Impact of Personalized Genetic Breast Cancer Risk Estimation With Polygenic Risk Scores on Preventive Endocrine Therapy Intention and Uptake

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ABSTRACT

Endocrine therapy is underutilized to reduce breast cancer incidence among women at increased risk. Polygenic risk scores (PRSs) assessing 77 breast cancer genetic susceptibility loci personalizes risk estimates. We examined effect of personalized PRS breast cancer risk prediction on intention to take and endocrine therapy uptake among women at increased risk. Eligible participants had a 10-year breast cancer risk ≥5% by Tyrer–Cuzick model [International Breast Cancer Intervention Study (IBIS)] or ≥3.0 % 5-year Gail Model risk with no breast cancer history or hereditary breast cancer syndrome. Breast cancer risk was estimated, endocrine therapy options were discussed, and endocrine therapy intent was assessed at baseline. After genotyping, PRS-updated breast cancer risk estimates, endocrine therapy options, and intent to take endocrine therapy were reassessed; endocrine therapy uptake was assessed during follow-up. From March 2016 to October 2017, 151 patients were enrolled [median (range) age, 56.1 (36.0–76.4 years)]. Median 10-year and lifetime IBIS risks were 7.9% and 25.3%. Inclusion of PRS increased lifetime IBIS breast cancer risk estimates for 81 patients (53.6%) and reduced risk for 70 (46.4%). Of participants with increased breast cancer risk by PRS, 39 (41.9%) had greater intent to take endocrine therapy; of those with decreased breast cancer risk by PRS, 28 (46.7%) had less intent to take endocrine therapy ($P < 0.001$). On multivariable regression, increased breast cancer risk by PRS was associated with greater intent to take endocrine therapy ($P < 0.001$). Endocrine therapy uptake was greater among participants with increased breast cancer risk by PRS (53.4%) than with decreased risk (20.9%; $P < 0.001$). PRS testing influenced intent to take and endocrine therapy uptake. Assessing PRS effect on endocrine therapy adherence is needed.

Prevention Relevance: Counseling women at increased breast cancer risk using polygenic risk score (PRS) risk estimates can significantly impact preventive endocrine therapy uptake. Further development of PRS testing to personalize breast cancer risk assessments and endocrine therapy counselling may serve to potentially reduce the incidence of breast cancer in the future.

Introduction

Prospective randomized controlled trials and meta-analyses (1) support the use of selective estrogen receptor modulators, including tamoxifen (2, 3) and raloxifene (4), and aromatase inhibitors, including exemestane (5) and anastrozole (6), as means to reduce breast cancer incidence among women at increased risk. Reputable guideline groups worldwide have recommended preventive endocrine therapy for women at increased breast cancer risk (7–10).

Paradoxically, despite ample level 1 evidence and evidence-based guidelines supporting endocrine therapy use, the acceptance of preventive endocrine therapy continues to be poor (8). Recent studies have found that the strategy of preventive endocrine therapy has failed to gain widespread traction in women at increased risk for breast cancer at the population level (11, 12). The women who decline preventive endocrine therapy commonly cite a fear of medications and adverse effects (13), fear of the term chemoprevention (14), poor understanding of the risk to benefit ratio, and uncertainty about their individual breast cancer risk as the rationale for their decision. Conversely, greater acceptance has

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been shown when a woman's physician recommends preventive medications (13, 15) on the basis of the risk to benefit ratio. In addition, the breast cancer risk prediction calculator tools in current clinical use have been shown to have low to modest discriminatory accuracy in predicting breast cancer risk for a woman (9). A more precise and biomarker-based test is needed to improve the ability to predict a woman's chance of breast cancer development over a defined time (16) and to guide preventive therapy decision-making.

Single-nucleotide polymorphisms (SNPs), common genetic variants, have consistently been associated with breast cancer risk in women. Although a single SNP does not reliably or accurately predict breast cancer (17), multiple SNPs discovered and validated for their risk evaluation in large studies can be combined to create a polygenic risk score (PRS) that captures the effects of multiple genetic variants, thereby improving predictive power.

In 2015, a large-scale genome-wide association study (GWAS; ref. 18) yielded a SNP77 PRS that was strongly associated with breast cancer, providing effective risk stratification of women with and without a family history of breast cancer. This PRS has been shown to be a strong risk factor for breast cancer independent of clinical risk factors and in high-risk populations, including women taking tamoxifen in the National Surgical Adjuvant Breast and Bowel Project P1/P2 (19) and those with dense breasts (20, 21).

Our study aimed to prospectively assess the role of PRS-based breast cancer risk prediction in the clinical care of women who are considering preventive endocrine therapy. Specifically, we sought (i) to determine whether the addition of PRS to clinical breast cancer risk calculator tools influences a woman's intention to take endocrine therapy and endocrine therapy uptake for breast cancer risk reduction and (ii) to explore the factors associated with that decision.

