UPDATE Gynecologic cancer

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Expert perspectives on studies that analyze HPV vaccination and cervical cancer rates, combination immunotherapy for recurrent endometrial cancer, and talcum powder's role in ovarian cancer risk

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Gynecologic malignancies continue to be a major cause of cancer-related mortality in women. In 2020, a number of developments changed practice in gynecologic oncology. In this Update, we highlight 3 important articles. The first showed that human papillomavirus (HPV) vaccination reduced the rate of cervical cancer. The next evaluated a novel targeted therapeutic approach using the combination of pembrolizumab and lenvatinib in women with recurrent endometrial carcinoma that progressed after prior systemic therapy. Finally, the third article showed that talcum powder was not associated with an increased risk of ovarian cancer. We provide here a brief overview of the major findings of these studies and how these results are influencing practice.

Evidence establishes that HPV vaccination cuts risk of invasive cervical cancer

Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383:1340-1348.

HPV infection is associated with 99% of cervical cancers, and approximately 65% to 75% of cases involve HPV 16 or 18.[1,2] The quadrivalent HPV (6, 11, 16, 18) vaccine was approved by the US Food and Drug Administration in 2006 for the prevention of cervical intraepithelial lesions and genital warts associated with HPV.[3-5] Previous studies of the HPV vaccine showed it to be effective in preventing HPV infection, genital warts, and high-grade precancerous cervical lesions, such as cervical intraepithelial neoplasia grade 2 (CIN2) and grade 3 (CIN3).[6-8] While the vaccine offers a number of advantages, the long-term goal of the vaccine—to reduce the incidence of invasive cervical cancer—was not shown until recently.

