PREVENTION

Tending the gut

Drugs, lifestyle changes and other measures might lower the risk of colorectal cancer — but the evidence is a long time coming.

BY LAUREN GRAVITZ

In a clinic at the University of Pittsburgh in Pennsylvania, gastroenterologist Robert Schoen has been injecting high-risk patients with a vaccine against colorectal cancer. With a series of three shots, he hopes to prime their immune systems so that they recognize, tag and destroy the disease in its earliest stages, before it can take hold and spread.

His trials¹ — the first to examine whether immunotherapy might be useful for preventing colorectal cancer as opposed to treating it — are part of a swell of research dedicated to cancer prevention that has taken hold in the past two decades.

“Prevention is the most important thing we can do from a public-health standpoint, but it’s also the most difficult area for getting randomized proof,” says Jason Zell, who studies the prevention and treatment of colorectal cancer at the University of California, Irvine. State-of-the-art, double-blind, placebo-controlled trials are always difficult when it comes to disease prevention. And in the case of cancer, the aim

is to thwart something that may not otherwise emerge for decades.

Colorectal cancer is largely preventable. Over the past 30 years, clinical trials and observational studies have suggested that everything from drugs to nutritional supplements, diet and exercise could help to stave off this lethal disease. The difficulties, however, lie in identifying what works, proving that it does, matching those people most at risk of cancer with the most appropriate interventions, and then persuading them to take the necessary action. And the whole process must be done in a way that is overwhelmingly safe.

Initially, many scientists believed that the best hope for preventing colorectal cancer lay in common elements of our diet. But even supplements that originate in everyday foods may not be as benign as they initially appear. Folate (from which folic acid is derived) may provide protection in the earliest stages of disease, but it actually seems to encourage the growth of tumour cells once they arise. And a large-scale trial aimed at preventing lung cancer showed that not only was β -carotene ineffective for

prevention, it seemed to increase both risk of disease and risk of stroke.

Moreover, few scientists have the funds or the institutional structure to power the large and lengthy studies required to demonstrate effective prevention. “It takes a while for the progression of events to happen, and it’s difficult to get a trial organized, completed and funded that can measure meaningful endpoints,” says gastroenterologist Paul Limburg, director of preventive services at the Mayo Clinic in Rochester, Minnesota. Very few such studies have been designed for colorectal cancer, he says. To test prevention in a more realistic time span, most use the best proxy they can: decreased incidence of precancerous polyps called adenomas.

For now, the best way to prevent colorectal cancer is a colonoscopy (see ‘Early alert’, page S4). The cancer almost always starts as benign polyps that grow in the lining of the large intestine. The

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disease is so slow-growing that regular colonoscopies can prevent between 76% and 90% of malignant cases from developing into something more serious.

The problem is that not enough people are tested. In the United States, only about 65% of those for whom regular colonoscopies are recommended actually have them. For the rest, and even for those who are regularly screened, the addition of preventive therapy — an approach often referred to as chemoprevention — could save lives. “It makes sense to have something in addition to screening,” says Limburg. “The ideal chemopreventive agent could delay screening or increase screening intervals.”

Researchers are trying to figure out the most effective approach, but it is complicated — there may be many molecular pathways that trigger the cancer, and even more potential molecular targets. “The number of mechanisms we have is almost equal to the number of scientists investigating the problem,” says Ernest Hawk, an oncologist and cancer-prevention researcher at the University of Texas MD Anderson Cancer Center in Houston.

INVESTIGATING INFLAMMATION

Despite all this complexity, colorectal-cancer researchers have been making progress. For colorectal cancer, “more than for any other cancer, there is evidence that there are agents we can use that would be effective,” says Andrew Chan, a who studies colorectal-cancer prevention at Harvard Medical School in Boston, Massachusetts.

Early research suggested that the best way to stave off colorectal cancer was to inhibit enzymes that foster inflammation, such as prostaglandin and the cyclooxygenases COX-1 and COX-2, which encourage abnormal cell growth. The anti-inflammatory agent with the best long-term data so far is the humble aspirin.

