The Impact of Hormone Replacement Therapy on the Detection and Stage of Breast Cancer

Julie Cheek, MD; Judith Lacy, MD; SuEllen Toth-Fejel, PhD; Katherine Morris, MD; Kristine Calhoun, MD; Rodney F. Pommier, MD

Hypothesis: Patients who receive hormone replacement therapy (HRT) and subsequently develop breast cancer are more likely to be diagnosed by palpation than mammography and have a higher stage of cancer at initial diagnosis.

Design: Retrospective case series.

Setting: University hospital.

Patients: Two hundred ninety-two patients with breast cancer who were postmenopausal.

Interventions: Clinical examination, mammography, and definitive therapy.

Main Outcome Measures: Hormone replacement therapy use, mode of cancer detection, tumor size, nodal status, stage, and survival.

Results: Patients receiving HRT prior to diagnosis had significantly more incidences of mammographically detected tumors, ductal carcinoma in situ, T1 lesions, negative nodes, and better survival rates than nonusers.

Conclusions: A history of HRT use had only beneficial and no discernible adverse effects on breast cancer detection and outcomes. These effects of HRT seem to be due to the development of less aggressive tumors rather than earlier detection.

Arch Surg. 2002;137:1015-1021

Hormone replacement therapy (HRT) is widely used for the relief of menopausal symptoms as well as for the prevention of osteoporosis. Although HRT is beneficial for these reasons, previous studies have reported an increased risk of developing breast cancer in women who have received long-term HRT prior to diagnosis.1-4

Another major concern regarding HRT and breast cancer is that patients receiving HRT will have denser breast tissue,1,5-13 making mammographic detection of tumors more difficult. As a result, tumors in patients who have received HRT would be detected more often by palpation as opposed to screening mammography. Palpable tumors are statistically more often node negative, conferring a better prognosis. Contrary to this belief, studies have demonstrated that patients with breast cancer who have received HRT have a better prognosis than those who have never received HRT.4,14-16

Two theories have been presented to describe the mechanism responsible for a better prognosis in patients with breast cancer who have received HRT. First, some authors advocate the theory that HRT users undergo more frequent screening.14,16-18 Second, others state that patients with breast cancer who have received HRT prior to diagnosis develop tumors that behave less aggressively.4,14 The aim of our retrospective review of patients with breast cancer who were postmenopausal was 3-fold: to investigate the relationship between HRT and mammographic detection, to examine the theory that breast tumors in HRT users are biologically less aggressive, and to explore the mechanisms by which a history of HRT use improves survival in women diagnosed as having breast cancer.
PATIENTS AND METHODS

The medical records of all postmenopausal women diagnosed as having breast cancer at Oregon Health and Science University (Portland) between March 1994 and January 2002 were reviewed. Women were identified as postmenopausal if they had achieved either natural or surgical menopause. Patients were not excluded if they had a history of breast cancer. Collected data included HRT status at the time of diagnosis, method of breast cancer detection, pathologic TNM staging, hormone receptor status, tumor histologic properties, interval between screening mammograms, family history of breast cancer, and status at last follow-up. Hormone receptor status was classified as positive or negative as interpreted by the pathologist. Positive family history was defined as having 1 or more first-degree relatives diagnosed as having breast cancer.

Hormone replacement therapy users were defined as patients who had ever received HRT prior to a diagnosis of breast cancer, or who were receiving HRT at the time of diagnosis. Nonusers were defined as patients who had never received HRT. All HRT doses and modes of delivery were accepted. Permission for the study was received from the institutional review board.

Hormone replacement therapy status was correlated with patient age at diagnosis, method of tumor detection (screening mammography vs palpation), primary tumor size, histologic axillary nodal status, axillary nodal stage, tumor histologic properties, histologic grade, hormone receptor status, and frequency of screening mammograms. Statistical significance (P≤.05) was determined by the Fisher exact test and χ² analysis. Statistical calculations of differences in tumor size and intervals between screening mammograms between the groups was determined by a t test. Disease-specific survival was determined by the Kaplan-Meier method. The statistical significance of differences in survival distributions was determined by log-rank analysis.

RESULTS

There were 292 patients identified. One hundred forty-four women had received HRT at the time of diagnosis and 148 women had not received HRT. Mean patient age at diagnosis was 66 years (range, 38-96 years). There was no significant difference in age at diagnosis between the groups.

