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REVIEW ARTICLE

Patient Decisions About Breast Cancer Chemoprevention: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose
Women at high risk of breast cancer face the complex decision of whether to take tamoxifen or raloxifene for breast cancer chemoprevention. We investigated what is known about decisions of women regarding chemoprevention.

Methods
Using MEDLINE, CINAHL, and PSYCINFO, plus reviewing reference lists of relevant articles, in December 2009 we identified 13 studies that addressed patient decisions about breast cancer chemoprevention, were published in 1995 or later, were peer-reviewed primary clinical studies, and reported rates at which participants showed interest in (hypothetical uptake) or accepted (real uptake) chemoprevention medications.

Results
Nine studies provided information about hypothetical breast cancer chemoprevention decisions (mean uptake rate, 24.7%) and five provided information about real decisions (mean uptake rate, 14.8%). The range of rates was wide, and each of the hypothetical uptake studies assessed interest differently. A logistic regression model found significant correlation with uptake of decision type (hypothetical versus real, odds ratio [OR] = 1.65; 95% CI, 1.26 to 2.16), educational or decision support intervention (provided *v* not, OR = 0.21; 95% CI, 0.17 to 0.27), and cohort risk for breast cancer (high-risk *v* general population, OR = 0.65; 95% CI, 0.56 to 0.75). Perceived vulnerability to breast cancer was consistently correlated with increased uptake, and concern for adverse effects was correlated with reduced uptake. All studies used a correlational/descriptive design, and most studies used convenience sampling strategies.

Conclusion
Breast cancer chemoprevention uptake rates are low and variation is wide. Hypothetical uptake rates are higher than real uptake, and interventions markedly reduce uptake. Research is needed that uses reproducible sampling methods and examines decision support strategies that lead to quality decisions.

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INTRODUCTION

For women in the United States, breast cancer is the most common nondermatologic cancer and the second leading cause of cancer death. In 2009, an estimated 192,370 new cases of breast cancer were diagnosed, and an estimated 40,170 women died from breast cancer.[1] Women who are at high risk for breast cancer face multiple decisions regarding breast cancer risk management. One decision is whether to take medication to lower their risk.[2,3] Recent updates of clinical practice guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend that women without preexisting breast cancer who are considered to be at high risk for breast cancer and low risk of adverse events may be offered tamoxifen to reduce the risk of invasive cancer. In postmenopausal women, raloxifene may also be considered.[4,5] The high risk for breast cancer can be established by breast biopsy showing high-risk benign breast disease, a family history consistent with high risk, or modified Gail score.[3,6] It has been estimated that more than 2 million US women could benefit from chemoprevention medication.[7] However, in the United States, even in the most favorable of situations, acceptance of these medications is low.[8-10]

A woman's decision about breast cancer chemoprevention is complex.[11,12] This is because the efficacy of tamoxifen and raloxifene in preventing breast cancer is limited to estrogen receptor–positive tumors; there is increased risk from these medications for important medical conditions, including

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endometrial cancer, thromboembolic events, and vasomotor adverse effects[2,3,4]; and the recommendations are different for pre- and postmenopausal women. This places the chemoprevention decision squarely in the category of preference-sensitive decisions. In contrast to effectiveness-based decisions (decisions about health services for which proven benefits are large compared with harms, so that there is an obvious best choice), preference-sensitive decisions are concerned with health services for which the best choice is not clear, either because the benefit/harm ratios are low or because they involve how a person values the potential benefits and harms. This has implications for appropriate strategies of risk communication and patient decision support.[11,13-15] For preference-sensitive decisions, a quality decision is defined as one that is informed and leads to a decision that is consistent with a person's values.[16-18]

