

Table 2.2. Case-control studies of estrogen-only menopausal therapy and breast cancer

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Brinton et al. (1998) Atlanta, GA USA 1990–1992	1031 women, aged 20–55 yrs, identified through rapid case ascertainment and checked against cancer registries	919 population controls identified by RDD, frequency matched by geographic area and age to the expected distribution in cases	In-person interview.	Incident breast cancer (in situ or invasive)	Estrogen only HRT	98	0.70 (0.5–0.9)	Age, race, combined variable of number of births & age at first childbirth, history of a mammogram, menopausal status	

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Henrich et al (1998) USA 1987–1992	109 postmenopausal women 45 years or older who had screening mammography performed	545 controls identified by mammographic screening with normal- or benign-appearing breasts. Matched by age within 1 year, the presence or absence of a history of a previous mammogram, year of the mammography, screening site (mobile unit or hospital), and payment status (charge or no charge) for those from the mobile units.	Self-administered questionnaire	<i>in situ</i> or invasive breast cancer	Estrogen alone	25	1.66 (0.98–2.82)	Matching factors accounted for in conditional logistic regression analysis. Unclear if other covariates were included in the model.	(Women were assisted in filling out the qx by specially trained radiology technicians who were knowledgeable about different estrogen preparations, and dates of use. and regimens.)
					<i>Type of estrogen</i>				
					Conjugated	17	1.49 (0.80–2.76)		
					Non-conjugated	12	1.86 (0.89–3.91)		

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Li CI et al (2000) Seattle, WA USA 1988–1990	537 female residents of King County, Washington who were ages 50–64 years; identified from SEER registry	492 women randomly selected through RDD; King County residents without a history of breast carcinoma; frequency matched by 5-year age groups	In-person interviews	primary breast carcinoma	Type of HTR use				Age, type of menopause	current use of unopposed estrogen for at least 6 months was 1.5 (95% CI, 0.5–3.9) for lobular tumors and 0.7 (95% CI, 0.4–1.1) for ductal tumors. Similar results were found when cases of invasive tumor were analyzed separately.
					<i>Estrogen only</i>					
					lobular	22	1.4 (0.6–3.2)			
					ductal	114	0.6 (0.4–0.9)			
<i>Invasive estrogen only</i>										
lobular	14	1.2 (0.4–3.1)								
ductal	100	0.5 (0.4–0.8)								
Ross et al. (2000) Los Angeles, USA, 3 periods during 1987–96	2653 cases from CSP: Group I (1987-1989, aged 55–64 years); Group II (1992, aged 55–69 years); Group III (1995–1996, aged 55–72 years)	2429 controls selected, individually matched by age (+/-3 years), race-ethnicity and neighbourhood of residence, and interviewed	In-person interview with questionnaire	Breast	Duration (months)				type of menopause and age at menopause, age at menarche, family history of breast cancer, history of benign breast disease, nulliparity, age at first full-term pregnancy, use of oral contraceptives, body weight, and alcohol use, ERT and CHRT simultaneously	
					No HRT		873	1.0		
					ERT					
					1–60		353	1.02		
					61–120		151	0.94		
					121–180		105	0.93		
					≥181		133	1.24		
					per 5 year			1.06 (0.97–1.15)		
					<i>Per 5 year use by stage</i>					
					All			1.06 (0.97–1.15)		
In situ			1.41 (1.18–1.80)							
Localized			1.03 (0.94–1.13)							
Advanced			0.98 (0.87–1.11)							

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Chen et al. (2002) Seattle, Washington, USA 1990–1995	705 postmenopausal women enrolled in the Group Health Cooperative of Puget Sound (GHC), who were aged 50 to 74 years and diagnosed with primary invasive breast cancer	692 randomly selected age-matched female members of GHC	GHC computerized pharmacy database	primary invasive breast cancer	Estrogen only HRT	132	1.17 (0.85–1.60)	age at reference, year of diagnosis, and number of mammograms before diagnosis	Nested case-control study; p-for trend includes non-users of HRT
					Current oral estrogen				
					<i>Months used in recent 5 yrs</i>				
					≤ 36	27	1.13 (0.64–2.01)		
					37–59	36	1.45 (0.84–2.49)		
60	35	1.84 (1.04–3.27)							
p for trend		0.02							

