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ORIGINAL ARTICLE

Breast cancer genetic risk profile is differentially associated with interval and screen-detected breast cancers

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Key message

To our knowledge, this is the first report looking into the genetic differences between screen-detected and interval cancers not detected at screening. It is an affirmation that screen-detected and interval cancers may have unique underlying biology, and our results have made advance in our understanding of genetic susceptibility to these distinct breast cancers. We believe that genetic risk discrimination has potential relevance in clinical care where interval cancers, which are usually rapidly growing and aggressive, do not currently benefit from mammography screening.

Abstract

Background

Polygenic risk profiles computed from multiple common susceptibility alleles for breast cancer have been shown to identify women at different levels of breast cancer risk. We evaluated whether this genetic risk stratification can also be applied to discriminate between screen-detected and interval cancers, which are usually associated with clinicopathological and survival differences.

Patients and methods

A 77-SNP polygenic risk score (PRS) was constructed for breast cancer overall and by estrogen-receptor (ER) status. PRS was inspected as a continuous (per standard deviation increment) variable in a case-only design. Modification of the PRS by mammographic density was evaluated by fitting an additional interaction term.

Results

PRS weighted by breast cancer overall estimates was found to be differentially associated with 1,865 screen-detected and 782 interval cancers in the LIBRO-1 study (age-adjusted OR_{perSD} [95% confidence interval]=0.91 [0.83-0.99], p=0.023). The association was found to be more significant for PRS weighted by ER-positive breast cancer estimates (OR_{perSD}=0.90 [0.82-0.98], p=0.011). This result was corroborated by two independent studies (combined OR_{perSD}=0.87 [0.76-1.00], p=0.058) with no evidence of heterogeneity. When enriched for "true" interval cancers among nondense breasts, the difference in the association with PRS in screen-detected and interval cancers became more pronounced (OR_{perSD}=0.74 [0.62-0.89], p=0.001), with a significant interaction effect between PRS and mammographic density ($p_{interaction}$=0.017).

Conclusion

To our knowledge, this is the first report looking into the genetic differences between screen-detected and interval cancers. It is an affirmation that the two types of breast cancer may have unique underlying biology.

Keywords: polygenic risk score, personalized medicine

Introduction

A recent effort carried out by the Breast Cancer Association Consortium (BCAC), as part of the Collaborative Oncological Gene-Environment Study (COGS), has resulted in the collective identification of more than 40 new single nucleotide polymorphisms (SNPs), which nearly doubled the number of known susceptibility loci, and identified additional risk-associated variants specific to estrogen receptor (ER)-negative breast cancer [1, 2]. On an unpredecented scale in breast cancer genetics, the collaborative large-scale experiment involved over 40,000 breast cancer cases and 40,000 controls [2].

Empirical studies suggest that individual risk loci underlying complex genetic diseases confer small effect sizes, with most genotype relative risks in the range of 1.1–2.0 [3]. However, the combined effect of common variants *en masse* may collectively account for a substantial proportion of variation in risk that is useful for population-based programmes of breast cancer prevention and early detection [4, 5].

Polygenic risk scores (PRS) have recently been used to pool genetic effects among an ensemble of markers which are individually associated with small relative risks [6]. In a report by Mavaddat et al. [7], it was shown that PRS computed from the 77 genetic variants which reflect the state of the art GWAS findings of breast cancer stratifies breast cancer risk in women with and without family history of breast cancer [7]. A three-fold increased risk of developing breast cancer was found between women profiled in the highest 1% of the PRS, compared to the middle quintile.

Whilst the PRS is likely to be an important tool for the risk prediction of breast cancer overall, breast cancer itself is not just one disease. Breast cancers which develop within the time interval between screening examinations (interval cancers) are usually associated with more adverse biological features and poorer survival outcomes compared with breast cancers

that are diagnosed through routine screening mammography (screen-detected cancers) [8, 9]. After adjusting for age and screening interval, interval cancers are typically larger, more frequently node-positive at diagnosis, more likely to be of lobular histology and more often associated with a triple-negative phenotype [8]. Although errors by radiologists generally account for about 25% to 40% of interval cancers [10] (22% in the Stockholm screening program [11]), another explanation is that the rapidly growing, high-grade tumor has a different biology and was too small to be detected on the last mammogram [12, 13].