Mean patient follow-up was 24 months. The mean and median follow-up times for HRT users with tumors detected by mammography were 27 and 22 months, respectively, and for nonusers, 24 and 20 months. The mean and median follow-up times for HRT users with tumors detected by palpation were 25 and 23 months, respectively, and for nonusers, 22 and 17 months. The mean duration of use among the patients who received HRT was 16 years prior to diagnosis.

Hormone replacement therapy users had tumors with significantly better prognostic indicators and significantly better survival rates, reflected by differences in mode of detection. Among HRT users, 84 had detection by mammography and 60 had detection by palpation. Among nonusers, 63 had detection by mammography and 85 had detection by palpation (P=.01). The mean time interval between screening mammograms was 22.4 months for HRT users and 23 months for nonusers (P=.85).

The percentage of patients with ductal carcinoma in situ (DCIS) varied with HRT status. Among patients who had received HRT, 23 patients were diagnosed as having DCIS. Among patients who had not received HRT, 14 patients were diagnosed as having DCIS. The difference in the incidence of DCIS cases between HRT users and nonusers was statistically significant (P=.04). There were no significant differences in grade or tumor size of DCIS between the groups (Table 1).

There were significantly fewer cases of invasive breast tumors among HRT users (P=.04). Additionally, there were significantly higher incidences of T1 lesions, stage I tumors, and node-negative tumors among this group of patients (Table 1).

There were no significant differences in overall mean tumor size, number of positive nodes, hormone receptor status, histologic grade, and incidence of stage IV tumors based on HRT status (Table 1 and Table 2).

Among mammographically detected tumors, there was a significantly lower incidence of poorly differentiated tumors in HRT users (Table 3). There was no significant difference in the incidence of positive family history of breast cancer between the HRT users and nonusers among mammographically detected tumors (Table 1).

All disease-specific deaths occurred in patients with invasive tumors. Figure 1 shows the survival curves for patients with mammographically detected tumors and for patients with tumors detected by palpation. The 6-year survival rate for patients with mammographically detected tumors was 94%, compared with 78% for patients with palpable tumors (P=.02). The 6-year survival rate for HRT users was 92% compared with 80% for nonusers (P=.05) (Figure 2). Figure 3 shows survival curves for patients with tumors detected by palpation. The 6-year survival rate was 79% for HRT users compared with 76% for nonusers (P=.57). For patients

Table 1. Comparison of Hormone Replacement Therapy (HRT) Users With Nonusers for All Breast Cancer Cases

<table>
<thead>
<tr>
<th></th>
<th>HRT*</th>
<th>No HRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cases</td>
<td>144</td>
<td>148</td>
<td>.01</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>84</td>
<td>63</td>
<td>.43</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>60</td>
<td>42</td>
<td>.57</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>23</td>
<td>14</td>
<td>.9</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>19</td>
<td>10</td>
<td>.10</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>4</td>
<td>4</td>
<td>.25</td>
</tr>
<tr>
<td>Invasive tumors</td>
<td>121</td>
<td>134</td>
<td>.04</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>65</td>
<td>53</td>
<td>.10</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>56</td>
<td>81</td>
<td>.25</td>
</tr>
<tr>
<td>Stage I tumors</td>
<td>68</td>
<td>54</td>
<td>.02</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>44</td>
<td>29</td>
<td>.05</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>24</td>
<td>25</td>
<td>.05</td>
</tr>
<tr>
<td>T1 lesions</td>
<td>84</td>
<td>72</td>
<td>.02</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>52</td>
<td>34</td>
<td>.03</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>32</td>
<td>38</td>
<td>.07</td>
</tr>
<tr>
<td>Node-negative tumors</td>
<td>87</td>
<td>81</td>
<td>.02</td>
</tr>
<tr>
<td>Detected by mammography</td>
<td>54</td>
<td>41</td>
<td>.14</td>
</tr>
<tr>
<td>Detected by palpation</td>
<td>33</td>
<td>40</td>
<td>.08</td>
</tr>
<tr>
<td>Family history (mammographically detected invasive tumors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td>12</td>
<td>11</td>
<td>.18</td>
</tr>
<tr>
<td>No family history</td>
<td>33</td>
<td>23</td>
<td>.11</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients unless otherwise indicated.
with mammographically detected tumors, the 6-year survival rate for HRT users was 100% compared with 87% for nonusers ($P = .03$) (Figure 4). No differences were observed in any of the survival curves, and there were no changes in any survival-related $P$ values when DCIS cases were included in or omitted from the analysis.