The purpose of this systematic review is to determine what is known about women's decisions regarding breast cancer chemoprevention with tamoxifen or raloxifene. We classified studies that reported rates of participants actually taking chemoprevention medications as providing information about real decisions concerning breast cancer chemoprevention. Studies reporting "willingness," "interest," or "intent" to take chemoprevention medications were classified as providing information about hypothetical decisions. Specific research questions include the following: (1) What uptake rates for real and hypothetical decisions have been reported, is there variability in reported rates, and are hypothetical decision rates higher than real decision rates? (2) How have real and hypothetical decision rates been measured? (3) What factors, such as demographic variables and breast cancer risk, are associated with uptake rates? (4) Are there issues of study methodology that may influence and thus bias reported uptake rates? To address these questions, we identified studies, critically appraised quality, and synthesized evidence about breast cancer chemoprevention decisions made by patients, conforming to the PRISMA guideline for systematic reviews.[19]

Information from this systematic review may be helpful to health care providers who care for women at high risk for breast cancer, health systems setting policy, and future research in the following ways: (1) providing information needed for development and delivery of breast cancer prevention and control decision support services, as recommended by a recent comparative effectiveness review[3]; (2) increasing understanding of factors that are associated with chemoprevention uptake; (3) assisting readers of the chemoprevention literature to understand its strengths and weaknesses; and (4) improving awareness of the problems and pitfalls of chemoprevention uptake research.

METHODS

Search Strategy

We looked for all studies that (1) addressed real or hypothetical decisions made by patients about chemoprevention of breast cancer; (2) enrolled adult (18 years or older) participants; (3) were published in 1995 or later, the year tamoxifen was approved for chemoprevention in high-risk women; (4) were peer-reviewed primary clinical studies; and (5) reported uptake rates for real or hypothetical decisions about breast cancer chemoprevention. In July 2009, separate searches were performed in each of three databases: MEDLINE, CINAHL, and PSYCINFO. An update of this search was performed in December 2009. We did not include EMBASE or CANCERLIT because, using a trial search, they did not contribute additional studies to our search results. Search strategies were developed by an experienced research health sciences librarian. Because we did not want to miss relevant articles, our strategies purposefully were designed to emphasize high sensitivity rather than specificity, which resulted in many false positives. Our search strategy for MEDLINE was as follows: (*breast neoplasms/pc* or *breast cancer and prevent$.ti.*) and (*tamoxifen.tw.* or *reloxifene.tw.* or *antineoplastic agents, hormonal/tu* or *antineoplastic combined chemotherapy protocols/tu* or *chemoprevention or chemoprevent$.tw.*) and (*decision making* or *choice behavior* or *decision$.tw.* or *decid$.tw.* or *choos$.tw.* or *choice$.tw.* or *chosen.tw.* or *participat$.tw.* or *health knowledge, attitudes, practice*), limited to English language and humans, and earliest publication date of 1995. CINAHL and PSYCINFO search strategies were similar and are available from the authors.

The three files, one from each database, were combined into one file (yield: 320 references). Letters to editors, reviews, commentaries, and duplicates were removed, leaving one set of articles (yield: 246) to be screened for inclusion in this review.

Article Selection and Classification

Two authors (M.E.R., J.K.) independently evaluated each of the 246 articles for possible inclusion, initially using the title and abstract from the citation. Disagreements were resolved by discussion between the evaluating authors, which involved detailed review of the abstract and occasionally the full article. Of the 246 articles, four underwent this more detailed review. Reference lists of articles included in our review were subsequently examined for eligible studies not previously identified by the MEDLINE, CINAHL, and PSYCHINFO searches. One additional article was identified this way. Thirteen studies met all inclusion criteria and constitute the basis for this review.[20-32]

Data Abstraction

Information abstracted from each study included type of decision (real or hypothetical); author; country where performed; study design; sample type; sample size; who was recruited, how, and where; description of study intervention; description of usual care; method of measuring hypothetical decisions (exact wording of the question); operational definition of hypothetical decision uptake (how interest or intent was transformed into a dichotomous variable, yes/no); operational definition of real decision uptake (dichotomous variable, yes/no); uptake rates for hypothetical and real decisions; and factors evaluated for association with chemoprevention decisions.

