Breast Cancer Res Treat (2009) 117:25–29
DOI 10.1007/s10549-008-0175-2

PRECLINICAL STUDY

When genomic and standard test results diverge: implications for breast cancer patients' preference for chemotherapy

Noel T. Brewer · Alrick S. Edwards · Suzanne C. O'Neill · Janice P. Tzeng · Lisa A. Carey · Barbara K. Rimer

Received: 21 April 2008 / Accepted: 25 August 2008 / Published online: 11 September 2008

Abstract *Purpose* We examined how women incorporate potentially differing genomic and standard assessments of breast cancer recurrence risk into chemotherapy decisions. *Methods* 165 women previously treated for early-stage breast cancer indicated their interest in chemotherapy regimens to prevent recurrence of breast cancer in response to six hypothetical vignettes that presented breast cancer recurrence risk estimates from standard criteria and a genomic test, some of which were discordant. *Results* Standard and genomic test results each elicited greater interest in chemotherapy when they indicated high rather than low risk for recurrence (89% vs. 26%, and 87% vs. 22%, respectively, $Ps < 0.001$). Genomic test results had a larger impact on chemotherapy preferences than standard measures to predict recurrence. *Conclusions* Some women may be reluctant to forgo chemotherapy when genomic tests indicate low recurrence risk but standard criteria suggest high risk. Additional research including replication of the findings of this small, vignette-based study is needed.

Keywords Risk recurrence · Oncotype DX® · Genomics · Patient decision making · Chemotherapy

Genomic information is becoming increasingly important to clinical care [1–3] Genomic information can predict risk for prostate cancer [4], survival from non-small-cell lung cancer [5], and recurrence risk for early stage breast cancer [6–8]. One genomic test, Oncotype DX®, recently moved into clinical practice as an aid to decisions by patients and their physicians about chemotherapy for early stage breast cancer. The test analyzes a profile of 21 genes to establish risk for distant recurrence of breast cancer within 10 years among node-negative, estrogen receptor-positive breast cancer patients treated with adjuvant tamoxifen [8]. Validation studies show that patients with low recurrence risk scores from Oncotype DX® derived little, if any, benefit from chemotherapy, while patients with high recurrence risk scores received a large benefit from the addition of chemotherapy to standard tamoxifen regimens [9].

New genomic diagnostic tests will eventually augment or replace some current medical tests and methods of estimating risk. However, in the initial stages of the tests' introductions, which can span many years, patients and clinicians will face difficult decisions about how to integrate potentially discordant information from the standard methods for deriving information about patients and the new genomic tests. Currently, breast cancer recurrence risk assessments incorporate information from several prognostic factors, including patient age, tumor size, and tumor grade [10, 11]. We refer to these henceforth as the "standard tests" although we recognize that these are not tests per se.

Oncotype DX® offers new and potentially discordant information. In one study, half of women with early stage breast cancer categorized as high risk for recurrence by standard tests were recategorized as low risk for recurrence by Oncotype DX® [12]. Another study found that as many as 33% of women categorized as high risk by standard tests were categorized as low risk for recurrence by genomic tests [13]. Recategorizing women from high to low risk is likely to be more common in the US where clinical criteria for recurrence risk yield more estimates of high risk than

N. T. Brewer (✉) · A. S. Edwards · S. C. O'Neill · J. P. Tzeng · L. A. Carey · B. K. Rimer
Department of Health Behavior and Health Education, School of Public Health, University of North Carolina, 364 Rosenau Hall, CB 7440, Chapel Hill, NC 27516, USA
e-mail: ntba@unc.edu

the St. Galen's criteria favored in Europe [13]. Accurately placing women in a lower risk stratum is important, because women who are unlikely to benefit from chemotherapy could be spared the discomfort, cost and risks associated with treatment. Genomic tests changed treatment recommendations so that they no longer included chemotherapy for 23% of patients in one study and 34% of patients in another [14, 15]. Whether not choosing chemotherapy as a result of the new genomic tests is acceptable to patients is not yet well understood.

The present study examined how women incorporate results from a new genomic risk for recurrence (RFR) test and from the standard RFR tests into their preferences for chemotherapy. We expected that, when either of the two sources of risk information indicated higher risk for recurrence of breast cancer, women's preferences for chemotherapy would be higher. We also expected that genomic RFR test results would have a greater impact on women's chemotherapy preferences than standard RFR tests, because the former have better prognostic value.