In view of a need to distinguish the generally more aggressive tumours of interval cancers, which benefit little from mammography screening, from screen-detected cancers, this paper uses PRS to explore whether there is a genetic difference between them. We examine whether the genetic risk stratification of breast cancer by PRS can also be applied to discriminate tumours with different biology. Due to a possible masking effect in dense breasts, it has been suggested that interval cancers are only truly more aggressive than screen-detected cancers in nondense breasts [14]. Therefore, we also examined whether the association between PRS and detection mode is modified by mammographic density.

Patients and methods

Study subjects

The primary analyses were based on the Linné-Bröst 1 (LIBRO-1) study; a cohort of Swedish female breast cancer cases. All first instances of female incident primary breast cancer cases diagnosed in Stockholm from January 2001through December 2008 (*n*=11,696) were identified via the Regional Cancer Register. We excluded women who were outside the age range of between 40 to 72 years at diagnosis of breast cancer (*n*=1,249), and excluded those who were deceased (*n*=645) or without a contact address (*n*=454) at point of

recruitment. Exclusions were motivated by the upper age bound of the screening program and the possibility to receive informed consent. A total of 9,348 women remained in the study base and were invited to participate. Invitations were sent out early in 2009 together with study information, informed consent documents, blood sampling tubes and a link to our web-questionnaire. Informed consent was retrieved for 61% (n=5,715) of the invited population.

Cancer-free controls were comprised of 5,537 participants of the Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) mammography screening study (http://karmastudy.org/) recruited between 2010 and 2011 from Helsingborg and Stockholm in Sweden.

Genotyping

Samples from LIBRO-1 and KARMA were genotyped using a custom Illumina iSelect Array (iCOGS) comprising 211,155 SNPs. The 77 breast cancer SNPs [7] were based primarily on variants reported to be associated at a genome-wide level ($P<5\times10^{-8}$) by COGS or previous publications, with either breast cancer overall or diseases of different ER subtypes. Missing genotypes were imputed using 1000 Genomes (Phase I integrated variant set release (v3) in NCBI build 37 (hg19) coordinates).

Mammographic screening visits and mammographic density

Dates of mammographic screening visits and information about the outcome of each visit were obtained through merges to the mammography-screening database kept at the Stockholm-Gotland Regional Cancer Center [15]. The database contains attendance and outcome of all visits undertaken within the population-based mammography-screening program for Stockholm County. Since 1989, all Stockholm women ages 50-69 have been invited to screening at 24-month intervals. Women 40-49 were included since mid-2005, invited with 18-month intervals.

Screen-film mammograms were collected from radiology departments and digitized with an Array 2905HD Laser Film Digitizer (Array Corp, Tokyo, Japan). Percentage mammographic density (PD) was estimated with an ImageJ-based method previously described in [16] for pre-diagnostic images in the mediolateral oblique view of the cancer-free breast. Women who developed contralateral cancer within three months of diagnosis did not have their mammographic density measured. Missing values of PD were replaced by the medians of all known values of the respective variables.

After excluding women diagnosed without a prior screening visit (n=1,701), women diagnosed after a normal screening interval had passed (n=1,014) and 99 cases with uncertain method of detection, 2,901 interval- or screen-detected tumors were identified within the study period. Of these women, 2,647 (1,865 screen-detected and 782 interval cancers) were successfully genotyped on iCOGS.

Polygenic risk score (PRS)

To investigate the association between breast cancer risk and the joint effects of known breast cancer loci, we combined the 77 SNPs by summing the number of alleles of each SNP, weighted by the effect sizes reported in Mavaddat et al. [7] (Supplementary Table S1, available at *Annals of Oncology* online). A PRS was derived for each individual using the formula below [7]:

$$PRS = \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \ldots + \beta_n x_n$$

Where β_k is the per-allele odds ratio (OR) for breast cancer associated with the minor allele for SNP k, and x_k the number of alleles for the same SNP (0, 1 or 2), and n=77 is the total number of SNPs. Three separate PRS were constructed, corresponding to weights from breast cancer overall (PRS$_{overall}$), estrogen receptor (ER)-negative (PRS$_{ER-neg}$), and ER-positive

disease (PRS$_{ER-positive}$). SNP ORs estimated separately for each ER subtype in the iCOGS experiment were used to derive the subtype-specific PRS [7].

Supporting datasets

Replication of the findings was performed in two independent datasets: Sweden and Singapore Breast Cancer Study (SASBAC) [2] and MERCK [17]. Briefly, SASBAC is a population-based case-control study of postmenopausal breast cancer in women aged 50 to 74 years born in Sweden, and diagnosed between 1 October 1993 and 31 March 1995. Genotyping for the SASBAC dataset was performed on the iCOGS array.

