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Bacteria & Breast Cancer: The Evidence Is Mounting

BY MICHELLE PERRON

In the decade since the NIH centralized efforts to understand the power of the human microbiome, discoveries have ranged from the anticipated to the surprising. One of the latter was described recently in a study of breast tissue, oral cavity, and urinary tract microbiomes in patients with and without breast cancer (*Oncotarget* 2017;8(50):88122-88138).

The authors, who are based at the Cleveland Clinic Genomic Medicine Institute, the Taussig Cancer Institute's Comprehensive Breast Cancer Program, and Pathology and Laboratory Medicine Institute, found that local breast microbiota differ among patients with and without breast cancer, and that these microbiota exist as far away from the breast as the

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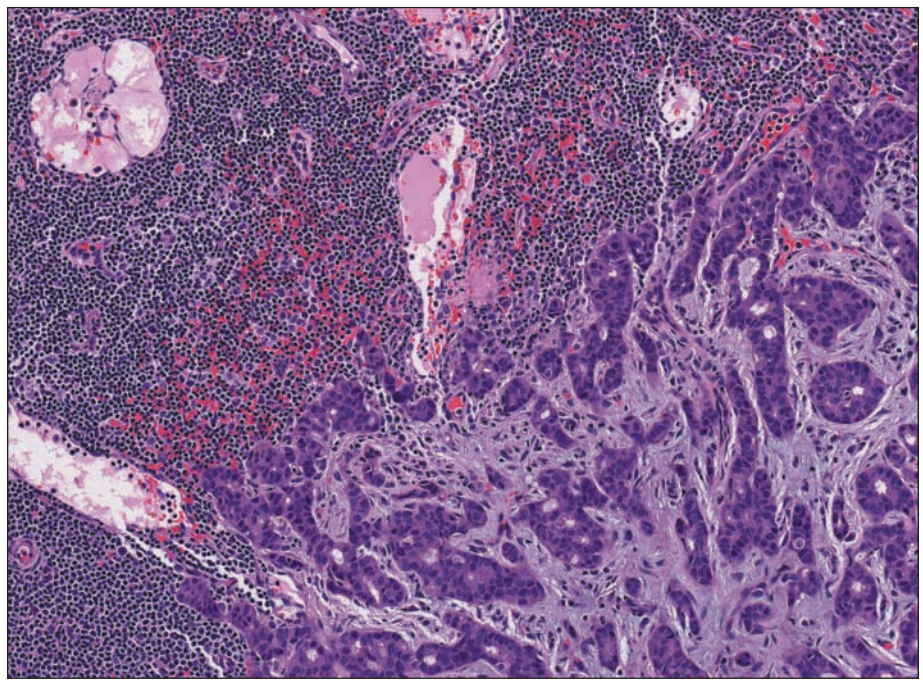

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Will New Screening Recommendations Impact Cervical Cancer Rates?

BY VALERIE NEFF NEWITT

The U.S. Preventive Services Task Force (USPSTF) sent shock waves through the women's oncology community in September 2017 when it issued its newest draft recommendations on screening for cervical cancer. The task force removed its former grade "A" recommendation for screening with cervical cytology (Pap) and high-risk human papillomavirus (hrHPV) co-testing every 5 years for women ages 30-65, replacing it instead with an every-3-years screening protocol of Pap testing alone, or an every-5-years screening with hrHPV testing alone.

CME Article

It is a decision that has left many experts shaking their heads—and wringing their hands. A reactive consensus statement issued in October from the Cytology Education and Technology

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Phase II CAR-T Study Reports Significant Remission Rates at 15-Months

A study involving the recently approved CD19-targeting chimeric antigen receptor (CAR) T-cell therapy shows that 42 percent of patients with aggressive large B-cell lymphoma remained in remission at 15 months following treatment with axi-cel.

The study, named ZUMA-1, also reported measurable responses in 82 percent of patients and complete responses in 54 percent. Fifty-six percent were alive at 15 months following therapy, with some remaining cancer free 2 years post-treatment.