Methods

Participants

Eligible participants were adult women who met the following criteria: previously diagnosed with Stage I/II primary breast cancer, completed surgery, and either had not received or had completed adjuvant chemotherapy. Patients who were currently receiving hormone therapy (tamoxifen) were eligible to participate in the study. We excluded patients from the study if they were not English-speaking or had a cancer recurrence, a life-threatening comorbid disease, a second primary cancer diagnosis, metastasis, or a history of serious psychiatric illness.

Procedures

Between February and August 2005, trained research assistants approached breast cancer patients at the University of North Carolina Breast Center and invited them to participate in the study. Patients who agreed to participate received an oral and written introduction to the recurrence risk test [16]. The Institutional Review Board of the University of North Carolina at Chapel Hill approved the study protocol and materials.

Measures

We used hypothetical scenarios to assess potential responses to RFR testing, similar to what was done in early studies undertaken to understand the potential uptake of and response to cancer susceptibility testing [17, 18]. All participants viewed scenarios (reported in the Appendix) that described hypothetical RFR test results obtained after a first diagnosis of breast cancer and stated their preference for chemotherapy, given the stated RFR test results.

The study employed a 2 × 3 within-subjects factorial design that varied genomic RFR test results (low risk or high risk) and standard RFR tests results (not stated, low risk or high risk). Thus, each participant read six hypothetical scenarios: (1) both the genomic and standard RFR tests showed low recurrence risk, (2) both tests showed high risk, (3) genomic test showed high risk and standard tests showed low risk, (4) genomic test showed low risk and standard tests showed high risk, and (5) and (6) genomic test showed low or high risk, but no standard test information was provided. For each vignette, respondents indicated their preferences for receiving chemotherapy using a 5-point response scale labeled from "definitely would not" to "definitely would."

Demographic information was assessed by survey. Missing information on age and race were obtained from women's medical charts. Health literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM) [19]. Based on information obtained during medical chart reviews, we calculated women's 10-year risk for breast cancer recurrence using Adjuvant!Online® [20] and assessed their history of chemotherapy treatment.

Data analyses

We analyzed chemotherapy preferences using a 2 (genomic RFR test results) × 3 (standard RFR test results) within-subjects analysis of variance. Post-hoc, paired *t*-tests explored the two-way interaction, the main effect of the three-level, standard tests result variable, and several comparisons relevant to understanding chemotherapy preferences in response to discordant results. To examine whether study findings differed by demographic subgroups, we repeated the 2 × 3 analysis of variance, adding each demographic variable as a moderator. Although statistical analyses used the continuous preference variable, we dichotomized the variable to provide descriptive data on preference for chemotherapy (comparing responses of "probably would" and "definitely would" have chemotherapy to other responses). All data analyses used SPSS (15.0, Chicago, IL). The critical alpha was 0.05, and all tests were two-tailed.

Results

Of 231 patients contacted, 165 completed the study (see Lillie et al. [16] for detailed analysis of non-responders).

Mean age was 59 years (SD, 10.6; range, 36–87). Women identified themselves primarily as white (85%) or African American (12%). Participants were generally well-educated (52% were college graduates). Health literacy levels were high, with a mean REALM score of 63.6, indicating high reading ability. The majority said they had spare money after paying their bills (64%). The women were a mean of 4 years post-diagnosis of breast cancer. The women's median 10-year breast cancer recurrence risk was 26%.

Women expressed greater preference for chemotherapy when standard RFR tests showed high risk rather than low risk (Fig. 1) ($F(2,328) = 217$, $P < 0.001$). When information about RFR from standard tests was absent, interest in chemotherapy was intermediate between that expressed when standard RFR was low and high. 26% of patients preferred chemotherapy when standard tests showed low risk, 89% when they showed high risk, and 56% when no risk was stated from the standard tests. Women also expressed stronger interest in chemotherapy when the genomic RFR test showed high risk rather than low risk ($F(1,164) = 418$, $P < 0.001$). 22% of patients preferred chemotherapy when the genomic test showed low risk and 87% when it showed high risk.