**COMMENT**

Our series demonstrated that patients who had received HRT had significantly more mammographically detected tumors, a finding that has been reported by others.\(^{14-16}\) Conversely, more nonusers had tumors that were diagnosed by palpation.\(^{15,16}\) Some authors have explained this finding as being due to more frequent screening in HRT users. For example, patients receiving HRT might be required to obtain annual screening mammograms as a prerequisite to continuing their HRT, whereas no such demand would be placed on patients not receiving HRT.\(^{14,16-18}\) However, our data show that the mean interval between screening mammograms was essentially the same between the groups. In fact, we found the average time interval between screening mammograms to be close to 2 years, as opposed to annually, in both groups. Thus, the increased frequency of mammographically detected tumors among HRT users cannot be attributed to an increased frequency of screening mammograms.

Other investigators have reported increased incidences of favorable prognostic features in the tumors of patients who had received HRT. Numerous authors have

### Table 2. Comparison of Pathologic Characteristics of Invasive Breast Cancer Tumors Between Hormone Replacement Therapy (HRT) Users and Nonusers*

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>No HRT</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive tumor cases detected by mammography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>24 (37)</td>
<td>16 (30)</td>
<td>.12</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>23 (35)</td>
<td>18 (34)</td>
<td>.15</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>9 (14)</td>
<td>14 (26)</td>
<td>.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (14)</td>
<td>5 (9)</td>
<td>.18</td>
</tr>
<tr>
<td>Invasive tumor nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>87 (72)</td>
<td>81 (60)</td>
<td>.02</td>
</tr>
<tr>
<td>Positive</td>
<td>32 (26)</td>
<td>52 (39)</td>
<td>.01</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>19 (13)</td>
<td>25 (17)</td>
<td>.11</td>
</tr>
<tr>
<td>Positive</td>
<td>95 (66)</td>
<td>108 (73)</td>
<td>.11</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (21)</td>
<td>15 (10)</td>
<td>.02</td>
</tr>
<tr>
<td>Invasive tumor size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;2$ (T1)</td>
<td>84 (69)</td>
<td>72 (54)</td>
<td>.02</td>
</tr>
<tr>
<td>$&gt;2$ (T2 + T3)</td>
<td>20 (17)</td>
<td>52 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean</td>
<td>200</td>
<td>2.39</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients unless otherwise indicated.

### Table 3. Summary of Statistically Significant Differences in Breast Cancer Cases Between Hormone Replacement Therapy (HRT) Users and Nonusers*

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>No HRT</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of detection</td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Mammography</td>
<td>84 (58)</td>
<td>63 (43)</td>
<td></td>
</tr>
<tr>
<td>Palpation</td>
<td>66 (42)</td>
<td>85 (57)</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>23 (16)</td>
<td>14 (9)</td>
<td>.04</td>
</tr>
<tr>
<td>Invasive tumors</td>
<td>121 (84)</td>
<td>134 (91)</td>
<td>.04</td>
</tr>
<tr>
<td>T1</td>
<td>84 (69)</td>
<td>72 (54)</td>
<td>.02</td>
</tr>
<tr>
<td>T2 + T3</td>
<td>20 (17)</td>
<td>52 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Node negative</td>
<td>87 (72)</td>
<td>81 (60)</td>
<td>.02</td>
</tr>
<tr>
<td>Stage I tumors</td>
<td>68 (56)</td>
<td>54 (40)</td>
<td>.02</td>
</tr>
<tr>
<td>Invasive tumors detected by mammography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 lesions</td>
<td>52 (80)</td>
<td>34 (64)</td>
<td>.03</td>
</tr>
<tr>
<td>Poorly differentiated tumors</td>
<td>9 (14)</td>
<td>14 (26)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients unless otherwise indicated.

![Figure 1](http://archsurg.jamanetwork.com/pdfaccess.ashx?url=/data/journals/surg/5366/) Survival curves of patients with mammographically detected tumors ($n = 118$) and tumors detected by palpation ($n = 137$); $P = .02$.

![Figure 2](http://archsurg.jamanetwork.com/pdfaccess.ashx?url=/data/journals/surg/5366/) Survival curves for hormone replacement therapy (HRT) users ($n = 121$) compared with nonusers ($n = 134$); $P = .05$. 

