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Review Article

Risks and Benefits of HRT Versus ERT in Order to Separate HRT from ERT

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Abstract

Aim: While the benefits of Hormone Replace Therapy (HRT) and Estrogen Replace Therapy (ERT) might overlap, their risks have to be separated particularly with regard to breast cancer. The risks of HRT are mainly Coronary Heart Disease (CHD) and Breast cancer. The main risk of ERT is the incidence of strokes which can be avoided by not using an oral estrogen but an Intra-uterine contraceptive but reducing the risk of endometrial cancer in women with a womb.

Methods: Studies that randomized peri-menopausal and menopausal women to either HRT or ERT versus placebo and one study that included similar women followed up prospectively for the incidence of the development of Alzheimer's Dementia (AD).

Results: The significant risks of HRT included CHD, stroke and pulmonary embolism. The risk of breast cancer only really existed after long term follow-up [(annualized incidence, 0.45% vs 0.36%; Hazard Ratio (HR) 1.28)]. The significant risks of ERT only included strokes. There was a lower risk of breast cancer in the long term [HR 0.77, 95% CI 0.62–0.95; p=0.02].

Conclusions: In women with a uterus, where HRT instead of ERT is mandated, the oral progestogen of HRT can be replaced by intrauterine device loaded with a Progestogen. Similarly, the oral Estrogen of HRT and ERT can be replaced by Estrogen sources like the patch, gel or implants that bypass the liver and bypass potential problems like strokes and pulmonary embolism.

Introduction

The risk of Breast cancer with combined oral Estrogen and Progestogen (HRT) has been shown by observational studies like the Collaborative Re-analysis Study (CR study, 1997)[1] and the Million Women Study (MWS, 2003).[2] Although these have been shown to be flawed[3-4] to show a cause and effect relationship that HRT causes breast cancer, the Women's Health Initiative Studies, point in the short term Roussouw[5] and in the long term Chlebowski[6] confirm the higher risk of breast cancer. However, it does not seem that the same higher risk is associated with Estrogen alone (ERT). In a randomized controlled trial against placebo, Anderson[7] in the short term and, Chlebowski[6] and Anderson[6,8] in the long-term showed that, compared to placebo, ERT was associated with a lower risk of breast cancer incidence and mortality. This manuscript clearly outlines the valid differences in risks and benefits between HRT (Estrogen plus Progestogen) and ERT (Estrogen alone) for peri-menopausal and menopausal women based on randomized controlled studies which are the main studies that reliably determine cause and effect relationships between use of HRT or ERT and severe diseases such breast cancer, coronary heart disease (CHD), strokes, depression, migraines, bowel cancer and hip fracture. It also highlights the options for women with a uterus with evidence from oral or intrauterine progestogen supplements or hysterectomy.

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Methods

The literature was searched for randomized controlled studies and prospective cohort studies that looked at peri-menopausal and menopausal women who had been prospectively followed up after HRT versus placebo or ERT versus Placebo. In a critical cause and effect analysis of the randomized trial evidence, Shapiro[9] showed that the report by Anderson[7] which examined the cause (ERT) and effect (Breast cancer) relationship satisfactorily met the parameters for a valid study. The evidence from the clinical trial suggests that unopposed estrogen does not increase the risk of breast cancer, and may even reduce it. The latter possibility, however, is based on statistically borderline evidence. Shapiro[10] similarly subjected the HRT randomized controlled trial[5] to critical cause and effect analysis. They concluded that HRT may or may not increase the risk of breast cancer, but the WHI did not establish that it does, supporting a potential lower risk of breast cancer. The evidence for Alzheimer's dementia (AD) was collected from the next best level of evidence, from prospective cohort studies.[11,12]

