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Preference For Breast Cancer Risk Reduction Hormonal Therapy
In Postmenopausal Women 50 -69 Years Attending Screening Mammography

by

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Abstract

The objective of this study was to elicit preference for breast cancer risk reduction hormonal therapy amongst women 50 – 69 years who attend screening mammography. The discrete choice experiment method was used and the attributes considered were effectiveness, cost and serious side effects. Five hundred women were invited to participate, 94 agreed and were sent the discrete choice experiment in the mail, and 79 completed questionnaires were returned. Participants preferred a drug that was more effective, less expensive, and did not increase the risk for endometrial cancer, venous thromboembolic events or bone fracture. Relative reductions in breast cancer risk between 18% – 33% were found to compensate for being at increased risk for the serious side effects. Predicted probability of choosing risk reduction hormonal therapy increased as the number of drug options increased. Feasibility of the discrete choice experiment method in this clinical context was demonstrated.

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Dedication

My thesis is dedicated to researchers and health care providers involved with cancer risk reduction efforts.

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List of Abbreviations

AH	Atypical hyperplasia
NSABP	National Surgical Adjuvant Breast and Bowel Program
NCI	National Cancer Institute
AI	Aromatase inhibitor
SERM	Selective estrogen receptor modulator
RCT	Randomized controlled trial
SD	Standard deviation
LCIS	Lobular carcinoma in situ
RR	Relative risk
95% CI	Ninety-five percent confidence interval
IBIS	International Breast Cancer Intervention Study
OR	Odds ratio
HRT	Hormone replacement therapy
HR	Hazards ratio
MORE	Multiple Outcomes of Raloxifene Evaluation
ASCO	American Society of Clinical Oncology
NCCN	National Comprehensive Cancer Network
QALY	Quality adjusted life year
TTO	Time trade-off
WTP	Willingness to pay
DCE	Discrete choice experiment
MRS	Marginal rate of substitution
VAS	Visual analogue scale
CHREB	Conjoint Health Research Ethics Board
RRR	Relative risk reduction

Chapter One: Introduction

1.1 Overview

Breast cancer is a major health concern for women, health care providers, policy makers and society. Evidence-based screening and risk reduction recommendations exist and vary according to predicted risk level. One risk reduction option available is drug treatment with tamoxifen; however, intentional and actual uptake reported in the literature is variable. In postmenopausal women, raloxifene has also been studied as a risk reduction drug, and the aromatase inhibitors are under investigation. Tamoxifen, raloxifene and the aromatase inhibitors are associated with differing benefits, side effects and costs. The discrete choice experiment method is an ideal, quantitative, stated preference strategy for studying how women value and trade-off between the characteristics of breast cancer risk reduction drugs.

1.2 Clinical background

1.2.1 Burden of breast cancer

Breast cancer is the most commonly diagnosed cancer in Canadian women, with 22,400 new cases predicted for the year 2008[1]. With screening and more effective treatments for early stage disease, the prevalence of survivors has been increasing. Currently, 1% of Canadian women are breast cancer survivors[1]. The management of early breast cancer, however, is not without impact for both the individual and society. Standard local management of early breast cancer is lumpectomy or mastectomy, sampling of axillary lymph nodes and in many cases, radiation[2-4]. To decrease the risk of metastatic recurrence and improve overall survival rates, adjuvant systemic therapies are also often

used, and may include 4-6 months of chemotherapy and/or 5-10 years of hormonal therapy[5-8]. Recently, trastuzumab, a humanized monoclonal antibody, has become a standard treatment in early breast cancer that over-expresses the protein HER2/neu. Trastuzumab is given intravenously every 3 weeks for one year starting concurrently with chemotherapy or after chemotherapy has been completed[9]. From an individual economic perspective, Lauzier et al have prospectively studied the short term impact of being diagnosed with early breast cancer amongst 800 women in Quebec[10]. They found that for the 459 women who had a paying job during the month before diagnosis, mean single time absence from work required was 7 months that resulted in a mean loss of 27% of projected usual annual salary after taking into account financial compensation received. From a societal economic perspective, Barron et al estimated the mean per patient per month cost during the year post diagnosis for breast cancer patients to be 2.38 times higher than matched non-breast cancer patients in a managed care setting in the United States[11]. Hospitalization contributed to most of the costs, followed by pharmacotherapy and then surgery. Finally, although mortality from breast cancer is decreasing, it is still of great importance when analyzing burden due to this disease. In 2008, it is estimated that 5300 Canadian women will die from breast cancer[1]. Cancer in general is the leading cause of premature death in Canada and breast cancer accounts for 17.8% of potential years life lost due to cancer in women[1].

1.2.2 Breast cancer risk assessment

Clearly, breast cancer is a major health issue. Screening programs exist for early detection, and risk reduction strategies are available. Recommendations vary according to

risk level with some being applicable to the general population of Canadian women where risk is currently one in nine over the lifetime[1], while other recommendations may only apply to those who can be identified to be at higher risk. Although models for breast cancer risk prediction have been developed and are used in clinical practice, this is still an active area of research.

Breast cancer risk prediction models must take into account factors which increase or modify risk. Age, endogenous and exogenous hormonal exposure, benign breast disease, mammographic breast density and family history are broad categories of the most established risk factors for breast cancer[12-14]. There is emerging data for lifestyle factors[15]. Alcohol consumption increases risk, but possibly only in women with inadequate folic acid intake[15]. Elevated body mass index and weight gain increase risk of postmenopausal breast cancer[15]. Physical activity appears to decrease risk[15].

Gail et al analyzed data from the Breast Cancer Demonstration Project and developed a model to predict the incidence of both non-invasive and invasive breast cancer in a general population of women undergoing mammographic screening[16]. This model incorporates the following risk factors: age, age at menarche, parity, age at first live birth if applicable, number of previous breast biopsies, diagnosis of atypical hyperplasia (AH) on breast biopsy, and number of first degree relatives who have been diagnosed with breast cancer. For the National Surgical Adjuvant Breast and Bowel Project's trial of preventive tamoxifen versus placebo (NSABP-P1), the model of Gail et al was altered to predict the incidence of invasive breast cancer only, and incorporated age-specific rates

from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (NCI) instead of the rates from the Breast Cancer Demonstration Project[17].

Within the placebo arm of NSABP-P1, agreement of observed and expected incident invasive breast cancers was excellent across the age groups[18]. This model is available online as the NCI Breast Cancer Risk Assessment Tool at:

[\(http://www.cancer.gov/bcrisktool/\)](http://www.cancer.gov/bcrisktool/) and can be used to predict 5-year and lifetime risks of invasive breast cancer in women who are at least 35 years of age. It is not applicable to women with in-situ breast cancers, women with previous invasive breast cancer or women from families where a dominantly inherited breast cancer susceptibility gene is highly suspected or confirmed[18].

The NCI Breast Cancer Risk Assessment Tool is the most utilized risk prediction model in clinical practice where a dominantly inherited breast cancer susceptibility gene is not suspected or confirmed. However, examination of a new model that also takes into estrogen and androgen levels, mammographic breast density, body mass index and waist-hip ratio is being studied by the Breast Cancer Prevention Collaborative Group[19].

1.2.3 Evidence for risk reduction hormonal therapy

For women with certain breast cancer risk factors, one strategy of risk reduction is drug treatment. Good quality studies for two drugs, tamoxifen and raloxifene, as breast cancer prevention agents have been completed and results published. Currently, another class of hormonal therapy, the aromatase inhibitors (AIs), are being evaluated as risk reduction agents.

Tamoxifen is a selective estrogen receptor modulator (SERM) that is commonly used to improve outcomes after an early breast cancer has been surgically removed (adjuvant treatment). The Early Breast Cancer Trialists' Collaborative Group has been conducting quinquennial metaanalyses of randomized controlled trials (RCTs) examining adjuvant tamoxifen versus placebo. In the 1998 publication that included 37,000 women from 55 RCTs, the risk of breast cancer recurrence was decreased relatively by 42% (SD = 3, $p < 0.00001$) and the risk of death from any cause by 22% (SD = 4, $p < 0.00001$), for women on tamoxifen compared with women on placebo at the 10 year follow-up mark.[20]. It was also found that the risk of a new contralateral breast cancer was reduced by 47% (SD = 9, $p < 0.00001$) with tamoxifen use[20]. The consistent finding that tamoxifen decreases the risk of contralateral breast cancer prompted its investigation as a drug that may help prevent or delay primary breast cancer in otherwise healthy women. The largest prevention trial, which randomized 13,388 women to tamoxifen 20 mg/day or placebo for 5 years, was NSABP-P1[17]. Eligible women were at least 60 years of age or had a history of lobular carcinoma in situ (LCIS) or were 35 and 59 years with a predicted 5-year breast cancer risk of at least 1.66%. With a median follow-up time of 54.6 months, tamoxifen decreased the risk of invasive and non-invasive breast cancer by 49% (RR 0.51, 95% CI 0.39 – 0.66) and 50% (RR 0.50, 95% CI 0.33 – 0.77) respectively for all age groups. The cumulative incidence of invasive breast cancer was 22 per 1000 women in the tamoxifen group and 43 per 1000 women in the placebo group. The cumulative incidence of non-invasive breast cancer was 7.7 per 1000 women in the tamoxifen group and 15.9 per 1000 women in the placebo group.

Three other prevention RCTs of tamoxifen versus placebo have been published. The next largest study in comparison to NSABP-P1, was the International Breast Cancer Intervention Study (IBIS-I)[21]. IBIS-I included 7139 women at high risk for developing breast cancer due to specific family history criteria or having had a diagnosis of either LCIS or AH. With similar median follow-up time to NSABP-P1, tamoxifen decreased the risk of invasive and non-invasive breast cancer by 25% (OR 0.75, 95% CI 0.54 – 1.04) and 69% (OR 0.31, 95% CI 0.12 – 0.82) respectively. Neither the Royal Marsden Hospital study[22] which included 2471 high risk women, nor the Italian study[23] which included 5408 average risk women with hysterectomy, showed a statistically significant benefit for tamoxifen compared with placebo with respect to incident breast cancer cases. Unlike NSABP-P1, the other three trials allowed for the use of hormone replacement therapy (HRT). Nevertheless, a metaanalysis of the four tamoxifen prevention trials has been conducted[24]. The pooled data suggest that tamoxifen compared to placebo decreases the risk of invasive or non-invasive breast cancer by 38% (HR 0.62, 95% CI 0.54 – 0.72). Besides impacting breast cancer risk, in NSABP-P1 tamoxifen led to a non-significant reduction in the risk of fractures involving the lower radius, hip and spine (RR 0.81, 95% CI 0.63 – 1.05; annual incidence 4.29/1000 versus 5.28/1000).[17] This outcome was not considered in all of the prevention trials and therefore was not analyzed in the metaanalysis. Given the use of HRT in the other trials, any benefit of tamoxifen on bone may have been obscured.

The side effects of tamoxifen are important to note and were examined in detail in NSABP-P1[17]. Hot flashes, which were “quite a bit or extremely bothersome,”

occurred in 45.7% of women on tamoxifen and 28.7% on placebo. Another common, nuisance toxicity was “moderately bothersome or worse” vaginal discharge occurring in 29% of women on tamoxifen compared to 13% on placebo. Tamoxifen significantly increased the risks of endometrial cancer (RR 2.53, 95% CI 1.35 – 4.97; annual incidence 2.3/1000 versus 0.91/1000), pulmonary embolism (RR 3.01, 95% CI 1.15 – 9.27; annual incidence 0.69/1000 versus 0.23/1000) and the need for cataract surgery (RR 1.57, 95% CI 1.16 – 2.14; annual incidence 4.72/1000 versus 3.00/1000). Non-significant trends with respect to increased risks of deep venous thrombosis (RR 1.44, 95% CI 0.91 – 2.30; annual incidence 49/1000 versus 34/1000) and stroke (RR 1.42, 95% CI 0.97 – 2.08; annual incidence 71/1000 versus 50/1000) were also observed. The metaanalysis also found that tamoxifen significantly increased the risks of endometrial cancer (HR 2.4, 95% CI 1.4 – 4.0) and venous thromboembolic events (HR 1.9, 95% CI 1.4 – 2.6)[24].

Raloxifene is a later generation SERM. In an RCT of raloxifene versus placebo (Multiple Outcomes of Raloxifene Evaluation Study or MORE study) in 7705 postmenopausal women with osteoporosis, raloxifene was found to decrease the risk of vertebral fractures (RR 0.7, 95% CI 0.5 – 0.8 for the 60 mg arm and RR 0.5, 95% CI 0.4 – 0.7 for the 120 mg arm) and increase bone mineral density in the spine and femoral neck[25]. A secondary outcome was breast cancer incidence. Raloxifene decreased the risk of invasive and non-invasive breast cancer (RR 0.35, 95% CI 0.21 – 0.58; 1.5 versus 4.3 per 1000 women-years)[26]. More women on raloxifene experienced hot flashes and venous thromboembolic events. However, raloxifene did not increase the risk of endometrial cancer. This finding was anticipated as animal studies have shown that

raloxifene antagonizes the mitogenic activity of estrogen and tamoxifen on the endometrium[26]. Women from this trial were invited to continue raloxifene (60 mg) or placebo for an additional four years and 4011 consented. The magnitude of breast cancer risk reduction was similar in the first and subsequent, four year study periods[27].

NSABP-P2 was an RCT that compared raloxifene and tamoxifen for preventing breast cancer in postmenopausal women at least 35 years old with predicted 5-year breast cancer risk $\geq 1.66\%$ [28]. 19,747 women participated. The incidence of invasive breast cancer was the same in both groups (RR 1.02, 95% CI 0.82 – 1.28; annual incidence 4.41/1000 versus 4.30/1000). There was a trend for more non-invasive breast cancer in the raloxifene group (RR 1.40, 95% CI 0.98 – 2.00; annual incidence 2.11/1000 versus 1.51/1000). In the raloxifene group, there were fewer cases of endometrial cancer (RR 0.62, 95% CI 0.35 – 1.08; annual incidence 1.25/1000 versus 2.00/1000), significantly fewer cases of venous thromboembolic events (RR 0.70, 95% CI 0.54 – 0.91; annual incidence 2.61/1000 versus 3.71/1000) and significantly fewer diagnoses of cataracts (RR 0.79, 95% CI 0.68 – 0.92; annual incidence 9.72/1000 versus 12.30/1000). The incidence of osteoporotic fractures was similar in both groups (RR 0.92, 95% CI 0.69 – 1.22; annual incidence 2.51 versus 2.73).

While SERMs such as tamoxifen and raloxifene block the interaction of estrogen with its receptor, AIs prevent the rate-limiting step in estrogen synthesis. AIs are potent suppressors of estrogen production in postmenopausal women only, and are becoming a component of standard adjuvant hormonal therapy in postmenopausal women with early,

hormone receptor positive breast cancer[8]. The AI, anastrozole, has been compared with tamoxifen after resection of early, ER positive breast cancer in a large RCT involving approximately 3000 women per arm[29]. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival and of interest, reduced the incidence of contralateral breast cancer (relative risk reduction 42%, 95% CI 12-62%). One discussion point from this study was “as tamoxifen compared with placebo shows a 50% reduction in the occurrence of breast cancer, anastrozole might prevent 70-80% of cases.” Other large RCTs have examined AIs after varying length courses of tamoxifen, in comparison to tamoxifen only for 5 years, in the setting of early, postmenopausal, hormone receptor positive breast cancer. These studies have also found favourable results for AIs with respect to improved disease-free survival and trends for decreased rates of contralateral breast cancer[30-32]. Due to the consistent finding of decreased contralateral breast cancer incidence with the AIs in the adjuvant studies to date, this class of drug is currently being evaluated as a primary prevention or risk reduction agent[33].

The side effects of AIs and tamoxifen differ and the data from Howell et al is exemplary. For anastrozole versus tamoxifen, hot flashes were less common (OR 0.80, 95% CI 0.73 – 0.89; incidence 35.7% versus 40.9%) and arthralgias more common (OR 1.32, 95% CI 1.19 – 1.47; incidence 35.6% versus 29.4%)[29]. In comparison to tamoxifen, anastrozole decreased the risk of venous thromboembolic events (OR 0.61, 95% CI 0.47 – 0.80; incidence 2.8% versus 4.5%) but increased the risk of fractures (OR 1.49, 95% CI

1.25 – 1.77; incidence 11.0% versus 7.7%).[29] The other adjuvant AI studies report similar side effect profiles[30-32, 34].