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reported increased numbers of T1 lesions,\textsuperscript{14-16,18-21} node-
negative tumors,\textsuperscript{4,15,18} and lower clinical stage at diagno-
sis\textsuperscript{4,13,16,18,21} in patients with breast cancer who had re-
ceived HRT. Our data show an increased frequency of
T1 lesions, node-negative tumors, and stage I tumors
among patients who had received HRT. We also found
more cases of DCIS among the HRT users. Conversely,
we observed significantly more T2 and T3 lesions among
patients who had not received HRT.

In our study, these parameters translate into better
survival rates for patients with invasive cancer who had
received HRT prior to their diagnosis. Other authors have
also reported a better prognosis for patients with breast
cancer who have received HRT.\textsuperscript{15-17,21} However, most au-
thors have attributed this better prognosis among HRT
users to earlier diagnosis by mammographic detection.
Few have considered the possibility that HRT causes tu-
mors to be less aggressive.

All of our findings, as well as those of other au-
thors, support the hypothesis that HRT induces a more
biologically favorable tumor. When we compared sur-
vival between groups of patients with mammographi-
cally detected invasive tumors, there was a significant
improvement in survival among HRT users. Hormone
replacement therapy users had a 100% survival rate at 6
years as opposed to 87% in nonusers. Both groups of
tumors were detected by screening mammography, thus
detected “early” by current convention. Yet, we ob-
served a survival benefit for those women who had
received HRT. We feel that this demonstrates that the
differences in outcome are more likely due to the de-
velopment of less aggressive tumors in HRT users rather
than earlier detection by mammography. Hormone re-
placement therapy was associated with fewer palpable
tumors and more mammographically detected tumors as
well as more DCIS and less invasive tumors. Although it
appears from Figure 3 that there was no survival benefit
from HRT on palpable tumors, it is critical to note that
HRT significantly diminished the number of palpable
tumors.

To identify the mechanism by which HRT effects these
changes, we compared hormone receptor status, tumor his-
tologic properties, and tumor grade between HRT users
and nonusers. In concordance with other investiga-
tors,\textsuperscript{3,14,18} we did not find a higher incidence of hormone
receptor–positive tumors in our HRT group. We found no
significant difference in the frequency of histologic sub-
types of breast cancer between the groups. In contrast
to other studies, we did not find a higher incidence of
well-differentiated tumors among HRT users.\textsuperscript{14-16,18} We
did find significantly fewer poorly differentiated inva-
sive tumors detected by mammography among HRT us-
ers, a finding that is supported by other authors.\textsuperscript{22} Thus
far, there have been no consistent findings that would
indicate a clear mechanism by which HRT improves the
outcome of breast cancer.

Our results have important implications for stud-
ies that examine the impact of HRT after a diagnosis of
breast cancer. Some studies have reported decreased mor-
tality rates among patients who received HRT after di-
agnosis and treatment of breast cancer.\textsuperscript{17,23,24} These stud-
ies were not controlled for HRT use before the diagno-
sis of breast cancer. In one study,\textsuperscript{17} 68% of patients receiv-
 ing HRT after a diagnosis of breast cancer had also re-
ceived HRT prior to their diagnosis. In contrast, only 47%
of patients who did not receive HRT after a diagnosis of
breast cancer had received HRT prior to their diagnosis.
Our study shows an improvement in outcome when HRT
was received prior to diagnosis. Therefore, it may be that
the patients who received HRT after breast cancer treat-
ment developed low-risk tumors as a result of receiving
HRT prior to diagnosis. It is possible that the observed
improved survival of patients who received HRT after a
diagnosis of breast cancer may be due to HRT use be-
fore the diagnosis of breast cancer. Accordingly, future studies of HRT use in patients with a history of breast cancer should be controlled for HRT use prior to diagnosis.

The Lancet meta-analysis\(^2\) showed that the absolute improvements in survival rates with adjuvant therapy were, at most, 4% for node-negative tumors and 8.6% for node-positive tumors at 10-years follow-up. The absolute difference in survival rates observed between patients receiving HRT and patients not receiving HRT was 13% at 5 years. Thus, the absolute difference in survival rates cannot be explained by differences in the use of any known adjuvant therapies.

Hormone replacement therapy has multiple favorable effects on breast cancer, resulting in a better outcome. We propose that these effects are due to a biological effect rather than early detection. While the mechanism of this beneficial effect of HRT on breast cancer is unclear, we did not demonstrate that it is due to an increased frequency of hormone-sensitive tumors or differing tumor histologic properties or grades.

