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Current Perspective

Hormone replacement therapy and the risk of breast cancer

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ABSTRACT

Hormone replacement therapy (HRT) has had a chequered history ever since its initial use to manage menopausal symptoms. It is clear that it has many other effects and here we review its impact on the risk of breast cancer. A clear risk is seen for current uses of combined oestrogen/progestagen pills, but this returns to normal shortly after treatment cessation. The role of oestrogen only replacement therapy is less clear, but most studies find a weaker, but still positive, association in current users.

Recent sharp reductions in HRT use have been correlated with declines in breast cancer incidence in the USA, but not so clearly elsewhere.

1. Background

Hormone replacement therapy (HRT) was introduced in the 1930s as a treatment for vasomotor symptoms associated with the menopause shortly after the isolation of oestrogen from urine in 1929 independently by Edward Doisy and Adolf Butenankt. In 1942 the FDA licensed Premarin which consisted of conjugated equine oestrogens extracted from mare's urine.[1] Early reports[2,3] indicated that it was associated with a large increase of endometrial cancer (5-fold), and led to the addition of a progestagen, which controlled this problem. Increases in venous thromboembolic events (VTEs) were also noted, but reports of benefits for heart disease, bone, and general well-being led proponents to hail HRT as making a woman not only feel better and be 'forever feminine', but also to live longer, and in the 1970s its use was extended from the 1–2 years typical for control of menopausal symptoms to 5–10 years or longer to achieve this panoply of putative benefits. The first reports of an increase of the risk of breast cancer came in 1976 from Hoover et al.[4] Early reports suggested that the risk was highest in users of oestrogen only preparations[5] and that addition of a progestagen might actually protect against breast cancer.[6] This was followed by the much larger and influential report from the Nurses Health study[7] which found an increased risk both for oestrogen only replacement therapy (RR = 1.32, 95% CI (1.14–1.61)) and oestrogen plus progestagen replacement therapy (RR = 1.41, 95% CI (1.15–1.74)). Subsequently, a comprehensive overview of all the available case-control and cohort data from 51 studies, involving 17,949 women who developed breast cancer and 35,916 controls who did not have breast cancer, was published.[8] The main findings of this study were that risk was confined to current and recent use of HRT (Fig. 1), and within the group of current/recent users, risk increased with duration of use and reached a 56% relative increase after more than 15 years of use. For current/recent users, the excess relative risk was estimated at 2.3% per year of use, leading to an excess absolute lifetime risk of 2/1000 for 5 years of use. It was

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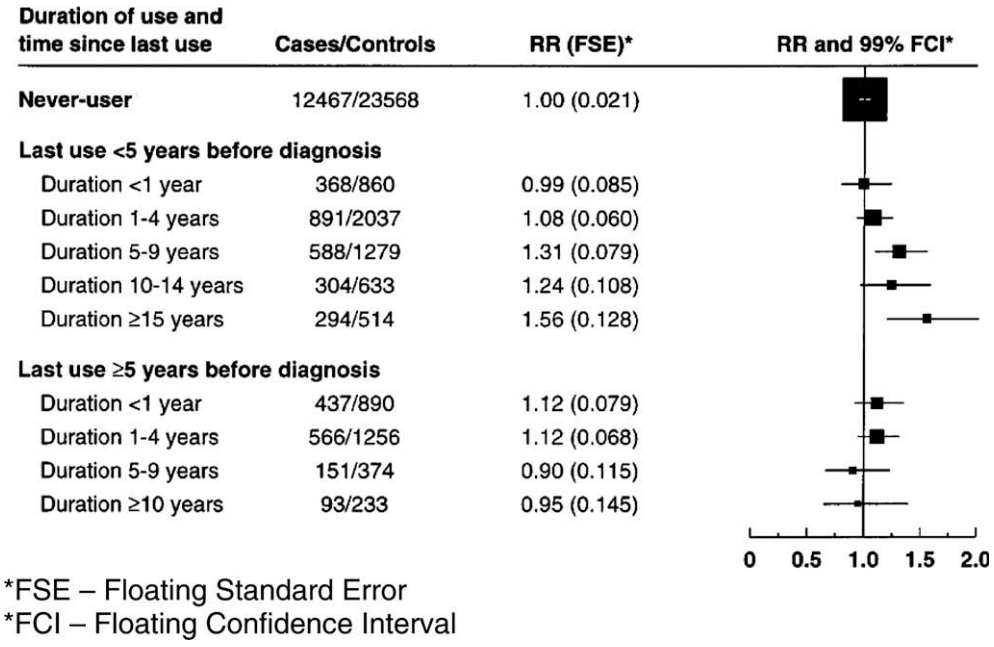

