Table 2.1 Cohort studies of estrogen-only menopausal therapy and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Colditz & Rosner (2000) USA Nurses' Health Study 1980–1994	58 520 women aged 30–55 years in 1980, followed through June 1, 1994 in the Nurses' Health Study. 1,761 incident invasive breast cancer cases were identified. Followed 1980–94	Mailed questionnaire	invasive breast cancer	Postmenopausal hormone use None ERT HRT	 5977 7322 9988	 1.0 ref 1.23 (1.06–1.42) 1.67 (1.18–2.36)	Age of menarche, menopause, pregnancy history, BBD, postmenopausal hormone use, body mass index, height, alcohol use, and family history of breast cancer	
Schairer *et al*., (2000) Breast Cancer Detection Demonstration Project, USA 1973–1995	46 355 postmenopausal women (mean age at start of followup, 58 years) identified from 29 screening centers throughout the United States. participants in the Breast Cancer Detection Demonstration Project (BCDDP); 2082 breast cancer cases identified during follow-up; follow-up between 1979–84	Mailed questionnaire or telephone interview	Incident breast cancer	Estrogen only *Ever use* *with* progestin unknown *Years since last use* Current 1–2 >2–4 >4–6 >6	 805 130 243 77 55 35 309	 1.1 (1.0–1.3) 1.3 (1.0–1.5) 1.1 (1.0–1.3) 1.4 (1.1–1.8) 1.2 (0.9–1.6) 0.9 (0.6–1.3) 1.1 (0.9–1.2)	Age, education, BMI, age at menopause, mammographic screening	Increases in risk with estrogen only were restricted to use within the previous 4 years (RR, 1.2 [95% CI, 1.0–1.4]; the relative risk increased by 0.01 (95% CI, 0.002–0.03) with each year of estrogen-only use. The primary type of estrogen used was conjugated estrogens (Premarin).

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Beral *et al*. (2003) UK Million Women Study, 1996–2001	1 084 110 UK women aged 50–64 years were recruited between 1996 and 2001 and were followed up for cancer incidence and death.	Mailed questionnaire	ICD C50	Oestrogen only	991	1.30 (1.22–1.38)	Age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.	Users of oestrogen-only preparations were further subdivided according to the specific oestrogen constituent of the HRT (equine oestrogen or oestradiol), its dose, and whether it was administered as an oral,. transdermal, or implanted formulation
				Duration of current use (yrs)				
				< 1	25	0.81 (0.55–1.20)		
				1-4	251	1.25 (1.10–1.41)		
				5-9	416	1.32 (1.20–1.46)		
				≥10	277	1.37 (1.22–1.54)		
				By constituent and dose				
				All equine oestrogen	426	1.29 (1.16–1.43)		
				≤0·625 mg	288	1.25 (1.11–1.41)		
				>0·625 mg	135	1.36 (1.14–1.61)		
				All ethinyloestradiol	454	1.24 (1.12–1.37)		
				≤1 mg ethinyloestradiol	367	1.25 (1.12–1.40)		
				>1 mg ethinyloestradiol	47	1.19 (0.89–1.58)		
				By formulation				
				Oral	606	1.32 (1.21–1.45)		
				Transdermal	324	1.24 (1.11–1.39)		
				Implanted	54	1.65 (1.26–2.16)		
Olsson *et al*., (2003), Sweden	Swedish registry data, 40 000 women aged 25–65, randomly selected from the South Swedish Health Care Region, followed until 2001; 556 malignant tumors developed during the follow-up period	Questionnaire Interviews	Malignant breast cancer	**Time to breast carcinoma in relation to the type of HRT use**				
				Estradiol only				
				natural menopause	NR	0.81 (0.34–1.96)		
				all women		0.71 (0.40–1.26)		
				Estriol				
				natural menopause	NR	1.45 (0.80–2.63)		
				all women		1.29 (0.79–2.13)		
				Type and duration of HRT				
				Women who ever used only one type of HRT				
				Estradiol only				
				Never user of HRT	NR	1.00		
				1–48mos		1.56 (0.38–6.38)		
				48+mos		….		
				Estriol				
				Never user of HRT	NR	1.00		

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				1–48mos		1.44 (0.63–3.28)		
				48+mos		2.29 (0.93–5.68)		
				Women who used different types of HRT				
				Estradiol only				
				Never user of HRT	NR	1.00		
				1–48mos		1.40 (0.56–3.48)		
				48+mos		1.05 (0.25–4.26)		
				Estriol				
				Never user of HRT	NR	1.00		
				1–48mos		1.44 (0.59–3.53)		
				48+mos		2.27 (0.99–5.20)		
				Type and duration of HRT			For other types of HRT exposures and for year of interview. Adjusted for year of interview Adjusted for family history, age at first full-term pregnancy, nulliparity, and age at menarche	Gestagen also considered Reference category not clear For estradiol use: it is clearly mentioned “estradiol only”, for estriol it is only mentioned “estriol”
				Estriadiol only				
				Never use		1.00		
				1–48 mos	526 (13)	0.77 (0.38–1.57)		
				48+mos	300 (8)	0.58 (0.22–1.55)		
				Estriol				
				Never use		1.00		
				1–48 mos	409 (9)	0.87 (0.41–1.85)		
				48+mos	256 (11)	1.98 (1.04–3.79)		

