Uptake of exemestane chemoprevention in postmenopausal women at increased risk for breast cancer

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Despite their efficacy, uptake of selective estrogen receptor modulators for breast cancer chemoprevention remains low. Exemestane, an aromatase inhibitor, has recently been identified as a potential chemopreventive option with fewer serious side effects compared with selective estrogen receptor modulators in postmenopausal women. The purpose of this study was to assess the uptake of exemestane in a breast cancer prevention clinic. A retrospective chart review was conducted to capture chemoprevention uptake by postmenopausal women presenting to the Yale Breast Cancer Prevention Clinic between November 2011 and November 2012. Descriptive statistics of the study population have been presented. Statistical analyses were carried out using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA) between December 2012 and February 2013. Of 90 postmenopausal women, 56 were eligible for chemoprevention. Their mean age was 56.8 years. Among the women, 39% had osteopenia or osteoporosis. Thirteen women chose to start chemoprevention medication (23%). Although 31\% of the chemopreventive medication administered included exemestane, only four of 56 postmenopausal women opted for exemestane (7\%). Chemoprevention uptake rates of postmenopausal women in the setting of a breast cancer prevention clinic are higher than that reported in the general population; however, they remain low overall despite the inclusion of exemestane as an option. A significant proportion of postmenopausal women have decreased bone density, which is a potential barrier to exemestane uptake. The results provide practical implications suggesting that exemestane may have limited impact on breast cancer chemoprevention uptake. Further investigations should focus on understanding the factors that influence, predict, and increase chemoprevention uptake. 

Keywords: aromatase inhibitors, breast cancer chemoprevention, chemoprevention uptake, exemestane, postmenopausal women

Introduction

Despite stabilization of breast cancer incidence rates and declining mortality in recent years, primary prevention of this disease remains a major public health issue, given that over 230,000 women are diagnosed with invasive breast cancer each year in the USA alone (Smigal \textit{et al.}, 2006; Reimers and Crew, 2012; Youlden \textit{et al.}, 2012). Approximately 75\% of breast cancer patients are estrogen receptor (ER) positive, and this percentage increases with age (Anderson \textit{et al.}, 2011). Although ER-positive tumors have a better prognosis than ER-negative tumors, ER-positive tumors are responsible for most breast cancer deaths owing to their higher prevalence and therefore comprise an important focus for prevention efforts (Decensi \textit{et al.}, 2012).

The selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene were the first drugs to gain recognition as effective agents for reducing the risk for ER-positive breast cancer in women at increased risk (Fisher \textit{et al.}, 1998; Cuzick \textit{et al.}, 2002, 2003; Powles \textit{et al.}, 2007). Several organizations including the US Preventative Task Force, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommend breast cancer chemoprevention for individuals at increased risk (Bevers \textit{et al.}, 2010; Moyer and Force USPST, 2013; Visvanathan \textit{et al.}, 2013). However, although SERMs have been shown to reduce breast cancer incidence by up to 50\% in clinical trials (Fisher \textit{et al.}, 1998; Vogel \textit{et al.}, 2006), this impressive result has not translated well into clinical practice. The uptake of SERM chemoprevention among healthy US women of ages between 40 and 79 years has remained low in both the general (1\%) and the high-risk populations (5\%; Visvanathan \textit{et al.}, 2009; Ropka \textit{et al.}, 2010; Waters \textit{et al.}, 2010). One reason commonly cited for poor chemoprevention uptake is patient concern over potential...
side effects, including increased risk of vasomotor symptoms, endometrial cancer, thromboembolic events, and cataracts (Cummings et al., 1999; Martino et al., 2004; Fisher et al., 2005; Vogel et al., 2010). These data clearly indicate the need for alternative agents with less toxicity if breast cancer chemoprevention is to be successfully integrated into practice (Gail, 2011).