1.2.4 Clinical practice guidelines pertaining to risk reduction hormonal therapy

Several groups have published recommendations with respect to the use of risk reduction hormonal therapy for breast cancer. A joint guideline from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was published in 2001 and was based on the interpretation of three tamoxifen prevention trials (NSABP-P1, Italian and Royal Marsden) and one raloxifene study (MORE)[6]. They found fair evidence to support skilled and experienced individuals counselling women with a predicted 5-year breast cancer risk of at least 1.66% on the potential benefits and harms associated with using tamoxifen to prevent breast cancer. With respect to tamoxifen, two important notes were made. First, they note that in NSABP-P1, the average predicted 5-year breast cancer risk was 3.2% and that as this risk increased above 5%, the benefits of tamoxifen were more likely to outweigh the harms. Second, they note that the modified Gail index had not been validated as a high risk case finding instrument and hence recommend against routine use in physician offices. For raloxifene, evidence considered did not support its use for breast cancer prevention outside of a clinical trial. The American Society of Clinical Oncology (ASCO) Technology Assessment of Pharmacologic Interventions for Breast Cancer Risk Reduction was published in 2002[35]. This group also considered the results of IBIS-I. The guideline recommends that women with a predicted 5-year breast cancer risk of at least 1.66% may be offered

tamoxifen to decrease the short term risk of breast cancer. They note that the greatest benefit with the least side effects can be expected for premenopausal women, women without a uterus and women at higher breast cancer risk. They recommend for counselling purposes, that outcomes with/without tamoxifen be translated into absolute terms. Evidence considered did not support the use of raloxifene or AIs for breast cancer prevention outside of a clinical trial.

The most current guideline on breast cancer risk reduction hormonal therapy comes from the National Comprehensive Cancer Network (NCCN) as of February 2008[36]. The NCCN guideline recommends that women with established breast cancer risk factors undergo risk assessment. Furthermore, it is suggested that discussion of risk reduction hormonal therapy be reserved for women identified to be at higher risk (for example those with a predicted 5-year risk of at least 1.7% using the modified Gail index), women who have a life expectancy of at least 10 years, and women who have normal breast cancer screening tests. It is recommended that in the absence of an available clinical trial, tamoxifen can be discussed with premenopausal women, and tamoxifen or raloxifene with postmenopausal women. The guideline also suggests that counselling should include presentation of benefit in terms of relative and absolute numbers, assessment of contraindications, and discussion of common and serious adverse events, with emphasis on age-dependent risks. Finally, it is clearly stated that for both premenopausal and postmenopausal women, use of an aromatase inhibitor for breast cancer risk reduction is inappropriate unless part of a clinical trial.

1.2.5 Intentional and actual uptake of risk reduction hormonal therapy

In 2003, it was estimated that 10 million women in the United States were eligible for risk reduction hormonal therapy with tamoxifen based on Food and Drug Administration approval guidelines but that only 2.5 million had a favourable risk-benefit ratio[37].

Furthermore, if these 2.5 million women took tamoxifen, approximately 28,000 new breast cancer cases could be prevented or deferred over a 5-year period. The potential impact of breast cancer risk reduction hormonal therapy from a societal perspective is significant. Since the publication of NASBP-P1 and the other prevention trials, interest in breast cancer risk reduction hormonal therapy, actual uptake, and the associated incentives and barriers, have become novel topics of study.

Reported interest in risk reduction hormonal therapy or intended uptake varies across the studies to date. A large telephone survey of women partaking in a breast cancer screening study, asked about interest in taking a drug to prevent breast cancer. The telephone interview did not include counselling or education about expected benefits or side effects of tamoxifen. Of 1273 women contacted, 23% expressed interest and it was found that perceived risk, breast cancer worry, being a current smoker or user of HRT were predictive[38]. Tjia et al focused on women age 60 – 65 years in their mailed questionnaire[39]. As for the telephone survey described above, specific details about benefits and toxicities were not provided. Of the 457 participants, 11.2% reported being interested in taking breast cancer chemoprevention and 47.9% were unsure. For women with a predicted 5-year breast cancer risk greater than 1.66%, lack of interest in chemoprevention was associated with low perceived risk and low breast cancer worry,

and for women with a predicted 5-year breast cancer risk of 1.66% or less, interest in chemoprevention was associated with greater breast cancer worry. A few mixed methods studies have been conducted to understand the attitudes and preferences of women eligible for preventive tamoxifen. In the larger study, a convenience sample of 250 women was recruited from community groups, health fairs, radio advertising and direct mailing of those on the observational arm of a study[40]. Participants underwent a standard education session, post educational session test of knowledge, and a structured interview. The education session described the potential benefits and risks of tamoxifen versus no treatment in terms of number of events per 1000 women over 5 years, and these benefits and risks were presented in multiple formats. 80% answered all of the post test questions correctly and only 2% had a difficult time understanding the benefits and harms. 17.6% were inclined to take tamoxifen. Factors associated with willingness to try tamoxifen were being confident in tamoxifen to reduce breast cancer risk, feeling that tamoxifen's beneficial effect on fractures is important, and having a household income less than 200% of the federal poverty level. In the smaller mixed methods study, 27 women potentially eligible for risk reduction hormonal therapy underwent in depth, semi-structured interviews and were asked to estimate the likelihood that they would take risk reduction hormonal therapy in the next 5 years[41]. The authors found that four conditions must be met in order for a woman to accept risk reduction hormonal therapy: belief in effectiveness, able to overcome reluctance to ingest a manufactured substance of uncertain safety, belief that the side effects will be tolerable and tending to be proactive and in control of health related matters. The estimated chance of taking risk reduction

hormonal therapy over the next 5 years ranged from 62% to 67% depending on the risk group.

Actual uptake of risk reduction hormonal therapy reported in the literature is also quite variable. The earliest uptake data comes from the NSABP prevention trials. For women who met the risk eligibility requirements, only 21 – 25% went onto screening for medical eligibility. However, of those who met medical eligibility requirements, approximately 96 – 98% were randomized. Outside of the prevention trials, data on uptake is scarce.

Clinic-based series report variable uptake: 1 of 27 (3.7%)[42], 2 of 43 (4.7%)[43], 6 of 41 (14.6%)[44, 45], and 57 of 137 (41.6%)[46]. Tchou et al found that history of atypical

hyperplasia or lobular carcinoma in situ, and older age were significant predictors of being offered and accepting treatment with tamoxifen[46]. In Port et al, the most

frequently cited reason for declining tamoxifen was fear of side effects[43]. Two other

uptake studies have had more involved protocols. In Bober et al, 129 women were recruited from a high risk clinic, individual physician practices and an introductory

meeting for the NSABP-P2 trial[47]. Participants received information during a counselling session and then were assessed immediately afterwards plus 2 and 4 months

later. At 2 months, 37 (28.7%) had decided to take preventive tamoxifen and 35 (27.1%) decided to participate in NSABP-P2. These numbers decreased only slightly at 4 months.

Factors associated with the uptake of risk reduction hormonal therapy were lower concern about side effects, more intrusive thinking about breast cancer, greater perceived vulnerability, higher perceived breast cancer risk and perceived physician

recommendation. Factors associated with decision satisfaction included having an

autonomous motivation style. Those dissatisfied with their decision were more likely to have greater breast cancer worry, depressive symptoms, perceived helplessness and lack of confidence. The authors express that the findings with respect to decision satisfaction, underscore the importance of shared decision making that supports a woman's sense of self-efficacy. In Taylor and Taguchi, 89 eligible women were identified from a surgical clinic[48]. These women were not called back for counselling but rather sent a letter outlining their 5-year and lifetime breast cancer risks with encouragement to discuss preventive tamoxifen with their family physician. Family physicians also received a letter outlining their patient's risk assessment along with the evidence available for risk reduction hormonal therapy. Between 2 and 14 months later, 48 women had discussed preventive tamoxifen with their family physician and 1 woman elected to take it. Five other women who also had osteoporosis or osteopenia were prescribed raloxifene. The most frequently reported reasons for declining tamoxifen were fear of serious side effects, low perceived breast cancer risk, and lack of physician recommendation.

1.3 Methods background

1.3.1 Stated preference methods

Stated preference is where a choice is indicated in response to a hypothetical situation[49]. One approach for comparing health interventions and services is cost-utility analysis where benefit is measured in quality adjusted life-years (QALYs). This approach requires that weights be attached to various health states. Stated preference methods have been used to obtain disease-specific, direct weights, and include choice-based approaches such as standard gamble and time trade-off (TTO)[50]. Another approach for comparing

health interventions and services is a stated preference method on its own - contingent valuation or willingness to pay (WTP). A more recently applied stated preference method in health care is conjoint analysis, such as the discrete choice experiment (DCE). DCEs present more realistic decisions to respondents compared with the other stated preference techniques, disease-state weights can be derived, they allow for indirect WTP estimates, and DCEs can measure non-health outcomes (provision of information, reassurance) and process of care factors (waiting time, location of treatment, continuity of care)[51]. In a health technology assessment of techniques for eliciting public views on the provision of health care[52], it is concluded that “there is no single, best method” and that “the method must be carefully chosen and rigorously carried out in order to accommodate the question being asked.” Standard gamble, TTO, WTP and conjoint-based methods were favourably assessed based on a comprehensive evaluation that took into account validity, reproducibility, internal consistency, acceptability to respondents, cost, theoretical basis, whether the technique offered a constrained choice and whether the technique provided a strength of preference measure[52].

1.3.2 Discrete choice experiment method

The DCE method originated from mathematical psychology and is used to quantify preference for non-traded goods and services[53]. It is an established method in marketing research, transportation economics and environmental economics and has been increasingly applied in the health care sector since the 1990's[53]. The theoretical basis underlying the DCE method is described next. From random utility theory, the utility U

that individual i derives from alternative j is composed of systematic (V) and random components (ϵ)[54]:

$$U_{ij} = V_{ij} + \epsilon_{ij} \quad (\text{equation 1})$$

The systematic component V is often modelled as a linearly additive function of the attributes as follows[54]:

$$V_{ij} = X'_{ij}\beta \quad (\text{equation 2})$$

X'_{ij} is a vector of explanatory variables and β is a conformable vector of coefficients.

Explanatory variables are those attributes specific to the intervention or service, but can also include others to describe individual characteristics. However, as utility is latent and cannot be directly measured, choice is taken as an indicator[54]. It is assumed that an individual i chooses option 1 if, and only if, its utility is higher than the utility of any other option in the set of J alternatives. The probability that utility is maximized in choosing option 1 is[54]:

$$\begin{aligned} P(Y_i = 1) &= P(U_{i1} > U_{ij}) \\ &= P(V_{i1} + \epsilon_{i1} > V_{ij} + \epsilon_{ij}) \\ &= P(V_{i1} - V_{ij} > \epsilon_{ij} - \epsilon_{i1}) \quad \forall j \neq 1 \quad (\text{equation 3}) \end{aligned}$$

Y_i is the dependent variable denoting the choice outcome.

Next the steps involved in conducting a DCE are presented. The good (or what will be herein called an intervention as more appropriate for the setting of health care), or service, being evaluated must be described in terms of attributes[49, 55, 56]. The attributes chosen should be relevant to the research question. A policy question may define the attributes. Other research questions may demand a literature review or exploration of important issues through qualitative research. One attribute is usually price (cost to the consumer) or a price-proxy (such as time required to complete or wait for an intervention or service, travel time to access an intervention or service, waiting time for results). Other common attributes found in health care based DCE studies include effectiveness of an intervention, accuracy of a test, location of a service, type of health care provider, and risks associated with an intervention or test. Ryan and Gerard reviewed 34 DCE studies pertaining to health care which were published from the start of 1990 through the end of 2000[57]. All studies reported the sources of the attributes and the rationale for choosing the attributes. The number of attributes ranged from 2 to 24, with a mode of 6. A monetary attribute was included in 19 studies and a time attribute in 25 studies.

Two or more levels must be assigned to each attribute. It has been suggested that the levels vary around the status quo so that they are plausible and actionable but at the same time should stimulate respondents to exhibit trading behaviour[49, 55, 56]. For example, if the price-proxy attribute for an intervention such as reconstruction following mastectomy for breast cancer is waiting time, and the current status quo is 12 months, the chosen levels might be 1, 6, 12 and 24 months. In this way respondents are faced with

potentially more and less desirable options that are still realistic from clinical and policy standpoints.

The principle of a DCE is to systematically vary attributes and levels to test hypotheses about behaviour. A profile is created when the levels of two or more attributes are combined. A binary choice experiment is when a series of profiles are presented, and the respondent is asked if he would choose the intervention or service: yes or no[53, 56]. A multiple choice experiment is when profiles (which differ by the attribute levels) are presented simultaneously, and the respondent is asked to choose one option[53, 56]. Multiple choice experiments may present forced choices where the respondent must pick one of the profiles, or they may allow the respondent to opt-out (i.e. choose none of the profiles). The number of possible profiles for a DCE is L^A (where L = number of levels and A = number of attributes). For example, if there are to be 3 attributes with 2 levels, and 2 attributes with 4 levels, then the number of possible profiles is $2^3 \times 4^2 = 128$. DCEs that incorporate all possible profiles are called full factorial designs and those that incorporate less are called fractional factorial designs. Developing a fractional factorial design can be done using computer software, website and catalogue designs or expert opinion. When determining a fractional factorial design, it must be decided whether only main effects will be considered or whether interactions will also be examined. Furthermore the following properties of a good design should be maintained: orthogonality or lack of correlation between the levels of two or more attributes; level balance meaning that the attribute levels occur with equal frequency within the experiment; and, if using a multiple choice format, minimal level overlap where attributes

do not appear at the same level for a particular choice[56]. If the number of choices will potentially be too burdensome for each respondent to complete, a block design can be utilized[56]. This means that two or more versions of the questionnaire are created and distributed to respondents in a stratified manner. In the review by Ryan and Gerard, 25/34 studies used a fractional factorial design, 19/34 used computer software to create the fractional factorial design and 25/34 only considered main effects[57].

Prior to the DCE questions, respondents are presented with pertinent background information about the subject in question and the attributes and levels to be examined[56]. The DCE can be administered using a self-complete questionnaire (either paper and pen, or web-based) or during a one-to-one interview[56]. Demographic and other relevant data, such as individual characteristics hypothesized to influence preference, are usually collected at the same time[56]. In the review by Ryan and Gerard, 27/34 studies used a self-complete questionnaire, 3 used a one-to-one interview and 3 used a computer-based interview[57].

For the analysis, an estimable choice model is derived from equation 3 by assuming a distribution for the random components. The conditional logit specification for the choice probabilities arises if the random components are assumed to be independent and identically distributed as extreme value type 1 random variates[54]. The type 1 extreme value distribution is as follows[58]:

$$f(\varepsilon) = \exp[-\varepsilon - \exp(-\varepsilon)] \quad (\text{equation 4})$$

Making this assumption, the probability P of individual i choosing option 1 in choice set J becomes[54]:

$$\begin{aligned} P(Y_i = 1) &= \exp(V_{i1}) / \sum_{j=1}^J \exp(V_{ij}), j = 1 \dots J \\ &= \exp(X'_{i1}\beta) / \sum_{j=1}^J \exp(X'_{ij}\beta), j = 1 \dots J \quad (\text{equation 5}) \end{aligned}$$

The method of maximum likelihood estimation is used to calculate the coefficients. The log likelihood function to be maximized has the following form[59]:

$$l = \sum_{i=1}^N \sum_{j=1}^J d_{ij} \ln[P(Y_i = 1)] = \sum_{i=1}^N \sum_{j=1}^J d_{ij} \ln[\exp(X'_{i1}\beta) / \sum_{j=1}^J \exp(X'_{ij}\beta)] \quad (\text{equation 6})$$

Here $d_{ij} = 1$ if individual i chooses alternative 1 and $d_{ij} = 0$ otherwise.

The coefficients estimated by the regression analysis represent the part-worths or marginal utilities of the attributes[49, 56]. For each attribute, the null hypothesis is that its associated utility, holding all other attributes constant, is zero. If the null hypothesis is rejected (significant p-value), then the attribute is considered to be an important influence of choice[49, 56]. The sign on a significant coefficient suggests direction of influence on choice[49, 56]. For example, a significant and positive coefficient suggests that the attribute increases the utility and probability of choosing the intervention or service.

Beyond statistical significance and sign, the estimated coefficients do not have meaningful interpretation and hence a gauge of practical significance with respect to the research question is not provided. One approach is to convert the coefficients (and their upper and lower confidence levels) to odds ratios which are then interpretable as the odds of choosing an alternative per increment of a continuous attribute, or the odds of choosing an alternative when a categorical attribute is present compared with when it is not. In both cases, odds are interpreted while holding all other attributes constant. The further an odds ratio is from unity and the tighter the confidence interval, the greater the potential practical significance in terms of an association between the attribute and choice.