The patient cohort of the MERCK study was selected using the population-based Stockholm-Gotland Breast Cancer Registry and the unique 12-digit personal number assigned to each Swedish resident. Women who were diagnosed with a primary breast cancer from January 1, 1997 through December 31, 2005, were identified. Patients developing distant metastatic diseases were selected and matched with metastasis-free breast cancer cases by adjuvant therapy, age and calendar period at diagnosis. Due to the enrichment for deadly metastatic breast cancers, the study has a comparatively larger proportion of interval cancers and higher number of excluded individuals due to young age (before screening age) compared to SASBAC and LIBRO-1. Genotyping for the MERCK study was performed on the Human1M-Duo BeadChip array.

All study participants gave informed consent and all studies were approved by the ethical committee at Karolinska Institutet.

Statistical methods

We first explored the relationship between PRS and breast cancer risk stratified by screen-detected/interval cancer status in the two case-control studies, LIBRO-1/KARMA and

SASBAC. Logistic regression models were used to estimate the 1) ORs and corresponding 95% confidence intervals (CI) for breast cancer risk by quartiles of the PRS based on controls, with the lowest quartile as the reference, or 2) the ORs and corresponding 95% CI associated with one standard deviation (SD) increments for PRS as a continuous variable. Analyses were adjusted for age at diagnosis for cases, or age at interview for controls.

To test for heterogeneity between screen-detected and interval cancers, we used a case-only design, comparing the two groups of breast cancer patients separated according to screen-detected/interval cancer status. Breast cancers detected at a screening visit were compared to breast cancers detected clinically in the interval between two screens.

Logistic regression models were used to estimate the ORs and corresponding 95% CI for interval vs screen-detected cancers by quartiles of the PRS based on screen-detected breast cancers, with the lowest quartile as the reference. Continuous PRS was standardized and the ORs and corresponding 95% CI associated with one standard deviation (SD) increments were also estimated. We adjusted for age at diagnosis, and PD. Modification of the PRS by PD (nondense [PD<25%] or dense [PD≥25%]) was evaluated by fitting an additional interaction term in the model. All tests of statistical significance were two-sided. All statistical analyses were carried out using the program R (Foundation for Statistical Computing, Vienna, Austria).

Results

The distributions of PRS by dataset are given in Supplementary Table S2 (available at *Annals of Oncology* online). In two independent case-control studies, PRS$_{overall}$ was found to be significantly associated with both screen-detected and interval cancers when compared against cancer-free controls, with an increased breast cancer risk for every increase in PRS$_{overall}$ quartile (Supplementary Table S3, available at *Annals of Oncology* online). When

we tested for heterogeneity using a case-only design, $PRS_{overall}$ was found to be differentially associated with 1,865 screen-detected and 782 interval cancers in the LIBRO-1 study (age-adjusted OR_{perSD} [95% CI]=0.91 [0.83 to 0.99], p=0.023, Table 1). The association was found to be more significant for PRS_{ER-pos} (OR_{perSD}=0.90 [0.82 to 0.98], p=0.011), but not significant for PRS_{ER-neg} (OR_{perSD}=1.02 [0.94 to 1.11], p=0.687). This result was corroborated by two independent studies with smaller sample sizes showing a clear trend with effects in the same direction and magnitude (Table 2, combined OR_{perSD}=0.87 [0.76 to 1.00], p=0.058) with no evidence of heterogeneity.

When $PRS_{overall}$ was categorized by quartiles based on the distribution in screen-detected cancers, patients were observed to be less likely interval cancers compared to screen-detected cancers with each increased quartile of $PRS_{overall}$ (Table 1). Women with the highest quartile of $PRS_{overall}$ were 20% less likely to be interval cancer cases (OR=0.80, 95% CI: 0.63 to 1.01, p=0.066), after adjusting for age at diagnosis. The association persisted after we adjusted for mammographic density. No discernible trend was observed for each increase in PRS_{ER-neg} quartile.

The relationship between PRS and screen-detected/interval cancer status was found to change depending on whether the affected woman has dense (PD≥25%) or nondense (PD<25%) breasts, for both $PRS_{overall}$ and PRS_{ER-pos} (Table 3, $p_{interaction}$=0.031 and 0.017, respectively). The corresponding observed effect sizes in nondense breasts were more pronounced than those observed in dense breasts ($PRS_{overall}$: OR_{perSD}=0.77 [0.64 to 0.92], p=0.004 for nondense breasts vs OR_{perSD}=0.97 [0.86 to 1.09], p=0.633 for dense breasts; PRS_{ER-pos}: OR_{perSD}=0.74 [0.62 to 0.89], p=0.001 for nondense breasts vs OR_{perSD}=0.97 [0.86 to 1.09], p=0.579 for dense breasts).