Fig. 1 – Relative risk (RR) of breast cancer according to duration of use within categories of time since last use of HRT [from: Collaborative Group on Hormonal Factors in Breast Cancer[8]].

also noted that the cancers found were more likely to be localised and have a good prognosis, and that there was little, if any, increase in risk for obese women. Here, the higher level of endogenous oestrogen associated with greater adipose tissue had already increased the risk of post-menopausal breast cancer,[9] so that there was less scope for further increases with HRT. Holli et al.[10] also confirmed a preponderance of good prognosis oestrogen receptor positive tumour in HRT users.

The next two major reports appeared at about the same time in 2002/3 and had slightly dissimilar findings. We will first review a large cohort study known as the Million Women Study,[11] and then consider two randomised trials conducted as part of the Women's Health Initiative.[12,13]

2. Million Women Study

In 1996, an Oxford-based group began collecting risk factor and follow up data (after informed consent) from women in the United Kingdom aged 50–64 who attended breast screening as part of the national programme. Details of HRT use were collected at entry and by 2001 the cohort had reached a size of 1,084,110 women. The initial results were reported in 2003[11] after a 2.6 year median follow up, at which time 6096 breast cancers had been recorded. Because of the prospective nature of the risk factor collection and the short follow up, the data were particularly useful for assessing recency of use. No excess of breast cancer was found in previous HRT users (RR = 1.01, 95% CI [0.95–1.08]), and this was true even for women who had stopped using HRT 1–5 years prior to cohort entry (RR = 1.04, 95% CI [0.95–1.12]), but a clear excess was seen in current users (Fig. 2). This was much larger for current users of combined oestrogen/progestagen preparations where the risk was 2-fold (RR = 2.00, 95% CI [1.91–2.09], but a clearly significant, although smaller, 30% risk was seen for current users of oestrogen only preparations (RR = 1.30, 95% CI [1.22–1.38]).

The risk of breast cancer for current users of combined formulations was duration dependent, ranging from a 45% relative increase for less than 1 year of use to a 131% relative increase for more than 10 years of use, with excess relative risks of 74% for 1–4 years use, and 117% for 5–10 years use. The excess lifetime absolute risk for 5 years of use of combined preparations was estimated at 6/1000, compared to 1.5/1000 for oestrogen only therapy. This study also found that the risk for lobular and tubular cancers, which generally have a good prognosis, was greater than for ductal cancers.[14] However, this was the first report to clearly establish that fatal breast cancer was also increased in current users (RR = 1.22, 95% CI [1.05–1.41]).

A more controversial finding was a 45% increased risk in current users of tibolone and a similar effect for other non-oestrogen based preparations (mostly progestagens only) (Fig. 2). The tibolone finding led to much debate and may have reflected the fact that this preparation is rarely used in the UK ,[15] and was probably more commonly used among women at increased risk of breast cancer, as it was thought not to have the breast cancer risk associated with oestrogen based replacement therapy.[16,17]

A recent trial (LIFT) confirmed a strikingly 70% lower risk of breast cancer, but also a doubling of strokes, leading to withdrawal of this compound.[18,19] This also led to the early closure of the LIBERATE trial in women with breast cancer.[20]

3. Women's Health Initiative

The Women's Health Initiative was a series of trials which began in 1993 to examine the effects of diet (fat reduction), hor-