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Bakken *et al*. (2004) Norway, The Norwegian Women and Cancer (NOWAC) study 1996–1998	A representative, national, population-based prospective cohort study. 31 451 postmenopausal women, aged 45–64 years, with complete information; follow-up information based on linkage to the Cancer Registry of Norway	HRT Postal questionnaire	Incident breast cancer	Estrogen only HRT < 5 years ≥ 5 years	 13 5	 2.5 (1.4–4.5) 1.0 (0.4–2.5) p trend = 0.2	Age, time since start of menopause, age at menarche, ever use of OCs, BMI, history of breast cancer in mother, regions with a screening program, age at first delivery and parity	

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Ewertz *et al*. (2005) Denmark 1989–2002	From the files of the CPR, we identified 83 873 women identified from the Central population register, 40–66 years of age; linked to the Danish Cancer Registry and the Pharmaco-Epidemiological Prescription Database to identify cases of breast cancer and assess HRT exposure occurring through 2002.	Pharmaco-Epidemiologic Prescription Database	Breast cancer	Oestrogen only HRT	50	1.35 (1.01–1.80)	Calendar period, number of children, and age at first birth	Since women with only 1 prescription may never have actually taken the drug, they were classified as nonexposed.
Fournier *et al*., France, (2005) E3N Study, 1990–2000	98 997 women born between 1925 and 1950, after exclusions: 54 548 postmenopausal women followed for an average of 5.8y until 2000, 948 primary invasive breast cancer	24-month intervals: self administered questionnaires, from 1992	Invasive breast cancer	Estrogen used alone Transdermal/percutaneous route Oral route	29 30 2	1.2 (0.8–1.7) 1.1 (0.8–1.6) 0.6 (0.2–2.4)	Time since menopause, BMI, age at menopause parity and age at first full-term pregnancy, familial history of breast cancer, personal history of benign breast disease, use of oral progestogens before, ever use of oral contraceptives and previous mammography	The referent group consisted of women who indicated that they had either never used any form of HRT or had started taking HRT less than 1 year before the end of follow-up

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Lee *et al*; (2006) Hawaii and California MultiEthnic Cohort, 1993–96	A cohort study among 55 371 African-American, Native Hawaiian, Japanese-American, Latina and White postmenopausal women aged 45–75 years old enrolled the Multiethnic Cohort Study between 1993–96. A total of 1615 incident invasive breast cancer cases were identified over an average of 7.3 years, followed until 2002		Breast ICD-0, 8500, 8520, 8522, 8050, 8260, 8503, 8211, 8480, 8481, 8510, 8512	Current ET[1] >0 to <5 years 5 to <10 years 10+ years Per 5 years of use Past ET[1] >0 to <5 years 5 to <10 years 10+ years Per 5 years of use	 18 60 183 180 31 26 	 1.02 (0.62–1.66) 1.35 (1.01–1.80) 1.55 (1.25–1.92) 1.10 (1.05–1.16) 1.05 (0.89–1.24) 0.95 (0.66–1.37) 0.89 (0.59–1.33) 0.99 (0.88–1.11)	Time on study	
Rosenberg *et al* (2006a), USA 1995–2003	Biennial questionnaires from 1995 through 2003 in the Black Women's Health Study, 32 559 women 40 years or older, 615 cases of breast cancer were reported.	Postal health questionnaires; medical records	Breast	Estrogen alone **Stratified by BMI** BMI<25 Estrogen alone *Duration (y)* Estrogen (<5) Estrogen (5–9) Estrogen (≥10) BMI 25-29 Estrogen alone *Duration (y)* Estrogen (<5) Estrogen (5–9) Estrogen (≥10) BMI ≥30 Estrogen alone *Duration (y)* Estrogen (<5) Estrogen (5–9) Estrogen (≥10)	134 34 14 6 13 54 18 14 15 46 20 12 11	1.10 (0.85–1.41) 1.41 (0.85–2.33) 1.30 (0.69–2.42) 1.15 (0.46–2.85) 2.71 (1.31–5.59) 1.17 (0.77–1.78) 0.97 (0.56–1.68) 1.50 (0.80–2.82) 1.37 (0.71–2.63) 0.85 (0.56–1.28) 0.82 (0.49–1.37) 1.02 (0.53–1.96) 0.88 (0.44–1.78)	Age, menopausal status, and age at menopause or hysterectomy	

[1] Each subject may contribute to more than one category of use. Analyses are simultaneously adjusted for the other categories of hormone therapy use

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Rosenberg *et al* (2008), Sweden 1993–95	3979 cases from a population-based case–control study; women born in Sweden aged 50–74 years at first diagnosis of breast cancer; cases identified although the Swedish Cancer Register followed until 2003		Breast	Never use	230	1.00	Age at diagnosis, recent mammography, adjuvant endocrine therapy and adjuvant chemotherapy, tumor size and lymphonode involvement	
				Current use	46	0.63 (0.42–0.95)		
				By duration				
				<5 yrs	28	0.74 (0.45–1.27)		
				≥5 yrs	18	0.52 (0.29–0.93)		
				By regimen				
				Estrogen progestin	37	0.59 (0.38–0.91)		
				Estrogen alone	8	0.78 (0.34–1.80)		
				Past use	34	1.03 (0.68–1.54)		
				By duration				
				<5 yrs	25	1.02 (0.64–1.63)		
				≥5 yrs	9	1.02 (0.48–2.17)		