
Hormone replacement therapy and breast cancer risk in a nationwide population-based cohort

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Background

- Hormone replacement therapy (HRT) alleviates the climacteric symptoms of menopause
- The association between the risk of breast cancer and HRT has been confirmed by a randomized controlled study (WHI trial) and several observational studies
- But, does HRT increase breast cancer risk in **ALL** postmenopausal women?

Background

- Asian population?
 - Most large scale studies were performed in Western countries
 - Different breast cancer epidemiology
- Breast cancer risk factors
 - Obesity
 - Breast density
 - Reproductive factors : OC use, parity, breastfeeding hx
- ✓ We investigated the association between **HRT and breast cancer risk** in a nationwide cohort with risk stratification according to **risk factors for breast cancer**.

Patients

- National Health Insurance Service (NHIS)
 - Almost all Korean citizens (97.2%) are covered by the NHIS
 - Regular health checkups every 1-2 years

- Study Cohort
 - Breast cancer screening + (bi)annual health checkups
 - 2009 – 2014
 - Postmenopausal women
 - Follow up until 2016 for breast cancer diagnosis

Methods

❖ Data collected

- Breast cancer screening program questionnaire
- Breast density by mammography, BI-RADs
- Health checkup data
 - Body weight, height, waist circumference
 - Smoking, alcohol, regular exercise
 - Hypertension, diabetes mellitus, dyslipidemia
- Breast cancer diagnosis
 - Rare, incurable disease registry of the NHIS
 - Exclusion: Diagnosed 6 months within health screening

❖ Statistical Analysis

- X^2 test, ANOVA
- Kaplan-Meier method, log-rank test
- Cox proportional hazards regression analysis

Study Population Flowchart

Participants with at least one health checkup
between 2009 and 2014 (n=27,235,770)

Excluded (n=22,677,394)

- Men (n=13,726,208)
- < 40 years old (n=2,969,839)
- Breast cancer screening not done (n=3,926,884)
- Breast cancer screening and regular health checkup was not performed within 30 days (n=198,194)
- Menopause (n=1,639,225)
- Missing data (n=176,773)
- Previously diagnosed of breast cancer (n=31,112)
- Diagnosed of breast cancer within 6 months of breast cancer screening (n=9,159)

4,558,376 subjects who were eligible for this study

No history of HRT
(n=3,862,292)

HRT < 2 years
(n=410,304, **9%**)

HRT 2 to <5 years
(n=158,514, **3.5%**)

HRT ≥ 5 years
(n=127,266, **2.8%**)

Results: Baseline characteristics

		Non-user, N(%)	HRT <2 yrs, N(%)	HRT 2 - <5 yrs, N(%)	HRT ≥5 yrs, N(%)	p-value
Total N		3,862,292	410,304	158,514	127,266	
Age (years)	- 50	159,567 (4.1)	28,001 (6.8)	6,679 (4.2)	2,631 (2.1)	<0.0001
	50 – 59	1,599,076 (41.4)	214,117 (52.2)	78,174 (49.3)	43,712 (34.4)	
	60 – 69	1,216,246 (31.5)	136,661 (33.3)	61,412 (38.7)	66,976 (52.6)	
	70 – 79	764,332 (19.8)	30,057 (7.3)	11,610 (7.3)	13,464 (10.6)	
	80 -	123,071 (3.2)	1,468 (0.4)	639 (0.4)	483 (0.4)	
Number of live births	None	76,073 (2.0)	12,053 (2.9)	5,018 (3.2)	4,474 (3.5)	<0.0001
	1	277,076 (7.2)	41,521 (10.1)	16,512 (10.4)	12,265 (9.6)	
	≥2	3,509,143 (90.9)	356,730 (86.9)	136,984 (86.4)	110,527 (86.9)	
Breastfeeding history	None	293,074 (7.6)	41,506 (10.1)	17,207 (10.9)	13,603 (10.7)	<0.0001
	< 6 mo	291,462 (7.6)	43,631 (10.6)	16,314 (10.3)	11,344 (8.9)	
	<12 mo	659,912 (17.1)	84,740 (20.1)	33,131 (20.9)	22,204 (17.5)	
	≥1 year	2,617,844 (67.8)	240,427 (58.6)	91,862 (58.0)	80,115 (63.0)	

