

Online Resource 2. Effect modification of breast cancer risk related to use of HT and baseline body-mass index, with adjustment for confounders and complete case analyses with adjustment only for attained age

	Body-mass index (BMI) ^a <25 kg/m ²				Body-mass index (BMI) ^a ≥25 kg/m ²			
	No. of cases/no. of participants	Model	HR	95% CI	No. of cases/no. of participants	Model	HR	95% CI
Any systemic HT								
Never use	943/75,467	Age-adjusted ^b	1		1,209/79,397	Age-adjusted ^b	1.21	1.11-1.32
		Adjusted ^c	1			Adjusted ^c	1.23	1.13-1.34
Current use	458/15,893	Age-adjusted ^b	2.07	1.85-2.32	412/13,256	Age-adjusted ^b	2.22	1.98-2.50
		Adjusted ^c	2.04	1.82-2.29		Adjusted ^c	2.22	1.97-2.50
HT use (current vs never) within strata of baseline BMI		Age-adjusted ^b	2.13	1.90-2.39		Age-adjusted ^b	1.80	1.61-2.02
		Adjusted ^c	2.10	1.87-2.36		Adjusted ^c	1.77	1.58-1.98
Systemic combination HT (EPT)								
Never use	943/75,468	Age-adjusted ^b	1		1,209/79,397	Age-adjusted ^b	1.21	1.11-1.32
		Adjusted ^c	1			Adjusted ^c	1.23	1.13-1.34
Current use	384/11,815	Age-adjusted ^b	2.35	2.08-2.65	333/9,168	Age-adjusted ^b	2.64	2.32-2.99
		Adjusted ^c	2.31	2.04-2.60		Adjusted ^c	2.62	2.31-2.97
HT use (current vs never) within strata of baseline BMI		Age-adjusted ^b	2.42	2.14-2.73		Age-adjusted ^b	2.13	1.88-2.41
		Adjusted ^c	2.37	2.10-2.69		Adjusted ^c	2.09	1.85-2.37

BMI = body mass index, calculated as weight (kg)/height (m)²; CI = confidence interval; EPT = estrogen plus progestogen treatment; HR = hazard ratio; HT = menopausal hormone therapy. ^a We excluded women reporting body weight <30 kg and >299 kg or height <120 cm and >203 cm. ^b Adjusted for attained age among participants without missing information on education, age at first birth, parity and alcohol consumption. ^c Adjusted for education, age at first birth, parity and alcohol consumption in addition to attained age.

Any systemic HT:

- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: -0.06 (-0.83, 0.70)
Adjusted: -0.06 (-0.36, 0.25)
- Measure of interaction on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test
Age-adjusted: 0.88 (0.75-1.03), LR chi²=2.36, LR p=0.12
Adjusted: 0.88 (0.75-1.03), LR chi²=2.39, LR p=0.12

Systemic combination HT (EPT):

- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: 0.08 (-0.30, 0.46)
Adjusted: 0.08 (-0.29, 0.46)
- Measure of effect modification on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test
Age-adjusted: 0.93 (0.78-1.10), LR chi²=0.79, LR p=0.38
Adjusted: 0.92 (0.78-1.10), LR chi²=0.82, LR p=0.36

Online Resource 3. Effect modification of breast cancer risk related to use of HT and the body-mass patterns “remained at normal weight” versus “overweight as young” with adjustment for confounders and complete case analyses with adjustment only for attained age

	Overweight as young ^a				Remained at normal weight ^b			
	No. of cases/no. of participants	Model	HR	95% CI	No. of cases/no. of participants	Model	HR	95% CI
Any systemic HT								
Never use	252/20,598	Age-adjusted ^c	1		748/58,091	Age-adjusted ^c	1.04	0.90-1.20
		Adjusted ^d	1			Adjusted ^d	1.10	0.95-1.28
Current use	74/3,165	Age-adjusted ^c	1.75	1.35-2.27	347/11,844	Age-adjusted ^c	2.19	1.86-2.59
		Adjusted ^d	1.71	1.32-2.22		Adjusted ^d	2.29	1.93-2.72
HT use (current vs never) within strata of body-mass patterns		Age-adjusted ^c	1.67	1.28-2.17		Age-adjusted ^c	2.14	1.87-2.44
		Adjusted ^d	1.60	1.22-2.08		Adjusted ^d	2.13	1.86-2.43
Systemic combination HT (EPT)								
Never use	252/20,598	Age-adjusted ^c	1		748/58,091	Age-adjusted ^c	1.04	0.90-1.20
		Adjusted ^d	1			Adjusted ^d	1.11	0.96-1.29
Current use	60/2,195	Age-adjusted ^c	2.06	1.56-2.74	291/8,859	Age-adjusted ^c	2.47	2.08-2.93
		Adjusted ^d	2.02	1.52-2.68		Adjusted ^d	2.59	2.17-3.10
HT use (current vs never) within strata of body-mass patterns		Age-adjusted ^c	1.94	1.46-2.59		Age-adjusted ^c	2.42	2.11-2.79
		Adjusted ^d	1.86	1.39-2.48		Adjusted ^d	2.41	2.09-2.77

