Use of hormone replacement therapy (HRT) and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases[1]. A Critique.

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Design and Methods

This paper describes two nested case control studies using data from the two largest UK primary care databases. QResearch and Clinical Practice Research Datalink (CPRD) GOLD, utilising linked data from Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality data and cancer registry data (QResearch only). From the QResearch database, all cases of incident breast cancer were identified using general practice, hospital admission, mortality, and cancer registry records. From CPRD, when linked general practice, hospital admission (up to 31 December 2017), and mortality data records (up to 13 February 2018) were used to identify cases, and, when not linked, general practice records only. HRT prescription information was extracted for all estrogens, progestogens, and tibolone from practice records.

Results

59 999 and 38 612 (98 611) cases of breast cancer were identified in QResearch and CPRD respectively, matched by age to 457 498 female controls. Compared with never use, long term use of systemic HRT (>/= 5 years) was found to be associated with an increased risk of breast cancer. The adjusted OR was 1.15 (95% CI 1.09 to 1.21) in women using estrogen and 1.79 (1.73 to 1.85) for combined estrogen and progestogen therapy. In those using combined estrogen and progestogen therapy, the increased risk was highest for norethisterone (1.88; 1.79 to 1.99) and lowest for dydrogesterone (1.24; 1.03 to 1.48). Past long term estrogen therapy and past short term combined therapy were not associated with an increased risk as opposed to past long term combined MHT usage which remained slightly increased (1.16; 1.11 to 1.21). In terms of absolute numbers this equated to 3-8 extra cases per 10 000 women years with estrogen only, and 9-36 extra cases per 10 000 women years in estrogen and progestogen users, depending on age group. No increase in risk was associated with vaginal estrogen preparations.

Commentary

Positive outcomes of study

As with the Collaborative Group on Hormonal Factors for Breast Cancer (CGHFBC) meta analysis[2] lower breast cancer risks were found in women using dydrogesterone containing HRT preparations. In fact, there was no increase in risk of breast cancer detected in women using dydrogesterone containing HRT for less than 5 years, 0.97 (0.88 to 1.08). This supports the hypothesis that there may be a weaker, or no promotional effect on breast cancers from less androgenic progestogens / progesterone when combined with estrogen in HRT. Smaller increased risks for combined HRT were found compared to the CGHFBC meta-analysis with more pronounced declines in risk on cessation of HRT compared to the CGHFBC analysis. The higher

risks from long term HRT exposure detected in the CGHFBC may have been because 40% of the data were derived from the Million Women Study in which participants were derived from a population who had all undergone mammography and represented a more "at risk" population.

Critique of study

This study had a number of limitations which reduced the value of the data and its application to modern HRT prescribing.

- The effects of HRT on breast cancer risk were assessed to the exclusion of the other risks and benefits, as they were in the Collaborative Group on Hormonal Factors for Breast Cancer (CGHFBC) meta analysis[2].

- It had all the known important limitations of a retrospective nested case control study

    - the data were derived from routinely collected information not collected for this primary outcome, therefore the data sets lacked reliable age at onset of menopause and in some cases missing information on smoking status, alcohol consumption and BMI, with no data on parity and physical activity
    - the groups could only matched for known confounders, in contrast to a randomised controlled trial, where unknown and unmeasured baseline characteristics are most likely to be balanced

- There was no information on HRT use before women joined their current primary care practice, adherence to HRT or the degree of switching between HRT regimens.

- Estrogen use was reported as a single outcome with no differentiation between oral and non-oral estrogen use.

- Unlike the CGHFBC analysis, differences between continuous and sequential HRT were not investigated because they are typically prescribed at different times at menopause and this was an age matched case control study.

- There was a discrepancy in the degree of HRT exposure in the CPRD data in this study compared to the CPRD data in the CGHFBC analysis (34% v 40%), which raises a question as to the accuracy of at least one of these data sets.

- Data from micronized progesterone (MP) users were not included in the analysis. This was also a problem with the CGHFBC study in which there were very few MP cases included. Although MP use in the UK has only recently become more popular, it is unclear why there were no cases at all included in this cohort.

- The data from the majority of combined preparations in this and the CGHFBC studies were derived from historical prescribing practice, using systemic HRT preparations containing medroxyprogesterone, norethisterone and levonorgestrel, which does not accurately reflect modern day prescribing in terms of the type and dosage of preparations now used.

- There were no data on tumour types, hormone sensitivity, breast cancer survival rates and most importantly, all-cause mortality in women using HRT.

- Contrary to the results from this and the CGHFBC paper, the recent 20 year analysis from the WHI prospective randomised controlled trial (RCT) showed a reduction in breast cancer diagnosis in estrogen only users. In addition to this, the WHI investigators found reduced breast cancer mortality in estrogen alone users and no effect on breast cancer mortality in users of combined conjugated estrogen with medroxyprogesterone acetate[3].

Conclusion

The reports[1-2] from observational data which unilaterally examine the risks of breast cancer without simultaneously counterbalancing the multiple benefits of HRT damage the confidence of prescribing menopause healthcare providers (HCPs) and the confidence of women whose quality of life is negatively affected by distressing symptoms and other menopause related problems. Until adequate resources are spent on conducting the definitive RCT using the best types of HRT given current evidence, the "menopause community" be regularly subjected to the limitations and uncertainties of re-analysed, often flawed, data where the outcomes of outdated HRTs are scrutinised and biases cannot be fully controlled for. In the meantime menopause societies will have to continue to pick up the pieces for concerned HCPs and women as we have done on this and previous occasions, by putting the risks and benefits into perspective[4-5]. This is a pressing global public health issue that requires prompt due care and attention, with investment from multiple departments of health, or possibly the World Health Organisation, to finally resolve it. Although the degree of investment required precludes immediate action due to the Covid 19 pandemic, the potential protective health benefits of female hormones and of optimum health in midlife and beyond should put this issue high on the priority list.

References

1. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ.2020 Oct 28;371:m3873. doi: 10.1136/bmj.m3873. PMID: 33115755; PMCID: PMC7592147.

2. Collaborative Group on Hormonal Factors for Breast Cancer . Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet.2019;394(10204):1159-1168.doi:10.1016/S0140-6736(19)31709-X.

3. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA.2020;324(4):369–380. doi:10.1001/jama.2020.9482.

4. The International Menopause Society comment on: “Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence.”
https://www.imsociety.org/manage/images/pdf/5054afeb9b1bc763032333443f1c0bed.pdf

5. HRT and breast cancer statement in response to EMA Pharmacovigilance Risk Assessment Committee recommendations in May 2020 https://thebms.org.uk/2020/09/hrt-and-breast-cancer-statement-in-response-to-ema-pharmacovigilance-risk-assessment-committee-recommendations-in-may-2020/