

Hormone therapy and cancer risks

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HT and breast cancer: meta-analyses

| Authors | Articles | RR | CI |
|---------------------|----------|------|-----------|
| Armstrong, 1988 | 12 | 0.96 | 0.89–1.05 |
| Dupont, 1991 | 31 | 1.07 | 1–1.12 |
| Steinberg, 1991 | 34 | 1.30 | 1.2–1.6 |
| Grady, 1992 | 30 | 1.01 | 0.97–1.05 |
| Sillero, 1992 | 27 | 1.06 | 1–1.12 |
| Colditz, 1993 | 31 | 1.02 | 0.93–1.12 |
| Collaborative, 1997 | 51 | 1.14 | ± 0.031 |

HT and breast cancer: meta-analysis, CGHFBC

- 51 studies conducted in 21 countries
- 52,705 breast cancer patients versus 108,411 control women, but after exclusion of pre- or perimenopausal women
- 17,949 cases versus 35,916 controls
- A slight significant increase in the risk of diagnosing a breast cancer: RR = 1.14

Lancet 1997;350:1047–59

HT and breast cancer: meta-analysis, CGHFBC

- The risk varies according to duration of use but remains low: RR = 1.31 after 5–9 years and RR = 1.24 after 10–14 years of treatment
- The elevation in the risk disappears after cessation of HT
- In the event of HT, two additional breast cancers are observed after 5 years of use (0.2%), six after 10 years (0.6%) and 12 after 15 years (1.2%)
- The diagnoses of cancers in patients on HT are made at an earlier stage

Lancet 1997;350:1047–59

HT and breast cancer: randomized study, HERS

- Heart and Estrogen/progestin Replacement Study research group
- 2763 menopausal women with a coronary heart disease
- 0.625 mg conjugated equine estrogens + 2.5 mg MPA versus placebo
- RR = 1.30 (CI: 0.77–2.19)

JAMA 1998;280:605–13

HT and breast cancer: randomized study, HERS

- HERS I + II: 6.8 years of follow-up
 - breast cancer: 1.27 (0.84–1.94)
 - colon cancer: 0.81 (0.46–1.45)
 - lung cancer: 1.39 (0.84–2.28)
 - endometrial cancer: 0.25 (0.05–1.18)
 - other cancers: 1.29 (0.87–1.92)
 - all cancers: 1.19 (0.95–1.50)

JAMA 2002;288:58–66

HT and breast cancer: randomized study, PEPI

- PEPI: a double-blind randomized study
- 875 women randomized between placebo, 0.625 mg CEE, or CEE + MPA, or CEE + micronized progesterone
- No difference in the risk of emergence of breast cancer ($p = 0.29$)

JAMA 1995;273:199-208

HT and breast cancer: randomized study, WEST

- Estrogens alone (1 mg 17 β -estradiol versus placebo in 664 patients having had a stroke)
- Follow-up: 2.8 years
- RR = 1.0 (CI: 0.30-3.50)
- Two endometrial cancers versus none

N Engl J Med 2001;345:1243-9

HT and breast cancer: randomized study, WHI

- 16,608 menopausal women aged 50-79 years (average: 63 years) randomized between a placebo and a combination of 0.625 mg CEE + 2.5 mg MPA
- Minimum follow-up: 3.5 years, maximum: 8.5 years (median 5.2 years)
- About 15 years after menopause
- Prior HT use: 26%

JAMA 2002;288:321-33

HT and breast cancer: randomized study, WHI

- Hazard ratio = 1.26 (CI: 1.00-1.59), 166 cases versus 124
- Eight additional breast cancers per 10,000 treated person-years
- No difference regarding cancers *in situ*
- No increased risk if a family history of breast cancer
- Same monitoring rate by mammography in the two groups
- No difference reported in mortality

JAMA 2002;288:321-33

WHI: Breast cancer and risk according to duration of HT use

- Increased risk of breast cancer in the event of prior use of HT
 - no prior use (114/102), HR = 1.06 (CI: 0.81-1.38) after 3-7 years of use
 - < 5 years (32/15), HR = 2.13 (1.15-3.94) after 4-11 years of use
 - 5-10 years (11/2), HR = 4.61 (1.01-21.02) after 8-16 years of use
 - > 10 years (9/5), HR = 1.8 (0.60-5.43) after 13-17 years of use

JAMA 2002;288:321-33

WHI: breast cancer and duration of HT use

| Duration (years) | CEE + MPA | Placebo | Ratio |
|------------------|-----------|---------|-------|
| 1 | 11 | 17 | 0.62 |
| 2 | 26 | 30 | 0.83 |
| 3 | 28 | 23 | 1.16 |
| 4 | 40 | 22 | 1.73 |
| 5 | 34 | 12 | 2.64 |
| ≥ 6 | 27 | 20 | 1.12 |

WHI: HT and cancers (n = 16,608)

| Cancers | CEE + MPA | Placebo | Hazard ratio (CI) |
|-------------|-----------|---------|-------------------|
| All | 502 | 458 | 1.03 (0.90–1.17) |
| Breast | 166 | 124 | 1.26 (1–1.59) |
| Endometrium | 22 | 25 | 0.83 (0.47–1.47) |
| Colon | 45 | 67 | 0.63 (0.43–0.92) |

