유방암의 위험요인을 가지고 있는 폐경 여성의 호르몬 치료

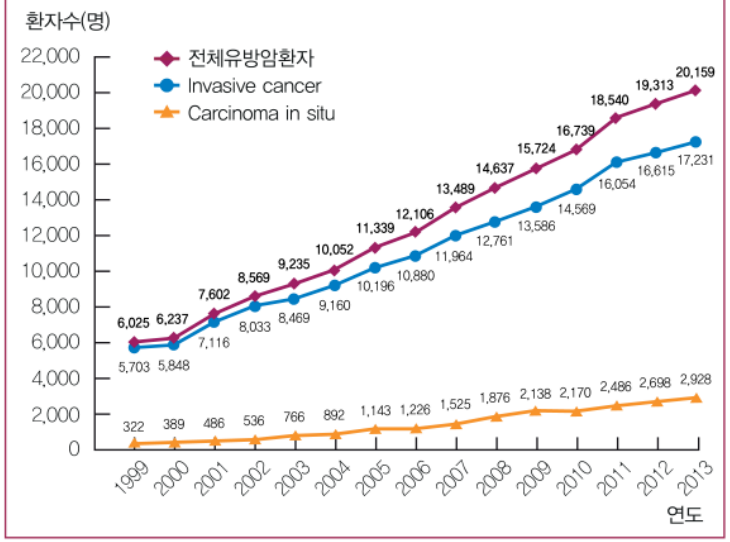
국립암센터

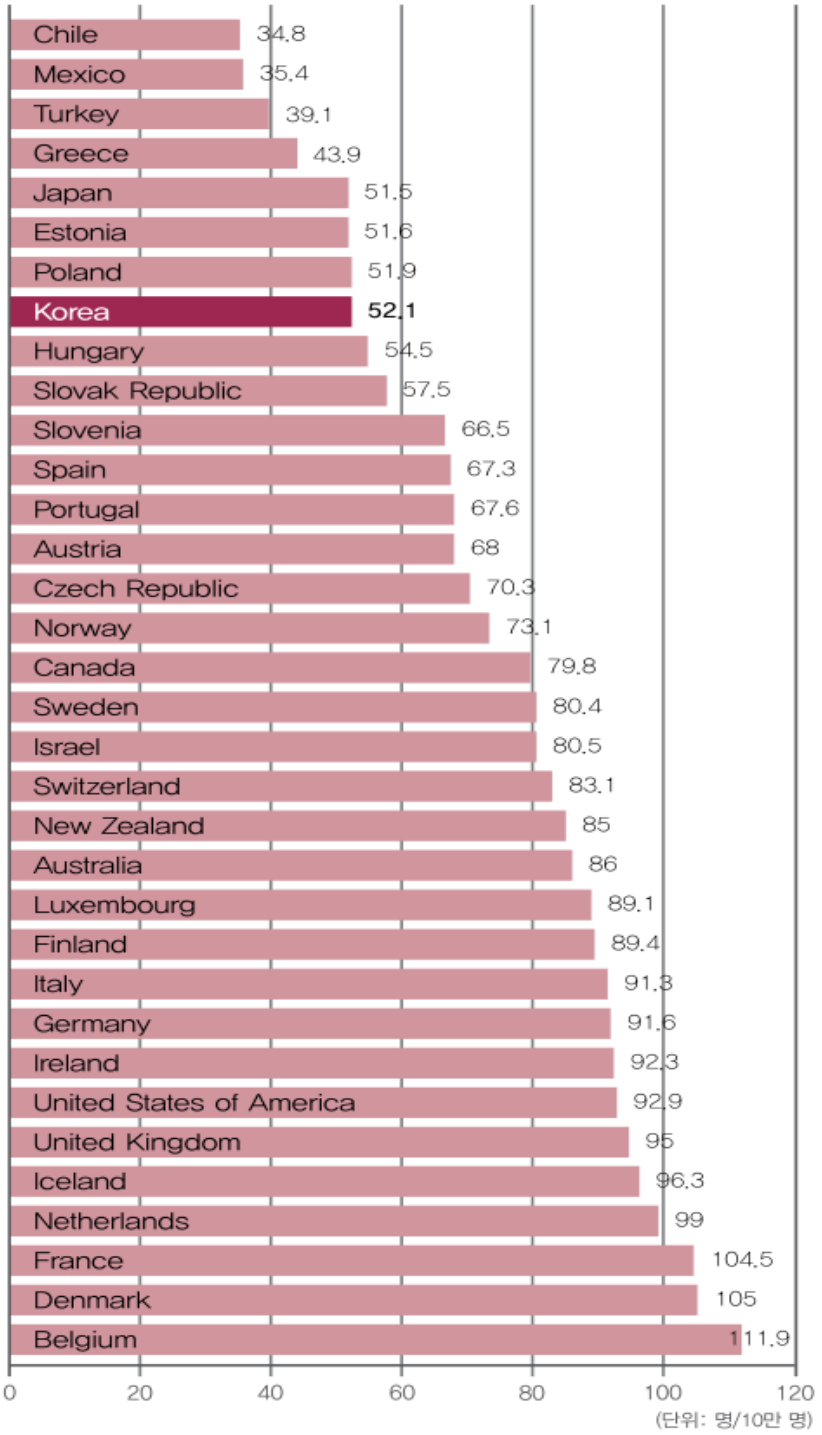
이 동 옥

2012 OECD 국가별 유방암 연령표준화발생률

- 유방암은 특히 전세계적으로 그 발생률이 빠르게 증가하는 질환으로서 2008년에 비해 2012년에는 그 발생률이 20% 증가
- 우리나라 유방암 환자 수는 2012년 16,615명으로 지난 10여 년 전에 비해 무려 3배 이상 증가
- 미국과 유럽 등 구미 지역의 3분의 1 정도지만, 이들 국가의 유방암 발생률은 감소 추세인 반면 한국의 유방암 발생률은 가파른 상승 곡선

[그림 5] 국내 여성 유방암의 연도별 발병 추이





유방암의 위험요인

- Reproductive factors
  - Early age at menarche
  - Late age at menopause
  - Late age at first full-term pregnancy
  - Nulliparity

Kelsey JL, Epidemiol Rev, 1993

- Others
  - Obesity
  - Alcohol intake
  - Nutrition
  - Increased mammographic density

- Gail model
  - Hx of breast cancer, DCIS, LCIS, previous radiation therapy to chest for Hodgkin lymphoma
  - BRCA1 or 2 mutation carrier
  - Age, Race
  - Age at the first menstrual period
  - Age at the first live birth
  - No. of breast cancer pts. among first-degree relatives – mother, sisters, daughters
  - Breast Bx Hx: No. of biopsy, Atypical hyperplasia

NCI, www.cancer.gov

Breast cancer risk factors – Nurses' Health Study 1980-2010

	RR	95% CI
Age at menarche≤12	1.17	1.11-1.24
13	1.09	1.03-1.16
≥14	1.00	-
BMI at age 18yrs <19.0	1.16	1.08-1.25
19.0-20.9	1.18	1.11-1.26
21.0-22.9	1.10	1.03-1.18
≥23.0	1.00	-
Height, inches<63.9	1.00	-
≥64.0 (162.6cm)	1.12	1.07-1.17
