As a student at Harvard Medical School, Charles S. Fuchs, MD, MPH, the new Director of Yale Cancer Center and Physician-in-Chief at Smilow Cancer Hospital, found his path while working on a hospital’s oncology floor. He thought, “I want to pursue a career in cancer medicine and cancer research, because that’s where the greatest need exists.”

Within the field itself, he saw the greatest need in gastrointestinal cancers, and became internationally renowned for his clinical and laboratory research at Harvard Medical School and the Dana-Farber Cancer Institute before coming to Yale. Dr. Fuchs points out that the gastrointestinal cancers, in aggregate, account for nearly 25 percent of all new cancer diagnoses in the United States, as well as approximately 30 percent of all cancer deaths. Colorectal cancer alone affects 134,490 people each year and kills 49,200.

“Gastrointestinal malignancies represent a major contributor to the burden of cancer in this country,” said Dr. Fuchs. “I saw this as an opportunity and an enormous need, both for fundamentally understanding the biology and for improving ways to prevent and treat gastrointestinal cancers to improve outcomes for patients.”

He believed he could lessen this burden most effectively by working with large epidemiological cohort studies. Historically, most such cohorts were formed to study heart disease, but Dr. Fuchs realized they were also treasure chests of data on cancer. For instance, he might find clues as to why colon cancer is about 40 times more common in the U.S. than in less developed areas, such as sub-Saharan Africa. His prime suspects: diet and lifestyle.

“He began with the Nurses’ Health Study, which collected extensive health and medical data on 121,700 registered nurses every two years starting in 1976. Dr. Fuchs received permission from the study to do molecular analysis on tissue samples of colon cancers. Then he looked for links between tumor characteristics, risk factors associated with diet and lifestyle, and outcomes.

“We learned a lot,” he said. For instance, a diet high in red meat, carbohydrates, and refined grains increases the risk of colon cancer, as do common byproducts of such a diet, including obesity and diabetes. By contrast, a diet high in fruits, vegetables, legumes, fish, poultry, and whole grains decreases cancer risk. A sedentary lifestyle was associated with greater risk of cancer, while regular exercise decreased risk. So did a daily aspirin and high levels of vitamin D. These findings have been confirmed many times by other studies, and have greatly influenced opinions on colon cancer risk and prevention. He practices what he researches—he exercises, eats a healthy diet, and takes a daily aspirin and vitamin D.

Next, Dr. Fuchs turned to a related question about these risk factors: after a patient is diagnosed with colon cancer, do diet and lifestyle continue to matter in terms of a patient’s recovery, survival, and the chances of cancer recurrence?

“Despite great interest in this question, there were no studies that adequately offered any answers,” explained Dr. Fuchs. He created cohorts of newly diagnosed colon cancer patients and followed them to assess whether their diet or lifestyle or use of supplements influenced their long-term survival, independent of the other cancer therapies that they received.
In the 18 years since, Dr. Fuchs and his colleagues have studied thousands of patients and identified many factors that clearly influence the outcomes of colon cancer patients. For instance, aspirin. Dr. Fuchs found that even after patients were diagnosed with colon cancer, those who took aspirin had a much lower risk of recurrence. The result was so clear that he launched a clinical trial to determine if adding aspirin-like compounds to standard therapies might improve outcomes for these cancer patients.

“...Dr. Fuchs is highly dubious about most supplements that claim to fight cancer, but he makes an exception for vitamin D. “It affects what genes are turned on or off in a cell,” he said. “Colon cancer cells actually possess receptors for vitamin D, and if you expose colon cancer cells to vitamin D in the laboratory, it inhibits their growth.” Based on a simple blood test, Dr. Fuchs learned that colon cancer patients with higher levels of vitamin D have much better outcomes, even if they begin taking the vitamin after diagnosis. Something similar is true for marine omega-3 polyunsaturated fatty acids, more commonly called fish oil, which have been associated with lower risk of colorectal cancer. Dr. Fuchs found that patients who exercise are more likely to be cured, even if they don’t begin an exercise regimen until after their diagnosis. Conversely, obese people, already at greater risk of getting colon cancer, are more likely to have a recurrence after being diagnosed.