Quality Review of Articles

Each of the included articles was reviewed for methodologic quality, using a previously established quality review system applicable to all study designs.[33-38] Seven standards were used that focused on methodologic issues relevant to study quality and minimizing bias in studies of uptake rates. Because our literature search did not identify any randomized trials, cohort studies, or case-control studies, additional standards in our established quality review system that address randomization, blinding, cross-over/contamination, and comparability of groups at baseline were not applied. The standards, their rationale, and study design for which each is relevant are as follows: standard 1: To allow understanding of who the study subjects are, the methods section provides clearly stated subject inclusion and exclusion criteria (applicable to all study designs); standard 2: To allow an estimation of reproducibility and whether study results can be applied to other groups (external validity), the sampling strategy is described clearly enough so that it would be possible to assemble the same or similar group if the study were to be repeated (applicable to all study designs); standard 3: To allow an understanding of the potential effect of incomplete participation and sampling bias, the number of individuals who refused to participate is reported (applicable to all study designs); standard 4: To allow for assessment of the potential effect of study dropouts, the number of enrolled individuals who withdrew is reported and, if there were study dropouts, the proportion of dropouts was less than 10% (not applicable to correlational/descriptive studies); standard 5: To provide an understanding of who was included in a study and to help determine whether study groups, when present, are comparable, descriptive statistics (at least age and breast cancer risk factors) are reported for the study participants according to study group (applicable to all study designs); standard 6: To provide an understanding of study outcomes, outcome measures are clearly defined and measured in the same way in all participants of any one study (applicable to all study designs); standard 7: To provide documentation of the clinimetric quality of

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outcome measures, description of or references to reliability and validity of the measure are provided (applicable to all study designs).

Two of the authors (J.T.P. and J.K.) independently assessed the articles' study design and rated them for compliance with quality standards relevant to that design. Each article received a rating of 2 (complete compliance), 1 (partial compliance), 0 (noncompliance), or NA (not applicable) for each standard. The ratings of the two reviewers were compared, and discrepancies were resolved by discussion to achieve consensus. If agreement could not be achieved, a third reviewer (M.E.R.) evaluated the article.

Statistical Analysis

For each study, we entered into a database number of subjects, number of subjects choosing uptake, decision type (real or hypothetical), risk of breast cancer (high risk present in all subjects or general population), and educational or decision support intervention (provided to all subjects or not). In addition to calculating simple statistics, we fit a logistic regression model to the data, where the independent variables were decision type, risk of breast cancer, and intervention, chosen a priori. The coefficients of regression were log odds ratios (LOR). These coefficients were related to the dependent variable, uptake rate (r), by two transformations. The first was a transformation to an odds ratio (OR) and the second to a logarithm: LOR = log(r/[1 − r]). When building the model, estimating the parameters, and interpreting the results, we followed the methodologies explained in detail elsewhere.[33,39,40] We used SAS/STAT software, version 9.1 (SAS Institute, Cary, NC) to fit the model and estimate the parameters (PROC GENMOD).

RESULTS

Study Characteristics

The 13 articles meeting the criteria to be included in this review are summarized in Appendix Table A1 (online only; real decisions) and Appendix Table A2 (online only; hypothetical decisions). Although all 13 studies used a correlational/descriptive study design, the studies were different in many other ways. Four[21,24,29,31] provided information about real chemoprevention decisions, eight[20,22,25-28,30,32] about hypothetical decisions, and one study about both.[23] They were performed in six different countries, mostly in the United States (eight) and Canada (three). Of the 13 studies, one recruited participants from lists provided by an insurance company[20]; two recruited participants from patient rolls of large health care providers[23,32]; one recruited participants through community-based advertising[28]; and the remaining nine found their subjects in various clinic settings. Ten studies enrolled patients who were at high risk for breast cancer, including all of the real decision studies.[21,23,24,29,31] Five[23,26,28,29,31] provided an intervention to assist patients in the chemoprevention decision, of which two were real, two hypothetical, and one both.