CI = confidence interval; EPT = estrogen plus progestogen treatment; HR = hazard ratio; HT = menopausal hormone therapy

^a Participants reporting weighing above average at 7 and/or 15 years of age, regardless of baseline BMI ^b Participants reporting weighing below the average or average at 7 and 15 years of age and having BMI <25 kg/m² at baseline

^c Adjusted for attained age among participants without missing information on education, age at first birth, parity, usual alcohol consumption, and relative height at age 7 years. ^d Adjusted for education, age at first birth, parity, usual alcohol consumption, and relative height at age 7 years, in addition to attained age

- Any systemic HT:
- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: 0.41 (-0.07, 0.88)
Adjusted: 0.48 (0.00, 0.95)
 - Measure of effect modification on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test
Age-adjusted: 1.21 (0.90-1.61), LR chi²=1.64, LR p=0.20
Adjusted: 1.21 (0.91-1.62), LR chi²=1.75, LR p=0.19
- Combination systemic HT (EPT):
- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: 0.37 (-0.24, 0.97)
Adjusted: 0.47 (-0.14, 1.07)
 - Measure of effect modification on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test:
Age-adjusted: 1.15 (0.84-1.57), LR chi²=0.78, LR p=0.38
Adjusted: 1.16 (0.85-1.58), LR chi²=0.87, LR p=0.35

Online Resource 4. Effect modification of breast cancer risk related to use of HT and the life-course body-mass patterns “gained weight” versus “overweight as young”, with adjustment for confounders and complete case analyses with adjustment only for attained age

	Overweight as young ^a				Gained weight ^b			
	No. of cases/no. of participants	Model	HR	95% CI	No. of cases/no. of participants	Model	HR	95% CI
Any systemic HT								
Never use	252/20,598	Age-adjusted ^c Adjusted ^d	1 1		858/52,020	Age-adjusted ^c Adjusted ^d	1.32 1.41	1.15-1.52 1.22-1.63
Current use	74/3,165	Age-adjusted ^c Adjusted ^d	1.65 1.61	1.27-2.14 1.24-2.09	293/8,703	Age-adjusted ^c Adjusted ^d	2.31 2.36	1.96-2.74 1.99-2.80
HT use (current vs never) within strata of body-mass patterns		Age-adjusted ^c Adjusted ^d	1.67 1.60	1.28-2.17 1.22-2.08		Age-adjusted ^c Adjusted ^d	1.78 1.76	1.56-2.04 1.54-2.02
Systemic combination HT (EPT)								
Never use	252/20,598	Age-adjusted ^c Adjusted ^d	1 1		858/52,020	Age-adjusted ^c Adjusted ^d	1.32 1.41	1.15-1.52 1.21-1.63
Current use	60/2,195	Age-adjusted ^c Adjusted ^d	1.95 1.90	1.47-2.58 1.43-2.52	234/6,065	Age-adjusted ^c Adjusted ^d	2.74 2.85	2.29-3.28 2.37-3.43
HT use (current vs never) within strata of body-mass patterns		Age-adjusted ^c Adjusted ^d	1.94 1.86	1.46-2.59 1.39-2.48		Age-adjusted ^c Adjusted ^d	2.08 2.05	1.79-2.40 1.76-2.37

CI = confidence interval; EPT = estrogen plus progestogen treatment; HR = hazard ratio; HT = menopausal hormone therapy

^a Participants reporting weighing above average at 7 and/or 15 years of age-regardless of baseline BMI ^b Participants reporting weighing below the average or average at 7 and 15 years of age and having BMI ≥ 25 kg/m² at baseline

^c Only adjusted for attained age among participants without missing information on education-age at first birth-parity, usual alcohol consumption, and relative height at age 7 years. ^d Adjusted for education-age at first birth-parity, usual alcohol consumption, and relative height at age 7 years, in addition to attained age

Any systemic HT:

- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: 0.39 (-0.09-0.86)
Adjusted: 0.45 (-0.03-0.93)
- Measure of effect modification on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test
Age-adjusted: 1.08 (0.81-1.45), LR chi²=0.28, LR p=0.60
Adjusted: 1.09 (0.81-1.46), LR chi²=0.33, LR p=0.57

Combination systemic HT (EPT):

- Measure of effect modification on additive scale: RERI (95% CI)
Age-adjusted: 0.47 (-0.14-1.09)
Adjusted: 0.55 (-0.07-1.17)
- Measure of effect modification on multiplicative scale: Ratio of HRs (95% CI) and likelihood-ratio test
Age-adjusted: 1.07 (0.78-1.46), LR chi²=0.16, LR p=0.69
Adjusted: 1.07 (0.78-1.47), LR chi²=0.18, LR p=0.68

Online Resource 5. Estimated RERI from previous publications reporting combined effects of HT use and BMI (or weight adjusted for height [1])-adapted from Hvidtfeldt et al [2]

Reference	Study size	Presented analyses	Subgroups	RR ₁₁ /OR ₁₁ /HR ₁₁ combined effect (95% CI)	RR ₁₀ /OR ₁₀ /HR ₁₀ HT (95% CI)	RR ₀₁ /OR ₀₁ /HR ₀₁ BMI (95% CI)	RERI ^a
Wu (2007) [1]	1,277 cases/1,160 controls	Combined effect of HT use and weight adjusted for height. P for interaction		OR 2.18 (1.09-4.35)	OR 1.10 (0.57-2.2)	OR 1.41 (0.90-2.20)	0.67
Ritte (2012) [3]	114,223 women/8,325 cases	Combined effects of HT use and BMI. P for interaction	ER+/PR+	RR 2.39 (<i>P</i> <0.05)	RR 2.42 (<i>P</i> <0.05)	RR 1.75 (<i>P</i> <0.05)	-0.78
			ER-/PR-	RR 1.51	RR 1.86	RR 1.40	-0.75
Canchola (2012) [4]	52,642 women/2,321 cases	Combined effects of HT use and BMI. P for interaction		RR 2.14 (1.59-2.89)	RR 1.92 (1.55-2.38)	RR 1.32 (0.96-1.82)	-0.10
Rosenberg (2006) [5] (not in [2])	2,289 cases (1,888 ductal-308 lobular-93 tubular) /3,065 controls	Combined effects of HT use and BMI	Ductal	OR 1.9 (1.2-3.1)	OR 2.0 (1.2-3.3)	OR 1.8 (1.4-2.3)	-0.9
			Lobular	OR 2.2 (0.9-5.6)	OR 3.4 (1.4-8.3)	OR 1.9 (1.1-3.3)	-2.1
Hvidtfeldt (2015) [2]	30,789 women/1,579 cases	Combined effects of HT use and BMI. Additive hazards		HR 2.15 (1.66-2.79)	HR 2.11 (1.84-2.42)	HR 1.21 (1.00-1.47)	-0.17
Huang (1997) [6] (not in [2])	95,256 women/2,517 cases	Combined effect of HT use and weight gain	Weight gain 10.1-20.0 kg	RR 1.7 (CI not reported)	RR 1.8	RR 1.6	-0.7
			Weight gain >20.0 kg	RR 1.7	RR 1.8	RR 2.0	-1.1
Lahmann (2004) [7]	103,344 postmenopausal women/1,405 cases	Combined effect of HT use and BMI	BMI 25-29.9	RR 1.93 (1.58-2.35)	RR 2.04 (1.74-2.39)	RR 1.28 (1.11-1.48)	-0.39
			BMI ≥30	RR 1.39 (0.95-2.03)	RR 2.04 (1.74-2.39)	RR 1.28 (1.06-1.54)	-0.93
Lahmann (2005) [8]	98,352 women (57,923 postmenopausal)/1,358 cases	Combined effects of HT use and adult weight gain	Weight gain 2-15 kg	HR 2.49 (CI not reported)	HR 3.06	HR 1.22	-0.79
			Weight gain >15 kg	HR 2.73	HR 3.06	HR 1.53	-0.86

BMI = body mass index; CI = confidence interval; HR = hazard ratio; OR = odds ratio; RERI = relative excess risk due to interaction; RR = risk ratio