Breast cancer screening questionnaire

		Non-user N(%)	HRT <2 yrs N(%)	HRT 2 - <5 yrs N(%)	HRT ≥5 yrs N(%)	p-value
OC history	None	3,228,917 (83.6)	300,110 (73.1)	114,192 (72.0)	89,787 (70.6)	<0.0001
	<1 year	311,059 (8.1)	60,447 (14.7)	18,540 (11.7)	14,515 (11.4)	
	≥1 year	196,384 (5.1)	34,263 (8.4)	18,170 (11.5)	16,050 (12.6)	
	Unknown	125,932 (3.3)	15,484 (3.8)	7,612 (4.8)	6,914 (5.4)	
History of benign breast disease	Yes	222,674 (5.8)	41,070 (10.0)	17,247 (10.9)	14,173 (11.1)	<0.0001
	No	3,391,371 (87.8)	348,719 (85.0)	133,368 (84.1)	106,881 (84.0)	
	Not know	248,247 (6.4)	20,515 (5.0)	7,899 (5.0)	6,212 (4.9)	
Age of menarche	Mean ± SD	16.33 ± 1.88	16.04 ± 1.86	16.05 ± 1.85	16.2 ± 1.86	<0.0001
Breast Density	<25%	1,549,454 (40.1)	114,959 (28.0)	39,612 (25.0)	31,280 (24.6)	<0.0001
	25 - 50%	1,240,999 (32.1)	144,121 (35.1)	56,104 (35.4)	45,910 (36.1)	
	51 - 75%	835,917 (21.6)	116,898 (28.5)	48,429 (30.6)	39,252 (30.8)	
	76 - 100%	235,922 (6.1)	34,326 (8.4)	14,369 (9.1)	10,824 (8.5)	

Health check-up

		Non-user N(%)	HRT <2 yrs N(%)	HRT 2 - <5 yrs N(%)	HRT ≥5 yrs N(%)	p-value
Smoking	None	3,706,574 (96.0)	388,596 (94.7)	150,023 (94.6)	120,446 (94.6)	<0.0001
	Ex-smoker	41,139 (1.1)	6,867 (1.7)	2,808 (1.8)	2,429 (1.9)	
	Current smoker	114,579 (3.0)	14,841 (3.6)	5,683 (3.6)	4,391 (3.5)	
Alcohol consumption	None	3,371,830 (87.3)	337,631 (82.3)	130,114 (82.1)	106,790 (83.9)	<0.0001
	Mild	473,028 (12.3)	70,130 (17.1)	27,395 (17.3)	19,725 (15.5)	
	Heavy	17,434 (0.5)	2,543 (0.6)	1,005 (0.6)	751 (0.6)	
Regular exercise	No	2,362,649 (61.2)	217,170 (52.9)	79,691 (50.3)	63,745 (50.1)	<0.0001
	Yes	1,499,643 (38.8)	193,134 (47.1)	78,823 (49.7)	63,521 (49.9)	

Health check-up

		Non-user N(%)	HRT <2 yrs N(%)	HRT 2 - <5 yrs N(%)	HRT ≥5 yrs N(%)	p-value
BMI	- 18.4	92,226 (2.4)	8,109 (2.0)	3,276 (2.1)	2,233 (1.8)	<0.0001
	18.5 – 22.9	1,349,621 (34.9)	160,532 (39.1)	65,858 (41.6)	49,403 (38.8)	
	23 – 24.9	995,643 (25.8)	112,649 (27.5)	44,560 (28.1)	37,222 (29.3)	
	25 – 29.9	1,241,125 (32.1)	116,211 (28.3)	40,892 (25.8)	35,266 (27.7)	
	30 –	183,677 (4.8)	12,803 (3.1)	3,928 (2.5)	3,142 (2.5)	
Waist circumference	Mean ± SD	80.06 ± 8.52	78.56 ± 8.02	77.99 ± 7.8	78.42 ± 7.66	<0.0001
Hypertension	Yes	1,630,173 (42.2)	136,784 (33.3)	54,631 (34.5)	49,617 (39.0)	<0.0001
	No	2,232,119 (57.8)	273,520 (66.7)	103,883 (65.5)	77,649 (61.0)	
DM	Yes	543,067 (14.1)	41,876 (10.2)	15,580 (9.8)	13,959 (11.0)	<0.0001
	No	3,319,225 (85.9)	368,428 (89.8)	142,934 (90.2)	113,307 (89.0)	
Dyslipidemia	Yes	935,530 (24.2)	101,259 (24.7)	36,126 (22.8)	27,571 (21.7)	<0.0001
	No	2,926,762 (75.8)	309,045 (75.3)	122,388 (77.2)	99,695 (78.3)	