Research Question 1: What Uptake Rates for Real and Hypothetical Decisions Have Been Reported, Is There Variability in Rates, and Are Hypothetical Decision Rates Higher Than Real Decision Rates?

The mean uptake rate for the five studies reporting real decision rates was 14.8%; for the nine studies reporting hypothetical decision, it was 24.7%. There was a wide range of uptake rates for both the real (0.5% to 51.2%) and hypothetical decision types (5.7% to 60.0%). Our multivariate model found that, controlling for study intervention and breast cancer risk, hypothetical uptake was significantly greater than real uptake (OR = 1.65; 95% CI, 1.26 to 2.16, Table 1). The mean uptake for real decisions was skewed by one study[21] that reported a high rate (51.2%); the mean uptake rate of the remaining four real decision studies was only 5.8%. In the one study that reported both hypothetical and real rates from the same cohort, the hypothetical rate was 5.7% as compared with the real rate of 0.5%.[23]

Table 1. Multivariate Logistic Regression Model for Association With Uptake

Variable	OR	95% CI	*P*
Decision type			
Real (referent)	1.0		
Hypothetical	1.65	1.26 to 2.16	.0003
Intervention			
No (referent)	1.0		
Yes	0.21	0.17 to 0.27	< .0001
Risk for breast cancer			
General population (referent)	1.0		
High risk	0.65	0.56 to 0.75	< .0001

Abbreviation: OR, odds ratio.

Research Question 2: How Have Uptake Rates, Real and Hypothetical, Been Measured?

Real decision uptake rates were defined as a study reporting either that participants were taking tamoxifen or raloxifene or were enrolled in the Study of Tamoxifen and Raloxifene (STAR) trial,[8] in which all patients were randomly assigned to one of the two medications. Only one study followed participants forward in time to determine whether patients continued to take the medication.[21] In this study, at 4 months, six (8.3%) of 72 participants who initially elected to take chemoprevention were no longer taking it.

Details of how hypothetical decision uptake rates were measured are presented in Appendix Table A2. Each of the nine studies phrased the question differently and used different response choices. Some questions asked for a general opinion, such as the following[25]: "Is chemoprevention an acceptable option for preventing breast cancer?" Others were more direct, such as the following[26]: "Would you take tamoxifen every day for the next five years to lower your chance of getting breast cancer?" In five studies,[22,25-27,32] written questionnaires were used, of which two were mailed.[27,32] Other studies used an Internet survey,[23] an in-person interview,[28] a telephone interview,[20] or both in-person and telephone interviews.[30]

Research Question 3: What Factors, Such As Demographic Variables and Breast Cancer Risk, Are Associated With Uptake Rates?

Nine[20-23,24-26,28,32] of the 13 studies evaluated variables other than interventions for association with real and hypothetical decision uptake rates. These are summarized in Appendix Table A3 (online only), which includes results of both univariable and multivariable analyses when available. Correlates to uptake were modest in magnitude, with relative risks rarely above 2.0. Of personal demographic variables, age and race were not strongly correlated with uptake. Only one[22] of four studies found education level to be correlated with uptake, and in that study, education level was inversely correlated with interest. Two studies reported a correlation of lower income with greater interest.[28,32]

In only one of three studies[26] was 5-year Gail score correlated with increased interest. The most consistent variable showing a correlation with interest was perceived vulnerability to breast cancer, where

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all five studies reporting that variable found that increased perceived vulnerability was correlated with increased uptake.[20-22,28,32] Two studies reported that concern about medication adverse effects was associated with reduced uptake.[21,28]

Ten studies[21,23-31] assembled participants who were high risk rather than general population risk, whereas three studies[20,22,32] did not restrict their enrollment to high-risk women. For the high-risk cohorts, the risk level was usually determined by 5-year Gail score. Contrary to expectations, the mean hypothetical uptake rate for the studies enrolling high-risk subjects was 22.3%, compared with 29.6% in the other three studies. In our multivariate model, while controlling for decision type and educational intervention, studies enrolling only high-risk subjects reported lower uptake rates than the other studies (OR = 0.65; 95% CI, 0.56 to 0.75; Table 1).

