

Vol. 2, #3

FOCUS: Thyroid Cancer

*Treatment & Research
Updates*

[INSIDE]

Is the Increasing Incidence of Thyroid Cancer Really Due to
Overdiagnosis? 2

ALK and EML4 Genes Shown as Likely Cause of Rare Type
of Aggressive Papillary Thyroid Cancer 5

Thyroid Nodule Genetic Testing Found as Valuable, But
Guidelines Lacking 10

Is the Increasing Incidence of Thyroid Cancer Really Due to Overdiagnosis?

BY HEATHER LINDSEY

Further evidence that the increasing incidence of thyroid cancer in the United States may be due to overdiagnosis rather than to an epidemic of the disease was shown in a study published last month in *JAMA Otolaryngology Head & Neck Surgery* (2014;140:317-322).

"Patients and physicians should consider carefully whether to work up small, incidentally identified thyroid nodules that are not causing symptoms, said Louise Davies, MD, MS, of the VA Medical Center in White River Junction, Vermont, who coauthored the article with H. Gilbert Welch, MD, MPH. The decision should be made consciously and with an understanding of the benefits as well as potential harms of proceeding down the path of workup, she said via email.

Still, the issue of papillary thyroid cancer overdiagnosis remains complicated, said Raymon Grogan, MD, Assistant Professor



of Surgery and Director of the Endocrine Surgery Research Program at the University

of Chicago Medicine & Biological Sciences. "There is some evidence suggesting that overdiagnosis is contributing to rising thyroid cancer rates, but the fact is that we do not know the relative contribution of overdiagnosis as opposed to a 'true' increase in thyroid cancer rates."

Study Details

For the study, Davies and Welch used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to analyze data for patients diagnosed with thyroid cancer from 1975 to 2009 in nine geographic areas: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, the San Francisco-Oakland area in California, and the Seattle-Puget Sound area of Washington.

Since 1975, the incidence of thyroid cancer has nearly tripled from 4.9 to 14.3

continued on page 3

EDITORIAL BOARD

Chairman: Robert C. Young, MD
Emeritus Chancellor, Fox Chase Cancer Center

Clinical Advisory Editor for Hematology/Oncology:
Mikkael Sekeres, MD, MS, Director, Leukemia Program, Cleveland Clinic Taussig Cancer Institute; Chair, Hematology/Oncology Pharmacy & Therapeutics Committee; Chair, FDA Oncologic Drugs Advisory Committee

Clinical Advisory Editor for Oncology: Ramaswamy Govindan, MD, Co-Director, Section of Medical Oncology, Professor of Medicine, Washington University School of Medicine, Alvin J. Siteman Cancer Center

Joseph S. Bailes, MD, Partner, Texas Oncology; Chairman, Cancer Prevention and Research Institute of Texas Foundation

Paul A. Bunn Jr., MD, Exec. Director, International Assoc. for the Study of Lung Cancer; James Dudley Endowed Professor of Lung Cancer Research, Univ. of Colorado

Michael A. Caligiuri, MD
Director, Ohio State University Comprehensive Cancer Center; CEO, The James Cancer Hospital and Solove Institute

Harold P. Freeman, MD, Founder, President and CEO, Harold P. Freeman Patient Navigation Institute

Joyce Hendershott, MSW, ACSW, LISW-S
Associate Director, Patient Education Department, The Ohio State University James Cancer Hospital & Solove Research Institute

Richard T. Hoppe, MD, Professor, Radiation Oncology; Member, Stanford Cancer Institute, Stanford University

Robert J. Mayer, MD, Faculty Vice President for Academic Affairs, Dana-Farber Cancer Institute; Faculty Associate Dean for Admissions and Stephen B. Kay Family Professor of Medicine, Harvard Medical School

Frank L. Meyskens, Jr., MD, Daniel C. Aldrich, Jr. Endowed Chair and Professor of Medicine, Biological Chemistry, and Public Health; Vice Dean, School of Medicine; Director Emeritus, Chao Family Comprehensive Cancer Center, University of California, Irvine

Joseph V. Simone, MD, President, Simone Consulting

Ellen Stovall, Senior Health Policy Advisor, National Coalition for Cancer Survivorship

Paul A. Volberding, MD
Director, AIDS Research Institute, University of California, San Francisco; Director of Research, UCSF Global Health Sciences

Carolyn Weaver RN, MSN, AOCN, AHN-BC
Clinical Nurse Specialist, Patient Education Coordinator, Fox Chase Cancer Center

Norman Wolmark, MD
Chairman and Principal Investigator, National Surgical Adjuvant Breast and Bowel Project; Chairman, Dept. of Human Genetics, Allegheny General Hospital Cancer Center, Pittsburgh



EDITOR: Serena Stockwell
ASSISTANT EDITOR: Sarah DiGiulio
PRODUCTION MANAGER: Stacy Drossner
DESKTOP MANAGER: Peter Castro
PRODUCTION, iPad App: Sarah Lemore
MANAGER OF CIRCULATION: Deborah Benward