Numerous studies over the past 20 years have shown that taking a daily dose of aspirin for a decade or more can reduce the risk of colorectal cancer by more than 50%, probably by inhibiting COX-1 and suppressing prostaglandin. But the effectiveness of aspirin may be limited by genetics. A study² published in March 2015 found that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) failed to protect a small percentage of people who had specific genetic variations on chromosome 15. In addition, taking aspirin in the long term can cause gastrointestinal bleeding, so oncologists recommend taking it only if a person’s familial risk or history of polyps overwhelms the risk of bleeds.

Such side effects have led some groups to try to make aspirin safer for chronic use. At the University of Texas Health Science Center in Houston, Lenard Lichtenberger and his colleagues have found that lipids from membranes such as those lining the stomach and intestines guard the organs from injury. Aspirin eats away at that lining, so Lichtenberger has combined aspirin with lecithin — a natural phospholipid that helps to protect the mucous membrane without interfering with drug absorption.

The drug, developed for cardiovascular disease prevention by Houston-based PLx Pharma, was approved by the US Food and Drug Administration (FDA) in 2012 for the same uses as over-the-counter aspirin. The University of Texas team is conducting animal trials to evaluate whether it is as effective as aspirin at preventing colorectal cancer. The researchers hope to begin clinical trials in the next few years.

Beyond aspirin, the only therapeutics that have proven effective at lowering the risk of colorectal cancer are other NSAIDs, such as ibuprofen and COX-2 inhibitors. But whereas the evidence for aspirin is undisputed, these NSAIDs are on shakier ground. Their benefit is a bit lower — the reduction in disease risk is closer to 20–30% — and, like aspirin, most increase the risk of gastrointestinal bleeds and other side effects. Celecoxib, one of the best-studied of the group, decreases the risk of bleeding but increases the risk of cardiovascular complications such as heart attack and stroke.

One particularly promising NSAID is sulindac, an FDA-approved anti-inflammatory drug that not only inhibits COX enzymes but also helps to remove molecules called polyamines from the epithelial tissue that lines

the colon and other organs. Elevated levels of polyamines have been associated with carcinogenesis, and inhibiting them has prevented the development of colon and other cancers in mice.

Zell and his colleagues are investigating the preventive power of sulindac combined with eflornithine, a drug that inhibits the creation of polyamines. In a three-year trial involving 375 people with a history of precancerous polyps, the combination of

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sulindac and eflornithine reduced the recurrence of adenomas by 70%, and progression to advanced adenomas by 92%, compared with placebo³. Now Zell is leading

a trial of more than 1,300 people to find out whether the drugs can prevent the recurrence of colorectal cancer. By studying the two drugs in a four-arm trial — one placebo, one sulindac-only, one eflornithine only, and one both sulindac and eflornithine — Zell and his collaborators hope to find out whether the two drugs work better together than they do on their own. The trial is expected to end in 2019.

LIVING PROOF

Lifestyle, too, has preventive potential. People who exercise regularly and who eat a diet low in red and processed meats have much lower rates of colorectal cancer. Yet although healthy habits are consistently associated with decreased disease, proving that these activities were the cause of lowered risk is difficult.

Most lifestyle studies are observational in nature — they use data from interviews or questionnaires to gather information on such factors as daily medication, diet and exercise, and then assess whether there is a link between behaviour and outcome. Graham Colditz, a cancer-prevention researcher and epidemiologist at Washington University in St. Louis, Missouri, conducted one such study⁴ on the US population. “When we looked at national data comparing obesity, inactivity, red-meat and processed-meat intake, alcohol and cigarette smoking, we saw that 80% of colon cancer was really looking preventable,” he says.

His study found that specific dietary factors seem to be implicated in a small fraction of colorectal cancers: about 6% can be attributed to eating red meat, and 5% to alcohol consumption. How they trigger carcinogenesis remains unclear. Some research suggests that the high iron content in red meat promotes carcinogenesis by increasing cell growth, and others indicate that one of alcohol’s metabolites can interact directly with DNA. One recent study drives the point home. In a population of more than 77,000 people who refrained from smoking and drinking, those who ate fish but no other meat seemed to cut their risk of colorectal cancer nearly in half⁵.