Aromatase inhibitors (AIs) have been proposed as safer alternatives with potentially better acceptance as chemopreventive agents for ER-positive breast cancer. AIs have long been recognized to reduce contralateral primary breast cancers at least as efficiently as tamoxifen therapy in postmenopausal women who received these drugs as adjuvant therapy for invasive cancer (Fisher et al., 1997; Cuzick et al., 2003; Atalay et al., 2004; Chow et al., 2008; Ellis et al., 2011; Goss et al., 2011). This observation, in addition to the expectation of a more favorable side-effect profile, stimulated interest in evaluating exemestane and anastrozole in chemoprevention trials (Johannessen et al., 1997; Goss et al., 2004, 2007, 2011; Cuzick, 2008). Published in 2010, the MAP.3 (Mammary Prevention 3) trial was the first double-blind, randomized, phase III trial demonstrating the use of an AI in a prevention setting (Moy et al., 2007). In this trial, 25 mg exemestane administered daily for 5 years compared with placebo reduced the risk of invasive breast cancer (primarily ER-positive breast cancer) by 73% in postmenopausal women at increased risk (Goss et al., 2011; Visvanathan et al., 2013). The most commonly observed side effects included vasomotor symptoms, arthralgia, and vaginal dryness (Moy et al., 2007). In addition, chemoprevention of breast cancer with exemestane in postmenopausal women worsened the age-related decrease in bone mineral density by approximately three times compared with placebo, despite adequate calcium and vitamin D supplementation (Cheung et al., 2012). Yet, the majority of women adhered to therapy (~85%; Moy et al., 2007). Similar results were seen in the recently published IBIS-II (International Breast Cancer Intervention Study II) double-blind, randomized phase III trial that compared 1 mg anastrozole daily for 5 years with placebo in postmenopausal women at increased risk for breast cancer. Anastrozole reduced the risk for ER-positive breast cancers by 50%, with the most commonly reported side effects being an increase in musculoskeletal adverse events and vasomotor symptoms, with a confirmed increase in the frequency of hypertension, vaginal dryness, and dry eye. Full 5-year adherence to therapy was 70% in the anastrozole group (Cuzick, 2008).

These data support the efficacy of AIs as chemopreventive agents and indicate an acceptable safety profile; however, whether the acceptance of these agents will be better than that of SERMs remains to be seen. Although AIs have fewer serious side effects such as thrombosis or secondary cancers compared with SERMs, they have significant rates of vasomotor symptoms and arthralgia and may also contribute to osteoporosis (Crew et al., 2007; Walker et al., 2013). Uptake of AIs as chemopreventive agents in the clinic has not been reported to date. The goal of this study was to determine the overall uptake of exemestane among postmenopausal women at increased risk for breast cancer presenting to a breast cancer prevention clinic.

Methods
A retrospective chart review was conducted to capture patient characteristics, medical history, and chemoprevention uptake of all postmenopausal women presenting to the Yale Breast Cancer Prevention Center (YBCPC) between November 2011 and November 2012. Postmenopausal status was defined as follows: (i) self-reported natural menopause (12 months of amenorrhea in the absence of other biological or physiological causes) or (ii) self-reported surgical menopause (bilateral oophorectomy). The study protocol was approved by the Institutional Review Board at Yale University and a waiver was obtained for informed consent.

Study population
All women presenting to YBCPC were evaluated clinically and counseled about chemoprevention with either an SERM or exemestane by a single provider, trained as a breast medical oncologist (E.H.). Counseling with regard to chemopreventive options included evaluation of overall health, breast cancer risk, and bone density, and discussion of the benefits and potential risks of each treatment on the basis of available clinical chemoprevention guidelines (Bevers et al., 2010; Moyer and Force USPST, 2013; Visvanathan et al., 2013; http://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf). Breast cancer risk was assessed using the available literature and/or by risk modeling with the National Cancer Institute’s Breast Cancer Risk Assessment Tool (BCRAT; NCI). Risk assessment also included the use of the SERM risk/benefit indices published by Freedman et al. (2011) where applicable. Postmenopausal women deemed eligible for chemoprevention were those whose benefit from chemoprevention outweighed its known risks, those without prior or current SERM use, and those without any medical contraindications to chemoprevention. Women with known osteopenia or osteoporosis were considered eligible for chemoprevention but were offered an SERM rather than exemestane.

Data collected for each patient included age, race, personal and family history of cancer, the presence of a known genetic mutation, history of precancerous lesions (e.g. atypia), history of breast biopsy, age of menarche, age at parity, BCRAT/Gail model score, hysterectomy status, medication history, smoking history, alcohol history, breast density, bone mineral density, and the presence of vasomotor symptoms.
Statistical analyses

The primary objective of this study was to compare the overall chemoprevention uptake of tamoxifen, raloxifene, and exemestane among a group of postmenopausal women presenting to a breast cancer prevention clinic. Basic descriptive statistics were applied to characterize the study population and uptake rates. Statistical analyses were carried out using SAS version 9.3 (SAS Institute Inc.) between December 2012 and February 2013.

Results

Study characteristics

A total of 215 women were seen at YBCPC in the defined time frame. Ninety women were postmenopausal and therefore selected for a detailed chart review. Characteristics of the study population are provided in Table 1. The mean age of the postmenopausal women presenting for evaluation was 56.8 years (range 41–79 years). The majority of women were non-Hispanic whites (87.8%), whereas African-Americans (6.7%), Hispanics (2.2%), and Asian-Americans (1.1%) constituted a minority. Categories of breast cancer risk included one or more of the following: breast atypia (15.5%), lobular carcinoma \textit{in situ} (16.7%), prior ductal carcinoma \textit{in situ} (7.8%), family history of breast cancer (in first, second, and/or third degree relatives; 45%), and/or a known deleterious \textit{BRCA} \textit{1 or 2} mutation (24.4%).