DIRECTOR, PUBLISHING: Theresa M. Steltzer
VICE PRESIDENT, NURSING, HEALTH & WELLNESS PUBLISHING: Jennifer E. Brogan
VICE PRESIDENT, PUBLISHING: Jayne Marks
PRESIDENT AND CEO, WOLTERSKLUWER HEALTH MEDICAL RESEARCH: Cathy Wolfe
VICE PRESIDENT, ADVERTISING SALES: Fabien Savenay
SALES DIRECTOR, LWJ JOURNALS: Ray Lender
SENIOR NATIONAL ACCOUNT MANAGER: Ben Harkinson
Wolters Kluwer Health, Lippincott Williams & Wilkins
100 River Ridge Drive, Suite 207 Norwood, MA 02062; 781-440-4854
fax: 646-607-4253, benjamin.harkinson@wolterskluwer.com
CLASSIFIED ADVERTISING: Mike Rusch, 215-521-8404;
fax 215-689-2453; mike.rusch@wolterskluwer.com
REPRINTS: Bridget Quinn, 215-521-8807; fax: 215-405-3812
Bridget.Quinn@WoltersKluwer.com

EDITORIAL/PUBLISHING OFFICES:
333 Seventh Ave., 19th Fl., New York, NY 10001;
OT@LWWNY.com, oncology-times.com

OVERDIAGNOSIS?

Continued from page 2

per 100,000 people, with just about all of the entire increase in papillary thyroid cancer, which rose from 3.4 to 12.5 per 100,000 people.

The absolute increase in thyroid cancer among women, from 6.5 to 21.4, equaling 14.9 per 100,000 women, was almost four times greater than for men, from 3.1 to 6.9, equaling 3.8 per 100,000 men. The mortality rate has remained stable since 1975 at about 0.5 deaths per 100,000 people, according to the study results.

In 1988 to 1989, which is when SEER started collecting data about the tumor, 25 percent of thyroid cancers were one cm or smaller and 42 percent were larger than two cm. In comparison, in 2008 to 2009, 39 percent of tumors were one cm or smaller and 33 percent were greater than two cm.

In 2009, about 56,000 people were diagnosed with thyroid cancer. The median age of diagnosis was 49 for women and 53 for men. More than 90 percent of men and women underwent surgery for their disease, with approximately half receiving radioactive iodine therapy.

Ongoing Debate

The data and concepts in the paper have been a long-debate, Grogan noted, citing, for example, another SEER database



LOUISE DAVIES, MD, MS, notes that thyroid cancer incidence has nearly tripled since 1975, while mortality from the disease has remained stable.

analysis that he and his colleagues published last year in *Cancer Epidemiology, Biomarkers & Prevention* (2013;22:1252-1259) showing similar findings. That study, though, which focused on the clinical and economic burden, projected that the incidence of papillary thyroid cancer will double by 2019 and become the third most common cancer in women of all ages, at a cost to the U.S. health care system of approximately \$18 billion to \$21 billion.

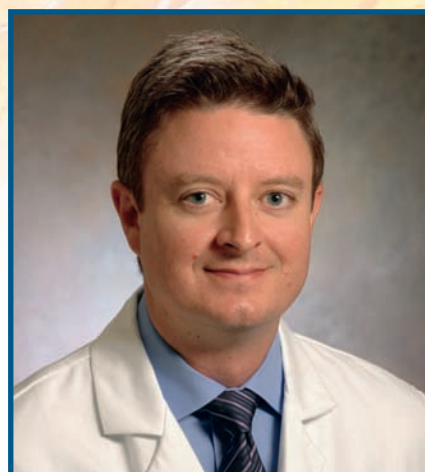
Grogan explained that although he and his coauthors agreed that overdiagnosis is an issue that needs to be fully characterized and remedied at the clinical level, they were concerned that opportunities to learn about the causes of thyroid cancer and possible prevention modalities may be being overshadowed.

Also asked for his opinion for this article, Dennis H. Kraus, MD, Director of the Center for Head & Neck Oncology, New York Head & Neck Institute, North Shore-LIJ Cancer Institute, said that while the Davies and Welch article is important and raises appropriate questions, he himself still struggles with the concept of calling the increase an epidemic of overdiagnosis—"I'm not entirely sure what that means," Kraus said. "I don't understand the idea of closing our eyes to patients with cancer, even though mortality hasn't gone up."

Defining the increase as an epidemic of overdiagnosis is doing a disservice to people who have had and those who will have bad outcomes from this cancer, Grogan added.

His colleague Briseis Aschebrook-Kilfoy, PhD, an epidemiologist in the Department of Health Studies at the University of Chicago, agrees. "There is evidence that more than just overdiagnosis is impacting thyroid cancer rates, and if we continue to blame the entire epidemic on overdiagnosis, we will never make progress on understanding the other factors that are likely contributing to the rising thyroid cancer rates," he said via email.