The five studies that included an intervention concerning chemoprevention[23,26,28,29,31] had lower uptake rates (mean hypothetical, 11.7%; mean real, 4.1%) than the eight that did not include an intervention[20-22,24,25,27,30,32] (mean hypothetical, 31.2%; mean real, 31.0%). Our multivariate model found that, while controlling for decision type and breast cancer risk, an educational or decision support intervention was associated with a greatly reduced uptake (OR = 0.21; 95% CI, 0.17 0.27; Table 1).

Research Question 4: Are There Issues of Study Methodology That May Influence and Thus Bias Uptake Rates?

The last column in Appendix Tables A1 and A2 present the quality ratings for the 13 studies. The first three standards were concerned with the assembly of study subjects, and there was general compliance with standard 1 (inclusion and exclusion criteria) and standard 3 (refusal rates). However, less than half of the studies used a sampling strategy that could reproducibly assemble study groups (standard 2). These convenience samples limit generalizability of study results.

An additional methodologic concern centers on the study designs used in the reviewed articles, all of which used a correlational/descriptive design. None were randomized controlled trials or cohort studies with comparison groups that provide evidence of causality. Therefore, it is difficult to make conclusions regarding the effect of interventions on uptake rates. Only one study assessed uptake at two different times to determine change over time.[21]

Finally, hypothetical chemoprevention uptake was ascertained in many different ways, making it difficult to compare rates among studies. Also, in most studies, documentation of the reliability and validity of the survey instruments used was not provided (etandard 7). Because only one study measured hypothetical and real uptake in the same group of patients,[23] we were unable to examine in detail the relationship between interest and actual uptake behavior.

DISCUSSION

Tamoxifen for more than a decade and raloxifene more recently have been recommended for breast cancer risk reduction in women at increased risk for breast cancer.[4,41] Despite the years that chemoprevention has been available, our systematic review found only 13 studies addressing women's decisions about tamoxifen or raloxifene therapy. However, from these studies we can draw some conclusions. Even in high-risk cohorts, usually defined as a 5-year Gail score risk greater than 1.6%, less than 25% of women were "interested" in, "willing to take," or "intended to take" chemoprevention. Also in high-risk cohorts, the mean real uptake rate was 14.8%. However, this value was skewed by one study[26] reporting an uptake rate of more than 50%. We believe that this high rate was the result of subjects who were identified at STAR trial recruitment meetings, where attendees were predisposed to participate in the trial that required taking chemoprevention medications. It is likely that other studies provide a more realistic measure of real uptake in clinical practice, one reporting on a group of high-risk women who recently had a breast biopsy negative for cancer,[31] one on a group of high-risk women identified in surgical practices and a breast cancer screening clinic,[29] and the third on a group of high-risk women who volunteered to use a chemoprevention decision aid.[23] In these three studies of high-risk women, on average only 4% elected to take chemoprevention. Despite the potential benefits of chemoprevention, few women are willing to accept it.

Most of the reviewed studies used hypothetical scenarios to assess levels of interest in chemoprevention. This methodology has a number of advantages for the researcher. It is relatively inexpensive, can be done quickly, can be administered in a variety of situations and conditions, and can be presented in a standardized way.[42] However, its major limitation is that the resulting outcomes are necessarily future intentions and anticipated behaviors, which have been shown in many situations to have only a modest association with eventual behavior.[33,42,43] A number of methodologic factors may influence hypothetical uptake accuracy, including the time between the assessment of interest and when chemoprevention will actually be offered, how hypothetical uptake is measured (eg, yes/no response *v* a Likert scale), and wording of the testing scenario.[42]