Incidence of breast cancer

- Median follow-up : **5.35 years** (Q1-Q3, 3.26-6.41)
- ✓ **26,797 (0.6%)** women newly diagnosed with breast cancer
 - 92.9% invasive breast cancer
 - 7.1% DCIS

HRT duration	Total N	Events (n)	Follow-up (Person-Yr)	Incidence per 1000	HR (95% CI)
None	3,862,292	21,262	18,771,852	1.133	1
HRT user	696,084	5,535	3,420,942	1.618	1.253 (1.216, 1.292)
< 2 years	410,304	2,792	2,014,117	1.386	1.079 (1.037, 1.123)
2 - <5 years	158,514	1,351	782,356	1.727	1.325 (1.254, 1.401)
≥ 5 years	127,266	1,392	624,468	2.229	1.722 (1.630, 1.819)

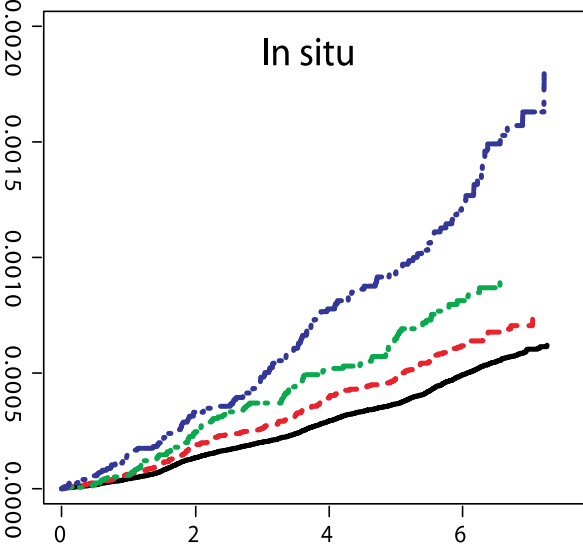
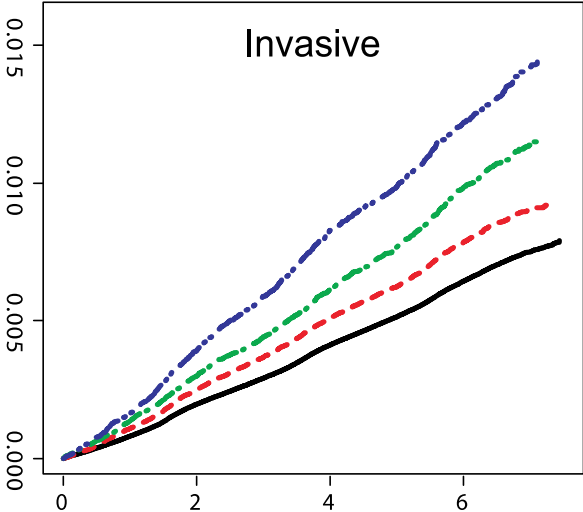
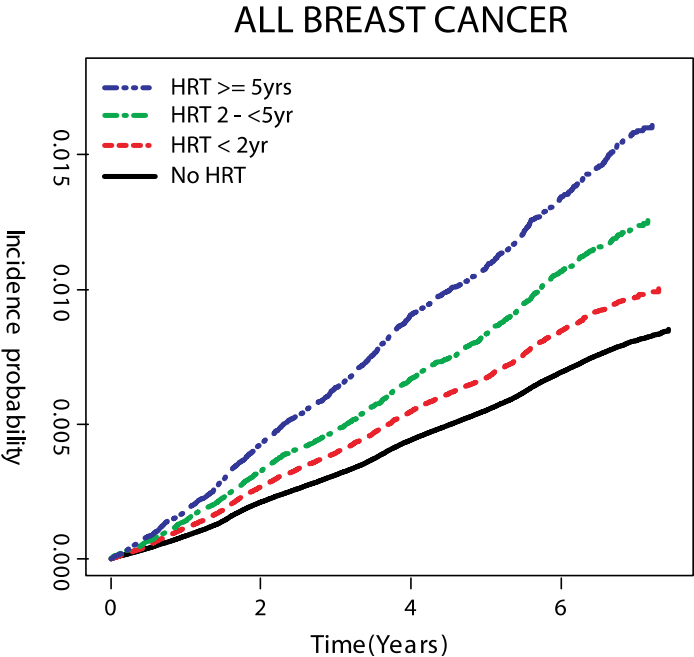
Model adjusted for age, parity (number of live births), breastfeeding history, breast density, oral contraceptive history, smoking, alcohol consumption, regular exercise, body mass index, height, diabetes mellitus, and age at menarche

