Human papillomavirus

MARCH 2019

TO THE EDITOR: I am an active primary care provider. After reading the update on human papillomavirus (HPV) in the March 2019 issue by Zhang and Batur,[1] I was hoping for some clarification on a few points.

The statement is made that up to 70% of HPV-related cervical cancer cases can be prevented with vaccination. I have pulled the reference[2] but cannot find supporting data for this claim. Is this proven or optimistic thinking based on the decreased incidence of abnormal Papanicolaou (Pap) test results such as noted in the University of New Mexico HPV Pap registry database[3]? The authors do cite an additional reference[4] documenting a decreased incidence of cervical cancer in the United States among 15- to 24-year-olds from 2003–2006 compared with 2011–2014. This study reported a 29% relative risk reduction in the group receiving the vaccine, with the absolute numbers 6 vs 8.4 cases per 1,000,000. Thus, can the authors provide further references to the statement that 70% of cervical cancers can be prevented by vaccination?

The authors also state that vaccine acceptance rates are highest when primary care providers announce that the vaccine is due rather than invite open-ended discussions. At first this shocked me, but then made me pause and wonder how often I do that—and when I do, why. I regularly do it with all the other vaccines recommended by the Advisory Committee on Immunization Practices. When the parent or patient asks for further information, I am armed to provide it. To date, I am struggling to provide data to educate the patient on the efficacy of the HPV vaccine, particularly the claim that it will prevent 70% of cervical cancers. Are there more data that I am missing?

Finally, let me state that I am a "vaccinator"—always have been, and always will be. I discuss the HPV vaccine with my patients and their parents and try to provide data to support my recommendation. However, I am concerned that this current practice regarding the HPV vaccine has been driven by scare tactics and has now turned to "just give it because I say so." The University of New Mexico Center for HPV prevention reports up to a 50% reduction in cervical intraepithelial neoplasias (precancer lesions) in teens.[3] This is exciting information and raises hope for the future successful battle against cervical cancer. I think it is also more accurate than stating to parents and patients that we have proof that we have prevented 70% of cervical cancers. When we explain it in this manner, the majority of parents and patients buy in and, I believe, enjoy and welcome this open-ended discussion.

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IN REPLY: We would like to thank Dr. Lichtenberg for giving us the opportunity to clarify and expand on questions regarding HPV vaccine efficacy.

Our statement "HPV immunization can prevent up to 70% of cases of cervical cancer due to HPV as well as 90% of genital warts" was based on a statement by Thaxton and Waxman, ie, that immunization against HPV types 16 and 18 has the potential to prevent 70% of cancers of the cervix plus a large percentage of other lower anogenital tract cancers.[1] This was meant to describe the prevention potential of the quadrivalent vaccine. The currently available Gardasil 9 targets the HPV types that account for 90% of cervical cancers,[2] with projected effectiveness likely to vary based on geographic variation in HPV subtypes, ranging from 86.5% in Australia to 92% in North America.[3] It is difficult to precisely calculate the effectiveness of HPV vaccination alone, given that cervical cancer prevention is twofold, with primary vaccination and secondary screening (with several notable updates to US national screening guidelines during the same time frame as vaccine development).[4]

It is true that the 29% decrease in US cervical cancer incidence rates during the years 2011–2014 compared with 2003–2006 is less than the predicted 70%.[5] However, not all eligible US females are vaccinated; according to reports from the US Centers for Disease Control and Prevention, 49% of adolescents were appropriately immunized against HPV in 2017,

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an increase over the rate of only 35% in 2014.[6] Low vaccination rates undoubtedly negatively impact any benefits from herd immunity, though the exact benefits of this population immunity are difficult to quantify.[7]

In Australia, a national school-based HPV vaccination program was initiated in 2007, making the vaccine available for free. Over 70% of girls ages 12 and 13 were vaccinated, and follow-up within the same decade showed a greater than 90% reduction in genital warts, as well as a reduction in high-grade cervical lesions.[8] In addition, the incidence of genital warts in unvaccinated heterosexual males during the prevaccination vs the vaccination period decreased by up to 81% (a marker of herd immunity).[9]