Methods

Patient population

Participants were recruited from one of the following sites: the Breast Diagnostic Clinic, Mayo Clinic, Rochester, Minnesota, or the Breast Cancer Screening Program (mammographic screening program) or Medical Genetics Counseling Program, CancerCare Manitoba, Winnipeg, Manitoba, Canada. Pamphlets describing the study aims and eligibility were placed in the aforementioned clinics, and patients self-referred for consideration for study participation or women who were determined to be high risk by their provider and were referred to a trial study coordinator.

Study-eligible participants were adult women (age 35–75 years) at increased risk for breast cancer, defined as a 5-year Gail Model score [National Cancer Institute Breast Cancer Risk Assessment Tool (BCRAT) version 4.0] of 3% or greater or a 10-year International Breast Cancer Intervention Study (IBIS) version 7.0 score (Tyrer-Cuzick) of 5% or greater. These breast cancer risk cut-off points were chosen for study eligibility to be in line with the U.S. Preventative Services Task Force Recommendations (22) and the American Society of Clinical Oncology Breast Cancer Risk Reduction guidelines (23). Women were deemed ineligible if they had a prior personal history of breast cancer, a known inherited breast cancer predisposition syndrome (e.g., *BRCA1/2*, Cowden syndrome), prior or current endocrine therapy, pregnancy or lactation at the time of study screening, or contraindication to endocrine therapy.

Breast cancer risk assessment (clinic visit 1 and year 1 and year 2 follow-up)

Participants underwent a baseline breast cancer risk assessment and counseling session by a participating provider (J.O. Kim, A. Cooke, C.A. Kim, D.L. Stan, B. Goldenberg, L. Neal, D. Grenier, L.A. Thicke, S. Pruthi). Physicians obtained a personal medical history, family history, and physical examination (including a clinical breast examination). Study participants received breast cancer risk reduction counseling that included discussion of the benefits and risks of endocrine therapy and the role of lifestyle and dietary modifications. In this session, breast cancer estimates from the breast cancer risk calculator tools (BCRAT/Gail version 4.0 and IBIS version 7.0) were reviewed in detail with the participant. Demographic, socioeconomic, and quality of life (Functional Assessment of Cancer Therapy-Endocrine Subscale) data were quantified at baseline with self-reported questionnaires. At the end of clinic visit 1, participants completed a self-reported questionnaire that quantified, with 5-point Likert scales, the intent to take endocrine therapy and the factors associated with the decision, including understanding of endocrine therapy efficacy and concerns about adverse effects.

In addition, participants completed a quality-of-life survey (Functional Assessment of Cancer Therapy–Endocrine Subscale) at year 1 and year 2. In these surveys, participants were specifically asked, "Are you currently taking a medication to prevent breast cancer?" If yes, they were asked "Which medication are you currently taking?" and "How long have you been taking your medication?"

Genotypic analysis

Study participants provided a 10-mL sample of whole blood that was processed for genotypic analysis at the Genomics Laboratory at Mayo Clinic (Rochester, MN). DNA extraction was performed with the MagNA Pure M96 automated extractor (Roche Diagnostics Corp). Regions of DNA flanking the SNPs that comprise the PRS were amplified in 4 multiplex polymerase chain reactions (Supplementary Table S1). After removal of residual nucleotides and primers with AMPure beads (Beckman Coultier, Inc), the SNPs were interrogated through locus-specific single-base extension primers. After desalting, the products of the single-base extension reaction were spotted onto a MassARRAY system chip (Agena Bioscience, Inc) and the alleles at each locus identified with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. This assay was validated according to the Clinical Laboratory Improvement Amendments requirements.

PRS

The genotype of each SNP was coded according to the dose of the risk allele (dose of 0, 1, or 2). PRS was calculated as a

weighted sum of the doses, with weights of the log odds ratio (OR) for the per-allele effect size of the SNP on breast cancer risk from the largest GWAS studies to date (18). To integrate the PRS with breast cancer risk assessment tool or IBIS risk predictions, we used the Individualized Coherent Absolute Risk Estimation (iCare) R package (https://dceg.cancer.gov/tools/analysis/icare). The package allows for incorporation of the log OR for the risk allele of each SNP and computes absolute risks through use of the SNP ORs to modify the baseline age-specific incidence rate (hazard rate) of breast cancer (24–26). Because the breast cancer risk assessment tool (Gail Model) reported risks at 5 years and lifetime residual risk and IBIS reported risk at 10 years and lifetime residual risk, we interpolated risks for both models to have risk estimates as 5 years, 10 years, and lifetime residual risk (to age 80 years). Integrated breast cancer risk estimates (i.e., Gail + PRS and IBIS + PRS) were computed for three time intervals (5-year, 10-year, and lifetime residual risk to age 80). They were summarized in a graphical report that was provided to the physician and the patient (example report in Supplementary Fig. S1). Supplementary Data S1 provides more details regarding the methodology used for the integrated PRS breast cancer risk estimates.