In this study, HRT had only beneficial and no discernible harmful effects on breast cancer detection or outcome. Fears of decreased mammographic detection of breast cancer in patients who received HRT prior to diagnosis were not substantiated in this study. In addition, concern that HRT induces aggressive tumor progression was refuted by improved survival rates. It is plausible that the beneficial effects of HRT on breast cancer could outweigh its reported risk of a slight increase in the incidence of the disease. These findings provide physicians with useful data when counseling patients on the risks and benefits of HRT with respect to breast cancer.

This paper was presented at the 73rd Annual Meeting of the Pacific Coast Surgical Association, Las Vegas, Nev, February 17, 2002, and is published after peer review and revision. The discussions are based on the originally submitted manuscript and not the revised manuscript.

Corresponding author and reprints: Rodney F. Pommier, MD, 3181 SW Sam Jackson Park Rd, L223A, Portland, OR 97201 (e-mail: pommier@ohsu.edu).

REFERENCES


Nathalie Johnson, MD, Portland, Ore: This is a very interesting and quite timely paper. Every day I discuss hormone replacement therapy with women who worry about the risk of breast cancer. Many are taking replacement for quality of life issues, but they do it with an underlying discomfort because of the attendant risk of developing malignancy of the breast. Of course, the next group of patients we encounter are the breast cancer survivors who are dealing with estrogen withdrawal and are searching for answers about use of any hormonal replacement, be it vaginal creams or phytoestrogens.

We know that estrogen works at the cellular level to promote the production of growth factors like transforming growth factor α and epidermal growth factor. In addition, it decreases the production of growth inhibitors like transforming growth factor β. Some of estrogen’s predilection to encourage malignant degeneration may be mediated by amplification of cell regulatory proteins called cyclins, which encourage abnormal growth.
by allowing cells to continue through the cycle unchecked and escape normal growth control. This could share similarities with the oncogene protein product HER-2-neu.

This brings me to my first question for the authors. In your study, you did not find significant differences in tumor differentiation or hormone receptor status between HRT users and nonusers. Did you collect data on HER-2-neu or p53, and, if not, are you planning to pursue this? If there are differences in the oncogene protein products, it may offer some clues for further study. You also found a trend towards more poorly differentiated tumors in non-HRT users. Were patients in this group younger, and did you find any association with oral contraceptive use?

As you stated, mammography in women on hormone replacement has been touted to be more difficult to interpret. Your study was in agreement with others in that there was a higher incidence of tumor detection by mammography in HRT users. The argument that HRT users are screened more frequently also did not hold up in your study, as they were screened at the same interval. Interestingly though, far more palpable tumors developed in the non-HRT group over the same screening interval, which would intuitively suggest that this group of patients had biologically more rapidly growing tumors. You did not control for S-phase, but Holli et al published a study in the Journal of Oncology in which they did find a statistically significant lower S-phase in patients on HRT.

You also found far more DCIS in your HRT users. All of these findings would support your conclusion that HRT seems to lend towards a biologically less aggressive breast malignant transformation. I would ask the authors for their theories on how this may occur and ask what might be some next steps in solving this interesting dilemma.

William H. Goodson, MD, San Francisco, Calif: First, it is great that somebody else is looking at the issue of how breast cancer is diagnosed. You can’t say often enough that even when you are using mammography, a very large proportion of patients’ cancers are first found at palpation. We tend to under-estimate the value of palpation; that is very important.

I wonder, however, about your results for several reasons. First, only about half of your total patients were first identified by mammography, which is considerably lower than what has been reported in other series. For example, a recent series from the Massachusetts General by Michaelson found that 58% of breast cancers were found by mammography. Our own series has found about 50% by mammography. I am trying to figure out why you have just a hair over half found by mammography. So my first question is why do you think this is so low?

My second question is whether this may be related to mode of practice. Were these patients seen by gynecologists? Were they seen by persons who would routinely get a mammogram before an office visit? If you are thinking about that question, and particularly if you are trying to assign a biological meaning to this, the basic question is not whether cancers were first found by mammogram but whether—at the time of diagnosis—did they have a positive mammogram or not? If a physician’s practice is to have the patient get the mammogram before they come to the office, some will more often be found first by mammography. However, that doesn’t tell you anything about the biology. You have to know whether or not your proportion of cases that had a positive mammogram was actually different in those on HRT or not, because if the proportion is the same, then it is necessary to rethink whether there is a biological effect or not.