Parity/age at first birth		
Nulliparous	1.23	1.12-1.35
≥1 child, <25.0yrs	1.00	-
1-4 children, 25.0-29.9yrs	1.13	1.07-1.19
1-4 children, ≥30.0yrs	1.34	1.24-1.44
>4 children	1.06	0.96-1.18
Age at menopause < 45.0	1.00	-
45.0-51.9	1.24	1.17-1.32
≥52.0	1.43	1.34-1.53

	RR	95% CI
Benign breast ds. Hx (-)	1.00	-
Hx (+)	1.45	1.39-1.51
FHx of breast cancer, No	1.00	-
, Yes	1.50	1.42-1.51
Breast feeding never	1.05	1.00-1.10
ever	1.00	-
Wt change since age 18yrs, kg		
Loss to 1.9kg gain	1.00	-
2.0 – 5.0kg gain	1.12	1.02-1.24
5.1 – 10.0kg gain	1.21	1.11-1.32
10.1 – 20.0kg gain	1.27	1.18-1.37
≥20.1kg gain	1.50	1.39-1.62
Menopausal HT, Never or past	1.00	-
Current user	1.35	1.28-1.42
Alcohol consumption, g/day		
0	1.00	-
0.1-4.9	1.03	0.97-1.09
5.0-15.0	1.13	1.05-1.21
>15.0	1.32	1.22-1.42

Tamimi RM, Am J Epidemiol, 2016

BRCA 1 or 2 mutation carriers

Risk reducing bilateral salpingo-oophorectomy in BRCA mutation carriers

- BRCA: “breast cancer gene”: important role in DNA repair and in the maintenance of telomere length
- Lifetime risk of cancer by age 70

	BRCA1 mutation	BRCA2 mutation
Breast cancer	60-65%	45-55%
Ovarian cancer	39-59%	11-17%

Antoniou A, Am J Hum Genet, 2003

Mavaddat N, J Natl Cancer Inst, 2013

- BSO reduced ovarian, fallopian tube, peritoneal cancer risks by 72-80%, and breast cancer risks by 46-48%.