The mean calculated 5-year breast cancer risk, on the basis of the BCRAT/Gail model, where applicable, was $5.3 \pm 4.0\%$. Approximately 38.9% of women had undergone a hysterectomy, and 54.4% had documented heterogeneous or extremely dense breast tissue. Thirty-one percent reported ongoing vasomotor symptoms at baseline, and 39% reported a known history of osteopenia or osteoporosis.

Upon clinical assessment, 34 of the 90 postmenopausal women were determined not to be candidates for chemoprevention because of significant medical comorbidities (e.g. active cancer diagnosis, $n = 19$), prior and/or current use of SERMs ($n = 11$), current hormone replacement therapy use ($n = 2$), and advanced age (age $> 75$ years, $n = 2$), leaving 56 women for analysis of chemoprevention uptake.

Thirty-four women (61%) of the 56 eligible candidates for chemoprevention had a normal or unknown bone mineral density, whereas 22 (39%) of them had documented osteopenia and/or osteoporosis (Table 2).

Decisions about exemestane treatment

Of the 56 postmenopausal women eligible for chemoprevention, 13 (23%) opted to start administering chemotherapy medication (Fig. 1). Of these, seven had normal bone density, whereas six had either osteopenia or osteoporosis. Eight women accepted raloxifene, one accepted tamoxifen, and four accepted exemestane (Table 3). Although 31% of the women who accepted chemoprevention uptake opted for exemestane, only four...
reluctant to take on this risk. While these women may be
purposes in this setting, and many patients may be
to offer exemestane solely for breast cancer prevention
of up to 2.0, many practicing clinicians may be reluctant
on bone density measurements. While the MAP.3 and
eligible for chemoprevention had documented bone loss
proportion (39%) of postmenopausal women otherwise
of AI chemoprevention in clinical practice. First, a large
trials.

**Table 3** Selection of chemopreventive drug type among those
patients opting for chemoprevention (n = 13)

| Total uptake [N (%)] | Normal/unknown bone density [N (%)] | Osteoporosis/osteopenia [N (%)] |
|----------------------|------------------------------------|--------------------------------|
| Tamoxifen            | 1 (7.7)                            | 0 (0)                           |
| Raloxifene           | 8 (61.5)                           | 3 (23.1)                        |
| Exemestane           | 4 (30.8)                           | 4 (30.8)                        |

(7%) of the 56 postmenopausal women eligible for breast
cancer chemoprevention were ultimately started on exe-
memestane in a clinical setting. The reasons commonly
mentioned by patients to their provider (E.H.) for
deciding against chemoprevention were primarily related
to concerns over potential side effects such as develop-
ment and/or worsening of vasomotor symptoms, worsen-
ing of baseline arthritic discomfort, secondary cancer risks,
thrombosis risks, and/or potential worsening of bone
density.

**Discussion**
To our knowledge, this is the first report that examines
the application of exemestane as a chemopreventive
agent in a breast cancer prevention clinic. Although the
overall prevention uptake rate was found to be 23% and
is higher than the generally reported prevention uptake
rate in the community, it still remains low. Among those
who were eligible for chemoprevention, only 7% started
on exemestane. Our findings suggest that AIs will have
limited impact on the prevention of breast cancer, despite
their impressive efficacy results from clinical
trials.

We identified three potential barriers to the acceptance
of AI chemoprevention in clinical practice. First, a large
proportion (39%) of postmenopausal women otherwise
eligible for chemoprevention had documented bone loss
on bone density measurements. While the MAP.3 and
IBIS-II trials included women with bone mineral density
of up to 2.0, many practicing clinicians may be reluctant
to offer exemestane solely for breast cancer prevention
purposes in this setting, and many patients may be
reluctant to take on this risk. While these women may be
the ideal candidates for an SERM, as they have a favor-
able effect on bone density, with studies demonstrating
up to a 32% reduction in fracture incidence, other
potentially frightening side effects (e.g. thromboembolic
complications, endometrial cancer) limit their acceptance
(Anon, 1998; Fisher et al., 1998; Smigal et al., 2006).
Although exemestane may have less effect on bone density
compared with other AIs, 2 years of treatment with exem-
emestane in the MAP.3 trial was found to be associated with
a three-fold worsening of bone density loss in postmenopausal
women compared with placebo, despite calcium and vita-
min D supplementation (Cheung et al., 2012). With nearly
50,000 deaths each year ultimately attributed to hip fractures
(Deprey, 2009; Stevens and Rudd, 2013; http://www.cdc.gov/
homeandrecreationsafety/fulph/ahdulhtipfs.html), osteoporosis
represents a major competing threat to health in postmenopausal
women and cannot be ignored when considering
chemoprevention options, including AIs. Given that osteo-
penia is not an absolute contraindication to use of an AI in
the prevention setting, how an individual provider frames
these competing risks to the patient will certainly influence
AI uptake rates.