Review of PRS and risk reduction recommendations (clinic visit 2)

At clinic visit 2, the personalized PRS report was provided to the participant, and breast cancer risk estimates that included the PRS were reviewed and explained by a physician. The magnitude and direction of change in breast cancer risk estimates with the addition of PRS and the implications with respect to breast cancer risk reduction options were reviewed in detail with each participant, including the benefits and adverse effects of endocrine therapy. Clinic visit 2 occurred within 1 to 6 months following clinic visit 1. After clinic visit 2, participants repeated the self-reported questionnaire that reassessed their decision to take endocrine therapy, endocrine therapy uptake, and the factors associated with their decision. Type of endocrine therapy taken was classified by review of endocrine therapy prescriptions and by patient self-reported questionnaires during follow-up.

Endocrine therapy uptake was assessed through several processes. At Mayo Clinic in Rochester, endocrine therapy uptake was ascertained with a chart review of clinical encounters in the electronic health record at visit 2 and all follow-up clinical visits or other type of communications within 12 months from visit 2. In addition, for the CancerCare Manitoba study participants, to ascertain whether prescriptions were filled, an electronic query was performed of the Manitoba Drug Program Information Network (DPIN) for each patient for whom a prescription was made. The DPIN is a provincially mandated administrative database that captures all prescriptions that are dispensed in the Province of Manitoba (including all endocrine therapy). The date of endocrine therapy discontinuation was ascertained through review of the clinical encounters within the electronic health record, in documentation by the clinical trials nurse or health care provider either during a follow-up assessment or over the telephone during a virtual follow-up visit.

Statistical considerations

Baseline patient characteristics were tabulated for descriptive purposes. Distributions of clinical breast cancer risk calculator (Gail Model version 4.0 and IBIS version 7.0) estimates were visualized with box plots, and percentage change in breast cancer estimates through PRS was displayed with waterfall plots. The primary end point—the within-subject decisional change to the question "Knowing what you know now, how likely would you be to take a medication to prevent breast cancer?"—was calculated by subtracting the clinic visit 2 response from the clinic visit 1 response. Cross tabulation was performed of decision change to take endocrine therapy by direction of change in breast cancer risk estimate by PRS (dichotomized as increased vs. decreased). Differences in proportions between groups were assessed with the χ^2 statistic. Univariable and multivariable linear regression analyses were performed to explore the association between quantitative change in the decision to take endocrine therapy and the variables, including patient age, enrollment site, baseline IBIS lifetime risk, baseline concern of adverse effects, and percent change in risk estimates with PRS. For this assessment, we ranked the decision from 0 (definitely will not take endocrine therapy) to 4 (definitely will take endocrine therapy) and then measured the difference in these scores from baseline to clinic visit 2 (see Supplementary Data S2 for the complete follow-up survey).

Endocrine therapy uptake was cross tabulated by direction (increased vs. decreased) and percentage change cut-off points (<5% vs. ≥5% change and <10% vs. ≥10% change) in lifetime residual IBIS breast cancer risk estimates by PRS. Endocrine therapy uptake also was cross tabulated by absolute lifetime residual breast cancer risk strata, as calculated using Gail-PRS and IBIS-PRS models. Differences in endocrine therapy uptake by percentage change strata or absolute lifetime breast cancer risk strata were assessed with the χ^2 statistic. Logistic regression analysis for the end point of endocrine therapy uptake (yes vs. no) was conducted to assess for associations between baseline characteristics and percentage change in lifetime IBIS breast cancer risk estimates by PRS to endocrine therapy uptake. Associations with $P < 0.05$ were deemed statistically significant for purposes of this analysis.

Ethical considerations

This study was conducted with the prior written approval of the Mayo Clinic Institutional Review Board and the University of Manitoba Biomedical Research Ethics Board. All patients signed informed consent before enrollment. The study was registered on ClinicalTrials.gov (trial identifier, NCT02517593).

Results

In total, 151 study participants were enrolled from March 1, 2016, through October 30, 2017 [median (range) age, 56.1

Table 1. Baseline characteristics of the cohort.