Domchek SM, JAMA, 2010

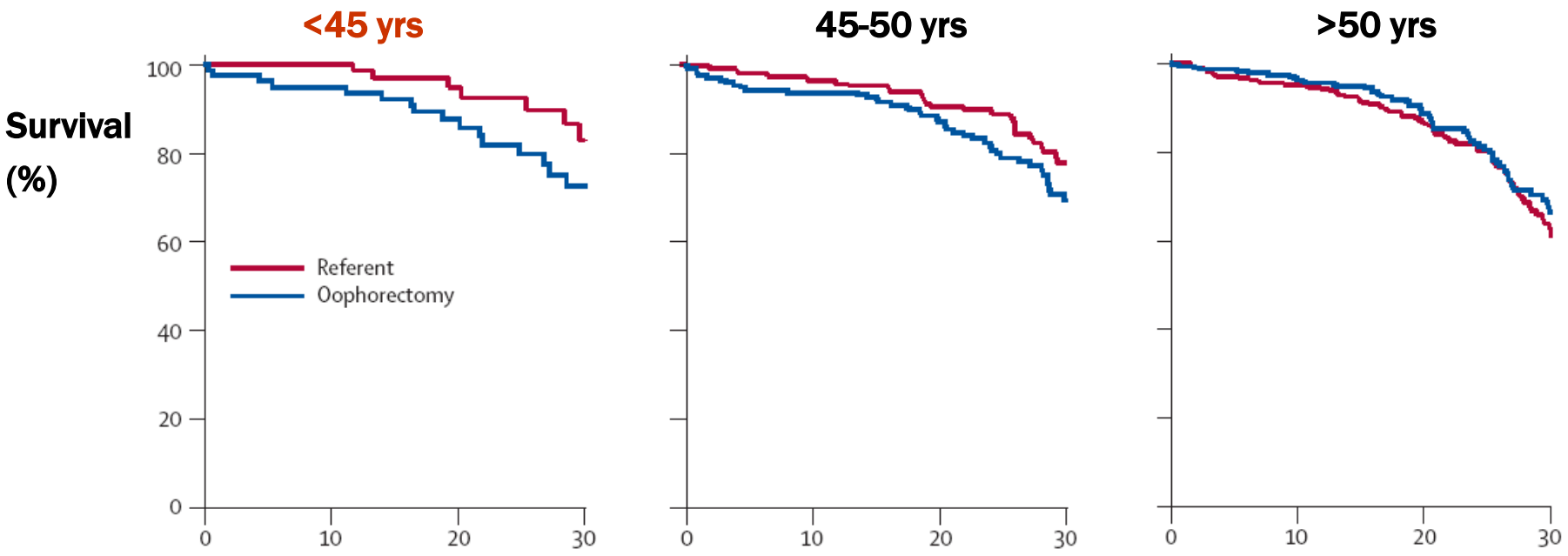
Finch AP, J Clin Oncol, 2014

- 40세 이전 BSO 시 4%에서 난소암이 발견되고 50세 이전 수술 시 14.2%에서 난소암이 발견됨 (occult cancer).

Finch AP, J Clin Oncol, 2014

Survival patterns after oophorectomy in premenopausal women

Survival by age at estrogen deficiency – Mayo Clinic Cohort Study



P=0.003

HR 1.93 (1.25-2.96)

Rocca WA, 2006, Lancet Oncol

Hormone therapy in BRCA 1 mutation carriers

- A case-control study of 432 matched pairs
- Mean duration of HT: 4.3 years
- HT ever user: Breast cancer OR 0.80 (95% CI 0.55-1.16, p=0.24)
- No difference by type of MP, recency of use, duration of use, and formation type.

