How Diet, Obesity and Even Gum Disease May Affect Immune System and Cancer

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BOSTON - The immune system is fickle, and easily influenced by more than just viruses and bacteria. It can be swayed by the seemingly unexpected, such as by what we eat, for example, and affected by surprising sources. At the American Association for Cancer Research's Frontiers in Cancer Prevention Research meeting, scientists are taking a closer look at the link between increasingly common lifestyle factors, the immune system and cancer, with the ultimate goals of preventing and better understanding cancer development.

A Prospective Study of Periodontal Disease and Pancreatic Cancer

Can diseased gums increase the risk of pancreatic cancer? Epidemiologists at the Harvard School of Public Health in Boston think it could, at least according to the findings of a study analyzing 16 years of health data on more than 52,000 men.

Dominique Michaud, Sc.D., assistant professor of epidemiology in the Harvard School of Public Health in Boston, and colleagues at Dana-Farber Cancer Institute and the University of Puerto Rico wanted to know if inflammation, and specifically, systemic inflammation from periodontal disease, might be related to pancreatic cancer.

According to Michaud, several studies have linked inflammation and cancer, and researchers have found a high risk of developing pancreatic cancer among individuals with pancreatitis, or inflammation of the pancreas. But the ties between periodontal disease and cancer have been more tenuous.

Previous studies have shown associations between tooth loss and cancer, and pancreatic cancer as well. But the validity of such studies was questionable because of confounding factors, including smoking, which contributes to both periodontal disease and cancer. An association with periodontal disease and heart disease has also been examined, with systemic inflammation being a potential mechanism behind the connection. Periodontal disease results in chronic inflammation over many years, both in the mouth and potentially, systemically, as well.

The researchers analyzed the health records of a fairly homogenous group of about 52,000 highly educated, male health professionals between ages 40

and 75 who participated in the Health Professionals Follow-up Study, which was created in 1986 to look at lifestyle factors related to cancer and other chronic diseases. They continue to be followed at present through mailed questionnaires, with a greater than 95 percent follow-up rate, Michaud said.

The researchers recorded 216 cases of pancreatic cancer in the 16 years of follow-up between 1986 and 2002. Men who reported having periodontal disease had a 63 percent higher risk of developing pancreatic cancer compared to those who did not report periodontal disease, after the team adjusted for smoking, diabetes, age, physical activity and diet. Those men who never smoked fared even worse, with a two-fold increase in risk. Men who reported a history of periodontal disease and tooth loss in the last four years showed a more than a 2.5-fold increase in the risk of developing pancreatic cancer compared to those without periodontal disease and recent tooth loss.

In a secondary analysis, the team looked at tooth loss at both the beginning of the study (baseline) and during the follow-up period. While tooth loss at baseline was not associated with a risk of pancreatic cancer, those who lost teeth during follow up showed an increased, albeit lesser, risk for pancreatic cancer. Tooth loss among older individuals is likely due to periodontal disease, Michaud explained, whereas tooth loss at enrollment in the study is more likely to reflect teeth that were lost or removed because of cavities.

"The results confirm our hypothesis that pancreatic cancer is related to periodontal disease, not merely tooth loss," Michaud said.

Other potential mechanisms, she said, include the fact that those with periodontal disease have high amounts of bacteria in the mouth and in the gut, and also tend to have higher amounts of nitrosamines, which have been proposed to increase pancreatic cancer risk.

"The work might provide new insights in understanding the role of systemic inflammation on initiation or promotion of pancreatic cancer," she said. Smoking, she noted, is a risk factor that could be acting as a promoter by causing inflammation.

"Establishing whether periodontal disease increases the risk and understanding the mechanisms behind these associations are important because we know so little about pancreatic cancer."

Pancreatic cancer, the fourth-leading cause of cancer death in this country, takes some 30,000 lives a year.

Diet-Induced Obesity Impairs Both Innate and Adaptive Immune Responses

Obese mice experience a far lower immune response than do normal weight mice to a vaccine typically given to cancer patients, according to studies by National Cancer Institute immunologists.

The diminished immune activity not only may explain the connection between obesity and heightened cancer risk, it also suggests that obesity might reduce the effectiveness of common vaccines, such as flu and tetanus.

According to Connie Rogers, Ph.D., MPH, a research fellow at the Laboratory of Tumor Immunology and Biology at the National Cancer Institute (NCI) in Bethesda, several studies over the years have implicated obesity with diminishing immune function. In the early 1990s, studies showed low antibody levels after vaccination in those who had a high Body Mass Index, or BMI, which is a measure of body fatness.

"We hypothesized that perhaps there are global immune impairments that occur in the face of obesity, and in turn, maybe this is one of several mechanisms that might lead to, or mediate, the relationship between obesity and tumor risk," she said.

Rogers and co-workers at NCI and at the University of Texas compared the immune system function of lean, overweight and obese mice. They created lean mice by slightly restricting their diets and watching carbohydrates. Mice that were given unlimited access to food with a mildly fat content, about 10 percent versus the usual 5 percent to 7 percent fat in their diet, became overweight. Mice that were given unlimited access to a diet made up of about 60 percent in fat, similar to consuming a diet plentiful in fast-foods, became overweight to obese.

"The mice differed in body fat," Rogers noted, "and we wanted to tease out whether it was the weight or body fat that impaired immune function, and if there was a fat threshold in regard to immune function."