Another means of interpreting the coefficients in a more meaningful way is to examine how individuals trade between two attributes. The marginal rate of substitution (MRS), or the rate at which an individual gives up one unit of an attribute for a one-unit increase in another attribute, is calculated by taking the ratio of the two coefficients[49, 56]. This is derived by partially differentiating the indirect utility function with respect to two attributes and then calculating their ratio[54]. If the denominator is the coefficient on the price attribute, then an indirect estimate of WTP is made[49, 56]. Ranking the attributes according to the magnitude of the coefficients is frequently observed in the health care-related DCE literature in describing relative importance. However, such an approach must be undertaken with caution as the attributes are more often than not measured differently (different units for continuous attributes or a mixture of continuous and categorical attributes).

The results of a DCE as thus far described can be further utilized[56]. Two or more interventions or services, with known attribute levels, can be compared in terms of relative overall utility or benefit, or according to overall WTP as measured by price or a price-proxy. Furthermore, probability of choosing one or more interventions or services, again with known attribute levels, can be predicted. Alternatively, a goal choice probability can be set, and the changes in attribute levels required to achieve the goal be explored.

1.3.3 Discrete choice experiments in health care

DCEs in health care have been used to measure preference for provision of services [51, 60, 61], screening programs [55, 62-65], and treatments [66-69], and have largely been from the perspective of potential users or patients. DCEs have also examined health care provider preference for treatment recommendations (in order to help explain variability in practice)[70] and for job attributes[71]. A comprehensive review of DCEs in health care is beyond the scope of this dissertation. A selection of DCEs are discussed next that have some relation to the current study in that preference for a risk reduction treatment or preference for a cancer screening program in relation to a women's health issue is measured.

The DCE most closely related to the current study examined women's preference for osteoporosis (fracture prevention) drug treatments[66]. The researchers recruited 120 women, age 60 years or older, from general practices in Rotterdam, Netherlands. These women had participated in a study on osteoporosis case finding and were classified as

low risk of hip fracture ($< 6\%$ over 10 years) or at high risk ($\geq 6\%$ over 10 years).

Attributes included were: drug effectiveness (expressed as relative reduction in risk of hip fracture over 10 years), nausea as a side effect, route of administration, treatment duration and out of pocket cost. Multiple choice format with an opt-out alternative was used.

Using conditional logit regression, they found that all attributes influenced choice and in the direction expected (i.e. effectiveness was a positive influence on choice). Inherent preference for drug treatment was identified but a 40% relative reduction in hip fracture risk was required to compensate for nausea as a side effect, and a 12% relative reduction in hip fracture risk was required before an out of pocket monetary contribution was considered acceptable. It was concluded that the target group of women should be willing to accept the currently available fracture prevention drug and that active osteoporosis case finding is supported.

Gerard et al have studied preference for breast cancer screening services amongst a convenience sample of women using a current service in Sydney, Australia[55]. They considered the following attributes: how the client is informed of eligibility, whether or not an information sheet is provided with invitation for screening, waiting time, appointment time choices, time spent traveling to appointment, how staff relate to client, privacy of changing area, time spent having screen, time waiting for results, and accuracy of results. The format was binary choice – yes or no. Random effects probit regression was used for the analysis and some interaction terms were considered. The most important attribute was accuracy but others were information sheet, travel time, screening time and privacy hence lending support to the importance of non-health outcomes and

process factors. Regression post estimation techniques were used to predict the probability of participation in the current service, a new service that would entail a few short-term changes, and a new service that would entail longer-term changes.

Ryan and Wordsworth used a DCE to measure preference for a cervical cancer screening program[63, 64]. A stratified random sample of women was selected from a database giving the names and addresses of all women 18 – 65 years eligible for cervical cancer screening in the Tayside area of Scotland. Attributes considered were time interval between tests, time for results, chance of being recalled, chance of having an abnormality, chance of dying from cervical cancer and cost of each test. The format was multiple choice with an opt-out alternative. Using random effects probit regression analysis, they found that all attributes were important influences of choice. Total WTP per test for a proposed new cervical screening program was calculated. Part of this study was to examine the sensitivity of the total WTP estimate to the attribute levels chosen. Hence two questionnaires were used that varied only in respect to the levels for 3 of the 6 attributes, each administered to roughly half of the respondents. Total WTP for the new cervical screening program did not differ between the groups. Their data was reanalyzed using another method that allowed for inclusion of individual characteristics in the model. From this analysis, it was found that the decision to screen or not was based only on individual characteristics and not on the attributes of the service itself. Hence from a policy perspective, their results suggested that improving the clinic would not improve participation.

1.3.4 Stated preference for breast cancer risk reduction hormonal therapy

Interest in breast cancer risk reduction hormonal therapy has been studied using basic survey techniques and in a few cases, more formal mixed methods approaches as described in 1.2.5. Only one study published thus far has attempted to systematically measure stated preference for a breast cancer risk reduction drug. Grann et al studied preference for a breast cancer prevention drug plus other health states: being at high genetic risk for breast and ovarian cancer, undergoing prophylactic mastectomy and/or oophorectomy, and having early or advanced breast or ovarian cancer[72]. A non-random recruitment procedure of women age 20 – 50 years was used and participants were divided into four groups: younger average risk women (<33 years), older average risk women (33-50 years), women known to be at high genetic risk (33-50 years), and women with breast cancer (33-50 years). Participants were asked to imagine being at high genetic risk, presented with nine vignettes relating to the health states of interest, and then subjected to two techniques for measuring preference. First, women were asked to rate the health state on a 0 to 100 visual analogue scale (VAS), and then they were asked a TTO question. They were told that a new treatment could eliminate the health state but that it would shorten the remaining life span (70 minus current age). They were then asked how many years of the remaining life span they were willing to trade to eliminate the health state. Preference for the health state according to the TTO question was calculated as $(1 - \text{time traded} / \text{remaining life span})$ multiplied by 100.

Some results from Grann's study are as follows. VAS ratings were consistently lower than the TTO scores. Evidence for convergent validity of the two methods was not

reported. The VAS rating for the chemoprevention vignette was not reported. The four groups did not differ significantly in terms of TTO scores for the chemoprevention state but did differ for the genetic risk, prophylactic surgery and cancer states. The two average risk groups preferred chemoprevention over preventive mastectomy but the high genetic risk and breast cancer groups did not. However, none of the groups preferred chemoprevention or preventive mastectomy over breast cancer.

Grann's study was done to provide preference weights for health states that could then be incorporated into a cost-utility analysis of risk reduction options available to women at high genetic risk for breast cancer. Their results suggest that the cost-utility analysis will be sensitive to whether the visual analogue scale or time trade-off weights are used, and the perspective that is taken (population, high genetic risk or breast cancer patient). Their instrument and methodology elicit concerns regarding validity. Overestimation of weights is suspected in some instances. The chemoprevention vignette provided respondents with a single estimate of effectiveness and excluded any discussion of potential side effects. Between 3 and 25% of participants per group did not trade time for freedom from any of the cancer states. With respect to generalizability, preference of women older than 50 years was not studied.

1.4 Current study

In the near future, it is expected that AIs, in addition to tamoxifen and raloxifene, will be available as risk reduction agents for postmenopausal women who meet threshold risk criteria. The literature thus far on how women value the benefits, side effects and costs of

preventive tamoxifen is limited. It is unknown how women value the upcoming breast cancer risk reduction drugs which are different from tamoxifen in terms of effectiveness, cost and side effect profiles. To formally assess preference for breast cancer risk reduction hormonal therapy in this hypothetical setting, the discrete choice experiment method was chosen for several reasons: (1) a quantitative method was desired; (2) it was felt to be novel for studying preference for drug treatment; (3) the research question fit the requirements of the method (for example it was possible to describe risk reduction drugs according to the same attributes); and (4) it was felt to have several advantages over other stated preference techniques. With respect to the latter reason, a DCE allows the researcher to examine: (1) preference for both the component characteristics that define the intervention and the intervention as a whole; (2) strength of preference for the component characteristics; and (3) probability of choosing different choice alternatives. Furthermore, the DCE method presents more realistic questions to respondents compared with standard gamble and TTO. This study was undertaken as a pilot in order to examine feasibility with respect to the population and topic concerned, and generate hypotheses from the results. The study proposal was approved by the Conjoint Health Research Ethics Board (CHREB), Faculty of Medicine, University of Calgary on February 26, 2007 (Appendix A).

1.5 Objectives

The primary objective was to elicit preference, using a discrete choice experiment, for breast cancer risk reduction hormonal therapy attributes (effectiveness, cost, and serious side-effects) in a pilot study of women age 50 – 69 years who attend screening

mammography through the Alberta Cancer Board Screen Test Program in the Calgary Health Region. Secondary objectives were as follows: (1) to assess the feasibility of the DCE method; (2) to predict choice of risk reduction hormonal therapy given hypothetical drug availability scenarios (tamoxifen, raloxifene, AIs); and, (3) to examine the generalizability of the DCE results by comparing participants and non-participants on demographic and breast cancer risk factors.

Chapter Two: Methods

2.1 Overview of study design

In this pilot study, preference for attributes of breast cancer risk reduction hormonal therapy was elicited using a discrete choice experiment administered to a sample of the target population via a one-time postal survey. Regression and post estimation techniques were applied to the DCE data. Demographic and breast cancer risk factor information on all invited women was obtained from the sampling frame database. Participant and non-participant groups were compared.

2.2 Target population

The target population was as follows: female gender, age 50 through 69 years, participation in breast cancer screening mammography, and absence of previous diagnosis of pre-invasive or invasive breast cancer. Only females are included as breast cancer risk reduction hormonal therapy has not been studied in males. The age range of 50 through 69 years was chosen because this is the target age range for screening mammography and potential clinical eligibility for AIs, in addition to tamoxifen and raloxifene. The screened population was chosen as it is this group to which breast cancer risk assessment and risk reduction hormonal therapy is most applicable.

2.3 Study population and sampling frame

Women meeting the criteria specified for the target population, residing in the Calgary Health Region, and having had a normal first time or repeat screening mammogram in the prior 12 months through the Alberta Cancer Board Screen Test Program were

eligible. The Screen Test Database was utilized as a sampling frame for two main reasons. First, Screen Test was willing, as an uninvolved party, to solicit interest in the study. Second, Screen Test systematically collects and records demographic and breast cancer risk factor information on all clients, and hence presented a convenient opportunity to collect this desired data.

2.4 Sample size and sampling procedure

Theoretical formulae for calculating sample size for a DCE have been proposed but are not readily applicable[49]. A reported heuristic is that 50 respondents are required to allow estimation of a reliable choice model consisting of main effects only[49]. Models containing interaction terms or experiments with sub-group analyses would require more respondents. A goal sample size of 50 was chosen for the current DCE as the proposed model did not contain interaction terms and sub-group analyses were not planned. From the Screen Test Database, 500 potentially eligible women were randomly selected and invited to participate. This strategy allowed for up to 90% of selected women to decline participation initially or at a later stage.

2.5 Recruitment procedure

The 500 eligible women identified by Screen Test were mailed an information letter about the study (Appendix B) with a pre-stamped, return postcard (Appendix C) asking permission for the research team to be in contact by telephone. At the time of telephone contact, potential participants were given further information about the study (Appendix

D). Two options for participation were presented: (1) attending an “in person” information and data collection session, and (2) participating via a postal survey.

2.6 DCE design

2.6.1 Instrument

The DCE questionnaire was accompanied by the Background Information booklet (Appendix E). The contents of this booklet spanned six pages and included: a reminder note on how participants were selected, the background information which is discussed in 2.6.2, and an introduction to the DCE (including details about attributes and levels, and an example of a choice set). The DCE Questionnaire booklet (Appendix F) spanned twenty pages. It included: introductory statements, 18 choice sets, a difficulty rating question, a section for open-ended comments, and a final question soliciting interest in obtaining study results. For the difficulty rating question, participants were asked to rate the difficulty of completing the DCE on a 5-point Likert scale labelled such that 1 = very easy, 2 = somewhat easy, 3 = moderate, 4 = somewhat difficult and 5 = very difficult. In both booklets, the respondent is asked to imagine being at above-average risk for developing breast cancer. A consistent example of above-average breast cancer risk occurred throughout the two booklets (i.e. 40 per 1000 women over 5 years).

The Background Information booklet and DCE questionnaire were assessed by two experts in the field of breast cancer for content validity. The instrument was administered to a convenience sample of graduate students (5), female breast cancer oncology nurses (2), and breast cancer patients (3), for assessment of time commitment, readability and

face validity. Evaluators provided written comments. Reported time commitment for a first pass reading of the Background Information booklet and to complete the DCE questionnaire ranged from 15 to 30 minutes. Changes were made to the Background Information booklet as follows. The main focus was simplification and some reorganization to improve readability. In consideration of face validity, two changes were incorporated. The reminder note on how participants were selected (Screen Test client, not because known to have elevated breast cancer risk) was moved from the back of the booklet to the start. Furthermore, naming tamoxifen as an example of a breast cancer risk reduction hormonal therapy was deleted. Changes to the DCE questionnaire were not required. It was, however, noted by evaluators and accepted by the researcher, that the DCE was potentially a complex task requiring a certain threshold level of literacy.

2.6.2 Background information

The intention of the background information was to introduce participants to breast cancer, breast cancer risk factors, how breast cancer risk and risk reduction can be described, and the potential benefits and side-effects associated with breast cancer risk reduction hormonal therapy. It has been suggested that disease-risk information for the public be clear, put into context and acknowledge uncertainty[73]. In terms of clarity, a numeric estimate of a specific outcome occurring during a specific time period, should be provided.

To describe the force of breast cancer, the risk of a 50 year old woman being diagnosed with breast cancer over 5 years was stated (adapted from provincial cancer statistics[74]).

The risks for a 60 year old woman and a 70 year old woman were also given in consideration of the target population. Risk was expressed as an absolute number as recommended by the ASCO Technology Assessment on Pharmacologic Interventions for Breast Cancer Risk Reduction. Specifically, “incident cases per 1000 women” was utilized. This approach is likely grounding as most women do not perceive their breast cancer risk to be higher than average, but most women do overestimate their numeric risk[75]. For context, women were told that breast cancer is the most commonly diagnosed cancer in women, mortality is much lower than incidence[1, 74], but that treatments can affect quality of life and are imperfect. Finally with respect to acknowledging uncertainty, it was suggested that breast cancer risk may be modified by various factors other than age[12-16].

The concept of risk reduction was introduced. It was demonstrated how a relative risk reduction statement translates into absolute numbers.

2.6.3 Attributes and levels

Attributes and attribute levels were determined through identification of key issues in the risk reduction hormonal therapy literature and DCE design. Literature on risk reduction hormonal therapy focuses on effectiveness and major side effects. Hence, breast cancer risk reduction, risk of endometrial cancer, risk of venous thromboembolic events and risk of bone fracture were selected as attributes. As DCEs routinely incorporate price or a price proxy, annual out of pocket cost was also selected as an attribute.

For breast cancer risk reduction, four levels were chosen and presented in terms of relative risk reduction (RRR) in the incidence of invasive breast cancer. The levels reflect the estimated range of benefit demonstrated to date for the drugs being represented. A RRR of 25% reflects the benefit of tamoxifen in IBIS-I[21], a RRR of 40% reflects the benefit of tamoxifen in the metaanalysis[24], a RRR of 50% reflects the benefit of tamoxifen in NSABP-P1[17] and presumably the benefit of raloxifene as per NSABP-P2[28]. A RRR of 70% reflects what might be expected of an AI as per the adjuvant trial of anastrozole versus tamoxifen[29].

Levels for the serious side effects were categorized. For endometrial cancer and venous thromboembolic events, the risk was either “increased” or “unchanged.” For bone fracture, the risk was either “decreased” or “increased.”

In keeping with suggested guidelines for presenting disease-risk information to the public, attribute levels for breast cancer risk reduction and the side effects were further described in terms of absolute numbers. For breast cancer risk reduction, how a woman with above-average breast cancer risk of “40 in 1000 over 5 years” benefits was shown. For instance, if the level for breast cancer risk reduction was 25%, then the description in absolute numbers was “40 in 1000 reduced to 30 in 1000.” For the side effect levels, a corresponding annual risk of “x in 1000” was provided. Rates for the levels “risk unchanged” and “increased risk” for the side effect attributes endometrial cancer and venous thromboembolic events were extracted from the placebo and tamoxifen arms of NSABP-P1[17]. For endometrial cancer, only invasive disease was considered. For

venous thromboembolic events, rates for pulmonary embolus and deep venous thrombosis were combined. Rates were rounded off to whole numbers. The rate for the level “decreased risk” for the attribute bone fracture was extracted from the tamoxifen arm in NSABP-P1[17]. The rate for all fractures combined was considered. In healthy, postmenopausal women who have never been diagnosed with breast cancer, the risk of bone fracture with AIs is unknown. In women with early breast cancer, AIs increase risk for bone fracture by 1.5 to 2 times in comparison to tamoxifen or in comparison to placebo after exposure to tamoxifen[29-32]. The rate for the level “increased risk” for the attribute bone fracture was obtained by multiplying the fracture incidence for the placebo arm of NSABP-P1[17] by 1.5 to be conservative.