Variable	Mayo Clinic, Rochester, Minnesota ($n = 74$, 49.0%)	CancerCare Manitoba ($n = 77$, 51.0%)	Whole cohort[a,b] ($N = 151$)
Age, median (range), years	55.3 (42.6–70.0)	56.5 (36.0–76.5)	56.1 (36.0–76.5)
Menopause status			
Premenopausal	25 (34.2)	28 (36.8)	53 (35.6)
Perimenopausal	9 (12.3)	3 (3.9)	12 (8.1)
Postmenopausal	39 (53.4)	45 (59.3)	84 (56.4)
Data missing	1	1	2
Race/ethnicity			
White	72 (97.3)	68 (88.3)	140 (92.7)
Indigenous	1 (1.35)	3 (3.9)	4 (2.6)
Asian	1 (1.35)	1 (1.3)	2 (1.3)
Other	0	5 (6.5)	5 (3.3)
Prior breast biopsy, *n* (%)			
0	30 (40.5)	62 (80.5)	92 (60.9)
≥1	44 (59.5)	15 (19.5)	59 (39.1)
Atypical hyperplasia if prior biopsy ($n = 59$)			
Yes	20 (45.4)	2 (13.3)	22 (37.3)
No	20 (45.4)	11 (73.3)	31 (52.5)
Unknown	4 (9.1)	2 (13.3)	6 (10.2)
Age at first menstrual period			
7–11	16 (22.2)	13 (16.9)	29 (19.5)
12–13	43 (59.7)	45 (58.4)	88 (59.1)
14+	13 (18.1)	19 (24.7)	32 (21.5)
Unknown	2	0	2
Age of first childbirth, years			
No births	12 (16.2)	19 (24.7)	31 (20.5)
<20	1 (1.4)	5 (6.5)	6 (4.0)
20–24	19 (25.7)	6 (7.8)	25 (16.6)
25–29	22 (29.7)	21 (27.3)	43 (28.5)
≥30	20 (27.0)	26 (33.8)	46 (30.5)
No. of family members with breast cancer			
1	44 (60.3)	53 (68.8)	97 (64.7)
≥2	29 (39.7)	24 (31.2)	53 (35.3)
Unknown	1	0	1
Education level			
High school or vocational diploma	24 (32.4)	33 (44.0)	57 (38.3)
Bachelor's degree	28 (37.8)	19 (25.3)	47 (31.5)
Graduate degree or higher	22 (29.7)	23 (30.7)	45 (30.2)
Unknown	0	2	2
Income, US$			
<$35,000	1 (1.4)	3 (4.5)	4 (2.9)
$35,000–$75,000	11 (15.7)	14 (20.9)	25 (18.2)
>$75,000	58 (82.9)	50 (74.6)	108 (78.8)
Unknown	4	10	14

[a]Values are presented as number and percentage of patients unless specified otherwise.
[b]Percentages may not total 100% because of rounding.

(36.0–76.4) years; **Table 1**]. The cohort consisted of premenopausal (35.6%), perimenopausal (8.1%), and postmenopausal (56.3%) women who were predominantly of European ancestry (98.7%). A substantial proportion of the cohort had undergone prior breast biopsy (39.1%), and each participant had at least 1 family member with a history of breast cancer.

Baseline clinical breast cancer risk estimates [median (range)] at 5 years, 10 years, and lifetime residual risk (to age 80 years) intervals were 2.5% (0.6%–14.1%), 5.4% (1.8%–28.3%), and 17.0% (4.3%–82.6%), respectively, with the Gail Model and were 3.8% (2.0%–11.5%), 7.9% (5.0%–23.1%), and 25.3% (5.5%–92.2%), respectively, with IBIS (**Fig. 1**).

The distribution of percentage change from the IBIS lifetime breast cancer risk estimate with the addition of PRS was bidirectional in nature. Risk was decreased for 70 women (46.4%) and increased for 81 women (53.6%). Among the women with increases in breast cancer risk estimate including the PRS, the median (range) increase was +2.0% (+0.1%–+21.0%), +4.5% (+0.1%–+35.3%), and +11.5% (+0.2%–+55.3%) from the 5-year, 10-year, and lifetime residual risk (to age 80) IBIS scores, respectively. For women with decreased breast cancer risk estimates including the PRS, the median (range) decrease was −1.0% (−0.1% to −4.8%), −2.2% (−0.1% to −9.2%), and −5.8%