Discussion

In this study, we explored whether genetic data for 77 common breast cancer variants, summarized as a PRS, could discriminate between screen-detected and interval cancers. The positive association between breast cancer risk and PRS reported by Mavaddat et al. [7] was found to hold true for both screen-detected and interval cancers when compared to controls (Supplementary Table S3, available at *Annals of Oncology* online). In a case-only analysis, interval cancers were found to be associated with lower $PRS_{overall/ER-pos}$ in our primary Swedish dataset (LIBRO-1), and the results were corroborated by two smaller Swedish datasets, SASBAC and MERCK, with comparable beta estimates in the same direction. Results of the analyses on $PRS_{overall}$ and PRS_{ER-pos} were found to be largely similar, tending towards a decreased risk of being an interval cancer over screen-detected cancer for each increased quartile of PRS (Tables 1 and 3). No clear trend was observed between quartiles of PRS_{ER-neg} and screen-detected/interval cancer status (Tables 1-3). The relationships between $PRS_{overall/ER-pos}$ and screen-detected/interval cancer status were found to be significantly different in breasts of high or low density, with much larger effect sizes observed in nondense breasts (Table 3).

Whilst much work has been performed to compare the clinic-pathological characteristics, molecular biomarkers and survival outcomes of screen-detected and interval cancers [8, 9, 12, 13, 18-20], there is yet a study which examines for germline genetic variation between screen-detected and interval cancers. Within the available 77-SNP portfolio, we observed disparate associations between screen-detected and interval cancers, suggesting that screen-detected and interval cancers are indeed distinct in both underlying genetics and biology. Replications from two independent studies provide further evidence that screen-detected and interval cancers have different genetic profiles.

True interval cancers are defined as an interval cancer with a normal screening mammogram, with no reason for assessment, as opposed to false-negative examinations missed at a previous mammography [10]. Due to a possible masking effect in dense breasts, it has been suggested that interval cancers are only truly more aggressive than screen-detected cancers in nondense breasts [14, 18, 19]. We stratified the dataset into women with dense and nondense breasts to explore if the association between PRS and screen-detected/interval cancer status would be stronger among those with nondense breasts, which is likely to be enriched for true interval cancers. In agreement, the effect sizes and associated statistical significance we observed among women with low mammographic density were more pronounced than that when we included all the women (Table 3). Taken at face value, women with nondense breasts and high $PRS_{overall/ER-pos}$ were more likely to be associated with the more favourable screen-detected breast cancer.

At a tipping point of genetic discoveries for breast cancer, a study that looks into stratifying the disease further into distinct subtypes is timely. The examination of possible genetic differences between screen-detected and interval cancers is also novel. The major strength of this study is the extensive national registry data available in Sweden, which offers an unprecedented and unparalleled resource to look into a study population that represents a large sample of the Swedish population. Whilst screen-detected and interval cancers differ primarily in their method of detection, the proper and accurate definition of latter is highly dependent on a comprehensive screening history, which is made possible with the nationwide mammography screening programme in Sweden implemented several decades ago. We have also incorporated the use of the most comprehensive and updated, state-of-the-art list of breast cancer susceptibility loci to date in the construction of PRS.

A noteworthy limitation is that the list of SNPs is mostly restricted to the iCOGS chip (41 out of 77), which was heavily enriched for SNPs with prior evidence of association with

breast cancer as a whole. The existence of other loci that have not been harvested by the iCOGS chip or previous breast cancer GWAS thus cannot be dismissed. Future studies using SNP arrays with genome-wide coverage are thus warranted. In addition, depending on the local screening guidelines, the definition of interval cancer can be inconsistent, with the time interval between screening mammograms ranging from one to three years [21, 22]. Whilst we observed similar effect sizes across three independent Swedish studies where the screening interval is two years for the majority of the women, it is unclear whether our results are generalizable over varied definitions of interval cancer. It should be also be highlighted that interval cancers have similar features and outcomes as symptomatically-presenting cases (i.e. they are similar, not worse, in terms of outcome, as clinically-presenting women who did not screen) [23]. However, the studies which have compared interval cancers and symptomatic cancers to screen-detected cancers have been small in size and have not made clear distinctions between dense/nondense, or true/false-negative interval cancers. Future work can expand our understanding on whether such cases are also genetically different.