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Daling et al (2002) Atlanta, Detroit, Los Angeles, Philadelphia, Seattle USA 1994–1998	1749 postmenopausal Caucasian and African-American women who were diagnosed at age <65 years with their first invasive breast tumor	1953 postmenopausal control women identified through random-digit dialing; born in the USA; frequency matched women to the age, race, and geographic location	In-person interviews	Invasive breast cancer	Unopposed estrogen pill/patch			age, race, study site, and type of menopause	
					<i>Ductal</i>				
					Duration < 6 mo	83	0.8 (0.6–1.1)		
					only used ≥ 6 mo	301	0.8 (0.6–1.0)		
					ever used ≥ 6 mo	441	0.8 (0.6–1.0)		
					6 mo to < 5 yrs	189	0.8 (0.6–1.1)		
					≥ 5 yrs	251	0.7 (0.6–1.0)		
					<i>Lobular</i>				
					Duration < 6 mo	14	0.9 (0.5–1.7)		
					only used ≥ 6 mo	55	0.9 (0.5–1.6)		
					ever used ≥ 6 mo	84	1.1 (0.7–1.8)		
					6 mo to < 5 yrs	27	1.0 (0.6–1.7)		
					≥ 5 yrs	57	1.3 (0.8–2.2)		
<i>Other</i>									
Duration < 6 mo	4	0.5 (0.2–1.6)							
only used ≥ 6 mo	17	0.8 (0.4–1.7)							
ever used ≥ 6 mo	28	0.7 (0.4–1.5)							
6 mo to < 5 yrs	9	0.6 (0.3–1.5)							
≥ 5 yrs	19	0.8 (0.4–1.9)							
Kirsh & Kreiger (2002) Canada 1995–1996	404 postmenopausal cases of breast cancer, age 20-74 years, Ontario residents, selected from the Ontario Cancer Registry and histologically confirmed	403 age frequency-matched population controls selected from the Ontario Ministry of Finance Property Assessment database	Self-administered questionnaire	Incident primary breast cancer	Estrogen alone HRT			age, age at menopause, type of menopause, history of benign breast disease	
					<i>Duration (years)</i>				
					Ever	75	1.08 (0.70, 1.69)		
					< 1	7	0.34 (0.11, 1.10)		
					1-4	11	0.99 (0.40, 2.46)		
					5-9	14	1.00 (0.44, 2.24)		
					≥ 10	39	1.74 (0.93, 3.24)		
					Per year		1.03 (0.97, 1.09)		
					p for trend		0.31		

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Lumachi et al (2002) Study dates not given	404 women (median age 59 years, range 26–89 years)	389 healthy age-matched women (Group A), and 391 (Group B) symptomatic non-screened patients without breast cancer, who were referred to the Breast unit	Personal interview	Breast cancer	ERT ever ERT > 40 months	NG NG	2.80 (1.92-4.34) 5.56 (2.94-7.81)	age	
Newcomb et al. (2002), Wisconsin, MA, 1992–1994	5298 incident cases, 50–79 old with invasive breast ca. 1007 used only ERT	Community controls, age 50–79, selected at random within 5y age strata	Telephone interviews	Breast	ERT only <i>Duration (yr)</i> <5 ≥5 <i>Current users (yr)</i> <5 ≥5 <i>Time since last use (yr)</i> Current <5 5–9 10–19 20+	1007 402 605 157 443 600 84 54 161 107	1.23 (1.09-1.39) 1.08 (0.92-1.27) 1.36 (1.17-1.58) P=0.001 1.07 (.84-1.37) 1.34 (1.12-1.59) P=.002 1.25 (1.08-1.45) 1.76 (1.21-2.56) 1.22 (0.80-1.87) 1.12 (0.87–1.43) 1.04 (0.77-1.40) P=0.001	Age at menopause, type of menopause, age at full-term pregnancy, BMI, family history of breast cancer, education, screening mammography history, recent alcohol consumption, history of benign breast disease, age at menarche, recent physical activity	