The findings, reported in the Dec. 10 online issue of *The New England Journal of Medicine* (2017; doi:10.1056/NEJMoa1707447), and presented at the American Society of Hematology Annual Meeting in December, resulted from a 22-institution study led by Sattva Neelapu, MD, Professor of Lymphoma & Myeloma at The University of Texas MD Anderson Cancer Center, Houston, and Frederick Locke, MD, Vice Chair and Associate Member of the Department of Blood and Marrow Transplant and Cellular Immunotherapy at Moffitt Cancer Center, Tampa, Fla.

"With the FDA's recent approval of this therapy, we believe this is a major advance in the treatment of patients with relapsed or refractory large B-cell lymphoma and is likely to save or prolong lives of many patients," stated Neelapu. "This study demonstrated that axi-cel provides remarkable improvement in outcomes over existing therapies for these patients who have no curative options."

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PERIODICALS

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Will New Screening Recommendations Impact Cervical Cancer Rates?

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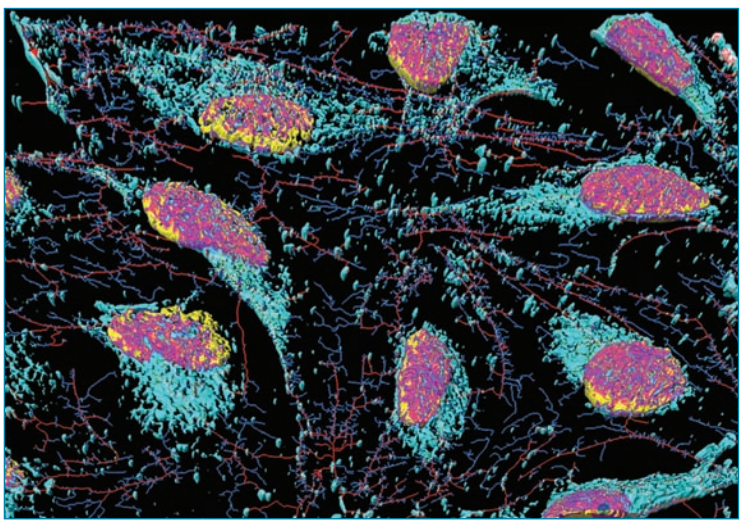
Consortium (CETC), comprised of the American Society for Clinical Pathology, American Society of Cytopathology, American Society for Cytotechnology, College of American Pathologists, International Academy of Cytology, and Papanicolaou Society of Cytopathology, said, "The CETC is concerned that if primary HPV screening every 5 years is endorsed by USPSTF, without co-testing as a screening option, this change may potentially impact safety and efficacy for cervical cancer prevention in the U.S." CETC then went on to make its own recommendations:

- Pap and hrHPV co-testing should be retained as a screening strategy for women aged 30-65 years.
- Primary HPV-only screening should be utilized only with testing platforms validated for that purpose and approved by the FDA.
- Any primary HPV screening should be applied every 3 years until there is more longitudinal data applicable to the U.S. screening population.

These CETC recommendations imply problems with the very foundation of the draft recommendations, built in part on data culled from non-U.S. studies.

Yet USPSTF defends its recommendations. "The new research and updated studies that the Task Force reviewed showed that getting both tests at the same time does not offer women more benefit than getting either a Pap test alone or an hrHPV test alone. Both tests are good on their own at identifying women at risk for cervical cancer early, when the condition is treatable, so the most important thing is that women are regularly screened using an effective strategy. Physicians should talk to women about their options for cervical cancer screening," noted Maureen Phipps, MD, MPH, a Task Force



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member, and Department Chair and Chace-Joukowsky Professor of Obstetrics and Gynecology and Assistant Dean for Teaching and Research in Women's Health at the Warren Alpert Medical School of Brown University, Providence, R.I.

Opposing Views

Still, critics find such explanations ring hollow.