For out of pocket cost, four levels were chosen and described in terms of annual cost in dollars. The market value for a year supply of drug plus biennial dispensing fees was approximately: \$160 for tamoxifen, \$640 for raloxifene and \$1840 for an aromatase inhibitor. If the drug was covered 100% by a third party, then the cost of dispensing the drug twice during a year was approximately \$40.

The attributes, levels and level description using absolute numbers where applicable are presented in Table 1.

Table 1: Attributes, levels and level description using absolute numbers

Attribute	Levels	Level description using absolute numbers
Breast cancer risk reduction	25%	40/1000 reduced to 30/1000
	40%	40/1000 reduced to 24/1000
	50%	40/1000 reduced to 20/1000
	70%	40/1000 reduced to 12/1000
Annual out of pocket cost	\$40, \$160, \$640, \$1840	N/A
Endometrial cancer	Risk unchanged	1/1000 per year
	Increased risk	2-3/1000 per year
Venous thromboembolic event	Risk unchanged	1/1000 per year
	Increased risk	2/1000 per year
Bone fracture	Decreased risk	5/1000 decreased to 4/1000 per year
	Increased risk	5/1000 increased to 7-8/1000 per year

2.6.4 Scenarios and choice sets

The attributes and levels resulted in 128 ($4^2 \times 2^3$) possible scenarios. A fractional factorial design to estimate main effects, assuming all interactions to be negligible, was adopted to give a manageable series of choice sets for the experiment. From a design catalogue, it was found that 16 scenarios were required in order to examine 2 attributes with 4 levels and 3 attributes with 2 levels. The fractional factorial design was created from “A Library of Orthogonal Arrays” accessed from:

<http://www.research.att.com/~njas/oadir/>. Orthogonality and level balance were checked.

The choice sets were then created using a matched, fold-over technique which meant that level overlap was avoided[56]. Two further choice sets were created as tests of internal consistency as described in 2.11. The choice sets were randomly ordered in the questionnaire. For all choice sets, respondents were asked whether they preferred “Drug A”, “Drug B”, or “Neither” (continued mammographic screening only). An example of a choice set is shown in Figure 1.

Figure 1: Example of choice set

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	40% <i>For example:</i> 40/1000 reduced to 24/1000	50% <i>For example:</i> 40/1000 reduced to 20/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$160 per year	\$640 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?

(Check 1 box only)

Drug A

Drug B

Neither

2.7 Data collection

2.7.1 DCE

The “in person” information and data collection session was not employed as this participation option was not selected by any of the potential participants. Those agreeing to participate via a postal survey were mailed a cover letter (Appendix G), the Background Information booklet, the DCE questionnaire, and a stamped, return envelope. A reminder post card (Appendix H) was sent 7 days after the initial mail-out. Non-responders identified 14 days after the date the reminder card was sent were contacted by telephone, asked if the package was received and if there was still interest in participating in the study (Appendix I). If interest expressed during this telephone contact, individuals were encouraged to complete and mail the questionnaire. A second package was sent 14 days after the telephone contact if the questionnaire had still not been returned.

2.7.2 Demographic information and breast cancer risk factors

Demographic and breast cancer risk factor data on the 500 women initially invited was obtained from the Screen Test Database in two aggregates: one aggregate of those who returned a completed questionnaire (participants) and one aggregate of those who declined or failed to return a completed questionnaire (non-participants). Demographic data included: age and education level. Breast cancer risk factor data included: age at menarche, number of live births, age at first live birth if applicable, number of previous breast biopsies, number of first degree relatives with breast cancer and mammographic breast density (recorded as category of % fibroglandular tissue on mammogram where <

25% = fatty, 25 – 50% = scattered fibroglandular densities, 51 – 75% = heterogeneously dense and >75% = extremely dense).

2.8 Data management

Data obtained from the DCE Questionnaire was entered into spreadsheet (Microsoft Excel 2003). Accuracy of data entry was re-checked on a 10% random sample of questionnaires. Data from Screen Test was received in a spreadsheet (Microsoft Excel 2003). Accuracy of data entry for this component, hence, could not be checked. The two spreadsheets were saved as separate “.csv” files and separately imported into Intercooled Stata Version 9 (Statacorp, College Station TX) for data cleaning and analysis.

2.9 Outcome measures

2.9.1 Feasibility of DCE method

Feasibility of the DCE method was examined by measuring (1) the extent of questionnaire completion defined as the proportion of choice sets answered across all respondents, and (2) the perceived straightforwardness of the DCE exercise defined as the proportion of participants who rated the questions overall as “very easy,” “somewhat easy” or “neither easy nor difficult” on a 5-point Likert scale.

2.9.2 DCE

Outcome measures with respect to the DCE were as follows. (1) The important attributes of risk reduction hormonal therapy were those with statistically significant coefficients from the regression analysis. (2) For the important attributes, whether each was a positive

or negative influence on choice was indicated by the sign of the coefficient. (3) Strength of preference for the important attributes was determined through marginal rate of substitution calculations using coefficients from regression analysis. The value of a 1% relative reduction in breast cancer risk was expressed as the dollar amount participants were willing to pay. The value of avoiding being at increased risk for each serious side effect was expressed both as the dollar amount participants were willing to pay and as the percent relative reduction in breast cancer risk participants were willing to trade. (4) The probability of choosing risk reduction hormonal therapy in different settings of drug availability (tamoxifen only; tamoxifen and raloxifene; all three drugs – tamoxifen, raloxifene and AIs) was calculated using a regression post estimation technique. The effect of varying the assigned level for venous thromboembolic event risk for raloxifene from “increased risk” to “risk unchanged” was examined.

2.9.3 Demographic information and breast cancer risk factors for participants and non-participants

Participants and non-participants were compared on the following demographic and breast cancer risk variables: (1) mean age; (2) proportion with any post-secondary education; (3) mean age at menarche; (4) proportion nulliparous; (5) mean age at first live birth where applicable; (6) proportion with a first degree relative with breast cancer; (7) proportion with a personal history of breast biopsy; (8) proportion with a predicted 5-year breast cancer risk $\geq 1.66\%$; and (9) proportion with extremely dense breast tissue ($\geq 75\%$ fibroglandular tissue) on most recent mammogram.

Predicted 5-year breast cancer risk was estimated using the NCI Breast Cancer Risk Assessment Tool. Screen Test could not provide data on past diagnosis of AH for women who reported a history of breast biopsy hence “unknown” was entered in this field where applicable. Furthermore, data on ethnicity was not requested and hence “white” was entered for all. In the Screen Test 2003/2005 Biennial Report approximately 80% of clients reported British or European ancestry[76].

2.10 Analysis

2.10.1 Regression analysis

The DCE data was analyzed with conditional multinomial logit regression for panel data (clogit) using Intercooled Stata Version 9 (Statacorp, College Station TX). The dependent variable was choice and the grouped variable was the question (choice set). Each choice set for each participant was associated with three alternatives or observations. The independent variables were the attributes. Clustering by participant was undertaken to adjust for within subject effects. For the model as a whole and for the attribute coefficients, statistical significance was considered when the p-value was less than 0.05.

The attribute levels and coding patterns used in the regression analysis are defined in Table 2. Breast cancer risk reduction and out of pocket cost were treated as continuous variables and the remaining attributes categorical and coded as dummy variables. Two dummy variables were required to accommodate the three levels associated with the bone fracture attribute. Although levels for the drug alternatives were always “increased risk”

or “decreased risk,” the “Neither” option corresponded to a third level “risk unchanged.”

The remaining attribute levels for the “Neither” option were also coded as zero.

Table 2: Coding patterns for attribute levels

Attribute/variable	Levels	Coding pattern
Breast cancer risk reduction	25%, 40%, 50%, 70%	0.25, 0.40, 0.50, 0.70
Out of pocket cost	\$40, \$160, \$640, \$1840	40, 160, 640, 1840
Endometrial cancer	Risk unchanged, Increased risk	0,1
Venous thromboembolic event	Risk unchanged, Increased risk	0,1
Bone fracture: increased risk	Risk unchanged, Increased risk	0,1
Bone fracture: decreased risk	Risk unchanged, Decreased risk	0,1

2.10.2 Analytical model

The following model was estimated:

$$v = b_1(\text{breast cancer risk reduction}) + b_2(\text{out of pocket cost}) + b_3(\text{endometrial cancer}) + \\ b_4(\text{venous thromboembolic event}) + b_5(\text{bone fracture: increased risk}) + \\ b_6(\text{bone fracture: decreased risk}) \quad (\text{equation 7})$$

The observable utility derived from breast cancer risk reduction hormonal therapy is v , the attributes or variables are shown in brackets and b_1 through b_6 represent the attribute coefficients. The coefficient b_1 represents the impact on utility of a 100% change in risk (given that relative risk reduction was coded as a fraction, i.e. 0.50 instead of 50%).

Hence, the coefficient b_1 divided by 100 represents the impact on utility of a 1% change in risk. The coefficient b_2 represents the impact on utility of a \$1 increase in annual out of

pocket cost. The remaining coefficients represent the impact on utility of the attribute being present versus not present. For instance, the coefficient b_3 represents the impact on utility of the drug alternative being associated with a state of increased risk for endometrial cancer.

2.10.3 Marginal rate of substitution calculations

Marginal rate of substitution was calculated by taking the coefficient on the attribute being valued over the coefficient on that attribute that is being used as a measure of value. For cost and effectiveness, the coefficient on breast cancer risk reduction was divided by the coefficient on out of pocket cost (b_1/b_2). However, to obtain annual willingness to pay for a 1% relative reduction in breast cancer risk, b_1 was first rescaled by dividing by 100. For effectiveness and the side effects, the coefficient on a side effect was divided by the coefficient on breast cancer risk reduction (i.e. b_3/b_1). However, to obtain the percent relative reduction in breast cancer risk participants were willing to trade to avoid being at increased risk for a side effect, b_1 was first rescaled by dividing by 100.

2.10.4 Regression post estimation technique

Probability of choosing risk reduction hormonal therapy in different settings of drug availability was calculated as follows. First, utility scores for tamoxifen, raloxifene, AIs and the “no drug” alternative were determined using the estimated model (equation 7) with substitution of the appropriate attribute levels into the attribute or variable positions.

Second, the utility scores calculated were substituted into equation 5 for the different settings of drug availability. The process was reapplied to examine the effect of changing the level for venous thromboembolic event assigned to raloxifene.

2.10.5 Participants versus non-participants

Differences in means for continuous data were assessed using the independent two-sample t-test and differences in proportions for discrete data were assessed using the independent two-sample Z-test of proportions. The comparison tests were 2-sided. Statistical significance was considered when the p-value was less than 0.05.

2.10.6 Open-ended comments

Open-ended comments were compiled into an electronic document (Microsoft Word 2003) in list-form. The list of comments was read and then re-organized into thematic categories that emerged. Themes, frequency of comments within the thematic categories, and examples were reported.

2.11 Internal validity

Methods for assessing internal validity of a DCE are evolving. Obtaining significant coefficients of the expected sign is supportive. A common practise has been to look for “irrational responses” to test questions. In a dominant choice test, one scenario presents superior levels on all attributes. Choosing the clearly inferior option is labelled as failure of the test and sometimes is considered to be “irrational or inconsistent behaviour.” With respect to internal validity, however, observing “irrational responses” could indicate a

design or implementation problem such as inadequate background information and instruction, influence of excluded attributes that should have been included, and influence of labelling choice alternatives[77]. For this study, two dominant choices were added to the questionnaire (questions 3 and 18). One further question naturally occurring in the DCE was also identified as a dominant choice (question 15). The proportions of participants failing one, two or three of the dominant choice questions were calculated. Choosing “Neither” was not considered failure of a dominant choice question. As an exploratory exercise, the regression was to be repeated after dropping data from participants who failed at least two of the dominant choice questions. It would have then been possible to examine the effect on the coefficients, 95% confidence intervals and p-values. For instance, if there was a substantial proportion of participants with “irrational responses,” then dropping their data would be expected to increase the magnitude of the coefficient on risk reduction, narrow the confidence interval and decrease the associated p-value. Lanscar and Louviere argue “irrational response” data may not be so and should be left in the analysis for reporting purposes. Besides issues of design and implementation, alternative approaches to consumer theory could be explanatory making the tests inconclusive[77]. Furthermore, truly “irrational behaviour” should be accommodated by the unobservable component of random utility theory[77].

Chapter Three: Results

3.1 Recruitment

Of the 500 potential participants randomly selected and approached through the Screen Test mail-out, 111 agreed to be contacted by the researcher, 285 declined and 104 post cards were never returned. Ninety-four were successfully contacted via telephone, all expressed interest in participating and all opted to participate by mail. Of the 94 potential participants who were mailed a study package, 79 returned a completed questionnaire giving a questionnaire response rate of 84.0%. The overall participation rate was 15.8% (79/500). Recruitment is illustrated in Figure 2.

Figure 2: Recruitment flow diagram



3.2 Characteristics of study population

Demographic and breast cancer risk factor data for participants and non-participants is outlined and compared in Table 3. Two non-participants were outside of the specified age inclusion range (both 78 years). Participants and non-participants appeared similar with respect to age, age at menarche, age at first live birth and proportion with extremely

dense breast tissue ($\geq 75\%$ fibroglandular tissue) on mammogram.. Proportions with post secondary education, family history of breast cancer and personal history of breast biopsy appeared higher in the participant group. Proportions nulliparous and with a predicted 5-year breast cancer risk $\geq 1.66\%$ were significantly higher in the participant group.

Table 3: Demographic and breast cancer risk factor data by participation status

	Participants (N=79)	Non-Participants (N=421)	P-value
Age ¹	59.13 years (50-68)	58.46 years (50-78)	0.31
Post-secondary education ²	72.15%	62.50%	0.10
Age of menarche ^{1,3}	12.53 years (10-16)	12.79 (10-16)	0.13
Nulliparous ⁴	33.33%	14.82%	<0.01
Age at first live birth ^{1,5}	23.98 years (16-39)	24.85 years (16-40)	0.26
First degree relative with breast cancer ⁶	14.47%	11.81%	0.52
Breast biopsy ⁷	18.99%	15.14%	0.39
Predicted 5-year breast cancer risk $\geq 1.66\%$	44.30%	31.59%	0.03
$\geq 75\%$ fibroglandular tissue on mammogram	20.25%	20.90%	0.90

¹Mean (range)

²For participants N=79 and for non-participants N=416

³For participants N=79 and for non-participants N=417

⁴For participants N=72 and for non-participants N=398

⁵Based on N=48 participants who had a live birth and N=339 non-participants who had a live birth

⁶For participants N=76 and for non-participants N=398

⁷For participants N=79 and for non-participants N=416

The distribution of predicted 5-year breast cancer risk is evident in Figures 3, and of mammographic breast density in Figures 4. The distribution of predicted 5-year breast cancer risk appears positively skewed. The distribution of mammographic breast density may also be positively skewed, however, this shape may be more difficult to detect as mammographic breast density is divided into only four discrete categories.

Figure 3: Predicted 5-year breast cancer risk by participation status

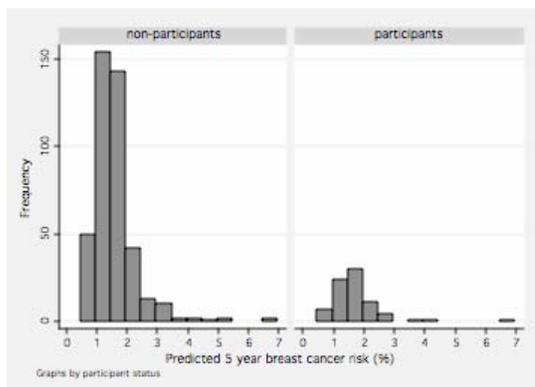
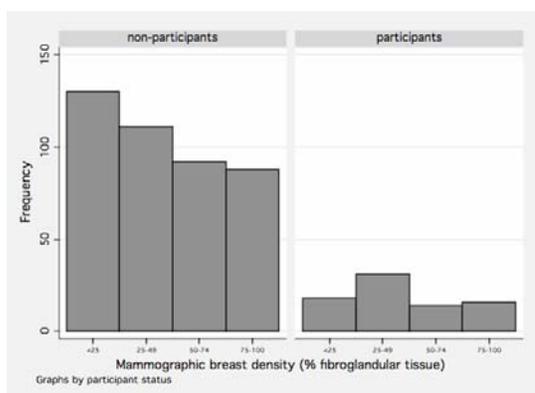


Figure 4: Mammographic breast density by participation status



3.3 DCE

3.3.1 Missing data

A total of 1422 choices (79 participants x 18 questions each) were posed. Only 7 of the 1422 questions (0.49%) were unanswered. Hence the completion rate was 99.51%. The missing data spanned 4 of the 79 participants (5.01%). One participant didn't answer one question (question 8) and three participants didn't answer two questions (questions 6 & 7 for 2 participants and questions 12 & 13 for 1 participant). Questions 6 & 7 and questions

12 & 13 appeared on facing pages within the questionnaire booklet suggesting that these choices may have been unintentionally missed. Furthermore, common themes amongst the unanswered questions could not be identified. For example, the more efficacious drug alternative was not consistently associated with higher cost or increased risk for one of the side effect attributes.