John A. Butler, MD, Orange, Calif: I have a question concerning your use of the term screening mammography. I noticed that in terms of the patients who were getting mammograms, the mean time was approximately 2 years for both groups. For most postmenopausal women, screening mammography is used yearly. So either the women of Portland were ahead of the curve in terms of the current controversy about the utility of screening mammograms, or maybe some of these people were not actually getting screening mammograms but were getting intermittent mammograms, and I wonder if you have that data concerning how many of these women were actually getting yearly mammograms.

The other issue I have is your last result, which talks about the beneficial effects of hormone replacement therapy on breast cancer. You’re talking about breast cancers that you diagnosed but you don’t really have the denominator in terms of the number of women on hormone replacement and the number of women who are not on hormone replacement who are at risk. Rather than your results showing the benefits of hormone replacement, I think it shows that if you have breast cancer, you are better off if you’ve had a long history of hormone replacement therapy, which may predict for a more benign clinical course.

Steven N. Parks, MD, Fresno, Calif: My questions also relate to the beneficial effects. Since you have shown “a beneficial effect” of hormone replacement on breast cancer, when you see someone with breast cancer today, are you stopping their hormone replacement?

The second question is a little more provocative. If in fact it is “beneficial,” are you starting hormones when you diagnose breast cancer?

1. Benjamin Paz, MD, Duarte, Calif: The questions you bring up are very important. But I have a problem with how you define having ever received hormonal replacement. It’s very hard and when you look at all of the studies of hormone replacement, they have the problem of quantifying the amount of estrogen taken. I cannot believe that a woman who took 20 years before estrogen is the same as the woman that is taking current estrogen replacement with Premarin. This could all be circumstantial evidence. A study that looks forward and with a collection tool that really documents how estrogens were used prospectively would probably show that women that did not receive estrogen; with the use of a tool, you will find that many of those women took estrogen and you probably did not know it.

David Z.J. Chu, MD, Duarte: I have 2 questions that may help decide whether the findings are due to early detection or a different biology. One is the family history. Are there any differences in terms of family history of breast cancer? The second, the mammographic detection: the time interval has been the same but the real issue is the time of the last mammogram before the diagnosis.

Ronald G. Latimer, MD, Santa Barbara, Calif: An observation and then a couple of questions. Some of us are old enough in this room to remember that estrogen was used as adjuvant hormone therapy and a third of breast cancer patients had a remission given just plain estrogen. That was done a long time ago and obviously is not in the present.

My question is, with hormone replacement therapy, ie, estrogen and progesterone, did you break it down in those women who were only taking estrogen vs those who were taking the combination? In addition, we do not have a range of how long they were taking the medication from 1 day to 12 years. What is the range?

Theodore X. O’Connell, MD, San Francisco, Calif: I have a question about the design of the study. At the beginning of the talk you said the outcome is better with tumors discovered by mammogram rather than palpation. Obviously patients who have smaller tumors will do better, but those same patients could have had a mammogram 3 months before that was negative and then you discover a palpable tumor. So the only way that you can prove that screening mammograms are good is to have 2 different groups, one a control group not having mammograms...
grams and one having a screening mammogram and showing that the outcome is different between the 2 groups. It’s the same thing with the study. The only way that you can come to sound conclusions is to have a prospective randomized study with half the women having estrogen replacement and the other half not, and seeing any outcome differences. Otherwise it becomes very difficult to decipher the data.

**Dr Pommier:** To answer Dr Johnson’s questions, HER-2-neu was not routinely determined at OHSU until the very end of the study period because it had no therapeutic implications before the advent of herceptin therapy.

The poorly differentiated tumors were evenly distributed by age. There were significantly fewer poorly differentiated tumors among women receiving HRT who had mammographically detected tumors but not palpable tumors. We did not look at the role of OCPs. This was a study designed to look at the impact of HRT taken after menopause.

Our overall percentage of mammographically detected tumors is about 50%, which is close to the national average. This is an average that results from a 40% rate among the non-HRT group, and a 60% rate in the HRT group. If one’s practice has a higher percentage of mammographically detected tumors, then it might mean that there were many women taking HRT in that region.

