## **Supplemental Table 4**: Retrospective, Observational Studies (n = 8) of Endometrial Cancer Incidence with Vaginal Estrogen Use in Menopausal Women

| **Reference** | **Registry/cohort** | **Study design and population** | **Endometrial cancer or hyperplasia**a |
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| Mørch et al, 201635 | * Danish Sex Hormone Register Study (1995-2009) cohort
* N = 1,108,213
* 914,595 were included in the analysis (9.8 years of mean follow up; 9 million women-years)
 | * All non-hysterectomized Danish women (50–79 years) without cancer
* Primary invasive endometrial cancers were identified in the database and were categorized into Type I and Type II tumors
* Hormone therapy was categorized by route of administration; if a woman began a new regimen, she was re-categorized to the new regimen when time on the new regimen exceeded that of the previous regimen
 | * Vaginal estrogen use versus non-use was associated with increased risk of endometrial tumors
	+ RR 1.96 (95% CI, 1.77–2.17); all types
	+ RR 1.98 (95% CI, 1.77–2.22); Type I
	+ RR 1.86 (95% CI, 1.32–2.63); Type II
* Vaginal estrogens were analyzed as one category without stratification by
	+ Product type
	+ Dose
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| Gunnison et al, 201536 (abstract) | * Kaiser Permanente Northern California membership database cohort study (2006-2012)
* ~600,000 included in the analysis
 | * Women ≥46 years
* Endometrial hyperplasia and cancer were identified from the Kaiser Permanente Northern California Cancer Registry
* Vaginal estrogen use within 3 years of diagnosis was identified
* Women who took systemic estrogen or progesterone within 2 years of diagnosis were excluded
 | * Overall incidence (per 10,000) of endometrial hyperplasia and cancer was
* 9.96, non-users
* 10.25, 1–3 dispensed prescriptions
	+ 9.96, ≥4 dispensed prescription
 |
| Neidecker et al, 200937 (abstract) | * North Carolina Medicaid prescription and medical claims cohort study (1998-2007)
* Risk was assessed over a 3-year follow-up period
 | * Women (18–64) with a prescription claim for vaginal estrogen (cream, tablet, ring; cases; n = 770) or a diagnosis of vaginal atrophy with no vaginal estrogen use (controls; n = 881)
 | * Incidence of uterine carcinoma
	+ 10/770 (1.3%) of vaginal estrogen users
	+ 11/881 (1.2%) of non-users
* Endometrial carcinoma risk was not significantly different between women using vaginal estrogen and those not
	+ OR 1.11 (95% CI, 0.47–2.65)
* Older age was a significant predictor of uterine carcinoma (age adjusted OR 1.11; 95% CI, 1.03–1.20, *P* = 0.008)
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| Weiderpass et al, 199938 | * Population-based, case-control study (1994-1995)
* 93% of women treated with estriol/dienoestrol
 | * Cases (50–74 years) of newly diagnosed histopathologically confirmed endometrial cancer (n = 708) identified through 6 regional cancer registries covering all of Sweden were matched to non-hysterectomized controls (n = 3,338) from a continuously updated Swedish population registry
 | * Endometrial cancer risk did not significantly increase with any vaginal estrogen ever vs never use
	+ OR 1.2 (95% CI, 1.0–1.6) overall
	+ OR 1.2 (95% CI, 0.9–1.7) for <5 years
	+ OR 1.2 (95% CI, 0.8–1.9) for ≥5 years
* Endometrial cancer risk with exclusive vaginal estrogen ever use vs never use
	+ OR 1.4 (95% CI, 1.0–2.0)
* Endometrial atypical hyperplasia risk was not significantly higher with any vaginal estrogen ever use vs never use
	+ OR 1.5 (95% CI, 0.8–3.0) overall
	+ OR 1.1 (95% CI, 0.5–2.8) for <5 years
	+ OR 2.3 (95% CI, 0.9–5.6) for ≥5 years
* No evidence of a differential effect of vaginal estrogens on tumor grade or myometrial invasiveness was found (data not shown)
* Any vaginal estrogen was used in 14.7% (104/708) of cases and in 11.3% (377/3,338) of controls; exclusive vaginal estrogen use was in 56/708 (7.9%) cases and 241/3,338 (7.2%) of controls
* Vaginal estrogen use included estriol 0.5 mg (49% of vaginal treatment), dienoestrol 0.5 mg (44%), or estradiol 25 µg (7%) applied daily in the initial 2–3 weeks, then twice weekly
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| Kelsey et al, 198239 | * Case-control study including data from 7 hospitals in Connecticut (1977–1979)
* Cases (n = 167) were women with endometrial cancer and controls (n = 903) were women admitted to the same hospitals for non-gynecologic surgery
 | * Women aged 45–74 years with endometrial cancer confirmed both by hospital pathologist and study pathologist
* Women identified hormone use using actual tablets and pictures of containers estrogen therapy compounds (confirmed with physician if a woman could not identify)
* Higher doses of vaginal estrogens would have been used
 | * Ever use of vaginal estrogens versus non-use was associated with increased risk of endometrial cancer
	+ OR 2.30 (95% CI, 1.1–4.6)
* Vaginal estrogens were analyzed as one category without stratification by
	+ Product type
	+ Dose
	+ Duration
	+ Time since last use
 |
| Horwitz and Feinstein, 197940 | * 2 case-control studies (1974–1976)
* Population I: Of the 238 cases and controls, 133 were interviewed
* Population II: Of the 298 cases and controls, 191 were interviewed
 | * Population I: Endometrial cancer cases (n = 119 from 561women with gynecologic cancer) were matched to controls (n = 119) obtained from the Yale Tumor Registry (US)
* Population II: Endometrial cancer cases (n = 149 from 6,869 women who had D&C or hysterectomy) matched with cases other than uterine cancer (n = 149) obtained from the Yale-New Haven Hospital (US)
* Higher doses of vaginal estrogens would have been used
 | * Ever use of vaginal estrogens versus non-use was not associated with an increased risk of endometrial cancer
* OR 0.90 (95% CI, 0.29–4.28; *P* = 0.560) in population I
	+ 6/83 (7%) of endometrial cancer cases and 4/50 (8%) of controls reported use of vaginal estrogen creams
* OR 0.82 (95% CI, 0.46–3.20; *P* = 0.439) in population II
	+ 9/104 (9%) of cases and 9/87 (10%) of controls used vaginal estrogen creams
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| Gray et al, 197741 | * Case-control study (1947-1976) from a private practice in Louisville, KY
 | * Women with endometrial carcinoma (excluding carcinoma in situ) were matched with women who had a hysterectomy for a benign condition (n = 205 each group)
* Higher doses of vaginal estrogens would have been used
 | * No significant increase in endometrial cancer with vaginal estrogen preparations
	+ RR 0.7 (95% CI, 0.1–3.6)
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aAll odds ratios (OR) and relative risks (RR) reported are adjusted as reported by the authors.

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