3.3.2 Opt-out data

For the majority of questions, participants chose either “Drug A” or “Drug B” over “Neither” (continued mammographic screening only). “Neither” was chosen for 393 of 1422 questions (27.64%). “Neither” responses were identified for all questions with a frequency ranging from 11 to 34 times and distribution shown in Figure 5. “Neither” responses spanned 45 of the 79 participants (56.96%), with a frequency of 1 to 18 per participant. The mode number of “Neither” responses per participant was 18, corresponding to 8 participants. The frequency distribution of “Neither” responses amongst participants choosing “Neither” at least once is shown in Figure 6.

Figure 5: Frequency distribution of “Neither” responses by question

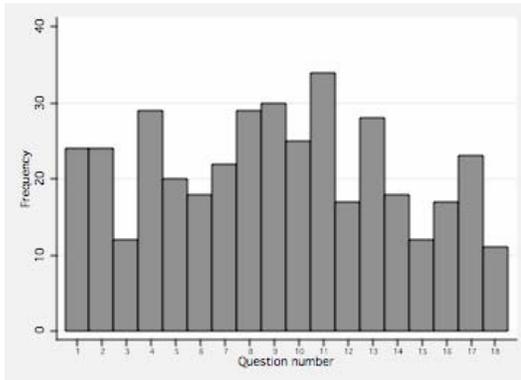
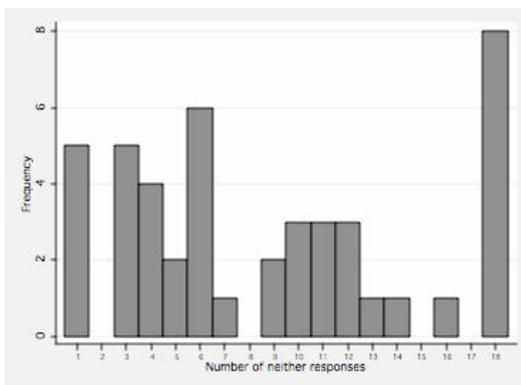


Figure 6: Frequency distribution of “Neither” responses per participant



3.3.3 Dominant choice tests

Only one participant failed 1 of the 2 implanted dominant choice tests. None of the participants failed both implanted dominant choice tests, or the naturally occurring dominant choice question. Hence, data from all participants was retained and the exploratory analysis without those who failed two or more of the dominant choice questions was not undertaken.

3.3.4 Regression analysis

The results of the final regression analysis are shown in Table 4. The number of observations is explained as follows. Seventy-nine participants were presented with 16 DCE choices (the 2 implanted dominant choices per participant were excluded prior to the regression analysis). As each choice is associated with 3 alternatives, this gives 3792 potential observations. However, there were 7 choices unanswered across all participants and again, each choice was associated with 3 alternatives. This gives 21 missing observations. Hence 3792 minus 21 yields the 3771 observations as shown. The Wald Chi-squared displayed at the bottom of Table 4 with its p-value < 0.0001 indicates that the model as a whole is statistically significant in that the attributes, taken together, have an effect on choice. The pseudo R-squared value was 0.1728. Although a direct empirical relationship has been observed between pseudo R-squared of a choice model and R-squared associated with ordinary least squares, pseudo R-squared should not be strictly interpreted as the proportion of explained variability[49]. Pseudo R-squared is better used to assess fit when moving from one model to another[78].

Except for decreased risk of bone fracture, all attributes of risk reduction hormonal therapy considered in the DCE were important for participants as indicated by the statistically significant p-values associated with the coefficients. The coefficient on breast cancer risk reduction was positive, suggesting this attribute increased participants' utility and the likelihood of choosing a drug. The coefficients on the other important attributes were all negative suggesting that these attributes decreased participants' utility. Hence, participants preferred a drug that was more effective, less expensive and did not increase

the risk for endometrial cancer, venous thromboembolic events or bone fracture. When the analysis was repeated without clustering by participant, the confidence intervals around the coefficients did get wider, however, the p-values were unchanged. Hence, interpretation of the coefficients was unchanged. This suggests negligible within subject effects.

Table 4: Results of regression analysis

Attribute	Coefficient	Lower 95% CI	Upper 95% CI	P-value
Breast cancer risk reduction	3.95234	3.230221	4.67446	<0.001
Out of pocket cost	-0.0005081	-0.000663	-0.0003533	<0.001
Endometrial cancer	-0.8221368	-1.02553	-0.618744	<0.001
Venous thromboembolic event	-0.7366241	-0.9220874	-0.5511608	<0.001
Bone fracture: increased risk	-1.323565	-1.760173	-0.8869569	<0.001
Bone fracture: decreased risk	-0.3708976	-0.8294224	0.0876271	0.113
Number of observations	3771			
Wald chi-squared	290.45			
P-value	<0.0001			
Pseudo R-squared	0.1728			

Exponentiation of the coefficients and the confidence interval estimates yields odds ratios as presented in Table 5. For a 100% relative reduction in breast cancer risk, the odds of choosing a drug was 52 times the odds of choosing no drug (holding all other attributes constant). For each 1% increment in relative reduction in breast cancer risk, the odds of choosing a drug versus not choosing a drug was increased by 1.04 (52.057038 raised to the power of 0.01). For a 20% increment, which is thought to represent the change in effectiveness in moving from tamoxifen or raloxifene to the AIs, the odds of choosing drug

versus not choosing drug was increased by 2.2 (52.057038 raised to the power of 0.2). For an increase in out of pocket cost of \$1, the odds of choosing drug was 0.9994203 the odds of choosing no drug, or alternatively the odds of choosing drug was decreased by 0.0005797 (1 minus 0.9994203). With an increment of \$200, representing the move from no out of pocket cost to paying only a biennial drug dispensing fee for five years, the odds of choosing drug is decreased by 0.11. With an increment of \$2000, representing the move from tamoxifen to raloxifene for five years, the odds of choosing drug is decreased by 0.69. With an increment of \$6000, representing the move from raloxifene to the AIs for five years, the odds of choosing drug decreases by 0.97. For the serious side effects, the odds of choosing drug was decreased by 0.5 to 0.7 if increased risk for the serious side effect was present.

Table 5: Results of regression analysis with odds ratios

Attribute	Odds ratio	Lower 95% CI	Upper 95% CI	P-value
Breast cancer risk reduction	52.057038	25.285244	107.17468	<0.001
Out of pocket cost	0.9994203	0.99933722	0.99964676	<0.001
Endometrial cancer	0.43949154	0.35860635	0.53862052	<0.001
Venous thromboembolic event	0.47872733	0.39768804	0.57628048	<0.001
Bone fracture: increased risk	0.26618466	0.1720151	0.41190732	<0.001
Bone fracture: decreased risk	0.69011461	0.43630122	1.091581	0.113

3.3.5 Strength of preference

Values for breast cancer risk reduction and being able to avoid each of the serious side effects expressed as dollar amounts are outlined in Table 6. Participants were willing to

pay \$77.80 each year per 1% relative reduction in breast cancer risk but lesser amounts to avoid being at risk for each of the side effects: \$26.05 to avoid being at increased risk for a bone fracture, \$16.20 to avoid being at increased risk for developing endometrial cancer, and \$14.50 to avoid being at increased risk for experiencing a venous thromboembolic event.

Table 6: Willingness to pay

Attribute	$b_{\text{Attribute}}/b_{\text{Out of pocket cost}}$	Marginal WTP
Breast cancer risk reduction ¹	0.0395234/-0.0005081	\$77.80
Bone fracture: increased risk	-1.323565/-0.0005081	\$26.05
Endometrial cancer	(-0.8221368/-0.0005081	\$16.20
Venous thromboembolic event	-0.7366241/-0.0005081	\$14.50

¹Coefficient on breast cancer risk reduction rescaled with division by 100 as noted in Section 2.10.2

Table 7 shows the percent relative reduction in breast cancer risk participants were willing to trade or give up in order to avoid being at increased risk for each of the serious side effects. Participants were willing to trade 33.49% in terms of relative reduction in breast cancer risk to avoid being at increased risk for bone fracture, 20.30% to avoid being at increased risk for developing endometrial cancer and 18.64% to avoid being at increased risk for experiencing a venous thromboembolic event.

Table 7: Willingness to trade effectiveness

Side effect attribute	$b_{\text{Attribute}}/-b_{\text{Risk reduction}}$	RRR breast cancer willing to trade
Bone fracture: increased risk	-1.323565/0.0395234 ¹	33.49%
Endometrial cancer	-0.8221368/0.0395234 ¹	20.80%
Venous thromboembolic event	-0.7366241/0.0395234 ¹	18.64%

¹Coefficient on risk reduction rescaled with division by 100 as noted in Section 2.10.2

3.3.6 Probability of choosing risk reduction hormonal therapy

Utility scores (v) for tamoxifen, raloxifene, AIs and no drug were determined using the estimated model:

$$v = 3.95234(\text{breast cancer risk reduction}) - 0.0005081(\text{out of pocket cost}) - \\ 0.8221368(\text{endometrial cancer}) - 0.7366241(\text{venous thromboembolic event}) - \\ 1.323565(\text{bone fracture: increased risk}) - 0.3708976(\text{bone fracture: decreased risk}) \\ (\text{equation 8})$$

Assigned attribute levels for the different drugs and the “no drug” alternative were substituted into the variable positions. The assigned attribute levels for the different drugs and the “no drug” alternative that were used are shown in Table 8.

Table 8: Assigned attribute levels for the different drugs and “no drug”

Attribute	Tamoxifen	Raloxifene	Aromatase Inhibitor	No drug
Breast cancer risk reduction	0.50	0.50	0.70	0
Out of pocket cost	160	640	1840	0
Endometrial cancer	1 (Increased risk)	0 (Risk unchanged)	0 (Risk unchanged)	0 (Risk unchanged)
Venous thromboembolic event	1 (Increased risk)	1 (Increased risk)	0 (Risk unchanged)	0 (Risk unchanged)
Bone fracture: increased risk	0 (Risk unchanged)	0 (Risk unchanged)	1 (Increased risk)	0 (Risk unchanged)
Bone fracture: decreased risk	1 (Decreased risk)	1 (Decreased risk)	0 (Risk unchanged)	0 (Risk unchanged)

Utility scores were then entered into equation 5 as previously described. Table 9 shows predicted probabilities of choosing risk reduction hormonal therapy according to three different settings of drug availability: only tamoxifen available, tamoxifen and raloxifene available, and all three drugs (tamoxifen, raloxifene and AIs) available. The predicted uptake of any drug was high: 49% for tamoxifen only, 73% for tamoxifen and raloxifene and 81% for all three drugs. Raloxifene is predicted to be favoured if tamoxifen and raloxifene are available. Raloxifene and the AIs are predicted to be equally favoured over tamoxifen if all three drugs are available.

Table 9: Probability of choosing drug according to availability¹

	Tamoxifen	Raloxifene	Aromatase Inhibitor	No drug
Tamoxifen available	49%	n/a	n/a	51%
Tamoxifen & raloxifene available	26%	47%	n/a	27%
All three drugs available	18%	32%	31%	19%

If the assigned level for venous thromboembolic event for raloxifene is varied to “risk unchanged,” the predicted uptake is increased from 47% to 65% if tamoxifen and raloxifene available, and from 32% to 50% if all three drugs available. These results are summarized in Table 10.

Table 10: Probability of choosing drug according to availability if level for venous thromboembolic event for raloxifene varied to “risk unchanged”

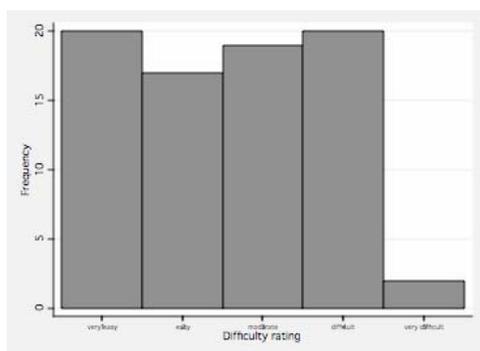
	Tamoxifen	Raloxifene	Aromatase Inhibitor	No drug
Tamoxifen available	49%	n/a	n/a	51%
Tamoxifen & raloxifene available	17%	65%	n/a	18%
All three drugs available	13%	50%	23%	14%

3.4 Participant feedback

3.4.1 Straightforwardness of DCE

All but one participant answered the difficulty rating question. The distribution of difficulty ratings is shown in Figure 7. The proportion rating the DCE as “very easy,” “somewhat easy” or “neither easy nor difficult” was 71.79% (56/78). Hence, 28.21% (22/78) rated the DCE as “somewhat difficult” or “very difficult.”

Figure 7: Frequency distribution of difficulty ratings



3.4.2 Open-Ended Written Comments

Six major themes emerged: risk reduction, side effects (unspecified and specified – bone fracture, endometrial cancer or venous thromboembolic event), cost, drug aversion,

difficulty with questionnaire and application to reality. For risk reduction, side effects and cost, the emphasis was either important or not important. Drug aversion was only considered in the absence of any specific reference to side effects. Written comment data for the risk reduction, side effects and cost themes is outlined in Table 11, and for the drug aversion, difficulty with questionnaire and application to reality themes, is outlined in Table 12. The importance of side effects, unspecified and specified, was raised most frequently. De-emphasis of the importance of endometrial cancer pertained to the participant having had a hysterectomy in 5 of 6 cases. As expected, none of the written comments de-emphasized the importance of breast cancer risk reduction. An equal number of written comments emphasized and de-emphasized the importance of out of pocket cost. For the difficulty with questionnaire theme, three sub-themes emerged: difficulty with imagining high risk scenario (1), difficulty with understanding concept (1), and difficulty with number of choices and/or variables (3).

**Table 11: Written comment data –
risk reduction, side effects and cost themes**

Theme	Important	Frequency	Examples
Risk reduction	Yes	7	I always chose the drug that was most effective in reducing breast cancer risk.
	No	0	
Side effects ¹	Yes	5	I will not take a drug to maybe prevent breast cancer because of the possible side effects of the drug.
	No	2	I would...not worry too much about treatable risks.
Bone fracture	Yes	3	I have other risk factors for bone fractures so this was also a determining factor.
	No	0	
Endometrial cancer	Yes	2	I think uterine cancer is as bad as breast cancer and would also not take that risk.
	No	6	I have had a hysterectomy so increased risk of uterine cancer was not a concern for me.
Venous thromboembolic event	Yes	3	Risk of blood clots important to me because of mother having this problem.
	No	0	
Cost	Yes	4	Money (if I have to pay) plays a big part with the answers.
	No	4	In no case is the cost so great that I wouldn't pay it.

¹Unspecified

**Table 12: Written comment data –
drug aversion, difficulty with questionnaire and application to reality themes**

Theme	Frequency	Examples
Drug aversion	4	The thought of taking any drugs is something that scares me a lot.
Difficulty with questionnaire	5	I am not high risk, have a hard time pretending I am. Didn't really understand concept. All the choices started to blur together.
Application to reality	2	I wish that we could be given such good summaries when we have to make similar decisions in real life. It gave me a lot of food for thought. We as women need to take a more active part in our health choices.

3.4.3 Interest in obtaining study results

Participants were given the option of being mailed the study results and 66 of 79 (83.5%) accepted.

Chapter Four: Discussion

4.1 Overview

In this pilot study of women age 50-69 years attending screening mammography, the discrete choice experiment was found to be a feasible method for eliciting preference for the characteristics of breast cancer risk reduction hormonal therapy. In addition to gaining insight into the important influences of choice, it was possible to examine how participants traded-off between effectiveness, cost and major side-effects. Furthermore, choice of risk reduction hormonal therapy in different settings of drug availability was predicted. The results were examined with respect to the demographic and breast cancer risk profile of the study population.