Chemotherapy preferences were more strongly affected by recurrence risk information from genomic than standard tests (partial $\eta^2 = 72\%$ vs. 58%, respectively). However, the effect of genomic RFR test results on chemotherapy preferences was more pronounced under certain conditions (interaction, $F(2,328) = 23$, $P < 0.001$). In the absence of RFR information from standard tests, the difference in interest in chemotherapy between the low and high genomic RFR test results conditions was largest (i.e., the leftmost bars of Fig. 1, difference = 1.36, 95%CI: 1.2–1.53). Influence of the genomic RFR test on preference for chemotherapy decreased when respondents considered a low risk result from standard RFR tests (middle bars, difference = 1.16, 95%CI: 1.01–1.32). It was smallest when respondents considered a high risk result from the standard RFR tests (rightmost bars, difference = 0.76, 95%CI: 0.65–0.88). All differences were significantly different from zero and from one another.

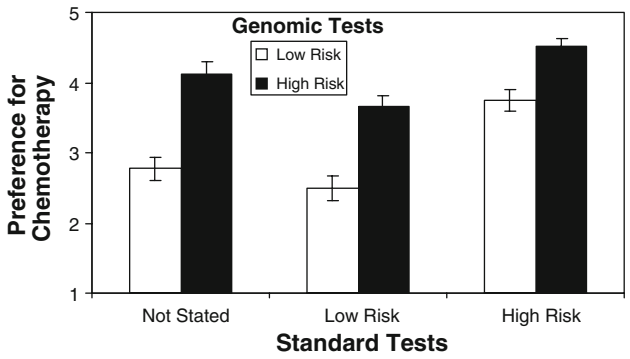

Fig. 1 Interest in chemotherapy was higher when either standard or genomic recurrence risk tests indicated a high risk for recurrence. Participants ($N = 165$) indicated preference for chemotherapy in all six conditions using a 5-point response scale labeled from "definitely would not" to "definitely would". Error bars report standard errors

One of our most important questions concerns whether women gave more weight to genomic or standard RFR test results when they were discordant. To answer this question, we made two comparisons. First, we compared chemotherapy preferences in the two "mismatched" results conditions (i.e., a low risk result from the standard test paired with a high risk result from the genomic RFR test [L-H] and vice versa [H-L]). Interest in chemotherapy was equivalent in these two conditions (represented by bars 4 and 5 of Fig. 1) ($t = 1.59$, $P = 0.11$). The important finding is that the critical condition where genomic tests indicated low risk, but standard tests indicated high risk, did not yield appreciably lower interest in chemotherapy. Second, we compared the two conditions where genomic tests indicated low risk, and standard tests results agreed or disagreed (L-L and L-H). Women's preferences for chemotherapy were higher when the standard tests showed high risk, even though they were countered by genomic results indicating the opposite (bar 3 vs. bar 5, ($t = 16$, $P < 0.001$).

We examined whether the interaction (i.e., the pronounced effect of higher risk genomic test results on preferences) differed for some subgroups of women. Chemotherapy decisions of women with higher health literacy were more affected by the magnitude of genomic RFR test results than women with lower health literacy (i.e., a larger difference in interest in chemotherapy when recurrence risk was low vs. high). This effect was found only when standard RFR tests were absent or indicated low risk but not high risk (3-way interaction, $F(2,324) = 5$, $P < 0.005$). The interaction did not differ by respondents' history of chemotherapy treatment, race, age, financial status, or their 10-year breast cancer recurrence risk.

Discussion

As the number and complexity of genomic tests expands, and these tests are more widely used in routine clinical care, the issue of how genomic test results can conflict with tests they complement or replace will become increasingly important. Our results suggest that new risk information from genomic tests may not always have the expected effect. Oncotype DX® test results can help women and their physicians more precisely understand whether chemotherapy would benefit them. However, women in our study indicated that if either standard or new genomic tests

indicated high risk they would have been more likely to want chemotherapy. This suggests that one of the main promises of this test, allowing some women to safely forgo the substantial discomforts and potential risks associated with chemotherapy, may be harder to fulfill than previously hoped. Some women may view chemotherapy as a potential lifeline and be unwilling to sacrifice any means to increase the probability of cure, even when the incremental benefit is exceedingly small or non-existent [21].

