HRT and breast cancer: recent findings in the context of the evidence to date

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'A common misperception is that HRT has been shown to have significantly different effects in younger compared with older women.'

Women and their doctors considering HRT use are much better placed today than they were a decade ago. The increasing availability and consistency of data on the risks and benefits of HRT has been accompanied by agreement between the key drug-regulatory authorities that HRT use should be targeted for moderate-to-severe menopausal symptoms only, and not for the prevention of disease.

Exposure to estrogen increases the risk of breast cancer

Overwhelming evidence from more than a century of research demonstrates that exposure to higher levels of estrogen increases the risk of breast cancer. This evidence includes findings of reduced breast cancer risk with: oophorectomy [1,2], natural menopause [3], use of estrogen antagonists such as tamoxifen [4] and low endogenous estradiol levels [5]. Furthermore, the consistently increased risk of breast cancer attributable to obesity in postmenopausal women can be explained by their elevated estradiol levels compared with postmenopausal women of healthy weight [6]. The findings regarding HRT and breast cancer are consistent with the overall picture of the relationship between hormones and breast cancer. Progestagens (also termed progestins) appear to augment the effect of estrogens. Exactly how estrogens and progestagens increase breast cancer risk is unknown. Estrogen increases the mitotic rate of cells in the breast [7], increasing the risk of mutation, and estrogen–progestagen HRT is thought to act as a cancer promoter [8].

Worldwide evidence to date on HRT & breast cancer

A key principle of evidence-based medicine is that clinical practice is guided by the quantitative sum total of the appropriate evidence to date, not the results of single studies or subgroups of single studies. It is particularly important that reviews of the evidence are independently conducted. For breast cancer, where the disease event is unpredictable and other risk factors can be reasonably accounted for, data from observational studies are reliable [9] and need to be combined with data from randomized, controlled trials (RCTs) in order to summarize the current relevant evidence.

This editorial uses data from the UK Public Assessment Report (UK Medicines and Healthcare Product Regulatory Authority) [101], the most recent independent quantitative review of the effect of HRT on serious disease, supplemented by data from other large-scale studies.

'Use of estrogen-only HRT increases the risk of endometrial cancer in women with a uterus.'

The evidence, to date, demonstrates that:

- Women currently using HRT have an increased risk of developing breast cancer [101];
- Breast cancer risk is elevated with the use of all HRT types, but is greater in users of combined estrogen–progestagen than in users of estrogen-only [101];
- The risk of breast cancer increases with increasing duration of use [3,10,101];
- The HRT-associated increase in breast cancer risk drops rapidly after ceasing use of HRT [3,10];
- The risk of death from breast cancer is elevated in women who are currently using HRT [10,11];
- Use of HRT by women with a previous diagnosis of breast cancer increases the risk of recurrence [12];
- Screening mammography is less effective in women currently using HRT, with increased false-positive screens and a greater chance that breast cancers will be missed at screening [13,14].

The only factor found to significantly modify the effect of HRT is body size; HRT results in a larger increase in the risk of breast cancer in women who have a lower compared with a

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higher BMI, specifically, in thinner women. Consistent with this is the finding that the effect of HRT on breast cancer is greater in Europe than in North America (where average BMI levels are higher) [101].

What is the effect of HRT on disease risk?

When quantitatively weighing up the risks and benefits of HRT, it is important to compare like with like; hence, robust analyses examine the absolute risk of potentially life-threatening diseases significantly increased or reduced by HRT and estimate a quotient for its net effect. In these terms, HRT significantly increases the risk of breast cancer, stroke, ovarian cancer and venous thromboembolism, and reduces the risk of fracture [15,16,101]. Use of estrogen-only HRT increases the risk of endometrial cancer in women with a uterus [101]. The UK Public Assessment Report found no significant effect of HRT on colorectal cancer or coronary heart disease [101].

A total of 5 years use of estrogen-only HRT results in:

- A 20% (95% CI: 10–40%) increase in breast cancer risk or two additional breast cancers per 1000 users aged 50–59 years, and three additional breast cancers per 1000 users aged 60–69 years [101];
- A net excess of five potentially life-threatening events per 1000 users aged 50–59 years (number needed to harm = 200), or six per 1000 users aged 60–69 years (number needed to harm = 167) among women without a uterus [101].

A total of 5 years use of estrogen–progestagen HRT results in:

- A 60% (50–70%) increase in breast cancer or six additional breast cancers per 1000 users aged 50–59 years, and nine additional breast cancers per 1000 users aged 60–69 years [101];
- A net excess of 14 potentially life-threatening events per 1000 users aged 50–59 years (number needed to harm = 71), or 22 per 1000 users aged 60–69 years (number needed to harm = 45) among women with a uterus [101].

The numbers above relate to the European context and demonstrate that among women aged 50–59 years, one potentially life-threatening adverse event is estimated to occur for every 200 women aged 50–59 years using estrogen-only HRT for 5 years and for every 71 women using estrogen–progestagen HRT for 5 years, which is not outweighed by a beneficial effect.