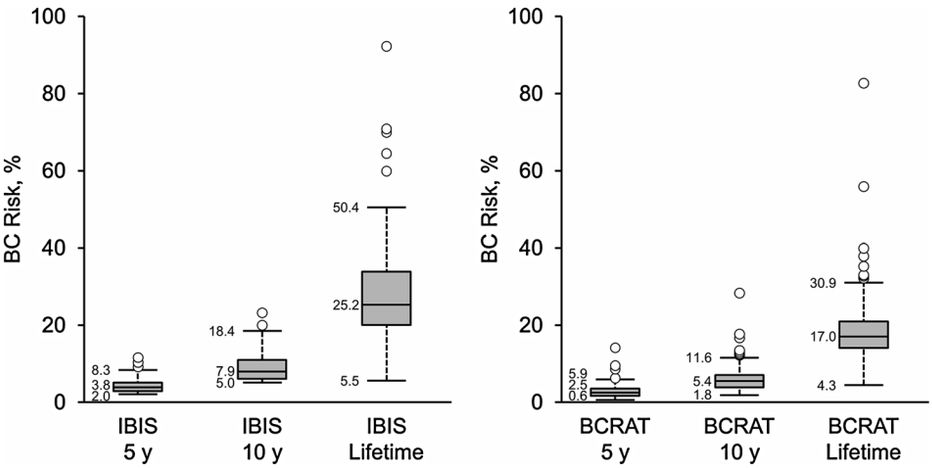

Figure 1.
Baseline breast cancer risk estimates from IBIS and Gail models at 5-year, 10-year, and lifetime residual (to age 80 years) intervals. Boxplots denote the median (horizontal black lines in each box), 25th and 75th percentiles (bottom and top of each box); the lower bar is the 25th percentile minus 1.5 times the interquartile range; the upper bar is the 75th percentile plus 1.5 times the interquartile range. BC indicates breast cancer; BCRAT, Breast Cancer Risk Assessment Tool; IBIS, International Breast Cancer Intervention Study.

(−0.1% to −24.3%) from 5-year, 10-year, and lifetime residual risk (to age 80) IBIS scores, respectively. Waterfall plots (**Fig. 2**) depict the distribution of percentage change in breast cancer risk estimates by PRS at these intervals. Thirty-seven participants (24.5%) had combined Gail-PRS 5-year risk estimates that were less than 1.66%, and 28 participants (18.5%) had combined IBIS-PRS 10-year risk estimates that were less than 5%.

Change in intent to take endocrine therapy (**Table 2**) differed on the basis of the direction of change in the breast cancer estimate with inclusion of PRS in the estimate ($P < 0.001$). Specifically, among women with increased breast cancer risk

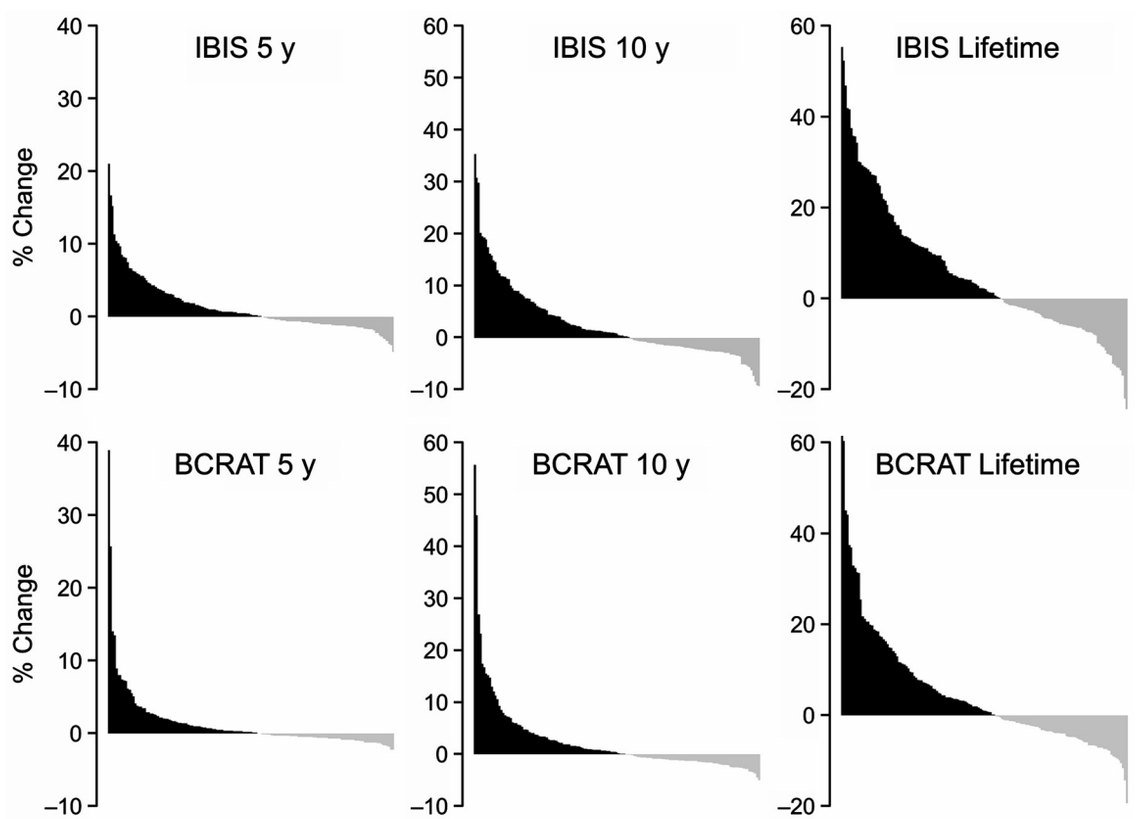

Figure 2.
Change in breast cancer risk estimates by PRS for IBIS and Gail models. BCRAT indicates Breast Cancer Risk Assessment Tool; IBIS, International Breast Cancer Intervention Study; PRS, polygenic risk score.