"The prevalence of high-risk HPV types varies with demographic populations and the current U.S. population is very diverse, in contrast to the patient populations in the prior European trials," claimed CETC in its consensus statement. It went on to explain: "A subset of carcinomas … as well as other tumor types may not be detected by HPV testing alone. A U.S. cancer registry study showed that 9.4 percent of cervical cancers were HPV negative and an additional 3.2 percent contained rare HPV subtypes (*J Low Genit Tract Dis* 2014;18(2):182-189). The incidence of cervical adenocarcinoma has increased significantly and these tumor types have a higher rate of testing HPV-negative (*Mod Pathol* 2014;27(12):1559-1567).

"The majority of the European trials in the literature used precancer (CIN2/3), not invasive cancer as an end point. A number of studies performed in the U.S. and other countries have found that about 9-10 percent of invasive cancers will test negative for HPV by commercially available tests (*Arch Pathol Lab Med* 2015;139(2):184-188). Studies performed in the U.S. population show that the addition of cytology screening will add sensitivity in many of these women. Data from one study suggests that cytology and hrHPV testing miss different subsets of invasive cancer, hence the higher sensitivity of co-testing (*Cancer Cytopathol* 2015;123(7):428-434)."

Mark Spitzer, MD, Clinical Professor of Obstetrics and Gynecology at Hofstra Northwell School of Medicine, Hempstead, N.Y., and a Past President of the American Society for Colposcopy and Cervical Pathology, also believes the Task Force has created the new recommendations based on faulty modeling and miscalculated "harms" associated with co-testing.

> "All members of the medical community need to be speaking with one voice to be sure women receive a clear message about the importance of screening for cervical cancer."

"While USPSTF correctly identified the detection of CIN-2/3 and CIN-3+ and prevention of cervical cancer and deaths as 'benefits,' it used the number of colposcopies and the number of tests conducted as a proxy for 'harms,' because these were easily measured," he noted. "And while they identified other harms, such as the psychological distress related to being told of a positive HPV result, they were not numerical and thus not included in the modeling. They also did not measure the distress associated with an extended screening interval or HPV-only screening."

Furthermore, in their modeling, "The Task Force operated on the premise that if a patient has an abnormal Pap test and you [the health care provider] follow it with a colposcopy, then you can guarantee that if the patient has disease you will find it," said Spitzer. "But in the real world no one believes that. The idea that colposcopy finds everything in follow-up to a Pap simply is not true." In contrast, co-testing as included in the previous guidelines, Spitzer noted, took smart advantage of available complementary tools (cytology, HPV testing, and colposcopy) to effectively detect cervical disease.

Spitzer, like CETC, also strongly faults the Task Force for utilizing data from randomly controlled trials of primary screening, primarily from Europe. He said most of these trials were conducted using conventional cytology that, for the most part, is no longer used in the U.S. Additionally, two of the European trials used HPV testing by PCR which is not approved by the FDA nor marketed in the U.S.

"Randomized controlled trials appear to be the Holy Grail for the Task Force," Spitzer lamented. "But we have excellent, large U.S. retrospective studies that should be taken into account."

Edward Evantash, MD, OB/GYN, Medical Director at Hologic, is also concerned about the Task Force's reliance on non-U.S. studies. He said that prior studies by Kaiser Permanente and Quest Diagnostics looked at over a million women and "…the Kaiser Permanente study found co-testing performed better than either HPV or Pap for protection against CIN3 at every interval. And when we look at data from the large Quest Diagnostics study, we find that women who presented with CIN3 had a far higher likelihood of being identified with co-testing compared to HPV alone or Pap alone."

Evantash added, "It is concerning that in its previous recommendation, co-testing every 5 years was a grade A; now co-testing is not even included in the Task Force's draft recommendations, despite the fact that we know co-testing offers the best detection of and assurance against developing high-grade pre-cancer or cancer at the subsequent interval."

Evantash also called into question the Task Force's suggestion that increased testing increases adverse events. "I wonder if the Task Force thought women had to undergo two separate test procedures. That is not the case; a Pap and a hrHPV are taken in a single specimen. A single swab of the cervix into a vial is all that is required, and from that vial we can get cytology as well as the hrHPV result. I don't know how

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it is looked upon as a 'negative' when we know this is the best testing method that is available and remains the preferred method of screening by the professional societies."

