

Medical News & Perspectives

Study Links Periodontal Disease Bacteria to Pancreatic Cancer Risk

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More than 50 000 people will be diagnosed with pancreatic cancer this year, and because the disease is often not diagnosed until an advanced stage, less than 10% of those diagnosed will still be alive in 5 years (<http://1.usa.gov/1wOVy73>). A new study, however, determined that people with 2 types of periodontal disease-causing oral bacteria have a greater risk of subsequently developing pancreatic cancer, thus pointing to a new avenue of research for investigating early markers of pancreatic cancer.

Several previous studies have linked poor oral health with an increased risk of developing pancreatic cancer (Meyer MS et al. *Cancer Causes Control*. 2008;19[9]:895-907), and the new study's research team suspected that oral pathogens might play a role.

"Studies have consistently shown this relationship. Our question was why. Our hypothesis was that oral bacteria is the underlying explanation because [periodontitis] is caused by oral bacteria dysbiosis," said Jiyoung Ahn, PhD, the study's principal investigator and associate professor of population health and environmental medicine at Langone Medical Center at New York University (NYU).

Pathogens Precede Cancer

The National Cancer Institute-funded study, not yet published, was presented at the 2016 American Association for Cancer Research meeting (<http://bit.ly/1rCf3SY>). For the study, researchers obtained saliva samples from participants in large-scale, long-term, prospective cohort studies (<http://bit.ly/1riJdKu>; <http://1.usa.gov/1SBFZIU>). They sequenced DNA extracted from saliva samples of 361 people who developed pancreatic cancer, as well as samples from 371 matched healthy participants. The researchers controlled for variances in age, race, sex, smoking status, alcohol use, body mass index, and diabetes, Ahn said.

The research team found that participants with *Porphyromonas gingivalis* in



their oral microbiome had a 59% greater risk of developing pancreatic cancer relative to those who didn't. Individuals with *Aggregatibacter actinomycetemcomitans* present in their oral microbiome also had at least a 50% increased relative risk of developing pancreatic cancer, although the association was not as statistically strong, Ahn said.

The increased risk remained the same after excluding pancreatic cancer cases that occurred less than 2 years after samples were obtained, making it unlikely that oral microbiome dysbiosis occurred after or concurrent with cancer development, Ahn added.

Researchers found both periodontal disease-causing pathogens in the oral microbiomes of individuals in the control and pancreatic cancer groups, Ahn explained. However, *P. gingivalis* was far more prevalent, found in the oral microbiome of 26% of control individuals and 35% of those who developed pancreatic cancer. In comparison, 4% of control participants and 9% of those who subsequently developed pancreatic

cancer harbored *A. actinomycetemcomitans* in their oral microbiome.

The NYU Langone study builds on other investigators' previous research that associated periodontal disease with pancreatic cancer. For example, a large European prospective cohort study found that people with high levels of *P. gingivalis* antibodies in their blood (>200 ng/mL) had a 2-fold greater risk of developing pancreatic cancer than those with lower levels of the antibodies (Michaud DS et al. *Gut*. 2013;62[12]:1764-1770). In addition, a prospective cohort study of more than 50 000 male health professionals, which provided a homogenous socioeconomic study population, determined that a history of periodontitis was associated with a 64% increased risk of developing pancreatic cancer and that the association was stronger for men who had never smoked, even though smoking is a risk factor for pancreatic cancer (Michaud DS et al. *J Natl Cancer Inst*. 2007;99[2]:171-175; <http://1.usa.gov/1SvUZel>).

Research has also shown a relationship between *P. gingivalis* and another type of cancer, esophageal squamous cell carcinoma. One study found that 61% of cancerous tissue samples taken from 100 patients were colonized with the bacteria, in contrast to none of the healthy esophageal tissue samples taken from 30 healthy participants. Infection with *P. gingivalis* was also positively associated with cancer metastasis and survival rate. However, the researchers could not determine whether *P. gingivalis* was a causative agent or whether the microenvironment of the cancerous tissue simply was hospitable to colonization by the bacteria (Gao S et al. *Infect Agent Cancer*. 2016;11:3).

Inflammation May Be a Driver

Unlike previous studies associating poor oral health with pancreatic cancer, the NYU Langone study determined that oral microbiome dysbiosis preceded the development of pancreatic cancer instead of developing after the cancer takes root.

"It is the first study to look at oral samples collected prior to disease onset," said Dominique S. Michaud, ScD, a professor of public health and community medicine at Tufts University Medical School in Boston, who was not involved in the NYU Langone study. "The findings confirm the positive association with *P gingivalis* that we previously observed using prediagnostic blood samples," added Michaud, the first author of the European *P gingivalis* antibodies study.

Nonetheless, it is premature to conclude that the 2 periodontitis-associated pathogens cause pancreatic cancer, Ahn cautioned. They could merely be a correlate of systemic inflammation or another process occurring within the body, she said.

"Inflammation is related to cancer. The bacteria could be causing inflammation in

the pancreas: that's one theory," Ahn said. "But maybe the bacteria in the mouth is just a marker for the susceptibility of the body to inflammation."

"This is very interesting work," Alison Klein, PhD, an associate professor of oncology at Johns Hopkins University School of Medicine and director of the National Familial Pancreas Tumor Registry, said of Ahn's study.

"I'd like to see mechanistic studies of how this [oral microbiome dysbiosis] goes on to cause pancreatic cancer or if it causes pancreatic cancer, as well as further validation in larger samples," added Klein, who was not involved in the NYU Langone study.

Additional studies are planned, Ahn said. In one study slated for later this year, researchers will inject *P gingivalis* and *A actinomycetemcomitans* into the pancre-

ases of mice with genetically engineered susceptibility to pancreatic cancer to explore how periodontitis-causing pathogens may influence pancreatic carcinogenesis.

The research team also hopes to expand its study of the association between the oral microbiome and pancreatic cancer by examining viruses in the oral microbiome of patients with pancreatic cancer, Ahn said.

Although the NYU Langone study results are intriguing, it's too soon to recommend that people step up their brushing and flossing as a preventive measure, Ahn said, noting that she has received numerous calls from people with pancreatic cancer or a family history of the disease asking if they should be on guard for periodontitis.

"I wish I could [offer more] answers. This is exciting as we figure it out," Ahn said. ■