While there's no question that physicians are overdiagnosing and overtreating very small papillary thyroid cancers, every four-cm papillary malignancy was at one time just four or five milli-



RAYMON GROGAN, MD:

"Defining the increase as an epidemic of overdiagnosis is doing a disservice to people who have had and those who will have bad outcomes from this cancer."

imeters, noted R. Michael Tuttle, MD, Professor of Medicine at Memorial Sloan Kettering Cancer Center (MSKCC). "So, we can't say ignore every 4 or 5 mm cancer," he explained, adding that about one percent of these growths develop distant metastases.

Overall, about 90 percent of small papillary cancers probably don't need to be treated, he said. "We don't want people to ignore small thyroid cancers, but the majority of them have very little potential to hurt you." Observation may be the better option in some individuals rather than treatment, which can be associated with side effects.

Potential Contributors

Much of overdiagnosis is probably coming from imaging of incidental thyroid nodules and subsequent use of fine needle aspiration (FNA), said Jack Jacoub, MD, a medical oncologist at MemorialCare Cancer Institute at Orange Coast Memorial Medical Center in Fountain Valley, Calif. "Detecting thyroid cancer incidentally isn't likely to change. Once patients have access to the health care system and are undergoing imaging for a variety of reasons, incidental detection is more likely to occur."

Still, Davies said, while the largest contributor to overdiagnosis of thyroid cancer is most likely imaging, other

continued on page 4

OVERDIAGNOSIS?

Continued from page 3

factors can play a role—for example, changing physician thresholds for ordering tests, inappropriate overuse of imaging studies, and changes in the way pathologists examine the thyroid specimens they receive after the thyroid gland is removed from the neck.

Also of note, Grogan pointed out, is that thyroid cancer rates are also rising in countries like Brazil and China where ultrasound and FNA are not be as readily available, countering the idea that imaging is contributing to the increased incidence. He and his colleagues also showed in a study published last year that there is an increase in thyroid cancer rates even in U.S. populations that don't traditionally have good access to care (*Ann Surg Oncol* 2013;20:2746-2753).

Curbing Overdiagnosis

While thyroid nodules will continue to be detected on ultrasound, what physicians can do to help curb overdiagnosis and overtreatment is to not conduct FNA biopsy for every growth, Tuttle said. And while this decision is up to radiologists and endocrinologists, a small suspicious nodule does not



MICHAEL TUTTLE, MD:

"While there's no question that physicians are overdiagnosing and overtreating very small papillary thyroid cancers, every 4 cm papillary malignancy was at one time just 4 or 5 mm, so, we can't say ignore every 4 or 5 mm cancer."

always warrant an immediate diagnosis. "It may be better to serially watch the nodule with ultrasound and then biopsy the few that demonstrate an increase in size."

The decision about whether or not to work up small, incidentally identified thyroid nodules that are not causing symptoms should be made consciously and with an understanding of the benefits as well as the potential harms of proceeding down the path of workup, Davies said.

Notably, in older patients who may have competing comorbidities and in whom the cancer may have been found incidentally, physicians may want to carefully weigh the risks and benefits of cancer treatment, Jacobus said. Some patients are more comfortable with a watch-and-wait approach than others are. In contrast, younger individuals with a new thyroid cancer might be more inclined to receive therapy than to undergo observation.

Prognostic Tools

Still, Grogan said, if overdiagnosis is actually occurring, it is not clear what physicians should be doing about it right now: "The biggest problem is that we don't have the appropriate prognostication tools," he said. "If two people come to my office with the exact same tumor, one might do well clinically, but the other may have a recurrence or die from this cancer. We have no way of understanding which person has the worse prognosis, so we have to treat them both in the same manner."

Understandably, patients often have difficulty accepting a watchful-waiting approach, he said. The hope is that proteomics or genomics will one day be able to provide information that can help determine which patients have high-risk papillary cancer to identify patients who need surgery and further treatment such as radioactive iodine.

Prognostic tools are not lacking, though, Davies maintains: "We know the survival rates for thyroid cancer, and there are several risk stratification systems available." Clinicians should be conscious about the decision to work up thyroid nodules, and should discuss



DENNIS H. KRAUS, MD: "I don't understand the idea of closing our eyes to patients with cancer, even though mortality hasn't gone up."

the pros and cons thoroughly with patients.

Research on Observation

Kraus pointed to two studies evaluating observation of patients with papillary thyroid cancer—one ongoing at MSKCC, and the other conducted in Japan and published four years ago (*World J Surg* 2010;34:28-35). Both studies are helping to address how physicians should monitor patients, which individuals should get surgery, and what is considered to be enough treatment.

Tuttle and his colleagues at MSKCC are observing a group of approximately 100 patients who have biopsy-confirmed thyroid cancer of less than 1 cm. Subjects are undergoing ultrasound every six months for two years and every 12 months thereafter. "After follow-up for about two to three years, 90 percent of the cancers are not changing at all," he said.

This type of trial is not for everyone, though, he said. "Some people can't stand the idea of cancer and want to rush to have surgery." Others, though, are fine with watchful waiting once they understand the risks and benefits of avoiding potentially unnecessary procedures and treatment.

Overall, the patients enrolled in the study are those who want to keep their thyroid and want to avoid taking hormones and in whom a delay in therapy will not make a difference. □