## **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
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| 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
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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.