Results

Roussouw[5] reported on the HRT component of the Women's Health Initiative, a randomized controlled primary prevention trial in which 16,608 post-menopausal women aged 50-79 years with an intact uterus were recruited at 40 US Clinical centers between 1993-1998. Participants received 0.625mg/day conjugated equine estrogens plus 2.5mg/day medroxyprogesterone acetate, in 1 tablet (n=8506) or placebo (n=8102). After a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of HRT vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the Global index statistic supported risks exceeding benefits. This report included data on the major clinical outcomes through 2002. The estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: Coronary Heart Disease, 1.29 (1.02-1.63) with 286 cases; Breast cancer, 1.26 (1.00-1.59) with 290 cases; Stroke, 1.41 (1.07-1.85) with 212 cases; Pulmonary embolism (PE), 2.13 (1.39-3.25) with 101 cases; Colorectal cancer, 0.63 (0.43-0.92) with 112 cases; Endometrial cancer, 0.83 (0.47-1.47) with 47 cases; Hip fracture, 0.66 (0.45-0.98) with 106 cases and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the Global index. Absolute excess risks per 10,000 person-years attributable to HRT were 7 more CHD events, 8 more Strokes, 8 more PEs, and 8 more Invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer Colorectal cancers and 5 Fewer hip fractures. The absolute excess risk of events included in the Global index was 19 per 10,000 person-years.

Anderson[7] reported on post-menopausal women who were randomized, into a double-blind, placebo-controlled disease prevention trial (the ERT component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. They enrolled 10,739 post-menopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity. The women were randomly assigned to receive either 0.625mg/day of conjugated equine estrogen (CEE) or placebo. After an average follow-up of 6.8 years, the intervention phase of the trial was ended early. The estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major available clinical outcomes were: CHD, 0.91 (0.75-1.12) with 376 cases; Breast cancer, 0.77 (0.59-1.01) with 218 cases; Stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; Colorectal cancer, 1.08 (0.75-1.55) with 119 cases and Hip fracture, 0.61 (0.41-0.91) with102 cases. Corresponding results for composite outcomes were: Total cardiovascular disease,1.12 (1.01-1.24); Total cancer, 0.93 (0.81-1.07); Total fractures, 0.70 (0.63-0.79); Total mortality, 1.04 (0.88-1.22) and the Global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years. The estimated excess risk for all monitored events in the global index was a non-significant 2 events per 10,000 person-years.

Anderson[7] therefore concluded that the use of oral CEE alone increased the risk of stroke, decreased the risk of hip fracture and did not affect CHD incidence in post-menopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk required further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not at the time be recommended for chronic disease prevention in post-menopausal women.

Anderson[8] sought extended surveillance from the 9,786 living participants in active follow-up, of whom 7,645 agreed. Using data from this follow-up to 2009, they assessed long-term effects of oestrogen use on invasive breast cancer incidence, tumour characteristics and mortality, using Cox regression models to estimate hazard ratios (HR's) in the intention-to-treat population.

After a median follow-up of 11·8 years (IQR 9·1–12·9), the use of ERT for a median of 5·9 years (2·5–7·3) was associated with lower incidence of invasive breast cancer (151 cases, 0·27% per year) compared with placebo (199 cases, 0·35% per year; HR 0·77, 95% CI 0·62–0·95; p=0·02) with no difference (p=0·76) between

intervention phase (0·79, 0·61–1·02) and post-intervention phase effects (0·75, 0·51–1·09). In sub-group analyses, they noted that breast cancer risk reduction with ERT was concentrated in women without benign breast disease (p=0·01) or a family history of breast cancer (p=0·02). In the oestrogen group, fewer women died from breast cancer (six deaths, 0·009% per year) compared with controls (16 deaths, 0·024% per year; HR 0·37, 95% CI 0·13–0·91; p=0·03). Fewer women in the oestrogen group died from any cause after a breast cancer diagnosis (30 deaths, 0·046% per year) than did controls (50 deaths, 0·076%; HR 0·62, 95% CI 0·39–0·97; p=0·04).