If patients were referred to us with a palpable lump, then the next step would be to get a diagnostic mammogram. Virtually all of the palpable tumors were seen on mammography. However, very few of the tumors that were detected by mammography were palpable by the clinician on concurrent examination.

The mammograms should be considered as screening mammograms even if they weren’t done annually. I don’t think we are achieving the goal of annual mammography anywhere in the country. Even if you look at the data from Sweden, where they have national health care and every woman will have a mammogram paid for annually, the average interval between screening mammograms is actually 18 months. No one is meeting the goal of annual screening mammography for all patients.

We currently do tell patients diagnosed with breast cancer to stop their HRT in order to comply with current standards of care and tamoxifen therapy. One of the next steps will be to try to give HRT back to patients after a diagnosis of breast cancer. It is absolutely correct that high-dose estrogen was an effective treatment for breast cancer before tamoxifen, and those who don’t know the history of breast cancer treatment are doomed to repeat it.

The history of HRT use was consistent and stable. We strived very hard to get these data, and we found them to be simpler than we thought. Essentially, women started HRT at menopause and they continued it for an average of 16 years. The average age at diagnosis was 66, so they essentially took it from the onset of menopause until they had a diagnosis of breast cancer. The other half of the patients were pure nonusers. So the data are really very clean in terms of users and nonusers. In addition, we haven’t yet correlated specific HRT regimens with outcomes.

The number of patients who had a positive family history was also evenly distributed between the HRT users and the nonusers. There appears to be a significant number of patients who, even though they had a positive family history of breast cancer, decided to use it.

I can address all of the remaining questions with the following closing remarks. Recently, there has been a great deal of publicity in the press about the Danish study that concluded that there may be no benefit of screening mammography in women with invasive tumors. These findings are disconcerting because they imply that our pathognomonically Halstedian concept of early detection simply doesn’t work. The results of our study persuade me to believe that may actually be true. We need a new paradigm to better fit the data. Perhaps women with mammographically detected tumors don’t have better survival because their tumors are caught earlier, as we have all been led to believe, but simply because they are biologically less aggressive tumors than palpable tumors. They are distinctly different than palpable tumors. Intuitively, this should already make sense to us. We have all seen patients with the so-called interval tumors that present as a palpable lump within a few months of a normal mammogram and a normal examination. We know that those tumors are aggressive and that those patients don’t do well. The opportunity for early detection in those patients never really existed. Perhaps mammographically detected tumors are a certain percentage of all breast cancers. Intuitively, that also ought to make sense. Nobody seems to question that inflammatory breast cancers are a mere 4% of all cancers. If this is the case, then screening mammography is not the appropriate strategy for changing outcomes because mammograms do nothing to alter that preexisting proportion of mammographically detected tumors.

This leaves little that can be done to affect outcomes. However, our study implies that there is something that can be done to affect the outcomes for postmenopausal women and that is to allow them to receive HRT. This actually increases the proportion of mammographically detected tumors. It increases the percentage of well-behaved tumors, as reflected by the increased number of T1 lesions, node-negative tumors, and stage I tumors. All of this is translated into better survival for patients who received HRT.

This isn’t a matter of early detection. It’s a biological effect. All of the benefit of HRT was confined to the group of patients with mammographically detected tumors. All of the mammographically detected tumors would be considered as having been detected early, in the Halstedian concept, by our current standards. Yet, there is an enormous survival advantage seen among the women who took HRT. This isn’t due to selection of more hormone-sensitive tumors. There are actually more patients with ER-/PR tumors in the group with mammographically detected tumors that took HRT than in the group that didn’t take HRT, but still, the HRT group had absolutely perfect 6-year survival. HRT didn’t impact the palpable tumors, which supports the concept that they are different.

We simply don’t yet know what causes this. The scope of our study was limited in that respect. Whatever the mechanism of HRT, the effect is profound. It yields a 13% improvement in absolute, not relative, survival rates and this is even extended to patients with ER-/PR-tumors. Both effects are more than can be expected from tamoxifen, whether it is adjuvant or preventative.

The next step is to look at genetic microarrays, comparing the genes and tumor markers, as Dr Johnson suggested, that are activated between the tumors of patients who are receiving HRT and those who are not, and between mammographically detected tumors and palpable tumors. Probably, that will tell us what the HRT does that is so favorable; possibly, it will tell us what we can do to also improve the outcomes for patients with palpable tumors. Hopefully, it will lead to better treatment and outcomes for all breast cancer patients.