In the US, the HPV subtypes found in the quadrivalent vaccine decreased by 71% in those ages 14 to 19, within 8 years of vaccine introduction.[10] An analysis of US state cancer registries between 2009 and 2012 showed that in Michigan, the rates of high-grade, precancerous lesions declined by 37% each year for women ages 15 to 19, thought to be due to changes in screening and vaccination guidelines.[11] Similarly, an analysis of 9 million privately insured US females showed that the presence of high-grade precancerous lesions significantly decreased between the years 2007 and 2014 in those ages 15 to 24 (vaccinated individuals), but not in those ages 25 to 39 (unvaccinated individuals).[12] Most recently, a study of 10,206 women showed a 21.9% decrease in cervical intraepithelial neoplasia grade 2 or worse lesions due to HPV subtypes 16 or 18 in those who have received at least 1 dose of the vaccine; reduced rates in unvaccinated women were also seen, representing first evidence of herd immunity in the United States.[13] In contrast, the rates of high-grade lesions due to nonvaccine HPV subtypes remained constant. Given that progression to cervical cancer can take 10 to 15 years or longer after HPV infection, true vaccine benefits will emerge once increased vaccination rates are achieved and after at least a decade of follow-up.

We applaud Dr. Lichtenberg's efforts to clarify vaccine efficacy for appropriate counseling, as this is key to ensuring patient trust. Immunization fears have fueled the re-emergence of vaccine-preventable illnesses across the world. Given the wave of vaccine misinformation on the Internet, we all face patients and family members skeptical of vaccine efficacy and safety. Those requesting more information deserve an honest, informed discussion with their provider. Interestingly, however, among 955 unvaccinated women, the belief of not being at risk for HPV was the most common reason for not receiving the vaccine.[14] Effective education can be achieved by focusing on the personal risks of HPV to the patient, as well as the overall favorable risk vs benefits of vaccination. Quoting an exact rate of cancer reduction is likely a less effective counseling strategy, and these efficacy estimates will change as vaccination rates and HPV prevalence within the population change over time.

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Aleukemic leukemia cutis

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TO THE EDITOR: I read with great interest the article "Aleukemic leukemia cutis" by Abraham et al,[1] as we recently had a case of this at my institution. The case is unique and quite intriguing; however, I found the pathologic description confusing and imprecise.

The authors state, "The findings were consistent with leukemic T cells with monocytic differentiation."[1] This is based on their findings that the tumor cells expressed CD4, CD43, CD68, and lysozyme. However, the cells were negative for CD30, ALK-1, CD2, and CD3.

First, I must contest the authors' claim that "the cells co-expressed T-cell markers (CD4 and CD43)": CD4 and CD43 are not specific for T cells and are almost invariably seen on monocytes, especially in acute monoblastic/monocytic leukemia (AMoL; also known as M5 in the French-American-British classification system).[2,3] Therefore, the immunophenotype is perfect for an AMoL, but since there was no significant blood or bone marrow involvement and it was limited to the skin, this would best fit with a myeloid sarcoma, which frequently has a monocytic immunoprofile.[3,4]

Additionally, this would not be a mixed-phenotype acute leukemia, T/myeloid, not otherwise specified, as that requires positivity for cytoplasmic CD3 or surface CD3, and that was conspicuously absent.[5] Therefore, the appropriate workup and treatment should have essentially followed the course for acute myeloid leukemia,[4] which is unclear from the present report as there is no mention of a molecular workup (eg, for *FLT3* and *NPM1* mutations). This would, in turn, have important treatment and prognostic implications.[6]

The reason for my comments is to bring to light the importance of exact pathologic diagnosis, especially when dealing with leukemia. We currently have a host of treatment options and prognostic tools for the various types of acute myeloid leukemia, but only when a clear and precise pathologic diagnosis is given.[5]

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IN REPLY: We greatly appreciate our reader's interest and response. He brings up a very good point. We have reviewed the reports and discussed it with our pathologists. On page 85, the sentence that begins, "The findings were consistent with leukemic T cells with monocytic differentiation" should actually read, "The findings were consistent with leukemic cells with monocytic differentiation." The patient was appropriately treated for acute myeloid leukemia.

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