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Weiss et al. (2002), USA, multicenter, population based. 1994-1998	1870, black and white women aged 35-64 years	1953 from the same metropolitan areas matched for race, and 5 year age group	In-person interviews	Breast	ERT use Never 0 to 6 mo. 6mo to 2 year 2 to 5 y 5+	672 113 110 131 353	1.0 0.83 (0.63-1.10) 0.85 (0.63- 1.14) 0.88 (0.66- 1.17) 0.84 (0.66- 1.06)	Adjusted for age atreference,race, studycenter,type of menopause	

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Li CI et al (2003) Washington state USA 1997-1999	975 women with ; ages 65-79 yrs; (196 lobular, 656 ductal, 114 other, 9 unspecified); identified through SEER registry; residents of King, Pierce, or Snohomish counties in Washington state	1007 population controls identified through HCFA records; residents of King, Pierce, or Snohomish counties	In-person interview	Incident in situ or invasive breast cancer	Exclusive ERT	360	1.0 (0.8-1.3)	Age, type of menopause	
					Ever	79	0.8 (0.6-1.2)		
					6 mo-4.9 y	79	0.8 (0.6-1.2)		
					5-14.9 y	90	1.2 (0.8-1.7)		
					15-24.9 y	86	1.3 (0.9-1.9)		
					≥25 y	105	1.0 (0.7-1.4)		
					Former	119	1.1 (0.8-1.5)		
					Current	241	1.0 (0.7-1.3)		
					6 mo-4.9 y	18	0.5 (0.3-0.9)		
					5-14.9 y	50	1.2 (0.8-2.0)		
					15-24.9 y	72	1.4 (0.9-2.2)		
					≥25 y	101	1.0 (0.7-1.5)		
					IDC				
					Ever	240	1.0 (0.8-1.4)		
					6 mo-4.9 y	56	0.9 (0.6-1.3)		
					5-14.9 y	60	1.2 (0.8-1.8)		
					15-24.9 y	61	1.4 (0.9-2.2)		
					≥25 y	63	0.9 (0.6-1.3)		
					Former	83	1.1 (0.8-1.6)		
					Current	157	1.0 (0.7-1.3)		
6 mo-4.9 y	12	0.5 (0.3-1.0)							
5-14.9 y	34	1.3 (0.8-2.1)							
15-24.9 y	51	1.5 (1.0-2.4)							
≥25 y	60	0.9 (0.6-1.4)							
ILC									
Ever	75	1.3 (0.8-2.0)							
6 mo-4.9 y	17	1.1 (0.6-2.0)							
5-14.9 y	19	1.5 (0.8-2.9)							
15-24.9 y	14	1.3 (0.6-2.6)							
≥25 y	25	1.3 (0.7-2.4)							
Former	22	1.2 (0.7-2.1)							
Current	53	1.3 (0.8-2.2)							
6 mo-4.9 y	6	1.1 (0.4-2.9)							
5-14.9 y	11	1.8 (0.8-3.9)							
15-24.9 y	12	1.5 (0.7-3.2)							
≥25 y	24	1.4 (0.7-2.7)							