4.2 Feasibility of DCE

Feasibility was considered from several perspectives. Completion rate and perceived straightforwardness of the DCE were specified outcome measures and will be examined in detail below. Response in terms of mode of data collection, and ethical repercussions, also pertain to feasibility and are hence mentioned in this section. Finally, feasibility issues pertaining to the related DCEs reviewed in 1.3.3 are discussed.

For participants, the completion rate of the DCE was high. Of the 1422 questions administered, only 7 were unanswered across only 4 women. It is probable that 6 of the 7 unanswered questions were skipped unintentionally as they were positioned on facing pages in the questionnaire booklet. The high completion rate was seen despite 28.2% of participants rating the exercise as “somewhat difficult” or “very difficult.” How

“difficulty” was ultimately interpreted by women is unknown. It may be that women were referring to the psychological task of imagining being at high risk for developing breast cancer as opposed to the technical exercise of comprehension and simultaneous choice-making. Explanatory information from the written comments was limited. One written comment highlighted the first interpretation, and four dealt with the latter.

Alternatively, perceived “difficulty” may have been overcome by a high rate of literacy as 72.15% of participants reported having some post secondary education.

With respect to mode of data collection, the mailed questionnaire was clearly an acceptable approach given the high return rate (84.0%). The “in-person” information and data collection session was clearly less desirable to potential participants. It is suspected that actual participation would have been less if only the “in-person” information and data collection session was offered. However, with this method, respondents would have had immediate feedback to questions surrounding the task. This could have potentially resulted in less measurement bias and may have given the researcher a better understanding of perceived “difficulty” in completing the DCE.

For this study, whether or not ethical repercussions arose may also indicate feasibility. It was acknowledged that discussion of breast cancer risk and risk reduction could potentially cause anxiety or alarm amongst participants despite a clear message that recruitment was based only on participation in Screen Test and not on prior knowledge of risk factor data. Participants were advised to see their family physicians if concerned about personal breast cancer risk. It was then stated that family physicians should call the

researcher if referral for formal breast cancer risk assessment and counselling was desired. Participants also had the direct contact number of the researcher. Given that the researcher did not receive any calls from family physicians or participants, is suggestive but certainly not conclusive, that significant anxiety amongst participants did not occur.

For comparison, feasibility issues pertaining to the DCEs reviewed in 1.3.3 are now discussed. Recall that De Bekker-Grobb et al studied preference for bone fracture prevention drugs in 120 women age 60 years and older who were recruited from 34 general practices in Rotterdam, Netherlands[66]. Women were approached about the study at the clinic and if agreeable, were mailed a questionnaire. The questionnaire response rate was 66%, 9 of 1872 questions were unanswered, and the vast majority (117 of 120) passed a dominant choice test. It is also stated that most women found the DCE questions very clear and had no difficulty in completing the questionnaire. Gerard et al examined preference for breast cancer screening services[55]. A convenience sample of women (63 of the 87 were age 50 years or older) were recruited from a metropolitan breast screening and assessment service in Sydney, Australia. Although not explicitly mentioned, women were approached at the screening and assessment service and if agreeable, were mailed a questionnaire. The questionnaire response rate was 48%, response data was complete, and all respondents passed a dominant choice test. Ryan and Wordsworth studied preference for cervical cancer screening amongst a stratified sample of women identified from a database that lists all women age 18 – 65 years who are eligible for cervical cancer screening in the Tayside area of Scotland[64]. Questionnaires were directly mailed to 2000 women and the response rate was 32% (641 of 2000). It

appears that of the 132 respondents dropped from the analysis, most were dropped because of a failed dominant choice test. Of interest, mean age was approximately 38 years. Results pertaining to missing data cannot be clearly ascertained. Thirteen percent rated completion of the DCE as “difficult” or “very difficult.” The low response rate and high dominant choice test failure rate in Ryan and Wordsworth’s study may have been related to: (1) sampling from the general population as opposed to from a clinic setting, and (2) recruitment of a somewhat younger group of women who may take a DCE less seriously than an older group of women.

4.3 Important attributes and strength of preference

The most important attribute in women’s selection of a risk reduction hormonal therapy was effectiveness. The larger the relative risk reduction, the more likely an individual was to choose a drug. Out of pocket cost and the serious side effects were important but negative influences of choice. Given the importance of increased risk of bone fracture, it was unexpected that decreased risk of bone fracture did not significantly influence choice (and had a negative sign). Type II error is one possible reason. For each variable in the regression, the null hypothesis is that it does not contribute to explanation of choice and hence its weight or coefficient equals zero. In the absence of sufficient power, the null hypothesis for a particular variable could be accepted when in fact, it is actually false. Alternatively, this finding could be real. The levels for decreased risk of bone fracture may not have been actionable due to the small absolute differences in risk presented or because of pre-existing osteoporosis prevention behaviour amongst participants. For instance, participants may already engage in calcium/vitamin D supplementation and

weight-bearing physical activity. Such behaviour could de-emphasize the importance of taking a drug that would offer protection from bone fracture but may not mitigate fear of taking a drug that would increase risk of the same problem.

Relative importance can be looked at in terms of how respondents trade-off, or substitute, between attributes. Willingness to pay calculations permit importance, or value, to be described in terms of price or a price-proxy. From this DCE, it was possible to describe the relative value of effectiveness, and the relative value of being able to avoid being at increased risk for the side effects, in terms of dollar amounts. Women were willing to pay \$77.80 annually for a one percent relative reduction in breast cancer risk and between \$14.50 and \$26.50 to avoid being at increased risk for each of the serious side effects. These dollar amounts emphasize the priority placed on effectiveness when choosing a drug. Further interpretation of willingness to pay should be undertaken with caution given the hypothetical nature of the DCE and given the fact that participants were sampled from a population where costs associated with health care are largely publicly funded and hence the exercise of valuing medical outcomes in terms of out of pocket dollar amounts without anchors or benchmarks was unfamiliar. However, it is of interest to explore the willingness to pay results. For example, if the relative risk reduction associated with tamoxifen is 50% and with the AIs is 70%, then it could be implied that women would be willing to pay an additional \$1,556 ($\77.80×20) per year for an AI, or \$7,780 for a 5 year course of an AI. The true incremental price in moving from tamoxifen to an AI for 5 years is about \$8000.

Importance of the side effects was examined from another perspective. Women were willing to trade 18.64% to 33.49% in terms of relative reduction in breast cancer risk in order to avoid being at increased risk for each of the serious side effects. An alternative viewpoint is that women required this range of effectiveness to accept taking a breast cancer risk reduction drug associated with these serious side effects. Again, it is of interest to explore these results. For example, the effectiveness associated with tamoxifen ranges from a relative risk reduction of 25% to 50% in preventing incident cases of invasive breast cancer[17, 21, 24]. Tamoxifen is associated with increased risk of endometrial cancer and venous thromboembolic events. If women require a threshold effectiveness of 20.8% to accept increased risk for endometrial cancer and 18.64% to accept increased risk for venous thromboembolic event, then uptake of tamoxifen in reality is conceivable.

For examining strength of preference, marginal rate of substitution calculations are advantageous as preference for the attributes can be compared against a common metric (i.e. out of pocket cost). However as both the numerator and the denominator are random variables, the estimated ratio is as well[79]. Thus marginal rate of substitution estimates are associated with uncertainty. Although uncommonly seen in the health-care related DCE literature, calculation of confidence intervals would acknowledge the uncertainty in these calculations and allow for comparison of marginal rate of substitution estimates across different attributes thus enabling ranking of attribute importance. One study used four different methods for calculating confidence intervals around WTP estimates from a simulated DCE and from empirical DCE data[79]. The delta, Fieller, Krinsky Robb and

bootstrap methods were found to be reasonably accurate and yielded similar results[79]. A less formal method of acknowledging uncertainty around marginal rate of substitution calculations is to look at worst case/best case scenarios. Using the current data, worst case and best case ratios can be calculated around the WTP estimate for effectiveness. For the worst case, the upper confidence interval of b_1 is divided by the lower confidence interval of b_2 . For the best case, the lower confidence interval of b_1 is divided by the upper confidence interval b_2 . With rescaling of b_1 as previously described, the range of WTP for effectiveness is \$70.50 to \$91.43 annually for each 1% relative reduction in breast cancer risk. Recall that the original estimate was \$77.80. Future work with data from the current study will involve formal calculation of confidence intervals around the marginal rate of substitution estimates.

4.4 Predicting choice of risk reduction hormonal therapy

The probability of choosing the different risk reduction drugs was estimated using a probabilistic model that incorporates utility scores based on the estimated model and assigned attribute levels for the different drugs. The estimated proportion of women choosing risk reduction hormonal therapy over continued mammographic screening was considerable. This proportion was 49% for the setting of only tamoxifen being available, and increased to 73% with the addition of raloxifene. As both tamoxifen and raloxifene are assumed to be equal in terms of effectiveness, and given that raloxifene is more expensive than tamoxifen, this increment is driven by preference for avoiding being at increased risk of endometrial cancer. Making an AI available in addition to tamoxifen and raloxifene, only increased this proportion to 81%. Here the increment is small.

Greater effectiveness of an AI drives the increment but is being counteracted by preference for avoiding being at increased risk of bone fracture and preference for a cheaper drug. More women would choose raloxifene than tamoxifen if both drugs were available, but approximately the same number would choose raloxifene and an AI if all three drugs were available.

However, the sensitivity of these estimates in relation to the attribute level for venous thromboembolic event assigned to raloxifene deserves exploration from a clinical standpoint. In order to maintain a manageable DCE from the design perspective, two attribute levels for venous thromboembolic event were chosen: “increased risk” or “risk unchanged.” It is well established that tamoxifen increases the risk, and AIs do not affect the underlying risk for this toxicity. Raloxifene on the other hand, appears to increase the risk for venous thromboembolic events but to a lesser extent than tamoxifen. Creating more than two levels for the venous thromboembolic event attribute may not have altered the estimated coefficient, utility scores or probabilities. Differences in the levels according to annual events per thousand women would have been very subtle. Varying the assigned level for venous thromboembolic event for raloxifene within the constraints of the DCE conducted and re-applying the probabilistic model may, on the other hand, overestimate predicted uptake of the different drugs. If it is assumed that raloxifene does not change the risk of venous thromboembolic event, the estimated uptake increases from 47% to 65% in the setting of both raloxifene and tamoxifen being available, and increases from 32% to 50% with the availability of all three drugs. It is thus possible that the probability of choosing raloxifene is somewhere between 47% and 65% if both raloxifene

and tamoxifen were available, and is somewhere between 32% and 50% if all three drugs were available.

4.5 Strengths and limitations of study

4.5.1 Internal validity

Internal validity refers to capacity to draw correct inferences from data. Several points can be made in favour of internal validity for this DCE. The instrument was tested for content and face validity. Drug effectiveness and risks for serious side effects were presented in more than one format, including absolute numbers. For each choice, participants could opt-out which is a realistic approach when looking at a disease risk reduction strategy. Attribute levels for the opt-out alternative were presented. For the most part, logical and significant results were obtained and “irrational responses” were not observed. Most participants engaged in some trading behaviour in that only 8 participants consistently chose “Neither.” Repeat analysis after excluding these categorical non-traders did not visibly impact the coefficient estimates (data not shown). However, limitations with respect to design may have negatively impacted internal validity and are discussed next. Furthermore, other strategies for examining internal validity are presented with some examples drawn from the DCE literature.

In presenting the attributes and their levels, it was attempted to be as explicit as possible. However, it is possible that alternative presentations, could have led to different results. First, the presentation of risk was different for effectiveness and the side effect attributes. Effectiveness was described in terms of relative risk reduction and the side effects were

described qualitatively. Both effectiveness and the side effects could have been described quantitatively using relative or absolute risk reduction/risk, or even number needed treat/harm. Second, out of pocket cost could have been presented as the cost associated with the recommended course of risk reduction treatment as opposed to the annual cost.

Important attributes of breast cancer risk reduction hormonal therapy may have been excluded. In particular, nuisance side-effects were excluded. Tamoxifen, raloxifene and AIs can be associated with hot flashes; tamoxifen with a higher incidence of vaginal bleeding; and, AIs with a higher incidence of arthralgias and other musculoskeletal complaints. Nuisance side effects were excluded for two main reasons. First, as the number of attributes in a DCE is increased, more choices are required for coefficient estimation. A higher number of choices produces a longer questionnaire and concern regarding participation, completion and use of simplifying heuristics arises. One solution is to employ a block design where each respondent answers a subset of the choices. However, a block design requires more participants. Second, it is a clinical impression that nuisance side-effects, in contrast to serious side-effects, may be greater deterrents of compliance as opposed to barriers of uptake. Exclusion of nuisance side effect attributes could have inflated coefficient estimates and/or reduced model fit.

In this study, it was not possible to include individual characteristics as attributes. For ethical reasons, this information was collected only in aggregate form from Screen Test for participant and non-participant groups. Hence individual characteristic data could not

be matched to individual DCE response data. Individual characteristic attributes essentially proxy for part of the unobserved component of utility. Hence exclusion may reduce model fit. Matched individual characteristic and DCE response data would have also permitted exploration of theoretical validity. Hypotheses could have been posed such as: (1) preference for breast cancer risk reduction is associated with family history of breast cancer or personal history of breast biopsy; and, (2) preference for avoiding being at increased risk of bone fracture is associated with age.

Internal validity of a DCE may also be adjudicated using convergent and criterion approaches. Convergent validity occurs if different methods generate similar results, and criterion validity occurs if results of a method predict an external criterion such as revealed preference. Although not pursued as part of the current study, a few health care DCEs reported thus far have been subjected to such tests. Ryan compared willingness to pay estimates for an assisted reproductive service generated from a dichotomous choice contingent valuation experiment and a choice experiment amongst past users of the service[80]. For the dichotomous choice experiment, after conducting a satisfaction survey regarding the attributes of the service, respondents were asked whether they would pay a specified amount for a further attempt at in vitro fertilization (yes or no) according to a bid vector. Attributes for the choice experiment and mean attribute values for the corresponding total willingness to pay calculation were derived from the satisfaction survey that preceded the dichotomous choice experiment. Willingness to pay estimates from the two different approaches were not significantly different. Telser and Zweifel used a DCE to measure preference for use of a hip protector in a sample of 522

individuals age 70 and older representative with regard to age and sex of the independently living Swiss subpopulation[69]. Using the DCE results, they calculated the value of a statistical life attributable to wearing a hip protector and preventing a fracture with inherent mortality risk. This value was age-adjusted and found to be comparable to other estimates based on revealed preference methods. After the face-to-face DCE, participants were offered a free trial of the hip protector and 83 accepted. The group that accepted the hip protector trial had a mean total willingness to pay that was significantly positive, and the group that declined the hip protector trial had a mean total willingness to pay that was significantly negative.

4.5.2 Analysis

The specified model was linear additive in the attributes and coefficients. However, there may be other ways that an attribute may enter the utility expression such as a logarithmic or quadratic function[49]. Furthermore, in this DCE, attribute interactions were excluded as inclusion requires more choices for estimation. In support of this decision however, main effects are thought to explain 70 – 90 % of preference structure[81].

Conditional logit regression is a commonly used analysis technique when there are more than two choice alternatives, and when a linear additive model is specified. In its favour, computation is relatively simple. The cluster option takes into account lack of independence of response data within each participant. Further assumptions however are implicit[49]. Specifically, the unobserved alternative specific component of utility can be broken down into sub-components relating to each specified attribute. These sub-

components are independent (i.e. not cross-correlated) and have the exact same distributions[49]. This is called the IID (independently and identically distributed) condition. The IID condition has an equivalent behavioural association that called the IIA (independence of irrelevant alternatives) assumption that implies all pairs of alternatives are equally similar or dissimilar[49]. For this DCE, an increase in the probability of choosing Drug A, should have resulted in an equal, proportional decrease in the probability of choosing Drug B or “Neither”[63]. However, it is possible that the drugs were perfect substitutes but that the “Neither” alternative did not compete, or that the drugs were closer substitutes with each other than the “Neither” alternative[63].

The nested logit approach can be used to examine whether the IIA assumption is admissible. This approach would have required matched individual characteristic and DCE response data as the decision of choosing drug or “no drug” would have been first modeled as a function of individual characteristics plus the expected utility of choosing a drug[63]. The inclusive value is a parameter estimate that results which is used to establish the extent of dependence or independence between linked choices (i.e. drug or “no drug,” and which drug)[49]. Alternatively, a model that uses random, instead of fixed, coefficient estimation, can be considered[49]. With random coefficient estimation the IID condition/IIA assumption is relaxed[49] and can lead to better model fit in some instances[62, 67].