Dr. Fuchs and his colleagues wondered why obesity and sedentary lifestyles increase the likelihood of a relapse of colon cancer. The answer may be insulin, a hormone that manages blood sugar. Obese and sedentary people overproduce insulin, but often not enough to keep blood sugar levels in check. The consequence is type 2 diabetes (also called adult-onset diabetes). “Why is that relevant?” asked Dr. Fuchs. “Because, in the laboratory, insulin can promote the growth of colon cancer.”

Next, he looked to see if type 2 diabetes are more likely to have poor outcomes from colon cancer. “The answer was yes,” said Dr. Fuchs. “They have a much higher risk of cancer recurrence.” Then he posed the same question by looking at diet. All food increases blood sugar levels; the increase varies with the food. Carbohydrates, for instance, drive up blood sugar and also cause weight gain. When a person’s total intake of food and its effect on blood sugar are measured, the result is called the dietary glycemic load. A high glycemic load diet has been linked to obesity, heart disease, and cancer.

Dr. Fuchs wanted to understand if a cancer patient’s ability to be cured was affected by such a diet. Again, the answer was yes, with a higher risk of either recurrence or death from the cancer. “Then we went to the heart of it, “ said Dr. Fuchs. “Because, in the laboratory, insulin can promote the growth of colon cancer.”

A Counterintuitive Breakthrough in Brain Tumor Therapy

Ranjit Bindra, MD, PhD, was puzzled. His patients were not responding as expected to a heralded new drug, enasidenib, for brain tumors, which targeted a mutation in the IDH gene, implicated in gliomas. When combined with chemoradiotherapy, in colon cancer patients at the time of diagnosis, and followed them. “We found that those with higher insulin levels in their blood were more likely to die from their cancer.”

He followed the implications of these findings farther. Since colon cancer patients with type 2 diabetes tend to have worse outcomes, they concluded that any risk factor for type 2 diabetes would be bad for colon cancer patients. Dr. Fuchs tested this idea against a well-known risk factor for brain cancer patients: obesity.

Dr. Fuchs wanted to understand if a cancer patient’s ability to be cured was affected by such a diet. Again, the answer was yes, with a higher risk of either recurrence or death from the cancer. “Then we went to the heart of it,” said Dr. Fuchs. “We measured insulin levels type 2 diabetes, heavy consumption of sugary drinks. He found the expected correlations: colon cancer patients who drank lots of sugar-sweetened beverages were more likely to have a recurrence or die from their cancer.

He noticed in the medical literature that coffee-drinkers were less likely to get type 2 diabetes. This made him wonder, given his previous research, if coffee-drinkers were also less likely to get colon cancer. The answer, again, was yes. Further, patients diagnosed with the disease lessened their risk of a recurrence if they drank more coffee.

“...Dr. Fuchs asked if his colleagues would be interested in testing this hypothesis. “I think so,” said Dr. Fuchs. “If we can find a treatment that could improve outcomes, that would be great.”

...Dr. Fuchs and his colleagues have studied thousands of patients and identified many factors that clearly influence the outcomes of colon cancer patients. For instance, aspirin. Dr. Fuchs found that even after patients were diagnosed with colon cancer, those who took aspirin had a much lower risk of recurrence. The result was so clear that he launched a clinical trial to determine if adding aspirin-like compounds to standard therapies might improve outcomes for these cancer patients.

“What’s interesting is that we found that patients diagnosed with colorectal cancer have a lower risk of dying from the disease if they increase their consumption of marine omega-3s. If other studies replicate this, the finding could have implications for future treatment regimens. Other factors associated with the risk of colon cancer can have consequences even after a diagnosis of the disease. For instance, Dr. Fuchs found that patients who exercise are more likely to be cured, even if they don’t begin an exercise regimen until after their diagnosis. Conversely, obese people, already at greater risk of getting colon cancer, are more likely to have a recurrence after being diagnosed.

Dr. Fuchs and his colleagues wondered why obesity and sedentary lifestyles increase the likelihood of a relapse of colon cancer. The answer may be insulin, a hormone that manages blood sugar. Obese and sedentary people overproduce insulin, but often not enough to keep blood sugar levels in check. The consequence is type 2 diabetes (also called adult-onset diabetes). “Why is that relevant?” asked Dr. Fuchs. “Because, in the laboratory, insulin can promote the growth of colon cancer.”

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