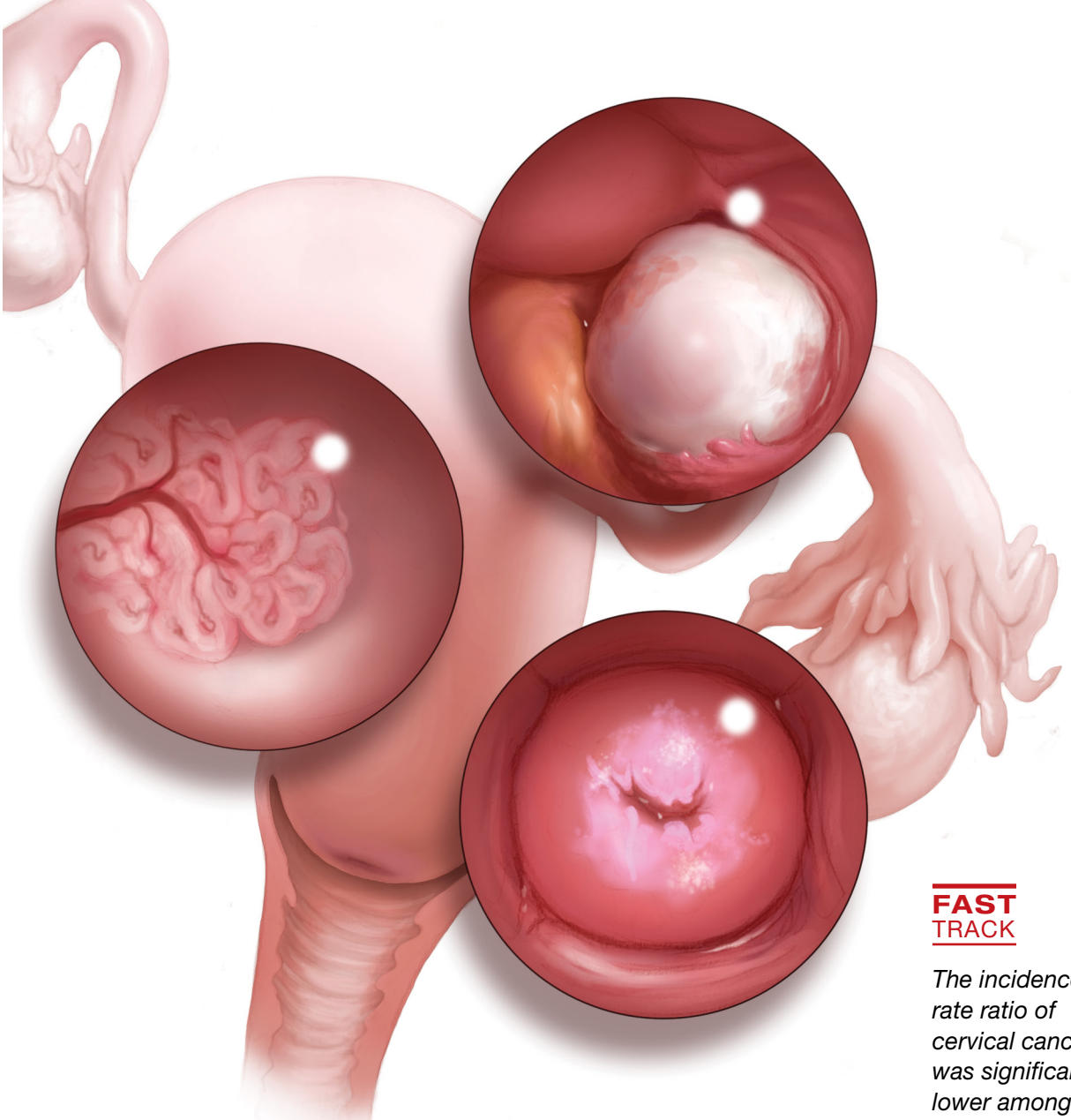

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Large study followed HPV vaccinated and unvaccinated women

Lei and colleagues conducted a registry-based cohort study from 2006 through 2017 of women aged 10 to 30 years who were living in Sweden.[9] They followed the women from their 10th birthday until they were diagnosed with cervical cancer, died, emigrated from Sweden, were lost to follow-up, or turned 31 years of age. In the study, the unique personal identity numbers assigned to all Swedish residents were linked to a number of large national administrative databases. Beginning in 2007 in Sweden, the quadrivalent vaccine was subsidized for use in girls aged 13 to 17, and a subsequent catch-up period that started in 2012 incorporated women who had not been vaccinated.

Cervical cancer rates were lowest in women vaccinated before age 17

A total of 1,672,983 women were included in the study; 527,871 received at least one dose of the HPV vaccine. During the study period, cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. Women who initiated vaccination before age 17 had the lowest rates of cervical cancer (4 cases per 100,000 persons), followed by women vaccinated after age 17 (54 cases per 100,000 persons) and then those who were not vaccinated (94 cases per 100,000 persons).

After adjusting for confounders, the incidence rate ratio (RR) of cervical cancer was significantly lower among vaccinated

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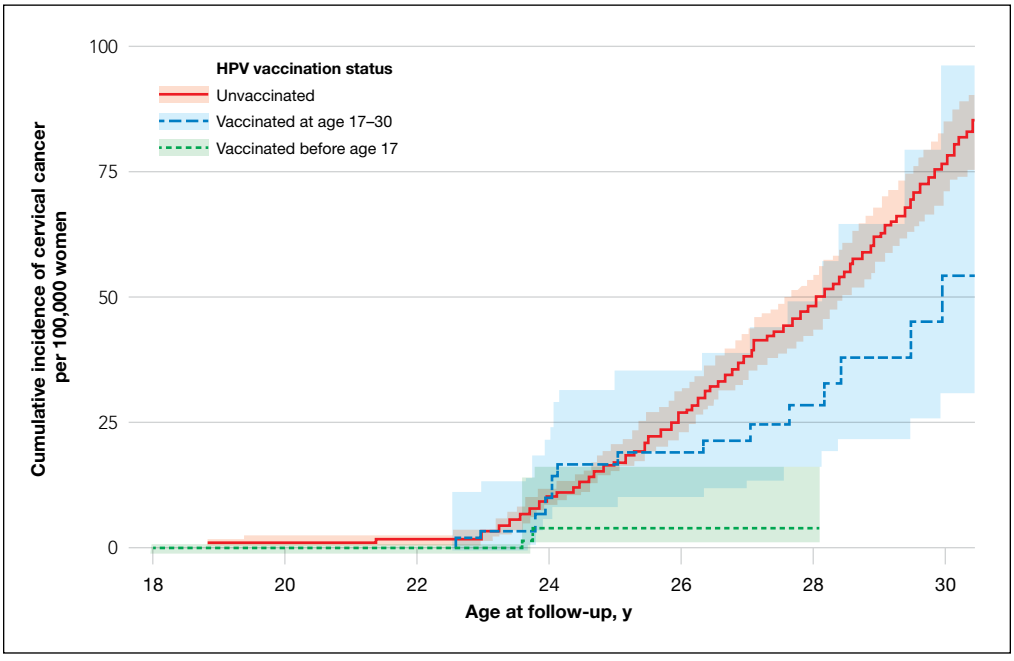
The incidence rate ratio of cervical cancer was significantly lower among HPV vaccinated women compared with unvaccinated women (RR, 0.37; 95% CI, 0.21–0.57)

