

# Largest Such Study Finds Smoking Increases Risk of Developing Second Smoking-Related Cancer

BY MARY BROPHY MARCUS

**L**ung, bladder, kidney, and head and neck cancer survivors who smoked before their first cancer diagnosis have up to a five-times higher risk of developing a second smoking-related cancer compared with survivors who never smoked, a large study has shown.

For the study, published online ahead of print in the *Journal of Clinical Oncology* ([doi.10.1200/JCO.2014.56.8220](https://doi.org/10.1200/JCO.2014.56.8220)), a team led by Meredith S. Shiels, PhD, MHS, a research fellow in the Infections and Immunoepidemiology Branch of the National Cancer Institute, analyzed data from five large prospective epidemiologic cohort studies that included 15,084 patients: 2,552 with stage 1 lung cancer; 6,386 with bladder cancer; 3,179 with kidney cancer; and 2,967 with head and neck cancers.



• Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Shiels noted in an interview that prior to this research, most of the data on smoking and risk of second cancers among cancer survivors involved smaller studies. “Our study is the largest to date to examine these associations, and the first I’m aware of to look at pre-diagnostic smoking behaviors and second cancer risk among bladder and kidney cancer survivors,” she said.

A total of 866 second primary smoking-associated cancers were diagnosed among the survivors, and those who smoked 20 or more cigarettes a day prior to their cancer diagnoses had an up to five-fold higher risk of developing a second smoking-associated cancer compared with survivors of the same cancers who never smoked.

- The findings also showed, more specifically, that in those who smoked cigarettes before their first cancer diagnosis:
  - Stage I lung cancer survivors were 3.3 times more likely to develop a second cancer;
  - Bladder cancer survivors were 3.7 times more likely to develop a second cancer;
  - Head and neck cancer survivors were 4.5 times more likely to develop a second cancer; and
  - Kidney cancer survivors were 5.3 times more likely to develop a second cancer.

There was still an increased risk for those who smoked fewer than 20 cigarettes a day or who had quit before their first cancer diagnosis compared with never-smokers, but the risks dropped the longer it had been since quitting.

## New Light

Asked for his perspective for this article, Damon Vidrine, DrPH, MS, Associate Professor of Behavioral Science at the University of Texas MD Anderson Cancer Center, said the study sheds some new light on smoking-related second cancers.

“We probably suspected this would be the case, but to my understanding, this is first time we’ve seen empirical evidence that shows it. I think it’s meaningful. It certainly adds to our understanding that smoking is bad and that it is not site specific. It affects sites all over the body,” he said.

The authors concluded their study by noting that a recent survey of American Society of Clinical Oncology members found that only 58 percent of providers always advise their patients to quit smoking and only 39 percent usually provide treatment or refer patients for treatment for tobacco dependence. Yet, research suggests cigarette smoking is still common in cancer survivors, even among those diagnosed with tobacco-related cancers. Shiels and her 13 coauthors write that this may be because patients do not realize they are at a higher risk for complications, second cancers, and death if they keep smoking.

“We probably suspected this would be the case, but this is the first time we’ve seen empirical evidence that shows it.”

The five studies that the data were drawn from were the following:

- National Institutes of Health-AARP Diet and Health Study;
- Agricultural Health Study;
- Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study;
- Iowa Women’s Health Study; and

## Resources

**S**tephanie Land, PhD, Director of the NCI’s Tobacco Control Research Branch and Behavioral Research Program, said that doctors can help patients by providing counseling and cessation medication, or by suggesting they call 1-800-QUIT-NOW, or visit [www.smokefree.gov](http://www.smokefree.gov), or similar resources.

In addition, information from ASCO notes that the Society is committed to educating its members and providing resources to help patients quit using tobacco. For example, the Society has a policy statement that specifically urges integrating tobacco cessation into clinical care (*OT 8/25/13 issue*), as well as a detailed guide to help patients quit using tobacco. All the resources are available at [www.asco.org/tobaccocessationguide](http://www.asco.org/tobaccocessationguide).

“This certainly adds to our understanding that smoking is bad and that it is not site specific. It affects sites all over the body.”

“For those currently smoking at the time of diagnosis, there is still a lot to be gained from quitting,” said Vidrine, who added that there is evidence that suggests that quitting at the time of diagnosis increases survival and decreases adverse treatment outcomes.

Shiels noted that the number of cancer survivors in the U.S. is growing due to increased survival after many cancer diagnoses, and understanding of risk factors for second cancers is therefore crucial.

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“This is also the first study we’re aware of to look at pre-diagnostic smoking behaviors and the risk of second cancers among survivors of bladder and kidney cancers.”