Kotsopoulos J, Breast Cancer Res Treat, 2016

- A case-control study of 472 postmenopausal women
- HT ever user: Breast cancer OR 0.58 (95% CI 0.35-0.96, p=0.03)
- E only: OR 0.51, (95% CI=0.27-0.98, p=0.04)
- EPT: OR 0.66, (95% CI=0.34-1.27, p=0.21)

Eisen A, J Natl Cancer Inst, 2008

HT after RRSO in BRCA mutation carriers: survival outcomes

- Survival outcomes

Marchetti C, Menopause, 2013

Study	Design	BRCA1/2 mutation carriers who received HT after RRSO	Type of HT	HT duration (y)	Breast cancer risk
Rebbeck et al[55]	Prospective cohort study	93	E_2, PG + E_2	Not specified	HR, 0.37; 95% CI, 0.14-0.96
Eisen et al[56]	Case-control	57	E_2, PG + E_2	4	OR, 0.48; 95% CI, 0.19-1.21
Gabriel et al[57]	Prospective	33	E_2, PG + E_2	2.79	Women with breast cancer, 3/33; 9.09%

- Quality of life outcomes

Study	Design	BRCA1/2 mutation carriers who received RRSO in premenopause: HT	BRCA1/2 mutation carriers who received RRSO in premenopause: No HT	Sexual symptoms	Vasomotor symptoms	Well-being
Nathorst-Böös et al[47]	Case-control	33	33	No change between HT users and nonusers	Not specified	Favoring HT users ($P = 0.05$); anxiety and depression decreased in HT users
Madalinska et al[50]	Prospective	77	87	No change between HT users and nonusers	Favoring HT users ($P = 0.05$); hot flashes decreased in HT users	Not specified
Finch et al[37]	Prospective	29	44	Favoring HT users ($P = 0.015$); sexual discomfort decreased in HT users	Favoring HT users ($P = 0.0003$); hot flashes decreased in HT users	No change between HT users and nonusers

NAMS Practical Pearl, 2016

Clinical recommendations for menopausal previvors

- Existing albeit limited data indicate that risks of breast cancer are not increased with use of systemic HT by menopausal BRCA mutation carriers with intact breasts.

- Young previvors with or without intact breasts should not defer or avoid risk-reducing BSO because of concerns that subsequent use of systemic HT will elevate breast cancer risk.

Domcheck MD, Menopause, 2016

HT and breast cancer in young premenopausal women

The Two Sister Study

- Sister-matched case-control study of young-onset breast cancer
- A prospective cohort study
- Women without breast cancer who had sister diagnosed with breast cancer before age of 50: 1,419 cases and 1,665 controls

Hormone Therapy	Crude[a]		Multivariate-Adjusted[a,b]		Propensity Score–Adjusted[a,c]	
	OR	95% CI	OR	95% CI	OR	95% CI
Hormone therapy used[d]						
None	1.00	Referent	1.00	Referent	1.00	Referent
Unopposed estrogen	0.42	0.29, 0.62	0.56	0.33, 0.93	0.58	0.34, 0.99
Estrogen plus progestin	0.41	0.24, 0.70	0.61	0.32, 1.15	0.80	0.41, 1.59
Progestin alone	1.24	0.66, 2.35	1.42	0.73, 2.78	1.51	0.76, 3.00

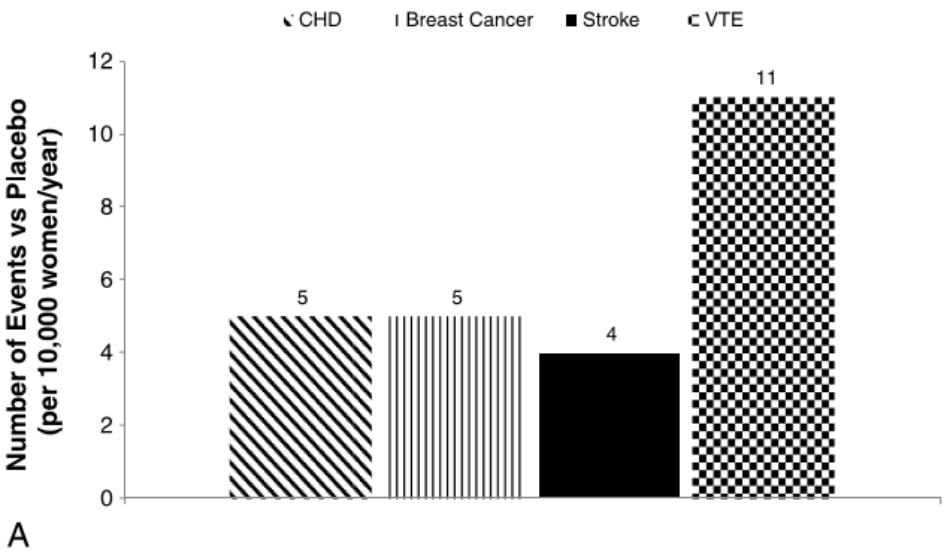
- Duration of use, age at first use, and recency of use did not modify results.