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Pesch B et al (2005), Bonn, Germany, 2000–2002	688 breast cancer cases aged 50-79 years	724 Caucasian population controls matched by residence and ±5yr of birth	Computer-assisted interviews	breast	For women in surgical menopause	42	1.13(.70-1.83)	BMI, family history of breast cancer, number of mammograms, years of oral contraceptive use, parity, lifetime months of breast feeding, age of menarche, age at first full-term pregnancy, age at menopause	It is assumed that all women with surgical menopause received unopposed estrogens HRT
					<i>HRT use</i>				
					Never	16	1.00		
					Ever	25	0.31(.07-1.45)		
					0-5	3	0.15(.02-1.14)		
					5-10	5	0.45(.02-8.96)		
10+	17	0.61(.09-4.17)							
						P=0.92			
Sprague <i>et al.</i> (2008) Wisconsin, Massachusetts, and New Hampshire, USA, 1997–2001	3499 cases, aged 20-69 years with a new diagnosis of invasive breast cancer	4213 population-based controls selected at random, state-specific frequency matched by age (5-year age groups)	Telephone interview with questionnaire	Breast (invasive)	Former Current estrogen only	283 651	1.00 0.96 (0.79-1.17)	Age, state of residence, weight at age 18 years, screening mammograms per year over the last 5 years, first-degree family history of breast cancer, personal history of benign breast disease, height at age 25 years, age at menarche, age at menopause, age at first full-term pregnancy, parity, oral contraceptive use, lactation duration, recent alcohol consumption, weight change since age 18 years, recent recreational physical activity (hours/week)	Reference group was former users of HRT.

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Wu <i>et al.</i> (2007) Los Angeles, USA, 1995–2001	1277 cases (450 Chinese, 352 Japanese, 475 Filipinos) from LA County SEER data, aged 25–74 years	1160 population-based controls (486 Chinese, 311 Japanese, 363 Filipinos) selected the neighborhoods, frequency matched by age (5-year age groups) and Asian-ethnicities	In-person interview with questionnaire	Breast	All postmenopausal			Birthplace and duration of residence in the US, education, age at menarche, number of live births, menopausal status and age at menopause, intake of tea and soy during adolescence and adult life and years of physical activity	Matched set variables: age and Asian ethnicity; reference was non-current HRT users in the lowest weight group.
					<i>Duration</i>				
					Never/short term	423	1.00		
					≥1-<5 years	31	1.31 (0.69-2.48)		
					≥5-<10 years	34	0.92 (0.51-1.66)		
					≥10 years	43	0.98 (0.55-1.74)		
					per 5 years		0.99 (0.83-1.19)		
					Natural menopause or bilateral oophorectomy				
					<i>Duration</i>				
					Never/short term	356	1.00		
≥1-<5 years	21	1.46 (0.66-3.25)							
≥5-<10 years	20	1.21 (0.55-2.66)							
≥10 years	30	1.42 (0.67-3.03)							
per 5 years		1.12 (0.89-1.42)							
Stratified by weight									
<i>Current ET alone users</i>									
≤49.9		0.90 (0.44-1.84)							
>49.9-55.4		1.09 (0.52-2.29)							
>55.4-61.3		0.81 (0.41-1.60)							
>61.3		2.83 (1.22-6.56)							

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Rosenberg et al. (2006b) Sweden 1993-95	2643 postmenopausal women ages 50 to 74 years, diagnosed with invasive breast cancer	3065 age frequency-matched controls randomly selected from the Swedish National Population Register	Postal questionnaire	Breast cancer	<u>ER⁻PR⁻</u>				
					<i>Estrogen alone</i>				
					No use	225	1.00		
					Ever	41	1.9 (1.3-2.7)		
					Current	23	1.9 (1.2-3.0)		
					Exclusive use				
					Ever	26	2.0 (1.3-3.1)		
					Duration				
					<5 y	13	1.6 (0.9-3.0)		
					≥5 y	10	2.4 (1.2-4.8)		
					Recency				
					Current	6	1.0 (0.4-2.4)		
					Past	17	2.7 (1.5-4.6)		
					<u>ER⁺PR⁻</u>				
					<i>Estrogen alone</i>				
					No use	200	1.00		
					Ever	30	1.6 (1.1-2.5)		
					Current	18	1.8 (1.0-3.0)		
					Exclusive use				
					Ever	18	1.6 (1.0-2.7)		
					Duration				
					<5 y	14	2.0 (1.1-3.7)		
					≥5 y	4	1.2 (0.4-3.3)		
Recency									
Current	4	0.9 (0.3-2.6)							
Past	14	2.4 (1.3-4.4)							
<u>ER⁻PR⁺</u>									
<i>Estrogen alone</i>									
No use	41	1.00							
Ever	13	3.2 (1.7-6.2)							
Current	8	3.5 (1.6-7.6)							
Exclusive use									
Ever	8	3.3 (1.5-7.2)							
Duration									
<5 y	1	0.6 (0.1-4.5)							
≥5 y	7	10.2 (4.2-24.6)							
Recency									
Current	4	3.5 (1.2-10.3)							
Past	4	3.5 (1.2-10.1)							
<u>ER⁺PR⁺</u>									
<i>Estrogen alone</i>									
No use	775	1.00							