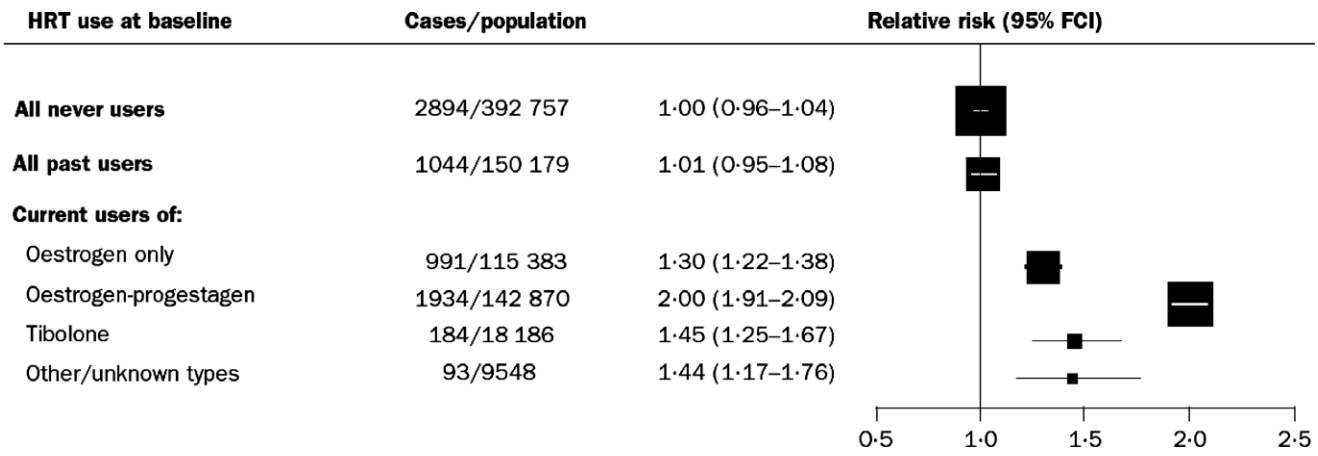

Fig. 2 – Relative risk of breast cancer in relation to recency and type of HRT used [from Beral V[11]].

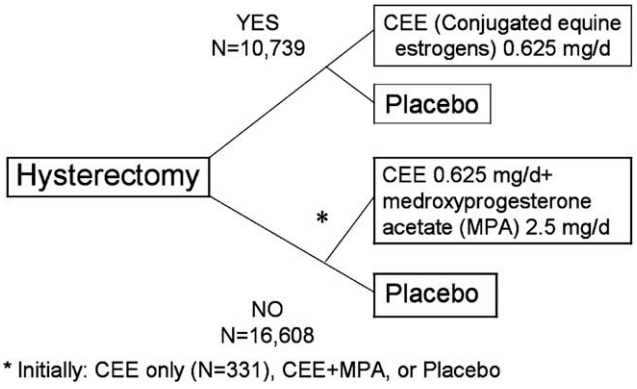

Fig. 3 – Women's Health Initiative Hormone - Design of two randomised trials in post-menopausal women [from: Writing Group for the Women's Health Initiative Investigators;[24] Chlebowski RT et al.[12]].

mone replacement therapy, and vitamin D and calcium on a range of health outcomes. Two trials involved HRT – one with oestrogen alone in hysterectomised women, and one evaluating combined preparations for women with an intact uterus (Fig. 3). These trials were not aimed at controlling menopausal symptoms, but entered women aged 50–79, with a view towards influencing a 'global health index', which included effects on coronary heart disease, breast cancer, fractures, stroke, pulmonary embolism, colorectal cancer and endometrial cancer (combined HRT only), as well as all cause mortality. Although the mean age of 63 years was higher than for symptomatic use, there was a broad spectrum of ages with about one-third of the women aged 50–59 years. The combined oestrogen plus progestagen HRT trial was stopped early in July 2002 after 5.6 years of follow up, when the global index became significantly inferior for the treated group. The oestrogen only trial also failed to show a global benefit (Table 1). However, an interesting difference between trials was seen for breast cancer risk (Fig. 4). Overall breast cancer risk was increased by 24% in the combined treatment trial (HR = 1.24, 95% CI [1.01–1.54], $P = 0.003$) whereas it was non-significantly decreased in the oestrogen only trial (HR = 0.78, 95% CI [0.60–1.01], $P = 0.06$). For the combined preparations the risk was similar across age groups[12] and increased with duration of use and was most apparent in women who had used HRT previously before entry into the trial (Table 2). The reduced risk for users of oestrogen only preparations was only seen in women who has not previously used HRT (HR = 0.61, 95% CI [0.43–0.85]).[13]

