Does the HRT-associated risk of breast cancer vary by histologic type and hormone regimen?

Possibly This case-control study found that the risk of breast cancer did vary, with:

- a significantly greater risk of lobular or tubular cancers than the risk of ductal carcinoma among women using hormone replacement therapy (HRT) at the time of diagnosis and
- a greater risk of breast cancer with the use of combined estrogen–progestogen therapy than with estrogen only.

Flesch-Janys D, Slanger T, Mutschelknauss E, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int J Cancer. 2008;123:933–941.

▸ EXPERT COMMENTARY
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FAST TRACK

Current users of HRT had a greater risk of lobular or tubular cancers than of ductal carcinoma, and combination therapy carried a greater risk of breast cancer than unopposed estrogen

Menopausal hormone therapy is an established risk factor for breast cancer. Flesch-Janys and colleagues zeroed in on this reality in an attempt to determine whether certain hormone regimens are associated with higher rates of breast cancer, and whether use of HRT is associated with certain histologic types of cancer.

Using data from their large population-based, frequency-matched control study from Germany (3,464 breast cancer cases, 6,657 matched controls), they found a higher risk of lobular cancer with use of norethisterone- and levonorgestrel-derived progestogens than with progestogens derived from progesterone.

Other studies have also suggested that women who use estrogen–progestogen therapy (EPT) are more likely to be given a diagnosis of lobular, rather than ductal, cancer, and that various dosages, routes of administration, frequency of use, and type of estrogen or progestogen differentially affect the type of breast cancer—although the reason for this intriguing observation is unknown.

Fournier and associates, for example, found that EPT regimens containing progesterone or dydrogesterone were associated with a lower risk of breast cancer than other types of progestogen.[1] The Women's Health Initiative (WHI) evaluated only one type of oral EPT and found too few lobular cancers to answer the question of whether breast cancers found in women in the EPT group differed by histologic type.[2]

Li and colleagues[3] and Flesch-Janys and associates found no statistically significant risk of breast cancer 5 years after EPT was discontinued. Heiss and colleagues reported that, 2.4 years after cessation of EPT, the risk of breast cancer remained stable for prior users in the WHI, compared with women taking placebo (5-year data are not yet available).[4]

Estrogen-only therapy in the WHI was not associated with an increased risk after 6.7 years of use.[5]

In the study by Flesch-Janys and associates, 67.9% of cases and 59.5% of controls had ever used HRT. Cases had a higher age at menopause and lower parity, and were less likely to have breastfed, more likely to have a family history of breast cancer, and more likely to have had benign breast disease.

Study design may invite bias

Case-control methodology is appropriate to study rare cases, examine conditions that develop over time, and generate preliminary hypotheses. Bias can occur, however, depending on the quality of existing records or self-recall and whether it is possible to collect information from all eligible controls.

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Recall bias can occur because cases tend to provide more accurate information than controls. In the study by Flesch-Janys and colleagues, trained interviewers conducted face-to-face interviews to limit recall bias, but the low response rate, particularly among controls, is of concern, as is the variety of HRT preparations used by participants. The lack of verification of histologic subtype or re-review of histology by blinded pathologists limits the generalizability of the findings.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Lobular carcinoma, found more often in this study, accounts for only about 15% of invasive breast cancers. It is usually hormonally sensitive and considered more treatable than ductal cancer. However, it is more difficult to detect by mammography and physical examination.

Encourage your patients to establish their risk of breast cancer using the Gail model or another tool; to perform breast examination; to undergo mammography; and, in a setting of high risk, to consider magnetic resonance imaging of the breasts. Counsel patients that the risk of breast cancer may be diminished by regular exercise, weight loss, smoking cessation, limitation of alcohol, and adequate intake of vitamin D.

If hormone therapy is indicated in a given patient, using a lower dosage or, potentially, different types of estrogen–progestogen regimens could minimize the risk of breast cancer, although more research on these measures is needed before recommendations can be made.

For women who are at high risk of breast cancer, you can offer Food and Drug Administration-approved chemoprevention with tamoxifen or raloxifene.

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