUTEIN</th>
<th>LYCOPENE</th>
<th>ZEAXANTHIN</th>
</tr>
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<tbody>
<tr>
<td>Red, orange, yellow and some dark green</td>
<td>Fruits: Apricots, cantaloupe, citrus fruits, nectarines, papayas, peaches, watermelon</td>
<td>Vegetables: Beet choy, broccoli, carrots, corn, greens (collards, kale, lettuce, spinach), pumpkin, red peppers, sweet potatoes, tomatoes and tomato products, winter squash</td>
<td>• act as an antioxidant</td>
<td>• inhibit cancer cell growth</td>
<td>• improve immune response</td>
</tr>
</tbody>
</table>

Foods containing carotenoids probably protect against cancers of the mouth, pharynx and larynx.

Carotenoids in dark leafy vegetables might inhibit the growth of cancers of the skin, lung, stomach and some types of breast cancer cells.

Lycopene in tomatoes and tomato products may reduce risk of prostate cancer.

Scientist in the Spotlight

Erin Giles, PhD

Research shows that excess body fat increases the risk of seven cancers, yet that risk may vary depending upon when in life we carry the excess body fat, says Erin Giles. Now with AICR support, Giles’ work is unraveling the mechanisms behind obesity may heighten breast cancer risk during certain windows of time.

After completing her undergraduate degree in biomedical science, Erin Giles applied to the graduate program in medical science at McMaster University in Hamilton, Canada. When asked to list a few key words on the application to describe her research interests, she listed “cancer” and “bone,” not knowing the inclusion of these words would end up shaping the course of her career.

“At the time, I didn’t think of cancer and bone as being connected, but it lead me to an interview with a faculty member at McMaster who studied breast cancer metastasis,” said Dr. Giles. “While getting into this field occurred somewhat by chance for me, I knew after earning my doctoral degree I wanted to conduct integrative research that was translational in focus.”

Giles, now a Postdoctoral Fellow at the Center for Human Nutrition at the University of Colorado, does exactly that by exploring the link between menopause, weight gain and breast cancer using a rodent model of obesity and postmenopausal breast cancer.

Linking Weight Gain at Menopause to Cancer
She recently published a study in Cancer Research comparing how lean and obese rats differed in their responses to weight gain after ovary removal. In contrast to lean rats, obese rats were unable to metabolize excess calories into their healthy tissues, causing the extra glucose and fat to fuel tumor growth. The researchers also found higher levels of the progesterone receptor, linked to tumor growth and the uptake of glucose, in tumors from obese rats. When the researchers treated the obese rats with the anti-diabetic drug metformin, they were able to improve glucose control and the ability of normal tissue to metabolize excess calories.

“Obesity is a growing problem worldwide, and being overweight or obese increases the risk of developing several types of cancer,” said Giles. “Some studies also suggest poorer survival rates for overweight and obese individuals.

“Despite this knowledge, we still don’t fully understand the obesity-cancer relationship. Our hope is that if we can further understand the mechanisms that underlie this relationship, we can then develop lifestyle and/or therapeutic interventions that can decrease cancer risk or improve outcomes for these patients.”

Menopause, in particular, said Giles, is a period of time when breast cancer risk is increased, especially in women who are obese. During menopause, lack of estrogen often results in the consumption of more calories, leading to weight gain. “By learning more about the mechanisms involved, we may be able to identify a window of time in which we can intervene before breast cancer develops,” she said.

“Our studies suggest that obese women might be able to lower their risk from postmenopausal breast cancer by taking measures during perimenopause to prevent weight gain and therapeutically control the metabolic effects of obesity,” she said. “These measures should include both reducing caloric intake and increasing physical activity, which is also very important.”

Research into Practice
To this end, Giles personally tries to take advantage of the outdoor activities Colorado has to offer. A varsity rower while in graduate school, she now runs, bikes, hikes and competes in triathlons. She qualified for the Boston marathon last year and is currently training to run the race in April of this year.

Moving forward, Giles also looks forward to continued research exploring the menopausal window and breast cancer risk. According to Giles, the most rewarding aspect of her research is its direct link to human health. “It’s important to me to see the findings of my studies put into practice and to result in actual health benefits,” she said.

Choices and Changes

Encouraging Healthy Habits for Survivors by Phone
It’s clear that physical activity benefits cancer survivors but – for many reasons – most survivors do not exercise regularly, falling into a similar physical activity pattern as the general US population. “Approximately three quarters of our breast cancer patients are not currently exercising,” says Melinda Irwin, PhD, Co-Leader of the Cancer Prevention and Control Research Program at Yale Cancer Center, a statistic that is mirrored in major health surveys on survivors.

The gold standard approach to promote healthy eating and exercising for cancer survivors is in-person counseling, but time, accessibility and cost make that prohibitive for many. Preliminary findings from an AICR-supported study conducted by Irwin and her colleagues at Yale University now suggest phone counseling may be as effective as in-person counseling.

The study focused on weight loss among overweight breast cancer survivors, with the focus on a healthy diet and physical activity. Survivors were randomly assigned to one of three groups: in-person counseling; phone counseling; or the usual-care group, where the women received pamphlets on healthy lifestyle recommendations.

At the six-month mark, it did not matter whether women received counseling by phone or in-person, both were equally and more effective for weight loss than the comparison group. Women who received counseling lost about seven percent of their body weight; the usual care group lost about two percent.

Participants who received counseling were given a pedometer and a goal, two factors that are incredibly motivating to increase activity, says Maura Harrigan, MS, RD, CSO, the project director of the study. “Having a goal to increase activity and for healthy eating, then having the accountability of a check-in … that helps the person really focus and gives them structure to increase their physical activity and make healthier food choices,” said Harrigan. “From my experience, if a person is ready to make changes it doesn’t matter if [the counseling] is in person or over the phone – they are ready.”

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