Abnormal mammograms at the 1 year follow up were almost twice as common in the combined HRT group versus

Table 1 – Women's Health Initiative - Clinical outcome hazard ratios (HR) for combined oestrogen/progestagen replacement therapy versus placebo

	Combined Oestrogen/Progestagen HR (95% CI)	Oestrogen only HR (95% CI)
CHD	1.29 (1.02–1.63)	0.91 (0.75–1.12)
Stroke	1.41 (1.07–1.85)	1.39 (0.10–1.77)
Pulmonary Embolism	2.13 (1.39–3.25)	1.34 (0.87–2.06)
Invasive Breast Cancer	1.26 (1.00–1.59)	0.77 (0.59–1.01)
Endometrial Cancer	0.83 (0.47–1.47)	1.08 (0.75–1.55)
Colorectal Cancer	0.63 (0.43–0.92)	0.61 (0.41–0.91)
Hip Fracture	0.66 (0.45–0.98)	1.08 (0.88–1.32)
Global Index	1.15 (1.03–1.28)	1.01 (0.91–1.12)
Dementia	2.05 (1.21–3.48)	1.49 (0.83–2.66)

From: Writing Group for the Women's Health Initiative Investigators;[24] The Women's Health Initiative Steering Committee;[25] Shumaker et al.[26]