Table 2. Change in endocrine therapy intent by direction of change in breast cancer risk estimate.

Change in intent to take endocrine therapy	Change in breast cancer risk estimate by PRS,[a] *n* (%)	
	Decreased (*n* = 70)	Increased (*n* = 81)
Less likely	28 (46.7)	11 (14.9)
No change	18 (30.0)	32 (43.2)
More likely	14 (23.3)	31 (41.9)
Data missing	10	7

Abbreviation: PRS, polygenic risk score.
[a]*P* <0.001.

when including PRS, 41.9% reported being more inclined to take endocrine therapy compared with 23.3% among women with decreased risk when including PRS ($P < 0.001$). In a complementary manner, among women with decreased risk by PRS, 46.7% were less inclined to take endocrine therapy compared with 14.9% of women with increased risk by PRS ($P < 0.001$).

Multivariable linear regression assessed whether quantitative decision change in intent to take preventive endocrine therapy was associated with the percentage change in the IBIS risk estimate that included PRS in the presence of potential confounding variables (i.e., age, enrollment site, baseline IBIS lifetime risk, and baseline concern of adverse effects). After multivariable adjustment, only percentage change in breast cancer risk estimate with PRS ($P < 0.001$) and enrollment site ($P = 0.005$) were statistically significant in the model, again showing that increased breast cancer risk with inclusion of PRS was associated with an increased frequency of the decision change to take endocrine therapy (Supplementary Fig. S2). Patients from Mayo Clinic in Rochester were more likely to take endocrine therapy than patients from CancerCare Manitoba. This difference in endocrine therapy acceptance between the 2 enrollment sites may relate to unmeasured differences in treatment-seeking biases of study participants accrued from the referral populations of Mayo Clinic (quaternary care) and CancerCare Manitoba (community and tertiary care).

A total of 57 participants (37.7%) took endocrine therapy following clinical visit 2, in which IBIS-PRS and Gail-PRS breast cancer risk estimates were reviewed in detail with each patient. Of the 57 patients who initiated endocrine therapy, the taken endocrine therapy medications were tamoxifen (54.4%), exemestane (38.6%), raloxifene (5.3%), and anastrozole (1.8%). Endocrine therapy uptake differed by the direction and magnitude of change in breast cancer risk estimates after PRS was incorporated. Of participants whose lifetime residual breast cancer risk estimate increased by PRS over the initial IBIS estimates, endocrine therapy uptake was 52.4% compared with 20.9% among those with decreased breast cancer risk estimates by PRS ($P < 0.001$). When stratified by percentage change cut-off points of less than 10% versus 10% or more in lifetime residual breast cancer risk after inclusion of PRS (**Table 3**), a dose–response gradient was observed whereby endocrine therapy uptake was lowest among participants in the greatest decrease in percentage lifetime breast cancer risk strata (13.3% uptake), and endocrine therapy uptake was highest among those in the largest increase in breast cancer risk estimates strata (59.6% uptake; $P < 0.001$). A similar dose–response gradient in endocrine therapy uptake was observed when using percentage change cut-off points of less than 5% versus 5% or more in lifetime residual IBIS breast cancer risk with PRS (Supplementary Table S2).

Univariable logistic regression analysis assessing the associations between patient variables (including all variables from **Table 1**) and the end point of endocrine therapy uptake showed no statistically significant associations of any of the potential explanatory variables. Univariable logistic regression of percentage change in lifetime IBIS breast cancer risk after incorporation of PRS (with use of 10% cut-off points) for the outcome of endocrine therapy uptake showed statistically significant decreased odds of endocrine therapy uptake among patients with moderate (OR, 0.2; 95% CI, 0.09–0.49) and large (OR, 0.1; 95% CI, 0.02–0.52) decreases in lifetime breast cancer risk by PRS compared with those who had large positive changes in lifetime breast cancer risk. Endocrine therapy uptake also differed by the absolute magnitude of lifetime IBIS-PRS risk estimates whereby participants in the lowest lifetime residual risk strata (<20% lifetime risk) had a smaller

Table 3. Endocrine therapy uptake and univariable logistic regression ORs for endocrine therapy uptake by direction and magnitude of change (10% cut-off point) in lifetime residual breast cancer risk by PRS.

Drug uptake	Change in lifetime residual breast cancer risk estimate by PRS,[a] *n* (%)			
	Decreased		Increased	
	−10% and Lower (*n* = 15)	−9.9%–0.0% (*n* = 52)	0.0%–+9.9% (*n* = 36)	+10% and Higher (*n* = 48)
Yes	2 (13.3)	12 (23.1)	15 (42.9)	28 (59.6)
No	13 (86.7)	40 (76.9)	20 (57.1)	19 (40.4)
Data missing			1	1
OR (95% CI)	0.10 (0.02–0.52)	0.20 (0.09–0.49)	0.51 (0.21–1.24)	Reference

Abbreviations: OR, odds ratio; PRS, polygenic risk score.
[a]*P* <0.001.