To our knowledge, this is the first report looking into the genetic differences between screen-detected and interval cancers. It is an affirmation that screen-detected and interval cancers may have unique underlying biology, and our results have made advance in our understanding of genetic susceptibility to these distinct breast cancers. We believe that genetic risk discrimination has potential relevance in clinical care where interval cancers, which are usually rapidly growing and aggressive, do not currently benefit from mammography screening.

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Disclosure

No potential conflicts of interest were disclosed.

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Table 1. Association between polygenic risk score (PRS) and screen-detected or interval breast cancer. Abbreviations: Screen, screen-detected; p_{Wald}, Pvalue based on Wald test.

PRS quartile (range)	Screen	Interval	Univariate			Adjusted for age			Adjusted for age and PD		
			OR	95% CI	p_{Wald}	OR	95% CI	p_{Wald}	OR	95% CI	p_{Wald}
PRS$_{Overall}$											
Q1 (-3.277 to -0.659)	466	223	1.00	Reference		1.00	Reference		1.00	Reference	
Q2 (-0.659 to -0.012)	466	192	0.86	0.68 to 1.09	0.206	0.86	0.68 to 1.08	0.201	0.87	0.69 to 1.10	0.234
Q3 (-0.011 to 0.652)	466	188	0.84	0.67 to 1.06	0.150	0.85	0.67 to 1.07	0.157	0.84	0.66 to 1.06	0.145
Q4 (0.652 to 3.720)	467	179	0.80	0.63 to 1.01	0.064	0.80	0.63 to 1.01	0.066	0.82	0.65 to 1.04	0.110
Continuous variable	1865	782	0.91	0.83 to 0.99	0.022	0.91	0.83 to 0.99	0.023	0.91	0.84 to 0.99	0.036
PRS$_{ER-neg}$											
Q1 (-3.664 to -0.718)	466	197	1.00	Reference		1.00	Reference		1.00	Reference	
Q2 (-0.717 to -0.04)	466	207	1.05	0.83 to 1.33	0.678	1.05	0.83 to 1.33	0.669	1.07	0.85 to 1.36	0.568
Q3 (-0.04 to 0.621)	466	180	0.91	0.72 to 1.16	0.460	0.91	0.72 to 1.16	0.458	0.92	0.72 to 1.18	0.519
Q4 (0.621 to 3.392)	467	198	1.00	0.79 to 1.27	0.981	1.01	0.79 to 1.27	0.961	1.01	0.79 to 1.28	0.944
Continuous variable	1865	782	1.02	0.94 to 1.11	0.687	1.02	0.94 to 1.11	0.677	1.02	0.94 to 1.11	0.685
PRS$_{ER-pos}$											
Q1 (-3.482 to -0.665)	466	218	1.00	Reference		1.00	Reference		1.00	Reference	
Q2 (-0.664 to -0.01)	466	197	0.90	0.72 to 1.14	0.391	0.90	0.71 to 1.14	0.374	0.90	0.71 to 1.14	0.391
Q3 (-0.010 to 0.672)	466	189	0.87	0.69 to 1.09	0.230	0.87	0.69 to 1.10	0.242	0.86	0.68 to 1.09	0.213
Q4 (0.673 to 3.777)	467	178	0.81	0.64 to 1.03	0.089	0.82	0.64 to 1.03	0.091	0.83	0.66 to 1.06	0.132
Continuous variable	1865	782	0.90	0.82 to 0.97	0.011	0.90	0.82 to 0.98	0.011	0.90	0.83 to 0.98	0.020

Table 2. Association between polygenic risk score (PRS) and screen-detected or interval breast cancer in independent studies. Abbreviations: Screen, screen-detected; p_{Wald}, Pvalue based on Wald test; I^2: I2 heterogeneity index (0-100); p_{Het}, Pvalue for Cochrane's Q statistic.