Incidence of breast cancer

	HRT duration	Total N	Events (n)	Follow-up (Person-Yr)	Incidence per 1000	HR (95% CI)
Invasive breast cancer	None	3,862,292	19,790	18,771,852	1.054	1
	HRT user	696,084	5,107	3,420,942	1.493	1.247 (1.208, 1.287)
	<2 years	410,304	2,593	2,014,117	1.287	1.081 (1.037, 1.126)
	2 - <5 years	158,514	1,250	782,356	1.598	1.322 (1.248, 1.401)
	≥5 years	127,266	1,264	624,468	2.024	1.684 (1.590, 1.783)
DCIS	None	3,842,502	1,472	18,771,852	0.078	1
	HRT user	690,977	428	3,420,942	0.125	1.339 (1.200, 1.495)
	<2 years	407,711	199	2,014,117	0.099	1.059 (0.912, 1.230)
	2 - <5 years	157,264	101	782,356	0.129	1.364 (1.114, 1.671)
	≥5 years	126,002	128	624,468	0.205	2.223 (1.852, 2.669)

Model adjusted for age, parity (number of live births), breastfeeding history, breast density, oral contraceptive history, smoking, alcohol consumption, regular exercise, body mass index, height, diabetes mellitus, and age at menarche

Cumulative incidence of breast cancer



Subgroup Analysis

Subgroup		HR (95% CI)	P-value for interaction
Age	≤55	1.207 (1.145, 1.271)	<0.0001
	>55, ≤65	1.182 (1.132, 1.235)	
	>65	1.329 (1.237, 1.428)	
BMI (kg/m ²)	<25	1.286 (1.239, 1.335)	0.0035
	≥25	1.189 (1.129, 1.253)	
History of benign breast disease	No	1.242 (1.201, 1.285)	0.2013
	Yes	1.093 (1.011, 1.182)	
	Not know	1.309 (1.152, 1.488)	
Number of live births	0	1.197 (1.038, 1.382)	0.4614
	≥1	1.255 (1.217, 1.294)	
Breastfeeding history	No	1.330 (1.227, 1.443)	0.2319
	Yes	1.238 (1.199, 1.279)	

Model adjusted for age, parity (number of live births), breastfeeding history, breast density, oral contraceptive history, smoking, alcohol consumption, regular exercise, body mass index, height, diabetes mellitus, and age at menarche

Subgroup Analysis

Subgroup		HR (95% CI)	P-value for interaction
Oral contraceptive	No	1.276 (1.232, 1.321)	0.7745
	< 1 year	1.043 (0.953, 1.140)	
	≥ 1 year	1.328 (1.196, 1.476)	
	Not know	1.324 (1.150, 1.525)	
Age of menarche	< 14	1.250 (1.211, 1.290)	0.7527
	≥ 14	1.275 (1.149, 1.415)	
Breast density	< 25%	1.235 (1.151, 1.324)	0.0243
	25 - 50%	1.177 (1.117, 1.241)	
	51 - 75%	1.281 (1.219, 1.347)	
	76 - 100%	1.288 (1.182, 1.405)	

Model adjusted for age, parity (number of live births), breastfeeding history, breast density, oral contraceptive history, smoking, alcohol consumption, regular exercise, body mass index, height, diabetes mellitus, and age at menarche

Strengths and Limitations

- 😊 Large sample size
- 😊 Longitudinal nationwide population-based cohort
- 😊 Adjustment for breast cancer risk factors, comorbidities and lifestyle factors
- 😊 Screening bias elimination
- ☒ Lack of information on formulation and timing of HRT
- ☒ Lack of data on subtype and histologic type of cancer
- ☒ HRT data from self-reporting

Conclusion

- In this nationwide population-based cohort study, HRT use was associated with an **increased risk** of breast cancer.
- The risk of breast cancer increased **proportionally** with the **duration of HRT** and was greater in **normal-weight** women and women with **dense breasts**.
- Risk stratification should be performed when deciding whether to apply HRT for relief of menopausal symptoms.