# Tests Use Tumor DNA in Stool and Circulation for Diagnosis, Prognosis

BY ROBERT H. CARLSON

NEW YORK—Somatic mutations of DNA in cancer cells can be very effective biomarkers, largely because of their specificity. Two promising tests to detect tumor DNA were described here at the Chemotherapy Foundation Symposium, sponsored by Mount Sinai School of Medicine.

“We will see an evolution of mutations as diagnostic markers, and not just as predictive and prognostic markers,” said Luis A. Diaz, MD, Associate Professor of Oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, speaking here at the Chemotherapy Foundation Symposium, sponsored by Mount Sinai School of Medicine.

“It’s an evolving field but we’ll be seeing its impact on cancer in the very near future.” His overall topic was on the use of serum tumor DNA for “liquid biopsies.”

At the same session, Steven Itzkowitz, MD, Professor of Medicine and Oncological Services at the Icahn



STEVEN H. ITZKOWITZ, MD (shown speaking at a previous Chemotherapy Foundation Symposium), described recent research on the Cologuard stool DNA test, noting that since approximately one-third of people currently eligible for colonoscopy avoid it, the test would be most important for them—“who hopefully will at least accept this and then a colonoscopy if necessary.”

School of Medicine at Mount Sinai, discussed a diagnostic test for colon cancer that uses DNA found in stool.

Session co-moderator Jordan D. Berlin, MD, Professor of Cancer Research and Medicine and Clinical Director of the GI Oncology Program at Vanderbilt-Ingram Cancer Center, commenting on the multi-targeted stool DNA as screening tests for patients, said “This is real-time stuff that can be applied to practice.”

And he said he found the circulating DNA test “particularly cool.”

While neither test is ready for the clinic, both are worthy of being put in multiple clinical trials, he said.



LUIS A. DIAZ, MD: “We will see an evolution of mutations as diagnostic markers, and not just as predictive and prognostic markers. It’s an evolving field but we’ll be seeing its impact on cancer in the very near future.”



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He said circulating tumor DNA can be used for monitoring response, as in a recent Phase II study of GTX-C (gemcitabine, capecitabine, taxotere, and cisplatin) as first-line treatment in patients with metastatic pancreatic cancer, on which he was senior author—the study was presented in a poster at the most recent American Society of Clinical Oncology Annual Meeting (*Dung et al: ASCO Abstract 213*).

The researchers reported that GTX-C was highly active and well-tolerated in patients with metastatic pancreatic cancer, but they also measured KRAS mutations in the patients’ plasma.

Diaz told the audience here that the researchers saw circulating DNA levels spike when therapy started and the patient had a response—“Dynamic changes were identified much faster than with an antigen biomarker.”

He said that because the half-life of circulating tumor DNA is one to two hours, he foresees circulating tumor DNA levels being used like the infectious diseases model, where dynamic changes can be quickly monitored to predict responses. This would be particularly useful in treating cancer patients with targeted therapies, he said.

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“In oncology, mutations are beautiful biomarkers. They’re incredibly specific, and unlike PSA, which is released by normal cells, they’re discovered in both in tumors and in precancerous tumors.”

## Circulating Tumor DNA for Liquid Biopsy

Malignant tumors have an abundance of mutations—rearrangements, amplifications, translocation, deletions, etc.—that are released by the tumor into the circulation, Diaz said. “Cells are constantly turning over—very few tumors just sit there indolently. And when they undergo apoptosis or necrosis they release DNA into the circulation, and that’s what we’re trying to measure.”

Importantly, circulating DNA levels correlate with survival as a measure of tumor burden, tumor staging, and prognosis, he said.

Cell-free DNA testing made the news earlier this year when a study showed that fetal DNA circulating freely in the maternal blood stream could detect Down syndrome with an estimated false-positive rate of 0.3 percent and a positive predictive value of 45 percent (*Bianchi et al: NEJM 2014; 370:799-808*).

In oncology, Diaz said “mutations are beautiful biomarkers. They’re incredibly specific, and unlike PSA, which is released by normal cells, they’re

## SMOKING

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“We’ve known for 50 years that smoking causes cancers—there’s a huge body of important literature showing that. So it’s really important for health care providers to emphasize in general that anybody who is a smoker can benefit from quitting, including cancer

survivors, given the increased risk of developing a second smoking-related cancer.”

Graham Warren MD, PhD, Chair of ASCO’s Tobacco Cessation Subcommittee, said in a statement: “As doctors, we want to give our patients

the best chance at long-term survival as possible. This study is a reminder for us to aggressively support and encourage tobacco cessation at every step of the way, and should be a wake-up call for all smokers to take the necessary steps to quit.”