O'Brien, Am J Epidemiol, 2015

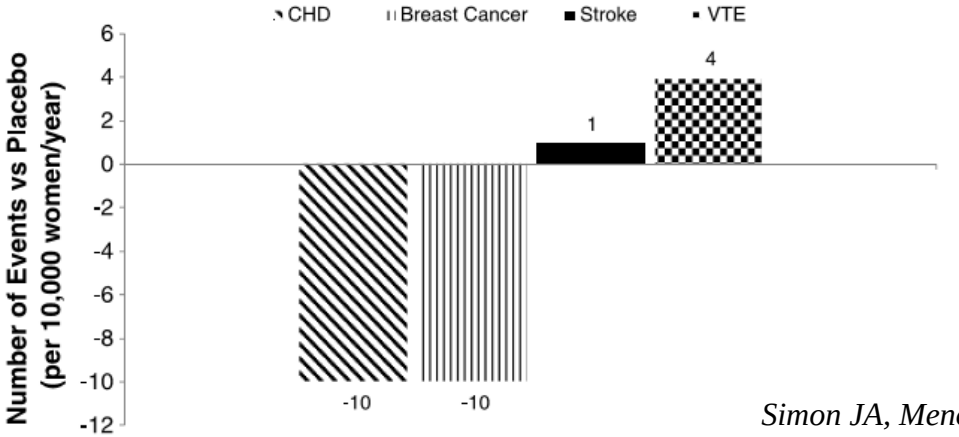
Progestogen?

WHI study, women aged 50-59 years

EPT



ET



No statistically significant interactions by race/ethnicity or BMI

Chlebowski RT, J Natl Cancer Inst, 2016

Simon JA, Menopause, 2014

Classification of progesterone

1. Natural progestogens
- progesterone

2. Synthetic progestogens (progestins)

2.1. Structurally related to progesterone

2.1.1. Pregnane derivatives

2.1.1.1 Acetylated
- Medroxyprogesterone acetate (MPA)
- Megestrol acetate
- Chlormadinone acetate
- Cyproterone acetate

2.1.1.2. Non-acetylated
- Dydrogesterone
- Medrogestone

2.1.2. 19 Nor-pregnane derivatives
- Nomegestrol acetate
- Nesterone
- Demegestone
- Promegestone
- Trimegestone

2.2. Structurally related to testosterone

2.2.1. Ethinylated derivatives

2.2.1.1. Estranes
- Norethisterone acetate (NETA)
- Ethynodiol diacetate
- Norethyndronel
- Lysterenol

2.2.1.2. 13-Ethylgonanes
- Levonorgestrel
- Desogestrel
- Norgestimate
- Gestodene

2.2.2. Ethinylated derivatives
- Dienogest
- Drospirenone

Stanczyk FZ, Endocr Rev, 2013

Different risk according to progestin? (1/2)

French E3N cohort study

- 80,377 postmenopausal women, from 1990 to 2002
- Mean F/U duration 8.1 years, 2,354 cases of breast cancer occurred
- ET OR 1.29 (95% CI 1.02-1.65)
- EPT : progesterone OR 1.00 (0.83-1.22)

  dydrogesterone OR 1.16 (0.94-1.43)

  other progestin OR 1.69 (1.50-1.91)
- No difference of breast cancer risk according to the route of E administration (oral or transdermal/percutaneous)

Fournier A, Breast Cancer Res Treat, 2008

Finnish case-control study

- Women aged over 50 years with HT Hx more than 6 months (n=221,551)
- After 5 years or more exposure
  - Norethisterone acetate (NETA) RR 2.03, CI 1.88-2.18
  - MPA RR 1.64, CI 1.49-1.79
  - Dydrogesterone RR 1.13, CI 0.49-2.22

Lyytinen H, Obstet Gynecol, 2009

Different risk according to progestin? (2/2)

- French population-based case-control study (n=1,555)