Table 4. Endocrine therapy uptake stratified by lifetime residual absolute Gail model–PRS or IBIS-PRS breast cancer risk estimates.

Lifetime breast cancer risk categories, %	Endocrine therapy uptake, *n* (%) No (*n* = 92)	Yes (*n* = 57)	Total (*n* = 149)	*P*
Gail-PRS				
<20	65 (74.7)	22 (25.3)	87 (100.0)	<0.001
20–<40	18 (40.9)	26 (59.1)	44 (100.0)	
≥40	9 (50.0)	9 (50.0)	18 (100.0)	
IBIS-PRS				
<20	33 (76.7)	10 (23.3)	43 (100.0)	0.001
20–<40	41 (67.2)	20 (32.8)	61 (100.0)	
≥40	18 (40.0)	27 (60.0)	45 (100.0)	

Abbreviations: IBIS, International Breast Cancer Intervention Study; PRS, polygenic risk score..

endocrine therapy uptake proportion (23.3%) than those in the largest lifetime residual risk strata (>40% lifetime risk) whose uptake proportion was much greater (60%; $P = 0.001$; **Table 4**). Among the patients who took endocrine therapy, 18 patients discontinued endocrine therapy within 1 year of its initiation, with the self-reported reasons for endocrine therapy discontinuation tabulated in the supplementary materials (Supplementary Table S3). The median duration from enrollment to year 2 follow-up was 2.35 years (range, 2.30–2.60 years).

Discussion

There is considerable interest in the role of low-penetrance susceptibility genes in the development of cancers, including breast (18), prostate (27), colorectal (28), and pancreas (29) cancers, and nonmalignant conditions such as Alzheimer disease (30), coronary artery disease (31, 32), and amyotrophic lateral sclerosis (33). Breast cancer and heart disease are unique among these diseases for which PRS tools are available, in that their risk can be reduced through such proven intervention measures as medication and lifestyle interventions. Because of myriad reasons (8); however, breast cancer-preventive endocrine therapies are underused (11) and often overlooked in the clinical setting (11).

With the advent of lower cost, high-throughput genetic sequencing, large GWAS studies have been completed (18) that have yielded PRS signatures for accurate polygene-based risk prediction and risk stratification for breast cancer development. Because the PRS is independent from clinical breast cancer risk factors, groups such as Cuzick and colleagues (34) have developed hybrid clinical-PRS risk assessment models for potential clinical use in the near future. Risk models that incorporate PRS may be able to refine risk estimates and thereby compel more women, especially those who would benefit the most, to take preventive endocrine therapy.

In this study, we observed that the counseling of women at increased breast cancer risk with the use of their individualized, PRS-based risk estimates was associated with a decision change to take endocrine therapy. The observed change in intent depended on the direction of change in the breast cancer risk estimate by PRS, whereby those with decreased risk estimates were less likely and those with increased risk estimates were more likely to consider taking preventive endocrine therapy. The direction and magnitude of the change in breast cancer risk estimates were also significantly associated with endocrine therapy uptake. This observed change in intent to take preventive endocrine therapy mirrors the observations of Marteau and colleagues (35), who found that patients perceived genetic risk estimates as being more accurate than clinical risk estimates, and of LaRusse and colleagues (36), who found that patients had a greater degree of reassurance that a condition would not develop if a genetic risk estimate, rather than a clinical risk estimate, found a low probability for disease. Similarly, in coronary artery disease, incorporation of information from a PRS into risk estimates results in patients at highest genetic risk being more likely to initiate and adhere to statin medications (37). Our findings also fit with the heuristic-systematic models of decisional change, which theorize that the greater the perception of personal relevance of information, the greater is the degree of change in the person (38).

The degree of endocrine therapy uptake seen in our study, 38%, was higher than the pooled overall endocrine therapy uptake estimate (16.3%) from a recent meta-analysis (8) of published studies. This degree of uptake is explained, in part, by a number of factors, including the fact that endocrine therapy uptake has been observed to be greater among clinical trial participants than in the clinical setting (25.2% vs. 8.7%, respectively; ref. 8) and if the recommendation to take endocrine therapy was made by a physician (13)—both of which were the case for this study. Both of these factors, inherent to our study, may relate to a degree of volunteer responder bias whereby intervention-seeking volunteers, who are potentially more accepting of treatment than the general public, self-selected to participate in our study. On the univariable level, the percentage change in breast cancer risk estimates by PRS was observed to have a strong association with convincing participants with positive inflections in their risk to take endocrine therapy and reassuring those whose risks decreased with PRS that the benefits of taking endocrine therapy may not merit the potential downside risks (i.e., toxicity) of endocrine therapy. These findings may be consistent with those of Donnelly and colleagues (39), who found that higher breast cancer risk estimate values were associated with greater interest in endocrine therapy acceptance. Ultimately, larger prospective studies of PRS use in various clinical settings will be required to produce more robust estimates of the impact of PRS test results on endocrine therapy uptake.