^aRERI was calculated as described by Rothman[9] and VanderWeele in:[10] $RERI=RR_{11}-RR_{10}-RR_{01}+1$ where RR₁₁ means relative risk with both exposures (here: current use of HT AND high BMI or weight gain)-RR₁₀ and RR₀₁ means relative risk in participants with one of the risk factors only (here: current use of HT OR high BMI or weight gain)-compared to those with no risk factors (here: not current use of HT AND not high BMI or weight gain). It is important to note that RERI can give the direction of the additive interaction (positive-negative-zero)-but can in general not be used to make statements about the relative magnitude of the underlying additive interaction for risk because RERI depends on the baseline risk-which may differ.[10-11]

Online Resource 6. Effect modification of breast cancer risk related to use of HT and baseline body-mass index among women under 55 years of age at baseline

	Body-mass index (BMI) ^a <25 kg/m ²			Body-mass index (BMI) ^a ≥25 kg/m ²		
	No. of cases/no. of participants	HR	95% CI	No. of cases/no. of participants	HR	95% CI
Any systemic HT						
Never use	737/66,786	1		730/64,378	1.06	0.96-1.17
Current use	166/8,717	1.67	1.41-1.98	130/6,942	1.67	1.38-2.01
HT use (current vs never) within strata of baseline BMI		1.67	1.41-1.98		1.58	1.31-1.91
Systemic combination HT (EPT)						
Never use	737/66,786			730/64,378	1.06	0.96-1.17
Current use	145/6,558	1.93	1.62-2.31	109/5,058	1.94	1.58-2.37
HT use (current vs never) within strata of baseline BMI		1.94	1.62-2.32		1.83	1.49-2.24

BMI = body mass index, calculated as weight (kg)/height (m)²; CI = confidence interval; EPT = estrogen plus progestogen treatment; HR = hazard ratio; HT = menopausal hormone therapy. ^a We excluded women reporting body weight <30 kg and >299 kg or height <120 cm and >203 cm. ^b Adjusted for attained age among participants without missing information on education, age at first birth, parity and alcohol consumption. ^c Adjusted for education, age at first birth, parity and alcohol consumption in addition to attained age.

Any systemic HT:

- Measure of effect modification on additive scale: RERI -0.06 (95% CI -0.46-0.34)
- Measure of effect modification on multiplicative scale: Ratio of HRs: 0.94 (95% CI 0.73-1.21) and likelihood-ratio test: LR chi²=0.20, LR P = 0.66

Systemic combination HT (EPT):

- Measure of effect modification on additive scale: RERI -0.06 (95% CI -0.55-0.44)
- Measure of effect modification on multiplicative scale: Ratio of HRs: 0.94 (95% CI 0.72-1.24) and likelihood-ratio test: LR chi²= 0.17, LR P = 0.68

Online Resource 7. Effect modification of breast cancer risk related to use of HT and baseline body-mass index among women aged 55 years and above at baseline

	Body-mass index (BMI) ^a <25 kg/m ²			Body-mass index (BMI) ^a ≥25 kg/m ²		
	No. of cases/no. of participants	HR	95% CI	No. of cases/no. of participants	HR	95% CI
Any systemic HT						
Never use	565/43,589	1		924/52,139	1.36	1.23-1.52
Current use	476/14,625	2.42	2.14-2.74	433/12,632	2.54	2.25-2.88
HT use (current vs never) within strata of baseline BMI		2.43	2.15-2.74		1.86	1.66-2.09
Systemic combination HT (EPT)						
Never use	565/43,589	1		924/52,139	1.36	1.23-1.51
Current use	395/10,775	2.72	2.39-3.10	344/8,477	3.03	2.65-3.46
HT use (current vs never) within strata of baseline BMI		2.73	2.40-3.10		2.21	1.96-2.51

BMI = body mass index, calculated as weight (kg)/height (m)²; CI = confidence interval; EPT = estrogen plus progestogen treatment; HR = hazard ratio; HT = menopausal hormone therapy. ^a We excluded women reporting body weight <30 kg and >299 kg or height <120 cm and >203 cm. ^b Adjusted for attained age among participants without missing information on education, age at first birth, parity and alcohol consumption. ^c Adjusted for education, age at first birth, parity and alcohol consumption in addition to attained age.

Any systemic HT:

- Measure of effect modification on additive scale: RERI -0.24 (95% CI -0.59-0.11)
- Measure of interaction on multiplicative scale: Ratio of HRs 0.76 (95% CI 0.65-0.90) and likelihood-ratio test LR chi²=9.47, LR P = 0.002

Systemic combination HT (EPT):

- Measure of effect modification on additive scale: RERI -0.06 (95% CI -0.50-0.37)
- Measure of effect modification on multiplicative scale: Ratio of HRs 0.81 (95% CI 0.68-0.97) and likelihood-ratio test LR chi²=5.10, LR P = 0.02

References

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