To provide context for these absolute and relative risks, in the European setting, ten in 1000 women aged 50–59 years and 15 women aged 60–69 years would be expected to develop breast cancer over a 5-year period [101]. One additional unit of alcohol per day increases the risk of breast cancer by 7% [17], and an extra unit of BMI (equivalent to a weight gain of approximately 2.6 kg for a woman of average height) is associated with a 4% increase in the risk of postmenopausal breast cancer [18]. Hence, 5 years of estrogen-only use is equivalent to approximately two-to-three additional alcoholic drinks per day or a 13 kg weight gain for a woman of average height. Overall, 5 years of estrogen–progestagen HRT is the equivalent of approximately eight extra drinks per day or a 39 kg weight gain. Having a mother or a sister with breast cancer is associated with a 65% increase in breast cancer risk for women aged 50 years and over [19], which is equivalent to 5 years of estrogen–progestagen therapy.

> 'Apart from the difference between estrogen–progestagen and estrogen-only HRT … at present, we must assume that breast cancer risks relating to the different formulations and doses of HRT are similar.'

HRT is highly effective in the treatment of hot flushes, night sweats [20] and vaginal dryness related to menopause. As difficult as it may seem, it is the severity of these symptoms that women must balance against the risk of serious disease attributable to use of HRT. The effects of HRT on other non-life-threatening conditions, such as increased risk of incontinence [21], gallbladder disease [22,23] and reduced peripheral fractures [24], should also be considered.

Does the effect of HRT differ according to a woman's age, how long it has been since menopause or the dose?

A common misperception is that HRT has been shown to have significantly different effects in younger compared with older women. Unfortunately, the available RCTs are too small to provide reliable evidence about the effects of HRT in women of different ages or according to many attributes of HRT use, and a finding of 'no significant effect' within specific groups is not meaningful evidence of safety [25]. Examination of

subgroups in RCTs is highly problematic and must include testing for statistical interaction or effect modification, according to predefined stringent levels of significance [25]. If no significant difference in the effect is detected, the effect of HRT in this subgroup must be considered to be equal to the overall effect in the whole group. Moreover, even subgroup analyses that yield marginally significant findings must be viewed with caution if they were not specified prior to analysis, or make up one of many such comparisons.

The relative risk of breast cancer (i.e., the percentage increase in risk) associated with HRT use does not vary significantly according to a woman's age [10]. However, as previously outlined, the background absolute risk of breast cancer does vary according to age, and this difference in background rates means that the same duration of use of HRT at an older age will result in a greater number of cases of breast cancer and other serious disease than use at a younger age.

'…HRT-associated risks are rapidly reversible after the use of HRT ceases.'

Apart from the difference between estrogen–progestagen and estrogen-only HRT, the risk of breast cancer relating to the current use of different chemical formulations and doses of systemic HRT has not been shown to differ significantly [10]. This means that, at present, we must assume that breast cancer risks relating to the different formulations and doses of HRT are similar.

Trends in use of HRT & breast cancer incidence

The Women's Health Initiative RCT of estrogen–progestagen HRT was discontinued 3 years early because of increased breast cancer and serious disease in the treatment arm [26]. Its main results were published in July 2002 [26] and led to a rapid fall in HRT use in many countries.

Global trends in breast cancer incidence have now confirmed the findings from observational studies and randomized trials. The fall in HRT use has been shown in several settings to be followed by a decline in breast cancer incidence, consistent with evidence from observational studies that HRT-associated risks are rapidly reversible after the use of HRT ceases [3,10]. In the USA, a 66% reduction in use of HRT was followed by a significant 11% reduction in breast cancer incidence from 2001 to 2004 among women aged 50 years or above, but not in younger women [27]. Similarly, in Australia, a 40% reduction in HRT use was followed by a significant 6.7% reduction in breast cancer incidence from 2001 to 2003, but no significant change in breast cancer incidence was observed in younger women [28].

These analyses of trends should consider the possible competing effects of changes in breast cancer screening that can also influence breast cancer incidence [28]. In the USA and Australia, changes in screening patterns were too small to account for the observed decreases in cancer incidence and, in the USA, a similar fall in breast cancer incidence occurred even when data were restricted to screening attenders [27–29]. Reports from Canada, Germany and New Zealand all indicate that breast cancer incidence rates have fallen recently among women aged over 50 years, but these trends were not assessed in the context of screening patterns [30–32,102].

By contrast, in England, two-view mammography for all screens was introduced in 2002/2003, which increased the detection of breast cancers [33] and, in Norway, the national breast screening program was increasing its geographic coverage between 1999 and 2004 [34]; these changes may have obscured any effect of HRT. In addition, the statistical power to detect changes in breast cancer incidence will be limited if the population is small, or if the prevalence of HRT (even at its peak) was low [35], as was the case in The Netherlands and northern Italy [36,37].

How long is too long? Guidance for clinicians & patients about HRT use

Since HRT-related risks increase with increasing duration of use, minimizing duration is important. As can be concluded from the information mentioned previously, 5 years use of HRT, particularly combined HRT, carries considerable risk. The US FDA [103], the UK Medicines and Healthcare Products Regulatory Agency [101], the Australian Therapeutic Goods Administration [104] and many other drug-regulatory agencies are in agreement that:

- HRT should only be used for the short-term treatment of menopausal symptoms (hot flushes, night sweats and vaginal dryness);
- Women considering the use of HRT should be informed of its risks and benefits;
- HRT should not be used for the prevention of disease or as first-line treatment for osteoporosis;
- HRT should be used for as short a period of time as possible, and the need for continuing use should be reviewed every 6 months [104] or annually [101].

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