Hormone replacement and breast cancer: Implications of the Iowa Women's Health Study

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ABSTRACT

Amid conflicting reports about the link between hormone replacement therapy and breast cancer, the Iowa Women's Health Study gives grounds for cautious optimism. According to the study, women on hormone replacement therapy had a higher incidence of breast cancer, but the excess cancers were of a "favorable" histologic type. This paper discusses clinical decision-making in light of the study results.

A recent study supports the safety of hormone replacement therapy

ACCORDING TO the recently published Iowa Women's Health Study,[1] women receiving hormone replacement therapy may have an increased risk of breast cancer, but in their study, mainly cancers of a "favorable" histologic type—a relatively uncommon category consisting of mucinous, medullary, tubular, or papillary carcinomas. The risk of these types of cancer, which accounted for only 5.4% of the cases of breast cancer in this trial, was approximately twice as high in women who had received hormone replacement therapy for more than 5 years compared with those who had not received it.

This study does not resolve the longstanding controversy about whether hormone replacement therapy causes breast cancer. However, it provides another bit of evidence that should give us cautious optimism about the safety of hormone replacement therapy.

This article looks at the findings of the Iowa Women's Health Study and other studies, examines common themes among the conflicting data, and suggests a reasonable approach for clinicians who want to prescribe hormone replacement pending more definitive data.

PREVIOUS STUDIES PROVIDE CONFLICTING DATA

Studies have shown that postmenopausal hormone replacement therapy reduces all-cause mortality.[2,3] However, the data conflict on whether there is a causal link between hormone replacement therapy and breast cancer. Various studies have come to the following divergent conclusions:

- Women receiving hormone replacement for more than 5 years have an increased risk of breast cancer.[4–7]
- There is no significant increased risk.[8–10]
- If women receiving hormone replacement indeed have a higher incidence of breast cancer, the tumors tend to be cancer in situ or cancers with a favorable prognosis.[7,11]
- Women who develop breast cancer while on hormone replacement therapy have a more favorable prognosis than women not on hormone replacement therapy, although this effect may wane with time from diagnosis.[12,13]

THE IOWA WOMEN'S HEALTH STUDY

The Iowa Women's Health Study[1] was designed to examine the effects of several risk factors on the incidence of breast cancer in postmenopausal women.

Methods

In 1985, the investigators mailed a questionnaire to 98,029 women age 55 to 69, who were randomly selected from the Iowa Department of Transportation driver's license list. Those who returned the questionnaire and were not excluded because of premenopausal status or previous mastectomy were entered in the study group (N = 37,105).

Risk factors. The questionnaire included questions about a number of factors associated with breast cancer risk: age, education, alcohol consumption, history of cigarette smoking, personal history of cancer, history of cancer in female relatives (number of relatives and their age at diagnosis were not included), menstrual history, reproductive history, height, current weight, and weight at age 18 (the last three being used to calculate the body mass index). Participants also received a tape measure and instructions on how to measure their hips and waist, from which the investigators calculated the waist-to-hip ratio.

Most important, the questionnaire asked about noncontraceptive hormone use: whether the participant had ever used hormone replacement therapy and for how long (≤ 5 years or > 5 years) and whether she was currently using hormone replacement therapy and for how long (≤ 5 years or > 5 years).

Follow-up questionnaires were sent in 1987, 1989, 1992, and 1997 to obtain information on incident self-reported disease and vital status.

Breast cancer cases were identified by checking the Health Registry of Iowa. The investigators coded the tumors according to histology, behavior (eg, in situ vs invasive), and histologic grade.

In 11 years, 1,520 documented cases of breast cancer occurred among the study participants. The investigators divided these cases into four groups:

- Infiltrating ductal or lobular carcinoma, 76.6%
- Ductal carcinoma in situ, 11.5%
- Invasive carcinoma of a histologic type with a favorable prognosis (ie, mucinous, medullary, tubular, papillary), 5.4%
- Others (lobular carcinoma in situ or nonepithelial or poorly defined tumors), 6.5%. These were excluded from analysis.

Statistical analysis consisted of calculations of the relative risk of the first three types of cancer listed above according to the various risk factors, including hormone use.

TABLE 1

Age-adjusted relative risk of breast cancer among women who ever used hormone replacement therapy

TYPE OF CANCER	RELATIVE RISK AND 95% CONFIDENCE INTERVAL WITH HORMONE REPLACEMENT	
	≤ 5 YEARS	> 5 YEARS
Invasive ductal or lobular carcinoma	1.05 (0.92–1.20)	1.07 (0.88–1.28)
Ductal carcinoma in situ	1.08 (0.77–1.52)	1.10 (0.68–1.77)
Invasive carcinoma of favorable histologic type	1.67 (1.02–2.71)	2.22 (1.22–4.02)

ADAPTED FROM GAPSTUR SM, MORROW M, SELLERS TA. HORMONE REPLACEMENT THERAPY AND RISK OF BREAST CANCER WITH A FAVORABLE HISTOLOGY. RESULTS OF THE IOWA WOMEN'S HEALTH STUDY. JAMA 1999; 281:2091–2097.