4.5.3 Theoretical concerns

DCE and other stated preference methods have been criticized from a theoretical perspective. It is assumed that individuals have complete and stable preferences for the good being valued, are willing/able to trade attributes during a valuation task, and actually put preferences and compensatory decision-making to use[82]. Lloyd has outlined evidence against the economic axioms of completeness and stability, and argues that individuals may employ an alternative decision-making strategy that defeats the DCE method and could make interpretation of coefficients and marginal rate of substitution calculations unclear[82]. Gigerenzer's theory of fast and frugal heuristics suggests that compensatory decision-making is too complex and that individuals consider the minimum amount of information necessary to make a decision[82]. In a DCE, an individual may compare two alternatives on the basis of a single attribute[83]. If this attribute can differentiate, then a decision is made immediately (lexographical preference). If not, only then is another attribute considered. Certainly evidence for failure to trade in DCEs has been documented but the concept of simplifying heuristics or lexographical preference has also been challenged[83]. Specifically, some evidence points to failure to trade being due to small trade-offs offered between alternatives[83, 84].

4.6 External validity

External validity refers to the extent to which results can be generalized to other groups or settings. It was acknowledged up front that external validity of this pilot study may be compromised.

Most women who received a questionnaire, actually participated (84.0%). However, if the entire population of women from whom permission to contact regarding the study was sought by the third party is considered, the overall participation rate was low (15.8%). Some individual characteristic data was obtained on participants and non-participants in aggregate form, and hence it was possible to compare the two groups on some levels. The groups were similar with respect to age, reported exposure to post-secondary education, age of menarche, age at first live birth and distribution of mammographic breast density. Although not statistically significant, it appeared that participants were more likely to have a first degree relative with breast cancer and a personal history of breast biopsy. Participants were significantly more likely to be nulliparous and have a predicted 5-year breast cancer risk of at least 1.66%. The finding that participants were more likely to be nulliparous could be explained a few different ways. Women without children may be more willing to engage in a research study possibly because they have more perceived time than women with children.

Alternatively, nulliparous women may be aware that lack of child-bearing is a risk factor for breast cancer, and thus more interested in participating in a research study relating to the topic of breast cancer risk reduction. The trend for participants being more likely to have a first degree relative with breast cancer and a personal history of breast biopsy, may also be accounted for by the latter explanation. Ultimately, the finding that participants were more likely than non-participants to have a predicted 5-year breast cancer risk of at least 1.66%, was driven by the greater proportion of participants being nulliparous, and possibly by the greater proportions of participants having a first degree

relative with breast cancer and personal history of breast biopsy. For the predicted 5-year breast cancer risk calculation, the same assumptions about past diagnosis of AH (unknown) and race (white) were made for both groups. It is possible that true differences between participants and non-participants in terms of these factors could have changed the proportions with predicted 5-year breast cancer risk of at least 1.66%. In any case, there were some systematic differences between participants and non-participants observed. Furthermore, it is possible that with participants being a higher risk group, estimates of preference for breast cancer risk reduction hormonal therapy and predictions of drug choice, are inflated. This effect could also arise from participation bias on its own.

A random sample of eligible women was drawn from the Alberta Cancer Board Screen Test database. Only women residing in the Calgary Health Region were eligible. There could be systematic differences between those who undergo mammogram screening through Screen Test in the Calgary Health Region and those who undergo mammogram screening through Screen Test elsewhere in Alberta. Some data elements collected for this study are comparable to data elements presented in the Screen Test 2003/2005 Biennial Report. First, the majority (71.4%) of women included in this report were of age 50 – 69 years[76]. The proportion having a first degree relative with breast cancer was 12.5%[76] and comparable to 14.47% for participants and 11.81% for non-participants. Likewise, the proportion with at least 75% fibroglandular tissue on mammogram was 17.4%[76] and comparable to 20.25% for participants and 20.90% for non-participants. However, the proportion of nulliparous women in the overall Screen Test population appeared to be

much lower at 9.1%[76] than 33.33% for participants and 14.82% for non-participants in this study.

Furthermore, as reported by the Public Health Agency of Canada for 2003/2004, approximately 10% of screening mammograms in Alberta occurred within an organized program (i.e. Screen Test)[85]. Thus, it is possible that there are systematic differences between those who undergo screening mammography through Screen Test and those who undergo screening mammography in the community in Alberta. The profile of women undergoing screening mammography outside of Screen Test in Alberta has not been reported. With such data, and had individual characteristics been included in the model, weighting of individual characteristics could have been pursued in attempt to increase generalizability. It should always be kept in mind, however, that demographic and breast cancer risk factor data is largely self-reported and hence subject to recall bias. In particular this might be why Screen Test does not ask their clients about past diagnosis of AH. Medical classification is presumably more difficult to accurately recall compared with events in the reproductive history.

4.7 Clinical significance and recommendations for future research

Cancer prevention is policy. The Alberta Cancer Board and Alberta's health, research, government and not-for-profit sectors, have committed to reducing the overall projected cancer incidence in the province by 35% by the year 2025[86]. Efforts to close the gap between knowledge and meeting the targets of cancer prevention policy should be prioritized.

Results from this study suggest that interest in risk reduction hormonal therapy may be high and that a substantial proportion of women age 50 to 69 years who undergo screening mammography are at sufficient risk to justify evidence-based risk reduction counselling. It was estimated that 73% of women, if deemed to be at elevated risk for developing breast cancer, would choose either tamoxifen or raloxifene if both were available. In reality, either of these medications can be prescribed for breast cancer risk reduction amongst eligible postmenopausal women. According to clinical practice guidelines[6, 35, 36], 33.4% of the invited population for this study was eligible for breast cancer risk reduction hormonal therapy counselling due to sufficient predicted 5-year risk ($\geq 1.66\%$). However, if breast density is also considered, a greater proportion of women may be deemed high risk. Breast density is a risk factor that is not fully explained by the components entered into the modified Gail index calculation[87]. Odds of developing breast cancer for women with $\geq 75\%$ fibroglandular tissue on mammogram is 4.7 (95% CI 3.4 -7.0) times higher than for women with $< 10\%$ fibroglandular tissue on mammogram[12]. In this study, 20.8% of the invited population had $\geq 75\%$ fibroglandular tissue on mammogram. Only 6.4% of the invited population had both predicted 5-year breast cancer risk $\geq 1.66\%$ and $\geq 75\%$ fibroglandular tissue on mammogram.

This study has shown that preference for the attributes of breast cancer risk reduction hormonal therapy can be elicited in a systematic way. Acknowledging limitations with respect to generalizability, it suggests that effectiveness may be the most important attribute for women when considering breast cancer risk reduction hormonal therapy.

Thresholds for effectiveness and accepting risk for a serious side effect are in line with minimal risk reduction expected with available drugs currently on the market. Out of pocket cost has a negative impact on choice. Such information on its own could be useful for the health care provider who is faced with counselling women about breast cancer risk reduction hormonal therapy. It can also be used to develop and test a breast cancer risk reduction hormonal therapy decision aid.

For breast cancer, lifestyle-related risk reduction strategies (in addition to risk reduction drug treatments) are supported by good evidence[88]. Risk assessment and risk reduction clinical services are emerging for women who have certain, established breast cancer risk factors. A logical next step is gaining an understanding of preference for the broader spectrum of risk reduction strategies, and for provision of risk assessment and risk reduction clinical services. Such an effort could involve a larger scale DCE. The current study supports the feasibility of the DCE method. Additional steps however, are recommended to optimize validity. A more representative sample of the target population should be sought. With the recent implementation of a provincial, organized screening mammography program, random sampling of women in the target age group with stratification for geographical location may be possible. Attributes and levels should be determined through additional literature review and a rigorous qualitative approach with women in the target population, relevant health care providers and policy makers. Individual characteristic data should be collected so that it can be matched to individual DCE response data and hence included in the model to understand the impact of these

characteristics on women's choices and/or used to explore theoretical validity. A sample of participants should be invited back to examine the credibility of the results.

4.8 Conclusions

The discrete choice experiment method was demonstrated to be a feasible technique for eliciting preference for the attributes of breast cancer risk reduction hormonal therapy amongst women age 50 – 69 years who participate in screening mammography through the Alberta Cancer Board Screen Test Program in the Calgary Health Region. For women in the study population, the most valued attribute of breast cancer risk reduction hormonal therapy was effectiveness however, the serious side effects and out of pocket cost, were important but negative influences of choice. Relative reductions in breast cancer risk of approximately 18% – 33% were found to compensate for being at increased risk for the serious side effects. Given the hypothetical scenario of being at elevated risk for breast cancer (40 in 1000 over 5 years), predicted probability of choosing risk reduction hormonal therapy was considerable and increased with drug availability. A higher proportion of participants compared with non-participants could be classified as being at elevated risk for breast cancer (5-year risk $\geq 1.66\%$) which may have inflated stated preference for breast cancer risk reduction hormonal therapy. However, a substantial proportion of both participants and non-participants had a predicted 5-year risk $\geq 1.66\%$ or extensive mammographic density ($\geq 75\%$ fibroglandular tissue on mammogram), and hence could be classified as being at elevated risk for breast cancer, and therefore eligible for risk reduction counselling. Gaps between interest in, and eligibility for, breast cancer risk reduction strategies should be addressed.

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APPENDIX A: LETTER FROM CHREB



FACULTY OF UNIVERSITY OF
MEDICINE CALGARY

→ S Lupichuk

2007-02-26

Dr. Heather E. Bryant
Division of Epidemiology, Prevention and Screening
Alberta Cancer Board
Tom Baker Cancer Centre
Calgary, Alberta

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dear Dr. Bryant:

RE: Preference for Breast Cancer Risk Reduction Hormonal Therapy in Women Age 50-69 Attending Screening Mammography

Ethics ID: E-20519

Student: Dr. S. Lupichuk

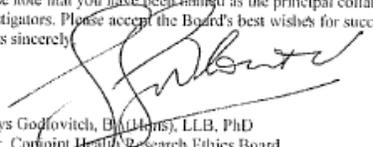
The above-noted proposal including the Background Information Questionnaire, Questionnaire, Information Letter, Project Proposal, Questionnaire Cover Letter, Telephone Scripts (Telephone Script and Telephone Script - Questionnaire Reminder), and Card (Response Post Card and Questionnaire Reminder Post Card and Appointment Reminder Card) has been submitted for Board review and found to be ethically acceptable.

Please note that this approval is subject to the following conditions:

- (1) appropriate procedures for consent for access to identified health information have been approved;
- (2) a copy of the informed consent form must have been given to each research subject, if required for this study;
- (3) a Progress Report must be submitted by February 26, 2008, containing the following information:
 - i) the number of subjects recruited;
 - ii) a description of any protocol modification;
 - iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
 - iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
 - v) a copy of the current informed consent form;
 - vi) the expected date of termination of this project.
- (4) a Final Report must be submitted at the termination of the project.

Please note that you have been named as the principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,


Glenys Godovitch, B.A.(Hons), LL.B, PhD
Chair, Conjoint Health Research Ethics Board

GG/emcg

c.c. Adult Research Committee
Lupichuk (Student)

Dr. P.S. Craighead (information)

Research Services

Dr. S.

Office of Information & Privacy Commissioner

APPENDIX B: LETTER FROM SCREEN TEST

October 12, 2006

Dear Screen Test Client:

The following research study is being conducted at the University of Calgary:

Preference for breast cancer risk reduction drugs.

The researchers hope to understand how women weigh the benefits and risks associated with taking drugs to help reduce the risk of developing breast cancer.

4.9

Your participation would involve either:

- Attending a 90 minute group session at the Tom Baker Cancer Centre in Calgary. There will be a short presentation and then you will be asked to complete a questionnaire.

OR

- Agreeing to complete the questionnaire at home and mailing it back.

Please mark on the post-card enclosed whether or not we may give your name and contact information to the researchers. Marking “yes” on the postcard does not mean that you have to participate. A researcher will contact you by telephone to give you more information. If you mark “no” then your name and contact information will not be released.

Please mail the post-card back as soon as possible.

Sincerely,

Jan Stevens

Manager, Screening Services
Division of Population Health and Information
Alberta Cancer Board, Holy Cross Site

APPENDIX C: RETURN POSTCARD TO SCREEN TEST

I agree to being contacted by telephone regarding participation in the following study being conducted at the University of Calgary:

Preference for breast cancer risk reduction drugs.

Yes, please contact me.

Are there days and times that are best for you?

No, please do not contact me.

APPENDIX D: TELEPHONE SCRIPT 1

Hello may I speak with (name of potential participant)?

This is (name of research assistant) calling from the University of Calgary.

You recently sent Screen Test a postcard saying that you were willing to be contacted about a study of women's preferences for breast cancer risk reduction drugs.

May I give you some more information?

This is a Master of Science project ongoing at the University of Calgary. We hope to understand how women weigh the potential benefits and risks associated with taking drugs to help reduce the risk of developing breast cancer.

May I tell you about the process?

Your participation would involve one of two options:

The first option is to attend a 90 minute session on one of two evenings between 7 PM and 8:30 PM in the Tom Baker Cancer Centre. The dates are: ... Up to 15 others will be there too. After a 20 minute presentation, you will fill out the questionnaire and hand it in. The questionnaire will take you less than 60 minutes to complete. In the last 10 minutes, the researcher can answer questions to the group as a whole. The researcher will also be able to answer questions one-on-one during the time everyone is working on the questionnaire and after the session is completed.

The second option is to complete the questionnaire by mail. You will be mailed a package containing the same background information and the questionnaire. The background information should take less than 20 minutes to read and the questionnaire less than 60 minutes to complete. You will mail the questionnaire back in the pre-stamped envelope provided. You can call us if you are having trouble understanding the background information or with any of the questions.

The background information presented at the session or mailed to you will contain facts about breast cancer and breast cancer prevention drugs. In the questionnaire, you will be given 17 choices asking if you would consider taking Drug A, Drug B or Neither. In these choices, the drugs will be described according to their ability to reduce breast cancer risk, their costs and side effects.

With either of the 2 options, all of the information you give is kept private.

I would also like to mention that this project is not funded by, or associated with, any drug company.

After hearing all of this, would you like to participate?

If yes...

Would you like to attend a session or complete the questionnaire by mail?

I would like to check that we have your correct address?

Thank-you. Written information about the study and a reminder about the session will be sent to you.

OR

Thank-you. Written information about the study, the background information and the questionnaire will be sent to you. If we don't receive your completed questionnaire back within several weeks, reminder information will be sent to you. We may also call to see if you need help filling out the questionnaire.

If no...

Thank-you for your time.

Good-bye

APPENDIX E: BACKGROUND INFORMATION**Preference for breast cancer risk reduction drugs**

Background Information

Important note

You have been asked to be part of this study because you are a woman between the ages of 50 and 69 who has had a mammogram through Screen Test, NOT because we think you have an above-average breast cancer risk. We will ask you to IMAGINE that you do have an above-average breast cancer risk and answer questions as you would if that were the case. If you are worried about your true breast cancer risk, please see your family doctor. Your family doctor may contact the researcher, Dr. Sasha Lupichuk at (403) 521-3347 if she or he believes you should be seen by a specialist for detailed breast cancer risk assessment and counselling.

What is breast cancer?

Breast cancer is a disease in which cells grow out of control, forming lumps or tumours. Cells can break off from a breast tumour and move to other parts of the body. Breast cancer often moves to lymph nodes, bone, liver and lung. If breast cancer is caught before it spreads, there is a greater likelihood that treatment (surgery and possibly radiation and/or drugs) will be successful and a woman will have a normal lifespan. Sometimes breast cancer can come back despite treatment and cannot be cured. A woman's lifespan in this case, would be significantly shortened.

Statistics

In Canada, breast cancer is the most commonly diagnosed cancer in women. It is expected that 22,000 Canadian women will be diagnosed with breast cancer in the year 2007.

Risk factors

A risk factor is anything that increases a person's chance of developing a disease. It is likely that breast cancer develops because of many risk factors acting together.