This report by Anderson[8] reinforced their findings of 20047 that their follow-up findings provide reassurance for women with hysterectomy seeking relief of climacteric symptoms in terms of the effects of oestrogen alone use for about 5 years on breast cancer incidence and mortality. However, they conclude that their data do not support use of oestrogen for breast cancer risk reduction because any noted and benefit probably did not apply to populations at increased risk of such cancer. Chlebowski[6] in a long-term follow up of these two placebo-controlled randomized clinical trials involving 27,347 post-menopausal women with prior randomized use of ERT (CEE) compared with placebo, among women with prior hysterectomy was significantly associated with lower risk of breast cancer (annualized incidence, 0.30% vs 0.37%; HR 0.78); and breast cancer mortality (annualized mortality, 0.031% vs 0.046%; HR 0.60), whereas prior randomized use of HRT (CEE plus Medroxyprogesterone acetate (MPA), compared with placebo, among women with an intact uterus, was significantly associated with higher risk of breast cancer (annualized incidence, 0.45% vs 0.36%; HR 1.28) and no significant difference in breast cancer mortality (annualized mortality, 0.045% vs 0.035%; HR 1.35).

In a prospective cohort Cache County Investigators study, Shao[11] showed a reduced risk of Alzheimer's disease (AD) in users of hormone therapy (HT), but trials have previously suggested higher risk. We examined whether the association of HT with AD varies with timing or type of HT use. Between 1995 and 2006, the population-based Cache County Study followed 1,768 women who had provided a detailed history on age at menopause and use of HT. During this interval, 176 women developed incident AD. Cox proportional hazard models were used to evaluate the association of HT use with AD, overall and in relation to timing, duration of use, and type (opposed vs unopposed) of HT. Women who used any type of HT within 5 years of menopause had 30% less risk of AD (95% CI 0.49-0.99), especially if use was for 10 or more years. By contrast, AD risk was not reduced among those who had initiated HT 5 or more years after menopause. Instead, rates were increased among those who began "opposed" estrogen-progestin compounds within the 3 years preceding the Cache County Study baseline (adjusted hazard ratio 1.93; 95% CI 0.94-3.96). This last hazard ratio was similar to the ratio of 2.05 reported in randomized trial participants assigned to opposed HT. The group, the association of HT use and risk of AD may depend on timing of use. Although possibly beneficial if taken during a critical window near menopause, HT (especially opposed compounds) initiated in later life may be associated with increased risk. The authors concluded the relation of AD risk to timing and type of HT deserved further study.

Conclusion

The significant risks associated with HRT are well known and prominent among them are CHD, breast cancer, stroke and pulmonary embolism. The risks associated with significantly lower risk are hip fracture, combined fractures and total mortality. While the global index statistic supported risks exceeding benefits in the shorter term report,[5] the global index statistic supported reduced mortality. However, the significant benefits associated with ERT are not as well known. In 2004, Anderson[7] concluded that although oral use of CEE alone significantly increased the risk of stroke, it decreased the risk of hip fracture and did not affect CHD incidence in post-menopausal women with prior hysterectomy over an average of 6.8 years. Estrogen alone (ERT) is the hormone needed in peri-menopausal and menopausal women without a uterus provided that oral ERT is avoided because of the known risk of strokes from the effect of oral estrogens which can increase coagulation by activating estrogen receptors in the liver and thereby modulating the production of a variety of circulating coagulation factors. However, because of irregular uterine bleeding or risk of endometrial cancer, a Progestogen was always added to make the combination we call HRT. Onwude[13] showed that there was no valid evidence to support additional Progestogen in terms of endometrial cancer and, if necessary, a progestogen loaded Intra-uterine device can be a suitable alternative as the standardized incidence ratio (observed-to-expected ratio) for endometrial adenocarcinoma was 0.50 (95% CI 0.35–0.70; 34 observed compared with 68 expected cases) after the first levonorgestrel-releasing intrauterine system purchase and even lower at 0.25 (95% CI 0.05–0.73 with 3 observed compared with 12 expected cases) after two purchases.[14,15] Although the endometrium was significantly protected, Soini[14] still showed a 16% increase risk of breast cancer, when compared with the general population with this intrauterine device used as a contraceptive in women.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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