	Any duration		Duration < 4 years		Duration ≥ 4 years	
	OR	95% CI	OR	95% CI	OR	95% CI
Never HT use	1	Ref.	1	Ref.	1	Ref.
E+natural P	0.80	0.44-1.43	0.69	0.29-1.68	0.79	0.37-1.71
E+Progesterone Der.	1.57	0.99-2.49	1.02	0.40-2.58	1.92*	1.13-3.27
E+Testosterone Der.	3.35*	1.07-10.4	1.64	0.38-7.15	9.47*	1.09-82.6
Tibolone	2.42	0.96-6.10	2.04	0.59-7.07	3.09	0.79-12.0
Continuous	2.52	0.77-8.32	2.41	0.36-16.1	2.70	0.60-12.2
Sequential	1.75*	1.09-2.79	1.40	0.54-3.65	2.00*	1.18-3.41

Cordina-Duverger E, PLOS one, 2013

Tibolone – Cochrane review

Comparison with placebo

- Women with no Hx of breast cancer (OR 0.52, 95% CI 0.21-1.25): four RCTs, 5500 women
- Women with Hx of breast cancer: increased risk of recurrence (OR 1.5, 95% CI 1.21-1.85): 2 RCTs, 3165 women

Comparison with EPT

- Breast cancer OR 1.69, 95% CI 0.78-3.67; five RCTs, 4835 women

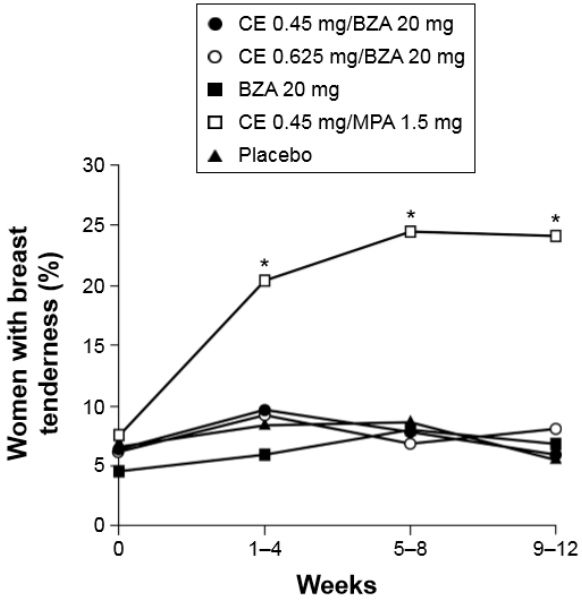
Cochrane review, 2016, Iss 10.Art No: CD008536.

TSEC (Tissue Selective Estrogen Complex)

- Pooled analysis of 5 RCTs with CEE 0.625 or 0.45mg/bazedoxifene 20mg (n=1583 and n=1585) and placebo (n=1241): RR 1.1 (95% CI, 0.3–3.8) with CE 0.45 mg/BZA 20 mg compared with placebo
- The longest SMART trials were 2 years, so longer term safety remains to be confirmed.

Mirkin S, J Womens Health, 2016

- BZA 20mg/CEE 0.45mg or 0.625mg demonstrated no increase of breast pain/tenderness compared with placebo
- No increase in mammographic density compared with placebo
- BZA/CE showed significantly lower incidence of breast pain that CE 0.45mg/MPA 1.5mg



Mirkin S, Int J Womens Health, 2013

Body Weight

Obesity and breast cancer -WHI

- 67,142 postmenopausal women age 50 to 79 yrs
- 3,388 breast cancer observed for 13 yrs F/U

Category BMI (kg/m^2)	Overweight 25 to <30	Obese, Gr I 30 to <35	Obese, Gr II+III ≥35
HR (95% CI)	1.17 (1.06-1.29)	1.37 (1.23-1.53)	1.58 (1.40-1.79)

- Obesity Gr II + III
  - larger tumor size (HR,2.12; 95%CI,1.67-2.69; P = .02),
  - positive lymph nodes (HR,1.89; 95%CI,1.46-2.45; P = .06),
  - regional and/or distant stage (HR,1.94; 95%CI, 1.52-2.47; P = .05),
  - death after breast cancer (HR,2.11; 95%CI,1.57-2.84; P < .001).
- Women with a baseline BMI < 25.0 who gained more than 5% of bodyweight over the follow-up period had an increased breast cancer risk (HR,1.36;95%CI,1.1-1.65),
- Women already overweight or obese: no association of weight change (gain or loss)
- No effect modification of the BMI-breast cancer relationship by postmenopausal HT

Neuhouser ML, JAMA Oncol, 2015

BWt and HT on breast cancer risk

- Breast cancer risk after HT appears to affect mainly lean postmenopausal women with dense breast starting HT soon after MP

Hou N, J Natil Cancer Inst, 2013

- Obese women or women starting HT after an interval 3-5 years have a lower excess HT-associated risk, although the baseline risk of obese women is higher compared to lean women.