A second major barrier to AI uptake in the clinical pre-
vention setting is the potential for significant side effects,
including vasomotor symptoms and arthralgia. Although
most of the toxicity of exemestane in the MAP.3 trial was
reported as grade 2 or less, symptoms including hot flashes,
musculoskeletal arthritis, and joint pain had mean grade 3
toxicity scores, which may impair the uptake of and
adherence to long-term preventive use of exemestane by
healthy women (Decensi et al., 2012). Interestingly, overall
health-related quality of life with exemestane did not show
a significant difference as compared with the control arm
(Decensi et al., 2012). IBIS-II showed similar results, with
significant musculoskeletal and vasomotor symptoms with
anastrozole but 75% adherence at 3 years (Cuzick, 2008;
Ropka et al., 2010). Yet, the clinical experience with poor
SERM chemoprevention uptake demonstrates that, despite
encouraging clinical trial results showing no significant
impact on the quality of life, women are reluctant to
administer medication for breast cancer prevention that
carries the potential for side effects (Ropka et al., 2010).
In addition, the absence of experience and hesitation in con-
trolling the side effects of available SERM chemopreven-
tive agents among internists, gynecologists, and family
medicine practitioners have been observed in clinical trials
(Rondanina et al., 2008), and often, it is the strength of the
physician’s recommendation that appears to influence
uptake in the high-risk population (McKay et al., 2005).

A third barrier to AI breast cancer chemoprevention
uptake is the inherent difficulty in communicating
accurate risk/benefit profiles to women at increased risk
of breast cancer. For a patient and provider to decide to
pursue any chemoprevention recommendation, the
woman’s risk of breast cancer must first be assessed and
then weighed against the potential risks and benefits of
chemoprevention. Although two models for breast cancer risk assessment, namely, the BCRAT/Gail Model and the IBIS model, are free and available online, only 18% of primary care physicians use them to calculate breast cancer risk (Guerra et al., 2009). Lack of confidence in primary prevention of breast cancer and time restriction during clinical visits have been cited as potential reasons for the software not being frequently utilized (Sabatino et al., 2007). There are no similar tools to personalize predictions of risks for side effects beyond the SERM Benefit/Risk Indices published in 2011 (Freedman et al., 2011). However, even if an accurate risk/benefit assessment is obtained, explanation of absolute versus relative risk reduction with the use of chemoprevention, in comparison with side effects and risks from the medications, can be time-consuming and challenging. Unfortunately, decision aids and reading material have had limited success in increasing SERM chemoprevention uptake, ranging from 0.5 to 5.6% (Port et al., 2001; Taylor and Taguchi, 2005; Fagerlin et al., 2010, 2011; Loehberg et al., 2010). It seems unlikely that the introduction of AIs will simplify risk assessment and decision making.

For breast cancer chemoprevention to succeed, the significant clinical trial results seen in P-1, STAR, MAP-3, and IBIS-II are not enough. Indeed, two approaches must be considered to move the breast cancer prevention field forward. One approach could be to focus efforts on identifying new agents with even more favorable toxicity profiles; even if such agents had lesser efficacy, their overall impact on breast cancer incidence rates would be large if they were broadly used. Alternatively, a similar large impact on breast cancer incidence would be seen if we are able to accurately identify the smaller population of women at highest risk for breast cancer, among whom the risk/benefit profiles are the most favorable. Ultimately, for SERMs and AIs to play a major role in breast cancer prevention, the latter approach must be pursued, with attention focused on improving risk modeling and identifying accurate and reliable biomarkers of breast cancer risk.

We believe our study to have several strengths. All patients were seen in a clinic setting specifically dedicated to breast cancer prevention. Breast cancer risk was universally defined by available risk modeling when appropriate, and patients were seen by a single provider, ensuring uniformity of approach. Limitations of the study include the relatively small sample size, the retrospective nature of the study, and the inability to determine details of patient decision making around AI and chemoprevention uptake from chart review. The fact that patients were seen by a single provider at a single site could also introduce bias; however, if present, it would potentially bias results toward chemoprevention uptake in general.

In conclusion, the uptake of the AI exemestane into the clinical breast cancer prevention setting was found to be low, with only 7% of eligible postmenopausal women pursuing exemestane treatment. A significant proportion of postmenopausal women at increased risk for breast cancer have decreased bone density, which appears to potentially limit the population in which AI could otherwise be utilized. Further research must be undertaken for AIs to successfully impact breast cancer incidence rates, with efforts focused on accurate identification of those women at highest risk for breast cancer.

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Conflicts of interest
There are no conflicts of interest.

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