## **Supplemental Table 3**: Prospective, Observational Studies (n = 2) of Endometrial Histology with Vaginal Estrogen Use in Menopausal Women

| **Reference** | **Treatment(s)** | **Study design and population** | **Endometrial cancer or hyperplasia** |
| --- | --- | --- | --- |
| Crandall et al, 201833 | * WHI-Observational Study (1993-2005) and Extension Study (2005-2010) * Of 93,676 in the total sample, 45,663 included in the analysis with a median follow-up time of 7.2 years | * Prospective cohort * Postmenopausal women (50–79 years) from 40 clinical centers * Women with prior breast, endometrial, or ovarian cancer, taking systemic hormone therapy at follow up, or without hormone use information or any follow-up data were excluded * Women with intact uterus who used vaginal estrogens (n = 3,003); non-users (n = 29,430) | * Endometrial cancer risk was not significantly different in vaginal estrogen users than in non-users   + Adjusted model 1 HR: 1.27 (95% CI, 0.69–2.33)   + Adjusted model 2 HR: 1.47 (95% CI, 0.75–2.90) * Incidence of endometrial cancer   + 1.3/1000 women-years; vaginal estrogen users (n = 3,003)   + 1.0/1000 women-years; non-users (n = 29,430) * Information regarding type (cream, ring, or tablet) or dose was not collected |
| Gambrell et al, 197934 | * Oral estrogen (n = 2,088) * Oral estrogen-progestogen (n = 3,792) * Estrogen vaginal cream (n = 574) * Other hormones (n = 201): progestogens (n = 172); androgens (n = 29) * Untreated (n = 1,515)   **Note:** n is number of women-years | * Analysis of prospective data collected 1976-1977 reported by Gambrell et al, 197848 and retrospective data from 1975 * Postmenopausal women treated at Wilford Hall USAF Medical Center, Texas from 1975 to 1977 (8,170 women-years of observation) * Endometrial curettage was performed when abnormal bleeding occurred | * 1.7/1000 total incidence of endometrial cancer at the center based on 14 cases during 8,170 women-years * Endometrial cancer incidence rates for each type of estrogen reported   + 1.7/1000, vaginal estrogen cream (1 case in 574 women-years)   + 3.8/1000, oral estrogens (8 cases in 2,088 women-years)   + 0.5/1000, oral estrogen-progestogens (2 cases in 3,792 women-years)   + 0 cases for other hormones   + 2.0/1000, untreated women (3 cases in 1,515 women-years) * Endometrial cancer occurred in one woman [above] using CEE vaginal cream (1 g 3x/week) for 7 months |

WHI, Women’s Health Initiative; HR, hazard ratio; CI, confidence interval; CEE, conjugated equine estrogen.

RR, relative risk; CI, confidence interval; US, United States; OR, odds ratio; D&C, dilation and curettage.