Our review supports the conclusion that, for chemoprevention, hypothetical uptake has not yet been demonstrated to be an accurate predictor of real uptake. Hypothetical uptake scenarios were different in each study, contributing to variability in rates. Five studies asked general questions about interest in or willingness to take a chemoprevention medication, whereas four specifically named tamoxifen. Some studies were designed to explore general interest in chemoprevention,[20,22,25,30,32] whereas others included decision support interventions followed by an explicit question about taking tamoxifen.[23,26,28] In the one study reporting both hypothetical and real uptake in the same group of women, the hypothetical uptake rate was more than 10 times the real uptake rate.[23] Our multivariate model found that hypothetical uptake was greater than real uptake, but with an OR of only 1.65 (Table 1). This difference may be due to the frequent convenience sampling, which resulted in highly selected groups being studied, and also because our multivariate model was limited in its ability to statistically control for additional differences between the real and hypothetical studies. Although research using hypothetical scenarios may be appropriate to assess interest in testing and treatments that are in development and not yet available for patient care, this is not the case for breast cancer chemoprevention. We believe that the future role for hypothetical assessments in chemoprevention research should be limited unless clear correlations between measures of hypothetical interest and real uptake can be established.

We found few factors that correlated strongly or consistently with uptake. There was little evidence that actual breast cancer risk, a logical

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factor, was related to increased uptake. The studies that enrolled high-risk women had a lower mean hypothetical uptake than those enrolling women from general populations, and only one of three studies reporting the correlation of Gail score to uptake found a statistically significant relationship. In contrast, a woman's perceived vulnerability to breast cancer, another logical factor, was consistently associated with uptake. Although a woman's perception of breast cancer risk may be a strong motivator to accept chemoprevention, the magnitude of her risk perception can be much greater than an objective measure of risk such as determined by the Gail score.[20,26] This raises the possibility that counseling high-risk women can lead to a feeling of relief when they discover that their risk perception was an overestimation, and they may then conclude that chemoprevention is not needed.

As expected, two studies found that concern about adverse effects of chemoprevention correlated with reduced interest.[21,28] Adverse effect risk aversion has been found to be an important deterrent in other studies of chemoprevention[23,44-46] and for preventive medical treatment decisions in general.[47] When faced with the chemoprevention decision, a woman must deal with the prospect of immediate adverse effects to accrue benefits at some unknown time in the future and with knowing that a minority of those who take chemoprevention will receive the benefits. Thus it is not surprising for a recent cost-effectiveness analysis to conclude that, when quality-of-life measures are taken into account, tamoxifen use is associated with an overall reduction of "quality-adjusted life years."[48] It is of interest that the studies that included an educational or decision support intervention reported much lower uptake rates than those that did not. Because such interventions must discuss risks and adverse effects of chemoprevention, it is likely that educational interventions and decision aids dissuade women from accepting chemoprevention.

Variation in uptake may also be attributable to a physician's description of the treatment and strength of recommendation.[49] In the reviewed studies, physician bias toward or against chemoprevention could only be inferred. The recommendation of a woman's primary care provider has been reported to be important in chemoprevention decisions.[44,45] Only one of the reviewed studies involved a primary care provider in the uptake decision.[31] The real uptake rate for chemoprevention in that study was only 1%. However, a recent survey found that a minority of primary care physicians have prescribed tamoxifen for chemoprevention.[10] If use of chemoprevention is to be increased, physician education is needed to make it part of their practice.

Our review reveals the limitations of what we know about uptake of breast cancer chemoprevention. We are left with more questions than answers concerning this complex, preference-sensitive decision. Future research is needed, enrolling women who are candidates for breast cancer chemoprevention using reproducible sampling strategies that allow the results to be generalized. Further study is needed regarding (1) how to assist patients in making a quality decision, including how knowledge about breast cancer, actual and perceived breast cancer risk, and risks and benefits of chemoprevention is best communicated; (2) effective processes for health care providers to counsel regarding the chemoprevention decision; and (3) developing and testing decision support interventions. It is preferable to study these issues in real decision situations rather than hypothetical scenarios to ascertain actual uptake rates and the factors that influence this decision. Finally, randomized controlled trials that include evaluation of decision support processes and decision quality as an outcome are needed to test decision support interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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