The researchers injected mice with a vaccine usually used for cancer patients and which targeted tumor antigens commonly seen in breast, prostate or colon cancers. By stimulating the immune system and measuring a specific response, they could compare the extent of obesity-induced immune function impairment in each animal body type.

"We needed to simulate the immune system and be able to measure a specific response," she said. The study also served "as a tool to probe the

immune system and to shed some light on whether obesity might be impacting patients we see who come in for cancer vaccine treatment."

The scientists gave mice a primary vaccination and two booster vaccines to mimic as closely as possible the schedule used in patients. They examined both the broad-based or innate immune responses, and the adaptive immune responses, including T- and B-cell responses to vaccination. While adaptive immune responses require prior exposure to a foreign protein such as a virus or bacterium, innate immunity does not.

"Interestingly, it looks like both innate immune responses such as natural killer cell function and T-cell proliferation to broad-based stimuli were impaired, and importantly, their adaptive immune responses to the vaccine were impaired," Rogers said. The group found that the obese mice failed to develop appropriate antibody levels and "their ability to proliferate in response to the vaccine antigens was impaired." Both are important for generating an adequate immune response to a vaccine.

Neither the lean mice nor the moderately overweight mice showed similar immune system impairments in response to vaccination, suggesting that the response might be a "stepwise decrease" in adaptive immunity, Rogers said.

"I think we now know that this obesity-induced impairment is fairly widespread, and affects many components of the immune system," she said. "The clinical and public health importance of this is that there are probably some significant long-term consequences. We targeted many components of the immune system, and several, such as general response to infection and tumor response to vaccine, for example, could be affected by this obesity-induced impairment in immunity."

"In the long term, we're considering the usual cancer patient who is in his sixties and probably overweight," Rogers said. "But a basic biological question and one with public health significance is that of general immune health of overweight or obese people. That has an impact on long-term health."

Rogers and her team have several questions to explore. "Now that we know about obesity-induced impairments in immune function, we want to know whether these can be reversed by interventions, such as diet and exercise," she said. "Is a person permanently immunologically impaired, or can losing weight, body fat or both, reverse the effects, or is some other mechanism involved?" Such studies involving diet and exercise currently are underway in animals.

A 23-Year Survival Analysis of Prediagnostic BMI and Risk of Lethal Prostate Cancer

A team of Harvard scientists has peered into 23 years of health data on more than 22,000 physicians and concluded that men who are overweight or obese years before being diagnosed with prostate cancer are more likely to die of the disease than those who are of normal weight.

While no studies have definitively shown that obesity and/or higher Body Mass Index, or BMI, which measures body fat, increases the risk of developing prostate cancer, these studies showed that obese men at the time of diagnosis were more likely to have a cancer recurrence.

But according to Jing Ma, M.D., Ph.D., a researcher at the Brigham and Women's Hospital-based Channing Laboratory and associate professor of medicine at Harvard Medical School, few studies have focused on obesity and the risk of dying from prostate cancer.

In fact, she said, there is "considerable debate in the urology and cancer fields regarding whether rising PSA (Prostate Specific Antigen) is a good indicator for whether people will eventually die from prostate cancer or not."

Ma and her co-workers at Brigham and Women's Hospital and at the Harvard School of Public Health examined 23 years of data from the Physician's Health Study, which began in 1982 as a randomized, double-blind trial of aspirin and beta-carotene. More than 22,000 U.S. male physicians were recruited for the trial to study the role of aspirin and beta-carotene in preventing heart disease and cancer.

About 15,000 men provided blood samples at enrollment, along with information on their body weight and height, and their BMI was calculated. Approximately 99 percent of the original participants were tracked through questionnaires for 23 years, including cause of death.

By the end of 2005, 2,367 men had developed prostate cancer, while 265 died of the disease. They found that 39 percent of the participants were overweight and 3.4 percent were obese at the beginning of the study, and that higher BMI was positively associated with the risk of dying from prostate cancer. They also showed that the risk of dying from prostate cancer increased 8 percent for each point increase in BMI.

A person with a BMI of between 25 and 29.9 is considered overweight, whereas someone with a BMI of 30-plus is called obese. The physicians were in relatively good shape compared to the U.S. population in general. U.S.

males between 50 and 69 are approximately 40 percent overweight and more than 30 percent are obese.

"It was surprising since it is a moderate association and the BMI was measured in 1982 and was on average eight to 10 years before developing prostate cancer," Ma said. "The beauty of the study is that we could factor out smoking at baseline, and tumor grade and stage didn't affect the trend."

"Some people might think that what they do today has little to do with cancer risk, especially for prostate cancer," Ma said, "and some individuals probably wouldn't believe that obesity has anything to do with prostate cancer. But we have found that if a man develops prostate cancer, being obese could put him at a higher risk of dying from the cancer. There is something many men can do about that."

She and her co-workers are exploring the underlying mechanisms that link being overweight and/or obese to prostate cancer progression. A better understanding of the risk factors that influence the disease's progression, said Ma, is imperative.

Prostate cancer is the most common type of cancer found in American men, other than skin cancer, and the third leading cause of cancer death in men. The American Cancer Society estimates that there will be about 234,460 new cases of prostate cancer in the United States in 2006, with approximately 27,350 deaths from the disease