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Li <i>et al.</i> (2006), Atlanta, Detroit, Los Angeles, Philadelphia, Seattle, USA 1994–1998	4279 women aged 35–64 with invasive breast cancer; cases ascertained through SEER database	4682 women without a history of breast cancer who were identified through random digit dialing (RDD), frequency matched by study site, race and age (± 5 years)	Interview	ICD 8500, 8520, 8522, 8510, 8512, 8211, 8201, 8501, 8480	Ductal				Age, race, study site, age at first full-term birth, age at menarche, first degree family history of breast cancer
					Never	553	1.0		
					Current E	315	0.7 (0.6–0.9)		
					Lobular				
					Never	55	1.0		
					Current E	35	1.0 (0.6–1.5)		
					Ductal-lobular				
					Never	28	1.0		
					Current E	28	1.3 (0.7–2.3)		
					Medullary				
					Never	15	1.0		
					Current E	4	0.5 (0.2–1.6)		
					Tubular				
					Never	10	1.0		
Current E	4	0.5 (0.1–1.6)							
Comedo									
Never	4	1.0							
Current E	8	4.1 (1.2–14.5)							
Mucinous									
Never	11	1.0							
Current E	8	0.8 (0.3–2.2)							

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Li <i>et al.</i> (2008) Washington state, USA, 2000–2004	1044 women aged 55–74, diagnosed with lobular, ductal or ductal-lobular breast cancer; identified through Seattle-Puget Sound SEER database	469 controls, aged 55–74 from the general population of female residents of King, Pierce and Snohomish counties	In-person interview	Breast	Ductal cases				
					Never use	117	1.0		
					Current EHT use	123	0.7 (0.5–1.0)		
					<3 y	4	0.4 (0.1–1.3)		
					3–4.9 y	7	0.8 (0.3–2.2)		
					5–9.9 y	15	0.4 (0.2–0.7)		
					≥10 y	97	0.8 (0.3–2.0)		
					Lobular and ductal-lobular cases	78	1.0		
					Never use	126	1.1 (0.7–1.5)		
					Current EHT use	3	0.4 (0.1–1.7)		
					<3 y	6	0.9 (0.3–2.9)		
					3–4.9 y	23	0.8 (0.5–1.6)		
					5–9.9 y	94	1.2 (0.8–1.8)		
					≥10 y				
					Lobular cases	51	1.0		
					Never use	82	1.0 (0.7–1.6)		
					Current EHT use	1	0.2 (0.0–1.9)		
					<3 y	3	0.7 (0.2–2.9)		
					3–4.9 y	15	0.9 (0.4–1.8)		
					5–9.9 y	63	1.2 (0.7–1.9)		
					≥10 y				
					Lobular and ductal-lobular cases	27	1.0		
					Never use	44	1.0 (0.6–1.8)		
					Current EHT use	2	0.8 (0.2–4.0)		
					<3 y	3	1.4 (0.3–5.7)		
					3–4.9 y	8	0.8 (0.3–2.0)		
					5–9.9 y	31	1.1 (0.6–2.0)		
					≥10 y	12	1.0		
					<50% Lobular	12	0.6 (0.3–1.5)		
					Never use				
					Current EHT use	8	1.0		
					≥50% Lobular	18	1.4 (0.6–3.4)		
					Never use				
					Current EHT use	2	1.0		
					<50% Lobular	8	2.6 (0.5–12.8)		
					Never use				
					Current EHT use				

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Abbreviations: GHC, Group Health Cooperative of Puget Sound; HRT, hormone replacement therapy, RDD, random digit dialing; ERT, estrogen-alone replacement therapy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma

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