Results

The results, adjusted for age, showed a statistically significant increase in the risk of developing an invasive carcinoma of favorable histologic type in women who had ever received hormone replacement therapy, compared with women who had never used it. (Keep in mind that this type of tumor accounted for only 5.4% of the cases of breast cancer in the study.) The other tumor types showed a statistically insignificant trend toward an increased risk (TABLE 1).

The results were somewhat different when adjusted for multiple risk factors (TABLE 2), but again showed a statistically significant risk of histologically favorable tumors in women who used hormone replacement therapy.

The investigators remarked that their study did not demonstrate the link between cancer in situ and hormone replacement

The increase in absolute risk must have been very small

TABLE 2

Multivariate-adjusted* relative risk of breast cancer among past and current users of hormone replacement therapy

TYPE OF CANCER	RELATIVE RISK AND 95% CONFIDENCE INTERVAL WITH HORMONE REPLACEMENT	
	≤ 5 YEARS	> 5 YEARS
Among past users		
Invasive ductal or lobular carcinoma	1.01 (0.87–1.18)	0.92 (0.65–1.28)
Ductal carcinoma in situ	0.91 (0.61–1.34)	0.29 (0.07–1.18)
Invasive carcinoma of favorable histologic type	1.44 (0.80–2.58)	2.68 (1.08–6.69)
Among current users		
Invasive ductal or lobular carcinoma	1.38 (1.03–1.85)	1.16 (0.90–1.49)
Ductal carcinoma in situ	0.94 (0.41–2.16)	1.35 (0.77–2.36)
Invasive carcinoma of favorable histologic type	4.42 (2.00–9.76)	2.63 (1.18–5.89)

*Adjusted for age, body mass index at age 18, waist-to-hip ratio, age at menarche, age at menopause, age at first birth, parity, family history of breast cancer in a first-degree relative, type of menopause, and alcohol intake

ADAPTED FROM GAPSTUR SM, MORROW M, SELLERS TA. HORMONE REPLACEMENT THERAPY AND RISK OF BREAST CANCER WITH A FAVORABLE HISTOLOGY. RESULTS OF THE IOWA WOMEN'S HEALTH STUDY. JAMA 1999; 281:2091–2097.

therapy as shown in some previous studies, but they noted an excess of breast cancers of a favorable histologic type. They hinted that hormone use might have a selective biological effect on less aggressive breast tumors. They drew a parallel between their observations and the observation that less aggressive endometrial cancers are seen among estrogen users.

PROBLEMS WITH THE STUDY

Two potential problems with the study come to mind.

Some "favorable" tumors may not be so favorable. Not all experts agree that one of the so-called less aggressive cancers, medullary carcinoma, has a favorable prognosis.[13–15] Medullary carcinoma accounted for 16 of the 82 "favorable" cases, and if these 16 cases were excluded, the increase in relative risk in this category would be diluted.

What is the absolute risk? The investigators presented their results in terms of relative risk, adjusted for other risk factors. However, the absolute risk may be a more useful number, especially if the complication (eg, cancer of a favorable histologic type) is uncommon. Unfortunately, the report did not divulge the actual numbers of women receiving hormone replacement therapy, nor the percentage of women on therapy who developed breast cancer, compared with those not on therapy. If one quarter of the study patients used hormone replacement therapy, the increase in absolute risk must have been very small, probably less than two excess cases of cancer per 1,000 users.

RECURRING THEMES FROM THE STUDIES

Among the many studies exploring the link between hormone replacement therapy and breast cancer, we note some repeating themes.

The larger the estrogen dose, the greater the risk.[16] The recent studies that did not show a significant association may reflect the trend to prescribe smaller doses of estrogen in recent years.

The longer the duration of hormone replacement therapy, the greater the risk. Several studies showed this trend.[5–8]

The risk increases with age.[5] Knowing this, and considering that the results of the Heart and Estrogen/Progestin Replacement Study[17] raise questions about starting hormone replacement therapy after a coronary event, physicians should be circumspect about starting estrogen in elderly patients and should consider alternatives to indefinite estrogen therapy if bone protection is the sole goal. However, there remains strong evidence of the favorable impact of hormone replacement on all-cause mortality and heart disease when given in an appropriate setting.[2,3]

Hormone replacement therapy may not increase the risk of ductal and lobular carcinomas. This conclusion is borne out by the

Iowa study[1] (except for a finding of an increased risk on multivariate analysis for current users for less than 5 years, TABLE 2), and by several other studies.[8–10]

TAILORING THERAPY TO THE INDIVIDUAL

Although the risk may be small, we should not dismiss it: any increase in the incidence of breast cancer must be viewed as an adverse effect of hormone replacement therapy. Our challenge is to tailor hormone replacement therapy so that each patient receives the maximum possible benefit with the least possible risk.

In doing so, our clinical decisions will be influenced by evolving knowledge on several fronts. Issues about hormone replacement and breast disease (as well as its effects on the heart and bones) may be better clarified by results of the Women's Health Initiative studies in progress.

Selective estrogen receptor modulators such as raloxifene may present an alternative to estrogen replacement for patients with a high risk of breast cancer who have no vasomotor symptoms, are at average or low risk for heart disease, but are at risk for osteoporosis.[18] In the meantime, given the caveats noted above, the current study does give us cautious optimism about prescribing hormone replacement therapy.

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Selective estrogen receptor modulators may present an alternative

CME ANSWERS

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