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The study by Lei and colleagues showed that HPV vaccination was associated with a substantially lower risk of invasive cervical cancer. While all women who received the vaccine had reduced rates of invasive cervical cancer, those who received the vaccine earlier (before age 17) showed the greatest reduction in invasive cervical cancer. On a population level, this study demonstrates that a program of HPV vaccination can reduce the burden of cervical cancer.

women compared with unvaccinated women (RR, 0.37; 95% confidence interval [CI], 0.21–0.57) (**FIGURE 1**).[9] In addition, women who were vaccinated before age 17 demonstrated the greatest benefit. For those vaccinated before age 17 versus those who were unvaccinated, the RR was 0.12 (95% CI, 0.00–0.34). For women vaccinated between age 17 and 30 versus unvaccinated women, the RR was 0.47 (95% CI, 0.27–0.75).

FIGURE 1 **Cumulative incidence of invasive cervical cancer according to HPV vaccination status**[9]



Abbreviation: HPV, human papillomavirus.

Promising option for patients with advanced endometrial cancer: Lenvatinib plus pembrolizumab

Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol. 2020;38:2981-2992.

Advanced stage endometrial cancer is associated with a 17% 5-year survival rate.[10] Paclitaxel with carboplatin is the standard first-line treatment

for advanced, recurrent, and metastatic endometrial cancer; for women who do not respond to this regimen, effective treatment options are limited.[11,12]

The immunotherapy approach

Immunotherapy is a more recently developed treatment, an approach in which the immune system is activated to target cancer cells. Pembrolizumab is a commonly used agent for many solid tumors.[13] This drug binds to the programmed cell death receptor 1 (PD-1) or PD-ligand 1 (PD-L1), a component of the immune checkpoint, which then allows the immune system to target and destroy cancer cells.[14]

Prembrolizumab is FDA approved for use in the treatment of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) solid tumors that have progressed after prior therapy and for which there are no satisfactory alternative treatment options.[15] Endometrial cancers frequently display microsatellite instability and mismatch repair defects.[16]

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptors 1, 2, and 3; fibroblast growth factor receptors 1, 2, 3, and 4; and platelet-derived growth factor receptor alpha, RET, and KIT.[17-19] In a phase 2 study of lenvatinib monotherapy for advanced previously treated endometrial cancer, the response rate was 14.3%.[20]

While some preclinical studies have examined the combination of immune checkpoint inhibitors with lenvatinib,[21-23] a recent study is the first to evaluate this combination in patients with advanced tumors.[24]

Prembrolizumab-lenvatinib combination therapy

Makker and colleagues conducted an ongoing multinational, open-label, phase 1B/2 study of lenvatinib 20 mg daily orally plus pembrolizumab 200 mg intravenously once every 3 weeks in patients with select solid tumors.[24] Women with previously treated endometrial carcinoma (N = 125) were included. Of the study participants, 49% were PD-L1 positive and 10% were MSI-H/dMMR. The primary end point was objective response rate (ORR) at 24 weeks, which was 38.0% (95% CI, 28.8%–47.8%).

The median duration of response was 21.2 months (95% CI, 7.6 months to not estimable). The ORR was similar in patients with PD-L1 expressing tumors (35.8%; 95% CI, 23.1%–50.2%), who are more likely to respond to immunotherapy, compared with those without PD-L1 expression (39.5%; 95% CI, 25.0%–55.6%). For patients with MSI-H/dMMR, there was a higher ORR (63.6%; 95% CI, 30.8%–89.1%, versus 36.2%; 95% CI, 26.5%–46.7%).

Median progression-free survival was 7.4 months (95% CI, 5.3–8.7 months) and median overall survival was 16.7 months (15 months to not estimable). Moderate to severe treatment-related adverse events occurred in 83 patients (66.9%), and 22 patients (17.7%) discontinued 1 or both study drugs because of adverse effects. Two deaths were judged to be treatment related.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study showed promising results for the combination of pembrolizumab with lenvatinib in women with advanced endometrial carcinoma who have progressed after prior systemic therapy. These data led to an accelerated approval by the FDA for the treatment of women with advanced endometrial carcinoma that is not MSI-H/dMMR, who have disease progression after prior systemic therapy, and who are not candidates for curative surgery or radiation therapy.[25] Currently, 2 phase 3 trials of lenvatinib plus pembrolizumab in advanced endometrial carcinoma are underway, which will shed further light on this combination therapy.