Chlebowski RT, J Natl Cancer Instr, 2013

- Women with natural MP and BMI < 25kg/m^2
  - Ever use of HT: breast cancer OR=1.95, 95% CI 0.32-2.88
  - Significant association for ER+, ER+PR+, luminal cancer subtype
- Women with natural MP and BMI ≥ 25kg/m^2
  - No association with breast cancer or subtypes
- Interaction tests for modifying effect of BMI was statistically significant

Cui Y, Clin Cancer Res, 2014

Breast cancer and menopausal hormone therapy

Breast cancer diagnosed during hormone therapy

Menopause: The Journal of The North American Menopause Society
Vol. 23, No. 11, pp. 1199-1203
DOI: 10.1097/GME.0000000000000698

Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study

Tomi S. Mikkola, MD, PhD,[1,2] Hanna Savolainen-Peltonen, MD, PhD,[1,2] Pauliina Tuomikoski, MD, PhD,[1] Fabian Hoti, PhD,[3] Pia Vattulainen, MSc,[3] Mika Gissler, M.SocSci, PhD,[4] and Olavi Ylikorkala, MD, PhD[1]

Lifestyle influences on the association between pre-diagnostic hormone replacement therapy and breast cancer prognosis—Results from The Danish 'Diet, Cancer and Health' prospective cohort

Marianne Holm[a,*], Anja Olsen[a], Niels Kroman[b], Anne Tjønneland[a]

[a] *Unit of Diet, Genes, and Environment, Danish Cancer Society Research Center, Denmark*
[b] *Department of Breast Surgery and Danish Breast Cancer Cooperative Group, Rigshospitalet, University of Copenhagen, Denmark*

Conclusions: HRT use at enrolment was associated with breast tumours of smaller size at the time of diagnosis and positive receptor status, and with a lower BC mortality. The found association between vitamin D from supplements and higher BC mortality warrants further exploration.