Our study findings are suggestive that PRS testing and utilization as a risk factor could be further developed as a tool to help refine the risk reduction and prevention counseling of women at increased breast cancer risk. High-risk women considering preventive endocrine therapy could conceivably be further stratified according to the degree of absolute benefit expected on the basis of an assessment of their personalized

PRS breast cancer risk estimates. The use of PRS in this manner would be analogous to the use of multigene-derived recurrence tools, such as Oncotype DX Breast Recurrence Score (ref. 40; Genomic Health Inc) or MammaPrint (ref. 41; Agendia), for patients considering adjuvant chemotherapy. These tools have clinical utility through an increase in the patient's confidence in treatment recommendations for chemotherapy versus hormonal therapy. In addition, these tools have helped with stratification of women into groups who would and would not be expected to benefit from chemotherapy. With the discovery of SNPs important to endocrine therapy benefit, PRS tools for breast cancer could be further refined and used as a potential means to personalize the approach to decision-making for women considering preventive endocrine therapy.

The PRS used in this study was trained and validated on large datasets of women of European ancestry. The validity of its risk estimates for women of non-European ancestry was unknown during the conduct of this study. Given that 98.7% of our cohort were women of European ancestry, the risk of substantial misclassification was minimal. Although PRS risk prediction is being developed for other ancestries, such as women of Hispanic (42), East Asian (43), and African (44) ethnicities or *BRCA1/2* mutation carriers (45), these studies have suggested that ORs associated with each SNP may differ among women of different genetic ancestries. In contrast, a recent report of SNP180 breast cancer PRS tools developed for a cohort of Latin American and U.S. Latina women (46) found that accuracy of the PRS was similar for those trained on the datasets of European women. Remarkably, the performance of this PRS did not differ substantially by degree of Indigenous American ancestry. Validation of PRS tools for women arising from diverse genetic ancestries would allow for expansion of the potential group of women for which PRS testing would be informative in the future. Finally, newer polygenic risk scores for breast cancer have been developed recently, including the SNP313, which was found by Mavaddat and colleagues (47) to possess improved discriminatory performance compared with the SNP77 PRS used in the this study. Thus, the updated breast cancer PRS will be important to consider for use in future clinical trials.

Limitations

Limitations of this study include its modest sample size and its volunteer population, who may represent a subset of the population who are potentially more likely to take preventive endocrine therapy than the general public. This volunteer bias may limit the generalizability of the study findings, and so further assessments are warranted of PRS breast cancer risk prediction in a larger, more heterogeneous population in settings that include community accrual sites in addition to tertiary care settings. Other limitations of these data include the lack of long-term endocrine therapy compliance data and the impact of quality of life while taking endocrine therapy on the endocrine therapy adherence in the setting of PRS-informed breast cancer risk estimates.

Finally, the role of PRS-based breast cancer risk estimation and stratification in the clinical setting is undefined because of knowledge gaps surrounding their use. These gaps include how they affect participation in other prevention behaviors (including mammographic screening and lifestyle and dietary modifications), the cost to benefit ratio, and the psychosocial effects for patients and families who undergo testing (8). Conceivably, the provision of a more personalized, PRS-informed approach to breast cancer prevention counseling may spur increased acceptance of preventive endocrine therapy and lifestyle modifications that in turn could reduce breast cancer incidence if used widely in populations at risk.

Conclusion

Breast cancer risk prediction that incorporates PRS significantly correlated with intention to take endocrine therapy and endocrine therapy uptake among women at risk. Further study is warranted to determine the effect of PRS risk estimates on long-term adherence to preventive endocrine therapy, screening behavior, lifestyle interventions, and assessing whether PRS testing can be used to increase acceptance of breast cancer prevention medication at the population level.

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Authors' Contributions

J.O. Kim: Conceptualization, writing-original draft, writing-review and editing. **D.J. Schaid:** Conceptualization, data curation, formal analysis. **C.M. Vachon:** Conceptualization, writing-review and editing. **A. Cooke:** Conceptualization, writing-review and editing. **F.J. Couch:** Conceptualization, methodology. **C.A. Kim:** Data curation, writing-review and editing. **J.P. Sinnwell:** Data curation. **L. Hasadsri:** Methodology, writing-review and editing. **D.L. Stan:** Writing-review and editing. **B. Goldenberg:** Writing-review and editing. **L. Neal:** Writing-review and editing. **D. Grenier:** Writing-original draft. **A.C. Degnim:** Writing-review and editing. **L.A. Thicke:** Writing-review and editing. **S. Pruthi:** Conceptualization, data curation, writing-original draft, writing-review and editing.

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