	Screen	Interval	Univariate			Adjusted by age		
			OR	95% CI	p_{Wald}	OR	95% CI	p_{Wald}
$PRS_{Overall}$								
SASBAC	694	197	0.88	0.75 to 1.03	0.106	0.87	0.74 to 1.03	0.102
MERCK	95	98	0.92	0.68 to 1.23	0.559	0.92	0.68 to 1.23	0.556
Combined	789	298	0.89	0.77 to 1.02	0.090	0.88	0.77 to 1.02	0.086
					$I^2=0$; $p_{Het}=0.794$			$I^2=0$; $p_{Het}=0.787$
PRS_{ER-neg}								
SASBAC	694	197	0.98	0.84 to 1.15	0.805	0.98	0.84 to 1.15	0.804
MERCK	95	98	0.97	0.72 to 1.31	0.857	0.97	0.72 to 1.31	0.857
Combined	789	298	0.98	0.85 to 1.13	0.762	0.98	0.85 to 1.13	0.761
					$I^2=0$; $p_{Het}=0.966$			$I^2=0$; $p_{Het}=0.967$
PRS_{ER-pos}								
SASBAC	694	197	0.86	0.73 to 1.01	0.067	0.86	0.73 to 1.01	0.064
MERCK	95	98	0.92	0.68 to 1.24	0.575	0.92	0.68 to 1.24	0.572
Combined	789	298	0.87	0.76 to 1.01	0.061	0.87	0.76 to 1.00	0.058
					$I^2=0$; $p_{Het}=0.706$			$I^2=0$; $p_{Het}=0.702$

Table 3. Association between polygenic risk score (PRS) and screen-detected or interval breast cancer, age-adjusted and stratified by percent mammographic density (PD). Abbreviations: Screen, screen-detected; p_{Wald}, Pvalue based on Wald test; $p_{interaction}$, Pvalue for interaction between percent mammographic density (dense/nondense) and PRS as a continuous variable.

	Nondense (PD<25%)						Dense (PD≥25%)						
	PRS quartile (range)	Screen	Interval	OR	95% CI	p_{Wald}	PRS quartile (range)	Screen	Interval	OR	95% CI	p_{Wald}	$p_{interaction}$
$PRS_{Overall}$													
	Q1 (-3.277 to -0.634)	155	46	1.00	Reference		Q1 (-3.243 to -0.713)	220	104	1.00	Reference		
	Q2 (-0.632 to 0.012)	155	39	0.85	0.52 to 1.37	0.502	Q2 (-0.713 to -0.059)	220	113	1.09	0.78 to 1.50	0.623	
	Q3 (0.013 to 0.749)	155	41	0.89	0.55 to 1.43	0.631	Q3 (-0.058 to 0.567)	220	92	0.89	0.63 to 1.25	0.494	
	Q4 (0.751 to 3.71)	155	27	0.59	0.35 to 0.99	0.047	Q4 (0.567 to 3.419)	220	112	1.08	0.78 to 1.49	0.648	
	Continuous variable	620	153	0.77	0.64 to 0.92	0.004	Continuous variable	880	421	0.97	0.86 to 1.09	0.633	0.031
PRS_{ER-neg}													
	Q1 (-2.802 to -0.688)	155	46	1.00	Reference		Q1 (-3.664 to -0.742)	220	96	1.00	Reference		
	Q2 (-0.684 to -0.08)	155	31	0.67	0.41 to 1.12	0.127	Q2 (-0.739 to -0.032)	220	123	1.28	0.93 to 1.78	0.132	
	Q3 (-0.079 to 0.569)	155	30	0.65	0.39 to 1.09	0.101	Q3 (-0.028 to 0.623)	220	102	1.06	0.76 to 1.49	0.718	
	Q4 (0.572 to 3.011)	155	46	1.00	0.63 to 1.60	0.987	Q4 (0.625 to 3.392)	220	100	1.05	0.75 to 1.47	0.785	
	Continuous variable	620	153	1.00	0.83 to 1.21	0.962	Continuous variable	880	421	1.02	0.91 to 1.14	0.702	0.860
PRS_{ER-pos}													
	Q1 (-3.482 to -0.630)	155	49	1.00	Reference		Q1 (-3.311 to -0.711)	220	108	1.00	Reference		
	Q2 (-0.627 to 0.039)	155	43	0.88	0.55 to 1.40	0.589	Q2 (-0.711 to -0.073)	220	98	0.91	0.65 to 1.26	0.560	
	Q3 (0.046 to 0.759)	155	33	0.67	0.41 to 1.10	0.115	Q3 (-0.072 to 0.564)	220	102	0.95	0.68 to 1.32	0.761	
	Q4 (0.761 to 3.777)	155	28	0.57	0.34 to 0.96	0.033	Q4 (0.566 to 3.206)	220	113	1.05	0.76 to 1.45	0.768	
	Continuous variable	620	153	0.74	0.62 to 0.89	0.001	Continuous variable	880	421	0.97	0.86 to 1.09	0.579	0.017