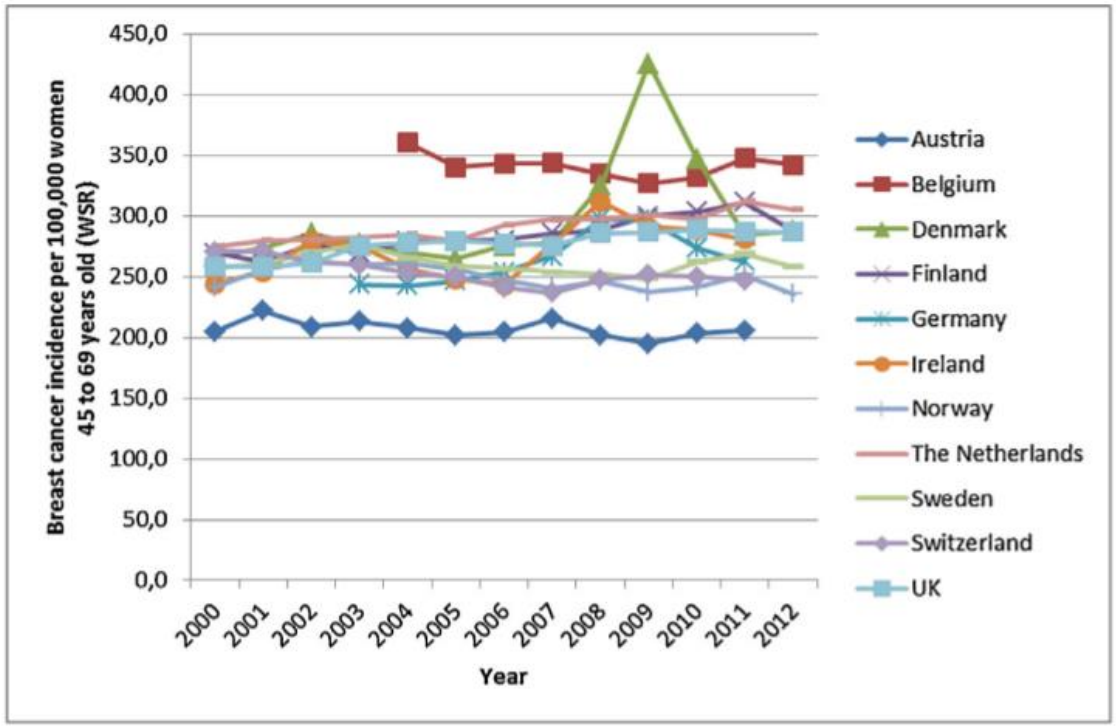
Maturitas 79 (2014) 442–448

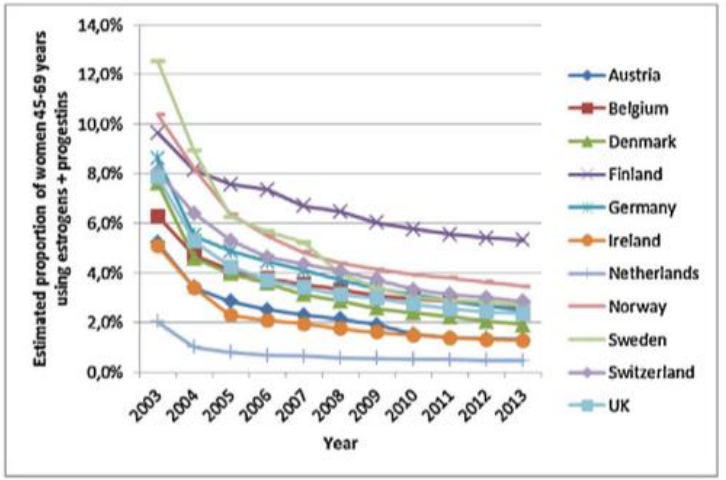
After stopping hormone therapy – E3N cohort

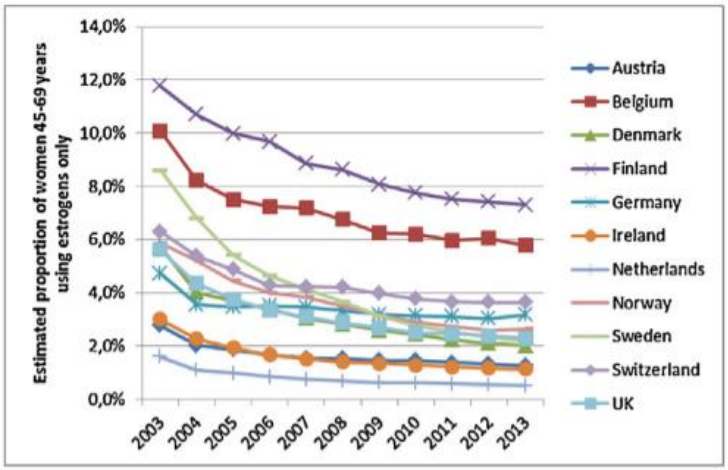
Time since last use	ET ≤ 5 years of use		ET > 5 years of use	
	HR	95% CI	HR	95% CI
Current use	1.11	0.89-1.38	1.22	0.96-1.54
3mon-5yrs since last use	1.10	0.91-1.33	0.79	0.46-1.34
5-10yrs since last use	1.11	0.92-1.33	1.54	0.92-2.57
>10yrs since last use	0.92	0.74-1.15	1.81	1.02-3.22
	E+Progesterone/dydrogesterone ≤ 5 years of use		E+Progesterone/dydrogesterone > 5 years of use	
Current use	1.13	0.99-1.29	1.31	1.15-1.48
3mon-5yrs since last use	0.96	0.82-1.12	1.15	0.93-1.42
5-10yrs since last use	0.85	0.71-1.01	1.08	0.80-1.46
>10yrs since last use	1.14	0.91-1.44	0.98	0.46-2.06
	E+Other progestogen ≤ 5 years of use		E+Other progestogen > 5 years of use	
Current use	1.70	1.51-1.91	2.02	1.81-2.26
3mon-5yrs since last use	1.08	0.92-1.25	1.36	1.13-1.64
5-10yrs since last use	1.13	0.97-1.31	1.34	1.04-1.73
>10yrs since last use	0.87	0.68-1.10	1.52	0.87-2.63

Fournier A, Breast Cancer Res Treat, 2014

Breast cancer incidence after WHI







Antonie C, Maturitas, 2016

Thank you for your attention

Management of non-oncologic issues for breast cancer survivors