Age is a risk factor. The risk of breast cancer increases as a woman gets older. The average risks for women of different ages are shown below:

Age:	Risk of breast cancer in the next 5 years:
50	10 per 1000
60	15 per 1000
70	20 per 1000

Other risk factors for breast cancer include:

- Monthly period before the age of 12
- First child-birth after the age of 30 or not having any children
- Menopause beyond the average age of 51
- Taking hormone replacement therapy (estrogen, progesterone) for more than 5 years
- Having had a breast biopsy showing abnormal cells
- Dense breasts on mammogram
- A family history of breast cancer
- Alcohol use

Breast cancer risk reduction drugs

Several drugs have been shown to decrease the chance of developing breast cancer. In other words, these drugs have been shown to help prevent breast cancer. Breast cancer risk reduction drugs are pills that are taken once every day for 5 years. The drugs differ in terms of their effectiveness in reducing the risk of developing breast cancer. Here is an example of effectiveness:

- Mrs. Jones is a 50 year old woman who has an above-average risk for developing breast cancer. Her risk in the next 5 years is estimated to be 40 per 1000.
- Drug X lowers her risk by 25%.
- If Mrs. Jones takes Drug X, her risk for developing breast cancer in the next 5 years is reduced to 30 per 1000.

Breast cancer risk reduction drugs may have other effects:

- Uterus cancer (cancer of the womb). Uterus cancer causes vaginal bleeding. It is usually caught in the early stages and is treated with hysterectomy (surgical removal of the womb).
- Blood clot in the legs or lung. Blood clots can cause temporary leg swelling, leg pain, chest pain or shortness of breath and are treated with a blood thinner for at least 6 months.
- Effects on bone health.
 - Some of these drugs offer protection from osteoporosis (weak bones) and fractures (broken bones).
 - Others increase the risk of osteoporosis and bone fractures. Osteoporosis is painless but fractures can be painful. Bone fractures can, however, be prevented with exercise, calcium, vitamin D and medications.

The research study

In the near future, women with above-average breast cancer risk may have the option of taking one of several breast cancer risk reduction drugs. In choosing a drug, a woman would have to understand the different benefits and risks. If some drugs are not fully covered by her health insurance plan (or if she doesn't have a plan), the out-of-pocket cost may also play a part in the choice she makes. This study will help us understand how women weigh the potential benefits, risks and costs associated with breast cancer risk reduction drugs.

For the first part of the questionnaire, please IMAGINE that you have an above-average breast cancer risk and you have the option of taking a breast cancer risk reduction drug for 5 years. You will be given a series of choices. For each choice, you can pick Drug A,

Drug B or Neither. All options include continuing on with regular mammograms. Drug A and Drug B differ according to certain characteristics as follows:

Characteristic:	Description:	Options you will see the in questionnaire choices:
Effectiveness	The average amount by which the drug is expected to reduce the chance of developing breast cancer.	<ul style="list-style-type: none"> ▪ 25% (e.g. 40 in 1000 reduced to 30 in 1000) ▪ 40% (e.g. 40 in 1000 reduced to 24 in 1000) ▪ 50% (e.g. 40 in 1000 reduced to 20 in 1000) ▪ 70% (e.g. 40 in 1000 reduced to 12 in 1000)
Cost	How much you will have to pay each <u>year</u> out-of-pocket.	<ul style="list-style-type: none"> ▪ \$40 ▪ \$160 ▪ \$640 ▪ \$1860
Risk of uterus cancer	The chance that you will get uterus cancer.	<ul style="list-style-type: none"> ▪ Risk unchanged (1 in 1000 per year) ▪ Increased risk (2-3 in 1000 per year)
Risk of blood clot in legs or lung	The chance that you will have a blood clot in your legs or lung.	<ul style="list-style-type: none"> ▪ Risk unchanged (1 in 1000 per year) ▪ Increased risk (2 in 1000 per year)
Risk of bone fracture	The chance that you will have a bone fracture.	<ul style="list-style-type: none"> ▪ Risk unchanged (5 in 1000 per year) ▪ Decreased risk (4 in 1000 per year) ▪ Increased risk (7-8 in 1000 per year)

Here is an example of a questionnaire choice:

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	<p>40%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 24/1000</i></p>	<p>50%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 20/1000</i></p>	<p>0%</p> <p><i>For example:</i></p> <p><i>Risk unchanged at 40/1000</i></p>
Will cost you...	\$160 per year	\$640 per year	\$0
Risk of uterus cancer...	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Increased risk</p> <p>(2-3 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of blood clots in legs or lung...	<p>Increased risk</p> <p>(2 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of bone fractures...	<p>Decreased risk</p> <p>(4 in 1000 per year)</p>	<p>Increased risk</p> <p>(7-8 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(5 in 1000 per year)</p>

Which drug would you choose?
(Check 1 box only)

Drug A

Drug B

Neither

You can see that:

- Drug A is cheaper and it does not increase the risk of getting uterus cancer or having a bone fracture (in fact, it protects against bone fractures compared with choosing Neither). On the other hand it is less effective (it doesn't reduce breast cancer risk as much as Drug B) and it increases the risk of having a blood clot.
- Drug B is more effective (it reduces breast cancer risk more than drug A) and it does not increase the risk of having a blood clot. On the other hand it is more expensive, and it increases the risk of getting uterus cancer and having bone fracture.
- Choosing Neither means that your breast cancer risk is unchanged and it doesn't cost you anything. Your risks for uterus cancer, blood clots and bone fractures are also unchanged.

Please go on to the questionnaire!

APPENDIX F: QUESTIONNAIRE

Preference for breast cancer risk reduction drugs

Questionnaire

Study Number



Making choices about breast cancer risk reduction drugs

- You are now asked to think about a series of choices about drugs that help reduce the risk of developing breast cancer.
- For each choice, Drug A and Drug B will be described in terms of ability to reduce the risk of breast cancer, out-of-pocket cost, risk of uterus cancer, risk of blood clots and effect on bone fractures.
- Remember that uterus cancer and blood clots are usually treatable.
- Bone fractures can often be prevented with exercise, calcium, vitamin D and medications.

Please IMAGINE that you have an above-average breast cancer risk and you have the option of taking a breast cancer risk reduction drug for 5 years. You will be presented with a series of choices. For each choice, you can pick Drug A, Drug B or Neither by checking one of the three boxes. All options include continuing on with regular mammograms.

Choice 1

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	<p>40%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 24/1000</i></p>	<p>50%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 20/1000</i></p>	<p>0%</p> <p><i>For example:</i></p> <p><i>Risk unchanged at 40/1000</i></p>
Will cost you...	\$160 per year	\$640 per year	\$0
Risk of uterus cancer...	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Increased risk</p> <p>(2-3 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of blood clots in legs or lung...	<p>Increased risk</p> <p>(2 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of bone fractures...	<p>Decreased risk</p> <p>(4 in 1000 per year)</p>	<p>Increased risk</p> <p>(7-8 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(5 in 1000 per year)</p>

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 2

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	50% <i>For example:</i> 40/1000 reduced to 20/1000	70% <i>For example:</i> 40/1000 reduced to 12/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$640 per year	\$1840	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 3

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	25% <i>For example:</i> <i>40/1000 reduced to 30/1000</i>	50% <i>For example:</i> <i>40/1000 reduced to 20/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$160 per year	\$40 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged 5 in 1000 per year

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 4

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	<p>40%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 24/1000</i></p>	<p>50%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 20/1000</i></p>	<p>0%</p> <p><i>For example:</i></p> <p><i>Risk unchanged at 40/1000</i></p>
Will cost you...	\$640 per year	\$1840 per year	\$0
Risk of uterus cancer...	<p>Increased risk</p> <p>(2-3 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of blood clots in legs or lung...	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Increased risk</p> <p>(2 in 1000 per year)</p>	<p>Risk unchanged</p> <p>1 in 1000 per year</p>
Risk of bone fractures...	<p>Increased risk</p> <p>(7-8 in 1000 per year)</p>	<p>Decreased risk</p> <p>(4 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(5 in 1000 per year)</p>

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 5

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	50% <i>For example:</i> 40/1000 reduced to 20/1000	70% <i>For example:</i> 40/1000 reduced to 12/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$160 per year	\$640 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lungs...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 6

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	25% <i>For example:</i> 40/1000 reduced to 30/1000	40% <i>For example:</i> 40/1000 reduced to 24/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$160 per year	\$640 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 7

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	40% <i>For example:</i> <i>40/1000 reduced to 24/1000</i>	50% <i>For example:</i> <i>40/1000 reduced to 20/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$40 per year	\$160 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 8

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	40% <i>For example:</i> <i>40/1000 reduced to 24/1000</i>	50% <i>For example:</i> <i>40/1000 reduced to 20/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$1840 per year	\$40 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lungs...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 9

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	70% <i>For example:</i> <i>40/1000 reduced to 12/1000</i>	25% <i>For example:</i> <i>40/1000 reduced to 30/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$1840 per year	\$40 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lungs...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 10

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	70% <i>For example:</i> 40/1000 reduced to 12/1000	25% <i>For example:</i> 40/1000 reduced to 30/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$160 per year	\$1840 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs and lungs...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 11

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	70% <i>For example:</i> <i>40/1000 reduced to 12/1000</i>	25% <i>For example:</i> <i>40/1000 reduced to 30/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$640 per year	\$1840 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs and lungs...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 12

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	25% <i>For example:</i> 40/1000 reduced to 30/1000	40% <i>For example:</i> 40/1000 reduced to 24/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$640 per year	\$1840 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs and lungs...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 13

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	50% <i>For example:</i> <i>40/1000 reduced to 20/1000</i>	70% <i>For example:</i> <i>40/1000 reduced to 12/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$1840 per year	\$40 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 14

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	25% <i>For example:</i> 40/1000 reduced to 30/1000	40% <i>For example:</i> 40/1000 reduced to 24/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$40 per year	\$160 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lung...	Risk unchanged (1 in 1000 per year)	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 15

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	<p>25%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 30/1000</i></p>	<p>40%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 24/1000</i></p>	<p>0%</p> <p><i>For example:</i></p> <p><i>Risk unchanged at 40/1000</i></p>
Will cost you...	\$1840 per year	\$40 per year	\$0
Risk of uterus cancer...	<p>Increased risk</p> <p>(2-3 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of blood clots in legs or lungs...	<p>Increased risk</p> <p>(2 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of bone fractures...	<p>Increased risk</p> <p>(7-8 in 1000 per year)</p>	<p>Decreased risk</p> <p>(4 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(5 in 1000 per year)</p>

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 16

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	50% <i>For example:</i> 40/1000 reduced to 20/1000	70% <i>For example:</i> 40/1000 reduced to 12/1000	0% <i>For example:</i> Risk unchanged at 40/1000
Will cost you...	\$40 per year	\$160 per year	\$0
Risk of uterus cancer...	Risk unchanged (1 in 1000 per year)	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lungs...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Increased risk (7-8 in 1000 per year)	Decreased risk (4 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 17

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	70% <i>For example:</i> <i>40/1000 reduced to 12/1000</i>	25% <i>For example:</i> <i>40/1000 reduced to 30/1000</i>	0% <i>For example:</i> <i>Risk unchanged at 40/1000</i>
Will cost you...	\$40 per year	\$160 per year	\$0
Risk of uterus cancer...	Increased risk (2-3 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of blood clots in legs or lungs...	Increased risk (2 in 1000 per year)	Risk unchanged (1 in 1000 per year)	Risk unchanged (1 in 1000 per year)
Risk of bone fractures...	Decreased risk (4 in 1000 per year)	Increased risk (7-8 in 1000 per year)	Risk unchanged (5 in 1000 per year)

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

Choice 18

	Drug A	Drug B	Neither
Reduces risk of breast cancer by...	<p>40%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 24/1000</i></p>	<p>70%</p> <p><i>For example:</i></p> <p><i>40/1000 reduced to 12/1000</i></p>	<p>0%</p> <p><i>For example:</i></p> <p><i>Risk unchanged at 40/1000</i></p>
Will cost you...	\$640 per year	\$40 per year	\$0
Risk of uterus cancer...	<p>Increased risk</p> <p>(2-3 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of blood clots in legs or lung...	<p>Increased risk</p> <p>(2 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>	<p>Risk unchanged</p> <p>(1 in 1000 per year)</p>
Risk of bone fractures...	<p>Increased risk</p> <p>(7-8 in 1000 per year)</p>	<p>Decreased risk</p> <p>(4 in 1000 per year)</p>	<p>Risk unchanged</p> <p>5 in 1000 per year</p>

Which drug would you choose?
(Check 1 box only)

Drug A**Drug B****Neither**

For the next question, please circle only one of the listed options.

How difficult were the above 18 choices to complete?

- 1. Very easy
- 2. Somewhat easy
- 3. Neither easy nor difficult
- 4. Somewhat difficult
- 5. Very difficult

Are there any comments you would like to make regarding this questionnaire?

Would you like to receive a summary of the study results by mail within the next year?

- 1. Yes
- 2. No

If you have questions or need help completing this questionnaire please call:

Dr. Sasha Lupichuk at (403) 521-3347

Thank-you for participating!

APPENDIX G: COVER LETTER

TITLE:

Preference for breast cancer risk reduction drugs in women age 50-69 attending screening mammography

INVESTIGATORS:

Dr. Sasha Lupichuk, MSc Candidate
Dr. Heather Bryant, Co-Supervisor
Dr. Gillian Currie, Co-Supervisor
Dr. George Browman, MSc Committee Member

SPONSOR:

Tom Baker Cancer Centre Clinical Trials Unit

BACKGROUND

In Alberta, breast cancer is the most commonly diagnosed cancer in women. In the near future, women with above-average breast cancer risk may have the option of taking one of several breast cancer risk reduction drugs. This is a survey study that will help researchers and doctors understand more about how women weigh the potential benefits and risks associated with taking a drug to help reduce the risk of breast cancer. 500 women age 50 – 69 years who had a mammogram through Screen Test have been randomly selected and invited to participate.

WHAT IS THE PURPOSE OF THE STUDY?

From this study, the researchers hope to understand the following:

- How women weigh the potential benefits, risks and costs associated with drugs that may help reduce the risk of developing breast cancer.

4.10

4.11 WHAT WOULD I HAVE TO DO?

Your participation would involve either:

1. Attending a 90-minute information and data collection session at the Tom Baker Cancer Centre. Up to 15 other participants will be there too. After a 20 minute presentation by the researcher, you will fill out a questionnaire and hand it in. The questionnaire will take you less than 60 minutes to complete. In the last 10 minutes, the researcher can answer questions.

OR

2. Agreeing to complete the questionnaire by mail. You will be mailed a package containing the background information and the questionnaire. The background information should take less than 20 minutes to read and the questionnaire less than 60 minutes to complete. You will mail the questionnaire back in the pre-stamped envelope provided.

WHAT ARE THE RISKS?

The topic of breast cancer risk and taking drugs to prevent breast cancer may cause anxiety or at least the desire to have more information about your personal situation. If either of these circumstances occurs, you should see your family physician. Your family physician can contact the researcher if questions still remain.

WILL I BENEFIT IF I TAKE PART?

If you agree to participate in this study there may not be any direct benefit to you. The information we get from this study may help doctors counsel women about breast cancer risk reduction drugs in the future.

DO I HAVE TO PARTICIPATE?

Your participation in this study is voluntary and you can withdraw from it at any time. The researcher may also decide not to include your data.

WHAT ELSE DOES MY PARTICIPATION INVOLVE?

You have the option of receiving the results of the study by mail in the future.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You do not have to pay for anything, nor will you be paid for participating.

WILL MY RECORDS BE KEPT PRIVATE?

Yes. The questionnaire data is collected anonymously. You will be assigned a study number which will be written on the questionnaire. Only the researcher will have access to the name-study number key.

AGREEMENT TO PARTICIPATE

Your decision to complete and return this questionnaire will be interpreted as an indication of your agreement to participate. In no way does this waive your legal rights nor release the investigators, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time.

If you have further questions concerning matters related to this research, please contact:

Dr. Sasha Lupichuk (403) 521-3347

If you have any questions concerning your rights as a possible participant in this research, please contact the Ethics Resource Officer, Office of Medical Bioethics, University of Calgary, at 220-3782.

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

APPENDIX H: REMINDER POSTCARD

Thank you for agreeing to participate in the following study being conducted at the University of Calgary:

Preference for breast cancer risk reduction drugs.

Please complete your questionnaire and mail it back as soon as possible.

If you have any questions, please contact Dr. Sasha Lupichuk at (403) 521-3347.

APPENDIX I: TELEPHONE SCRIPT 2

Hello may I speak with (name of potential participant)?

This is (name of research assistant) calling from the University of Calgary.

You recently were sent a questionnaire for a study about women's preferences for breast cancer risk reduction drugs.

We have not yet received a completed questionnaire from you. I am wondering if you are still interested in participating in this study?

If yes – Do you still have the questionnaire?

- If yes – do you have any questions about the background information or questions? If any questions do come up, please call, otherwise, we look forward to receiving your responses. Good bye.
- If no – may I confirm your address? You will be sent a 2nd questionnaire right away. Please call if you have questions. Good bye.

If no – thank you for considering this study. Good bye.