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Median progression-free survival with prembrolizumab-lenvatinib therapy was 7.4 months (95% CI, 5.3–8.7 months) and median overall survival was 16.7 months (15 months to not estimable)

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What is the risk of ovarian cancer in women who use powder in the genital area?

O'Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer. JAMA. 2020;323:49-59.

FAST TRACK

Among women who used genital powder, the incidence of ovarian cancer was 61 cases/100,000 person-years; for never users, the incidence was 55 cases/100,000 person-years

Women apply talcum powder to their genital area to keep skin dry and to prevent rashes. Powder can be applied by direct application, sanitary napkins, diaphragms, or tampons. Most powder products contain the mineral talc. Because it often is found in nature with asbestos, a known carcinogen, talc's carcinogenic effects have been investigated.[26,27]

Talc also might ascend through the genital tract and irritate the epithelial lining of the fallopian tubes or ovaries, possibly triggering an inflammatory response that may promote carcinogenesis.[28,29] Case-control studies have reported a possible association between genital powder use and ovarian cancer.[30,31] Since these studies, talc-related lawsuits and media coverage have increased.[32,33]

Large prospective cohorts provide data for analysis

In a pooled analysis of 4 large US-based observational cohorts between 1976 and 2017, O'Brien and colleagues noted that 38% of the 252,745 women included in the study self-reported the use of powder in the genital area.[34] With a median of 11.2 years of follow-up, 2,168 women developed ovarian cancer (58 cases/100,000 person-years). Among women who reported using genital powder, the incidence of ovarian cancer was 61 cases/100,000 person-years, while for women who reported never using genital powder, the incidence was 55 cases/100,000 person-years. This corresponded to an estimated hazard ratio (HR) of 1.08 (95% CI, 0.99–1.17).

Frequent powder use, long-term use, and never use. Similar findings were seen for those with frequent use versus never use (HR, 1.09; 95% CI, 0.97–1.23) and long-term use versus never use (HR, 1.01; 95% CI, 0.82–1.25). When restricting the group to women with a patent reproductive tract at baseline, the HR was 1.13 (95% CI, 1.01–1.26), but the *P* value for interaction comparing women with versus women without a patent reproductive tract was 0.15 (**FIGURE 2**).[34]

Bottom line. In contrast to a prior meta-analysis, in this study there was no statistically significant association between the self-reported use of powder in the genital area and the incidence of ovarian cancer. ●

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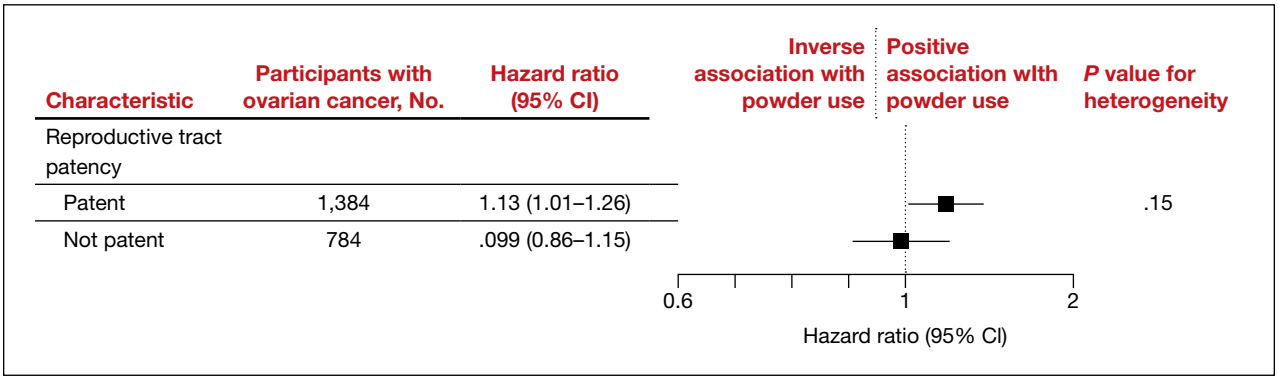
WHAT THIS EVIDENCE MEANS FOR PRACTICE

The study by O'Brien and colleagues is the largest study to date with the longest follow-up that examines the possible association between talc-based powder use and ovarian cancer. A strength of this study is the avoidance of recall bias by the selection of administrative data sets that had gathered information on talcum powder use from patients prior to the diagnosis of ovarian cancer. While these findings are reassuring, the study may have been underpowered to identify a small increase in ovarian cancer risk with talc use.

FIGURE 2 **Association between ever use of powder in the genital area and risk of ovarian cancer according to reproductive tract status**[34]



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