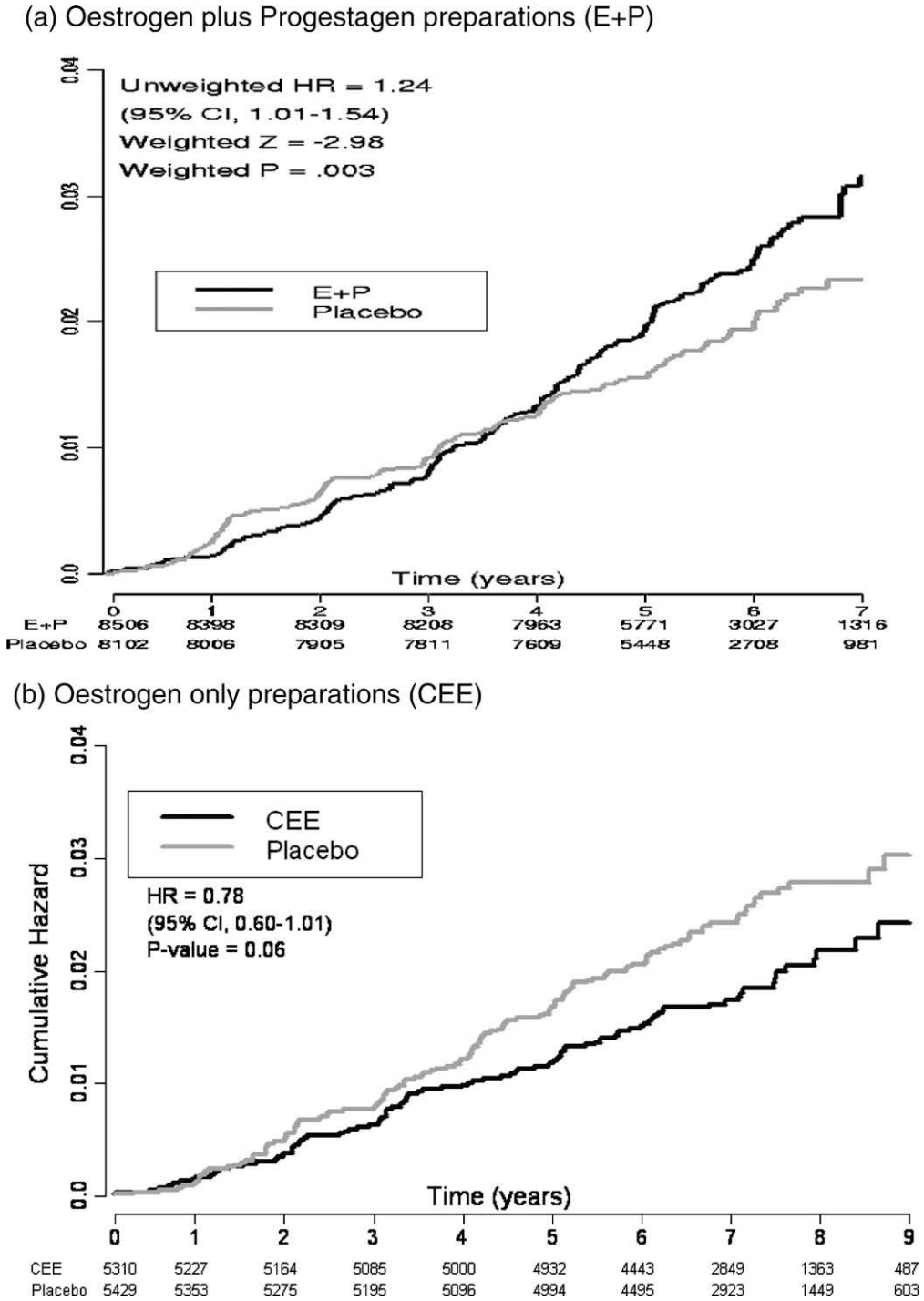

Fig. 4 – Kaplan–Meier plots for risk of invasive breast cancer in the two Women's Health Initiative trials of hormone replacement therapy [from: Writing Group for the Women's Health Initiative Investigators;[24] Chlebowski RT et al.[12]].

placebo (9.4% versus 5.4%, $P < 0.0001$). Somewhat surprisingly, tumours in the HRT arm were larger (mean 1.7 versus 1.5 cm, $P = 0.04$) and more often node positive (25.9% versus 15.8%, $P = 0.03$), but histology and tumour grade were similar to the placebo group.[12] Similar findings were reported for the oestrogen only trial.[20] Neither trial reported a greater proportion of oestrogen receptor positive tumours in the HRT arms as seen in previous studies.

4. National trends

Announcement of the Women's Health Initiative result led to a rapid 38% reduction in HRT in the USA from 2001 to 2004. Assuming that the effect of HRT on breast cancer occurs only in current users, a rapid fall in breast cancer might be expected. This indeed was the case, and oestrogen receptor positive tumours in women aged 50–69 were decreased

Table 2 – Influence of oestrogen/progestagen HRT on hazard ratios for breast cancer compared to controls and 95% confidence intervals by year on study and prior HRT use

	Prior hormone therapy (HT) use	
Year	No	Yes
1	0.48 (0.19, 1.20)	0.90 (0.26, 3.15)
2	0.65 (0.34, 1.25)	1.10 (0.47, 2.61)
3	0.96 (0.51, 1.82)	3.09 (0.84, 11.27)
4	1.45 (0.85, 2.45)	2.16 (0.66, 7.05)
5	1.61 (0.88, 2.94)	3.56 (1.18, 10.73)

From: Chlebowski et al.[12]

by 14.7%, with no effect on oestrogen receptor negative tumours.[21]

5. Use in women with breast cancer

The HABITS trial of 447 women randomly assigned to HRT or not was stopped early after an interim finding indicating a more than doubling of recurrences (HR = 2.4, 95% CI 1.3–4.2).[22] This led to the discontinuation of other trials in this population, despite no evidence of an increase in the Stockholm trial of similar size[23] where the hazard ratio was 0.82 (95% CI 0.35–1.9).

6. Conclusions

HRT has experienced two peaks of popularity followed by equally strong negative sentiments. It is now clear that combined oestrogen/progestagen preparations significantly increase the risk of breast cancer in current users, but the excess risk vanishes soon after cessation of therapy. Use of oestrogen only preparations carries a much lower risk, but the preponderance of evidence still suggests some excess, although one randomised trial found a slight but non-significant decrease in risk. There are other risks associated with HRT use and the bisphosphonates are better drugs for preventing osteoporosis. Thus, HRT use is best limited to its original indication of providing relief for symptoms of the climacteric, and long term use for cardiovascular benefits, or maintenance of bone density is no longer appropriate. Use in women with breast cancer probably carries an even higher risk, and should be limited to the shortest duration and lowest dose necessary to control menopausal symptoms.

Conflict of Interest

None declared.

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