Breast cancer and HRT

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What are the risks for breast cancer?

Although breast cancer occurs 100 times more frequently in females than in males, suggesting that breast cancer prefers tissue that is primed by female hormones, there are a significant number of other risk factors that are associated with its occurrence. These risk factors have cast doubt on the role of the sex hormones being primarily responsible for the initiation of breast cancer, namely:

a) The disease is more commonly diagnosed in post-menopausal women not on HRT than in pre-menopausal women.
b) It is a disease of the ageing. The older the woman, the more likely she is to develop breast cancer. At age 50 years, the rate of diagnosis is 1:50, whereas at 70 years, it is 1:20 and at 85 years it is 1:10. A 50 year old has a 10% lifetime probability of developing and a 3% probability of dying of breast cancer.
c) Pregnancy before the age of 25 years, even though associated with high levels of endogenous sex hormones, results in a reduced risk, especially if associated with breast-feeding.
d) An increasing number of pregnancies is also associated with a reduction. Women who have 5 or more children have about two-thirds the rate of breast cancer as women who have one child.
e) The oral combined contraceptive pill is not associated with an increased diagnosis of breast cancer.
f) A body mass index of greater than 30 kg/m^2 , or regular consumption of alcohol, will increase the incidence of breast cancer.
g) A menarche <12 years or menopause >54 years are associated with an increased incidence.
h) Increased breast density at the time of mammography. Recent reviews of 7 studies have indicated decreased mammographic sensitivity in hormone users, with a slight increase in false positive recalls. Post-menopausal women not on HRT, but with an increased breast density on mammography, require mandatory surveillance with annual mammography and ultrasonography as these patients may have a higher incidence of breast cancer.
i) A family history of two first degree family relatives with breast cancer doubles the individual's risk of developing the disease. Family history does not further increase the small risk of breast cancer said to be associated with HRT usage.
j) Oophorectomy before 35 years reduces the lifetime risk of breast cancer by 75% in women.

The Women's Health Initiative study (WHI) found that, in women who were taking continued estrogen-progestogen therapy, there was a 26% increase in invasive cancer. In this study, only a quarter of the participants had prior HRT use and the average participant's age was 63 years. The recently published data from the estrogen-only arm of the WHI did not show any increased risk for the development of breast cancer.

A synopsis of the currently held views is as follows:

a) Estrogen alone does not appear to increase the incidence of breast cancer.
b) Estrogen-progestogen combinations, are either associated with a small increase in the risk of breast cancer or, in fact, promote pre-existing tumour rather than initiating the tumour.
c) The increase in risk is seen only after 5 years of usage and not if used <5 years. The increase is only of invasive cancers and not of in-situ or non-invasive lesions.
d) This increase is only seen in past users and the effect is lost once the woman has stopped taking HRT for 5 years.
e) In terms of absolute increase in number of breast cancer per 1000 women who commence HRT at the age of 50 years, and use it for 5, 10 and 15 years respectively, the excess of breast cancers will be 2, 6 and 12. The absolute increase in the WHI was 8 per 10 000 women users per year.
f) From the observational studies, it appears that higher doses and longer duration of usage will impact on risk. Hence the need to use the lowest dose of HRT which is effective in controlling symptoms.
g) Risk estimates for breast cancer with HRT use are similar in the HERS I, HERS II, WHI and some observational studies. For example, the hazard ratio of 1.26 reported by the WHI is consistent with the risk ratio of 1.27 reported after 6.8 years of follow-up in HERS I/HERS II. These data suggest that breast cancer risk may be increased with long-term HRT use, but if this is so, the increase in risk is small.

Will Hormone Therapy cause breast cancer?

Over 50 epidemiological studies and six meta-analyses have examined the association between hormone therapy and breast cancer risk in the past 30 years, and the lack of a uniform

consistent conclusion means that any effect, if at all, has to be a small one.

Among studies that examined estrogen-only use, 82% found no effect on breast cancer risk, 13% reported a modest increase in risk, whilst 5% reported a reduced risk. Results of studies with estrogen and progestogen preparations followed a similar trend: 80% found no effect, 10% reported an elevated risk and 10% a reduced risk. The Collaborative Group on Hormonal Factors in Breast Cancer reanalysed 90% of the worldwide epidemiological evidence on the relationship between risk of breast cancer and use of HRT. The relative risk for ever-users was 1.14, for current or recent users 1.21, for current or recent users with 5 or more years of use 1.35, and the relative risk for past users was 1.07. The more recently published randomised studies, HERS I, HERS II and the WHI, have been addressed above. They all concur with the observational data – there is a small increase in risk, but only after approximately 5 years of usage.

What are the characteristics of breast cancer that develops whilst taking HRT?

From the mid 90s it became apparent from the observational studies that, even though there was this small increase of breast cancer in HRT users, as described above, there was an accompanying decreased mortality from breast cancer in these patients.

There is substantial evidence, from a number of studies, to support that women taking HRT, when their breast cancers were diagnosed, had smaller sized tumours, that were better differentiated, had a higher local restriction with less lymph node involvement. They were more likely to be lobular cancers, while the risk for the more aggressive ductal cancers remained essentially constant. Women who had an early menopause (<40 years) had the greatest benefit from HRT preventing fatal breast cancer. Although this is the commonly held general opinion, the WHI's findings were contradictory. The authors did not detect any differences in the histologic types of breast cancer and in their study there was an earlier appearance of less differentiated tumour. The authors of the study, however, do point out that, although the results were consistent with stimulation of growth in established breast cancers, they were of the opinion that the delay in diagnosing these tumours may have led to this greater number of less differentiated tumours than described in previous studies. The latter they ascribe to the larger number of abnormal mammograms in the HRT group than in the placebo group. The majority of the studies, including the WHI, have all shown substantially improved survival rates in women with breast cancer whilst on HRT. In the WHI, despite the greater likelihood of less differentiated tumours, there was not an accompanying increase in mortality.

Continuous combined HRT will lead to increased breast density in approximately 35% of patients, sequential combined HRT in 15% and estrogen alone in 10% of users. Does HRT impair mammographic screening? Overall, the studies suggest a decreased mammographic sensitivity, but with little impact on specificality. Even though the effectiveness of the breast cancer screening may be somewhat reduced, the outcome has not had adverse impact on breast cancer mortality. The increase in breast density associated with postmenopausal HRT appears to be a transient, reversible change, a change unlikely to have a persistent effect on cellular proliferation. After discontinuation of HRT, breast density rapidly decreases.

Two weeks of cessation allows regression of HRT induced density. Therefore, there is good reason to recommend discontinuation of HRT for two weeks prior to mammography in all women older than 65 years who have dense breasts and in all younger women who have been recalled because of a suspicious or abnormal mammogram. The general consensus at present is that breast cancers diagnosed in HRT users are better differentiated, of lower grade and stage, with better outcomes.

The contrary finding in the WHI may reflect the older age of its participants and certainly does not receive any support from any other study.

References: Available on request.