Interviewing women already treated for breast cancer allowed us to begin examining a pressing clinical research question before use of the test by women and their clinicians becomes widespread. Similar work was done with BRCA1/2 testing as it first moved into clinical practice [17, 18, 22]. However, our findings should be confirmed with women actively deciding about receiving chemotherapy for early stage breast cancer using Oncotype DX®. We acknowledge that there may be considerable differences between hypothetical scenarios and real life decisions.

Indeterminate or intermediate recurrence risk results are likely to be challenging, because the additional benefit of chemotherapy for women with intermediate recurrence risk according to Oncotype DX® is not yet known. Our study did not examine the effect of indeterminate or intermediate recurrence risk results on chemotherapy decisions, leaving an important question for future research. In previous work using bogus saliva tests for pancreatic disease, indeterminate results regarding future risk made participants more likely to perceive future negative outcomes than definitive results [23]. Past research on uncertainty of genomic test results also found that individuals trusted intermediate genomic test results less than low or high-risk results, and they would most regret having the genomic test if they received intermediate risk results [24–26].

We used a within-subjects design to maximize power due to the limited number of eligible participants, but a between-subjects study design may yield different findings [27]. To simplify in-clinic interviews, questionnaires all used the same scenario order, which may have yielded order effects; randomly ordering the scenarios would have distributed any potential order effects more evenly across the scenarios. Though we sought to present scenarios in the most understandable manner possible, the scenario introduction did not provide details of what constituted "other tests" and highlighted key words "high" and "low", potentially affecting participant responses.

Although we described the new genomic tests as being more accurate than standard means of assessing risk for recurrence, some women may not have fully understood this. We did not explicitly assess whether women trusted the new genomic tests more or less than standard tests, but women expressed relatively high trust in the genomic test described in our study (data reported by O'Neill et al. [26]). Nonetheless, it suggests that some women may not fully understand the benefit of this new genomic test in potentially allowing them to forgo chemotherapy. This highlights the potential need for clinicians to take added care in explaining the benefits of genomic testing for breast cancer recurrence risk, especially issues surrounding conflicting test results. Additional research is needed to understand how women understand recurrence risk information from genomic tests and how best to communicate this information. Physicians' messages to patients may carry as much or more weight as genomic risk estimates. If physicians reinforce the perception that women are better off with chemotherapy, the recurrence risk result may not matter for patents' decisions. However, recent data suggest that a change in treatment recommendations by medical oncologists, from including to not including chemotherapy, is a main outcome of genomic testing [28]. Legal, family, social and other factors may also influence physicians and women's decisions to opt for more treatment.

Acknowledgments We thank Sarah Lillie and Edward Morrill for their help in planning and conducting the study; the interviewer team for their help with data collection; Claire Dees, Beth Fogel, and other physicians and nurses of the University of North Carolina Breast Center for their assistance; and two anonymous reviewers for their helpful comments on an earlier version of the paper. Most importantly, we thank the women who participated in this study. Financial support for this study was provided in part by grants from the American Cancer Society (MSRG-06-259-01-CPPB) and the Lineberger Comprehensive Cancer Center. The funding agreements ensured the authors' independence in designing the study, interpreting the data, writing the report, and publishing it.

Appendix

The wording for the six scenarios that presented the results of the standard and RFR tests are below. Participants indicated their interest in chemotherapy using a 5-point response scale labeled from "definitely would not" to "definitely would".

Please continue to recall the time when you were first diagnosed with breast cancer.

1. If the Test result said your cancer had a high chance of recurring would you want to have chemotherapy?
2. If the Test result said your cancer had a low chance of recurring would you want to have chemotherapy?

The Recurrence Risk Test results can disagree with the result of other tests. The Recurrence Risk Test might show a **high** chance of the cancer recurring (suggesting chemotherapy is needed). But other tests might show a **low** chance (suggesting chemotherapy is not needed). In this case, the patient and her doctor have to choose which test results to rely on.

3. If all of the tests said **low** risk, would you want chemotherapy?
4. If the Recurrence Risk Test said **low** risk but the other tests said **high** risk, would you want chemotherapy?
5. If all of the tests said **high** risk, would you want chemotherapy?
6. If the Recurrence Risk Test said **high** risk but the other tests said **low** risk, would you want chemotherapy?

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