JAMA 2002;288:321–33

WHI: other results

- Coronary heart disease: HR = 1.29 (CI: 1.02–1.63)
- Stroke: HR = 1.41 (1.07–1.85)
- Pulmonary embolism: HR = 2.13 (1.39–3.25)
- Femoral neck fracture: HR = 0.66 (0.45–0.98)
- Total mortality: HR = 0.98 (0.82–1.18)
- Global risk–benefit index: 1.15 (1.03–1.28)

JAMA 2002;288:321–33

Sequential or continuous treatments?

| Studies | Sequential | Continuous |
|-----------------|------------------|------------------|
| Porch, 2002 | 1.04 (0.74–1.46) | 1.82 (1.34–2.48) |
| Weiss, 2002 | 0.98 (0.74–1.30) | 1.45 (1.09–1.91) |
| Olsson, 2003 | 1.44 (0.67–3.08) | 3.13 (1.70–5.75) |
| Ross, 2000 | 1.38 (1.13–1.68) | 1.09 (0.88–1.35) |
| Magnusson, 1999 | 1.03 (0.94–1.13) | 1.19 (1.09–1.31) |
| Newcomb, 2002 | 1.57 (0.95–2.60) | 1.54 (1.15–2.07) |

Relative risk and 'attributable' risk

- Risk of developing a breast cancer after 10 years of HT use increased by 23%
- In the USA, the risk of developing a breast cancer for a woman aged 50, not on HT for a period of 10 years, is 2.52 per 100 women
- Thus, the excess risk is 0.58 per 100 women, which is the attributable risk

HT and risk of breast cancer

- The absolute risk in the event of HT use for 10 years is $1.23 \times 2.52 = 3.1$ per 100 women
- The odds that a woman aged 50 not on HT and followed up for 10 years will not develop a breast cancer are 97.5%
- In the event of HT use, the odds are 96.8%

Breast cancer, mortality and HT Schaier's trial

- 2614 patients with breast cancer diagnosed between 1973 and 1981
- Reduced mortality in users under treatment at the time of diagnosis:
RR = 0.5 (0.3–0.8) for node-negative and
RR = 0.5 (0.3–0.8) for node-positive cancers
- This effect wears off in time (after 10 years for node-negative and 4 years for node-positive)

JNCJ 1999;91:264–70

Breast cancer, mortality and HT

Willis' study

- Prospective study: 422,373 followed-up women, 1469 breast cancers observed
- Reduction in mortality from breast cancer in women treated with estrogens, RR = 0.84 (0.75–0.94)
- The benefit is even more marked in women who reach menopause before 40 years, RR = 0.59

Cancer Causes and Control 1996;7:449–57

Breast cancer and mortality

Jernström's study

- 984 Swedish breast cancer patients
- Reduced mortality with HT use: RR = 0.73 (0.62–0.87), $p = 0.0005$
- Reduction confirmed by adjusting the results for the stage, the year of diagnosis and the patient's age at the time of diagnosis: RR = 0.78 (0.65–0.93), $p = 0.006$
- This reduction is observed no matter what the hormone receptor status might be and how the diagnosis was made
- In women aged 45–60 in whom breast cancer is the leading cause of mortality, HT reduces risk by 22.5%, which corresponds to the reduction in mortality observed with mass screening

Br J Cancer 1999;80:1453–58

Summary of studies on breast cancer, mortality and HT

| Studies | Year | RR | CI |
|-----------|------|------|-----------|
| Grodstein | 1997 | 0.76 | 0.56–1.02 |
| Willis | 1996 | 0.84 | 0.75–0.94 |
| Sellers | 1997 | 1.07 | 0.69–1.65 |
| Paganini | 1994 | 0.86 | 0.58–1.30 |
| Sourander | 1998 | 1.77 | 0.6–5.21 |
| Sturgeon | 1995 | 0.7 | 0.5–1 |

Summary of studies on breast cancer, mortality and HT

| Studies | Year | RR | CI |
|-----------|------|------|-----------|
| Ettinger | 1996 | 1.89 | 0.43–8.36 |
| Persson | 1996 | 0.5 | 0.4–0.6 |
| Hunt | 1996 | 0.5 | 0.4–0.6 |
| Vakill | 1983 | 0.48 | 0.13–1.22 |
| Schairer | 1999 | 0.5 | 0.3–0.8 |
| Jernström | 1999 | 0.73 | 0.62–0.87 |

Breast cancer, mortality and HT

- 20–30% overall reduction in mortality
- Reduction related to
 - the profile of treated patients?
 - a surveillance bias
 - a biological effect of estrogens on the tumor
 - estrogens might be the first SERMs
 - promoting effect but 'anti-metastasizing' effect?

Effects of estrogens on the tumor

- Promotion of slow-growing tumors
 - fewer mitotic cells (Squiterri)
 - more grade 1 and lobular cancers (Bonnier)
 - more ER+, PR+ tumors (Potter)
 - more less bulky tumors without nodal involvement and less aneuploid (Magnusson)

Conclusions

- This study confirms the probable promoting effect of HT on some pre-existing breast cancers
- The reported relative risk is very low; HT erases the protective effect of menopause
- Bearing in mind that we lack proper perspectives, it is noteworthy that no increased risk is reported for other cancers but a reduction is noted for colon cancer
- No difference in mortality
- What is one to make of this combination? What is the role of progestins?