Evantash conjectured that, should the new draft recommendations be adopted and followed, patients may well pay an unacceptable price. "This marks a step backward for women and allows the possibility for an increase in cervical cancer incidence in this country, as well as deaths from a very preventable disease."

Mixed Signals

Another concern voiced by critics is found in the elongated testing intervals within the draft recommendations, which allow for primary hrHPV testing every 5 years.

Writing commentary for HuffPost on Oct. 6, 2017, Juan Felix, MD, a specialist in gynecologic pathology and cytology, Medical College of Wisconsin, made the point that while prolonging screening intervals has been shown to lower costs, it also "…. has been universally shown to increase the rates of cervical cancer in women. In a large population of women in Northern California, extending screening intervals from 3 to 5 years doubled the number of cervical cancers in women tested with either HPV testing alone or co-testing with Pap plus HPV (*J Natl Cancer Inst* 2014; doi:10.1093/jnci/dju153). In this study, the investigators made the case for the more frequent 3-year interval, particularly when screening with HPV testing alone."

Spitzer, too, has concerns. "In the U.S. we have opportunistic screening—meaning when a woman shows up in the office we have the opportunity to screen. Women understand the annual Pap. Now we've tried to move that out to 3 years, and I do believe we are capable of re-educating women to go to 3 years. But the problem with the recommended 5-year intervals for primary hrHPV testing is this: What if women show up a year or two too late? We have no evidence that it is safe. In other countries, like Sweden or Norway, every person is in a medical database and they get letters and phone calls to make them compliant with national screening programs. Here we have no organized screening; there is no guarantee someone will get to the doctor at the 5-year point to be screened. It is wishful thinking."

Critics of the draft recommendations hope that pushback from professional associations and incisive commentaries delivered to the Task Force may be enough to cause it to rethink its draft proposal.

"All members of the medical community need to be speaking with one voice to be sure women receive a clear message about the importance of screening for cervical cancer," said Spitzer. "But many clinicians believe these draft recommendations are not in the best interest of their patients."

Evantash summed up his cautionary viewpoint. "We have seen cervical cancer go from one of the top killers of women decades ago to No. 14 in the ranking of cancers we see in U.S. women today. To make a change that could cause an uptick in the incidence and deaths of this disease is both disappointing and distressing. Co-testing works; we should be trying to extend this powerful screening to as many women as we can. To do any less is a step backward. To hear that we are stretching the intervals and reducing the number of tests available makes me concerned about the future. Co-testing is a success story. We should not do anything other than improve upon it."

Spitzer said if he could leave *Oncology Times* readers with two lingering thoughts, it would be these: "First, you need to screen with the best tools, and the most sensitive screening tool that we have is the co-test. Pap and hrHPV tests are complementary. HPV is clearly the most sensitive screening test we have and will detect disease that will be missed by Pap tests. But Pap tests are also useful and will detect some disease that is missed by HPV testing. There is some overlap, but the combination of the two, by definition, will pick up more than either test alone.

"Second, we need to develop some system within the U.S. that doesn't allow women to fall through the screening cracks. In 2012 and 2013, we created 5-year screening intervals using co-testing, but we do not yet have results from the first cohort of women using this 5-year interval. We have no way of knowing if it really works in our populations. Until we reach the point where we can be sure that women will arrive for screening at 5 years, we should continue to screen at 3 years and use the additional 2 years as a safety net."

Short of these cautionary suggestions, Spitzer said moving forward with the new draft recommendations will result in one of two things. "Either they will be ignored by women and their clinicians—which I believe is highly likely—or we may discover in 5, 6, or 7 years from now that the cancer rate has gone up. I am disappointed the Task Force did not consider these real-world limitations in developing these recommendations, but instead created models that only work in an idealized world. I hope the Task Force will listen to clinicians as we speak out in advocacy for our patients." OT

Valerie Neff Newitt is a contributing writer.

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