Obesity and physical inactivity also

Exercise can improve glucose metabolism and reduce the risk of developing colorectal cancer.

contribute significantly to colorectal-cancer risk, and here researchers have more confidence in the mechanism: they blame glucose metabolism. High levels of insulin, which the body uses to absorb glucose from the blood, seem to stimulate the growth of cancer cells, and the colon seems particularly sensitive to increased insulin. But exercise can halt or even reverse that cycle. The more physically active someone is, the more sensitive the body's cells become to the insulin, improving their ability to metabolize glucose. Moreover, contracting muscles use up more glucose. "We've looked at blood markers for insulin and seen that they relate to subsequent risk of colon cancer," Colditz says, "and exercise has a direct impact on glucose metabolism."

Among other research, data from the Harvard Nurses' Health Study — a long-term project that followed more than 200,000 nurses to assess how various factors influence health — found a strong connection between exercise and reduced risk of colorectal cancer, for both primary and recurring cancer.

The Canadian CHALLENGE trial, led by Kerry Courneya at the University of Alberta in Edmonton, is recruiting people without disease who have previously been treated for either stage II or stage III colorectal-cancer to find out whether they benefit from a physical-activity-based intervention. The researchers hope that this 6–8-year study will yield the most definitive answer yet about how exercise affects disease risk in colorectal-cancer survivors.

BUILDING A BETTER SHIELD

The link between insulin metabolism and cancer is prompting others to ask whether a medication that is already available could help to avert the disease. Michael Pollak, an oncologist at McGill University in Montreal, Canada, is testing metformin, a diabetes drug

that suppresses excess glucose production. Metformin is one of the most commonly prescribed drugs in the West and has a long and proven safety record.

Its effects on colorectal-cancer prevention, however, are still unknown. What limited evidence there is comes from *in vitro* studies showing that, in the presence of metformin, epithelial cells from the colon proliferate more slowly — the opposite of what happens when cells start to turn cancerous. Metformin also has been shown to increase glucose uptake in the colon.

Pollak has confirmed the first finding in studies using human patients: taking metformin for a month significantly decreased the turnover of colon epithelial cells. But large-scale follow-up studies to validate the preventive effect are still a way off. "We certainly know that metformin has an excellent safety record — we have a million person-years of follow-up with it," Pollak says. "We would love to put together a prevention trial, but that's a big undertaking and people want more evidence."

Two dietary supplements also raised hopes for prevention: calcium and vitamin D. But results have been mixed. Clinical epidemiologist John Baron at the University of North Carolina in Chapel Hill presented disappointing results at the American Association for Cancer Research conference in 2014. In a trial of more than 2,200 participants, he looked at the preventive potential of calcium and vitamin D, but found that neither of the supplements, nor a combination of the two, significantly reduced adenomas. "There are a

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lot of observational data suggesting that vitamin D would be dynamite," Baron says. "The results are a big disappointment." The same, he says, was true of calcium.

Such setbacks have left researchers feeling frustrated. "There is a lot of interest in diet and supplements for cancer prevention, particularly for cancers of the gastrointestinal tract," says Chan. "To date, however, there really are not any home runs."

Among all these unproven approaches to preventing colorectal cancer, the most intriguing may be the vaccine being developed at the University of Pittsburgh. Schoen believes that the immunotherapy approach that is gaining traction for cancer treatment — teaching a patient's immune system to recognize and attack antigens specific to cancer cells — can also stop colorectal cancer from developing in the first place. A vaccine given during the earliest stages of the disease, before adenomatous polyps have had the chance to progress into something more insidious, would prompt the immune system to develop an antibody against antigens expressed on precancerous cells.

Schoen's work focuses on a protein called MUC1, which is present on colorectal adenomas. In an early trial involving 40 people who had had advanced adenomas removed, the researchers administered three doses of the vaccine and measured the immune response. A year later, they gave the patients a booster. They found that nearly half of the subjects showed a significant immune response¹. According to Schoen and his colleagues, this 'memory' means that if a vaccinated person develops an adenoma that expresses MUC1, the immune system could potentially recognize the protein and attack the cells expressing it, preventing cancer from developing.

The initial results were so promising that Schoen and his colleagues are now conducting a multicentre trial to determine whether the vaccine can prevent the recurrence of adenomas.

In the end, many researchers believe that the best option for preventing colorectal cancer might be a combination of several approaches. "Prevention may not be one-size-fits-all," says Limburg. "In fact, it probably isn't." But with the right mix — and unlike with other cancers, such as those of the pancreas or the blood — it may well be possible to prevent colorectal cancer. ■

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