Personalizing Breast Cancer Screening Based on Family History & Polygenic Risk.

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Submitted

ABSTRACT

Background

Current breast cancer screening guidelines are age-based. However, at any given age there is variability in breast cancer risk. This study assessed screening approaches using first-degree family history (FH) and polygenic risk scores (PRS) to identify women for risk-based screening.

Method

Two established breast cancer models assessed the impact of risk-based screening on breast cancer deaths, life years gained, false-positive mammograms, and overdiagnoses for the 1985 U.S. female birth cohort. Digital mammography screening strategies varying in initiation age (30, 35, 40, 45, 50) and interval (annual, hybrid, biennial, triennial) were evaluated for women differing in risk due to their family history and European-ancestry PRS. The benefits and harms of risk-based screening were compared to current age-based guidelines for biennial screening from 50-74.

Results

Under the most effective screening strategies, the estimated increase in life years gained and reduction in breast cancer mortality due to risk-based screening were 6% and 3% (FH), 19% and 11% (PRS), and 24% and 14% (PRS+FH). The predicted rate of false-positives and overdiagnoses of 917 and 14.5 per 1.000 women screened over their lifetimes for age-based screening increased to 997 and 14.9 (FH), 1154 and 15.9 (PRS), 1157 and 16.3 (PRS+FH).

Conclusion

European-ancestry women at increased risk due to family history or polygenic risk could consider risk-based screening strategies starting before age 50 depending on their attitude towards the harms and benefits of breast cancer screening.

INTRODUCTION

Regular mammography screening has been shown to reduce breast cancer mortality. (1) However, it is uncertain whether current age-based screening recommendations (2, 3) are optimal, as there is variability in breast cancer risk at any given age. The risk of developing breast cancer approximately doubles for women with a first-degree family member with breast cancer.(4) Approximately 20% of the familial risk is attributable to high- or moderate penetrance mutations in genes including BRCA1, BRCA2, PALB2, ATM, and CHEK2.(5, 6) The majority of the remaining 80% is due to a combination of more common variations in the DNA sequence, e.g., single nucleotide polymorphisms (SNPs). Currently, about 170 common breast cancer risk SNPs have been identified.(7) While these individual variants are associated with small to modest risks, their combined effects considered as a polygenic risk score (PRS) can be substantial and could achieve a level useful for population screening.(8, 9)

The U.S. Preventive Services Task Force recommends that women discuss their individual risk and screening options with their healthcare providers, yet there are limited data to inform such discussions. Two ongoing trials, My-PEBS and the WISDOM trial are presently testing age-based vs. risk-based screening approaches that include genetic markers and family history information, but results are not expected until 2024-2025. (10) A recent study modeled the use of polygenic risk scores to determine the cost-effectiveness of screening women triennially above a certain risk threshold in the UK.(11) However, there are no studies that have estimated the impact of screening strategies tailored to risk from family history of breast cancer, polygenic risk, or both. To fill this gap, two established Cancer Intervention and Surveillance Modeling Network (CISNET) models which were used to inform current breast cancer screening guidelines(12, 13), estimated the lifetime effects of screening based on family history status and polygenic risk.(2) The projections in this study are intended to inform screening policy and provide background for clinical discussions about risk-based breast cancer screening.

METHODS

Model overview

Breast cancer simulation models developed by the Erasmus University Medical Center (14) and the Georgetown University-Albert Einstein College of Medicine (15) evaluated the lifetime effects of different screening strategies among the 1985 U.S. female birth cohort. Model descriptions and detailed information on model inputs and validation have been described.(12, 16-18) (Appendix 1)

Briefly, both models used incidence from four breast cancer molecular subtypes based on estrogen receptor (ER) and human epidermal growth factor receptor (HER)2 status.(17) Screen-detection of breast cancer was modeled using digital mammography sensitivity and stage distributions reported by the Breast Cancer Surveillance Consortium.(19) Treatment impact was derived from systematically reviewed treatment effectiveness (20) and reduced the probability of death from breast cancer. At any time, women diagnosed with breast cancer could die of the disease or competing other cause mortality. To evaluate the potential efficacy of different screening strategies, the models assumed that all women received genetic testing and were screened according to the selected strategy, and, if diagnosed with cancer, received sub-type specific adjuvant therapy.

Screening strategies

Nineteen digital mammography screening strategies that varied by age at initiation of screening (30, 35, 40, 45, 50) and screening interval (annual, biennial, triennial, hybrid) were evaluated. Hybrid strategies screen annually before age 50 and biennially starting at age 50. All strategies stopped screening at age 74. The primary comparator was biennial screening from ages 50 to 74 as this strategy is supported in the screening guidelines in many developed countries. (2, 21, 22)

Risk stratification

Family history

We defined five family history groups: women who learned in age ranges 30-39, 40-49, 50-64, 65-100 that they had a first-degree relative with breast cancer; and women with no family history of breast cancer in their lifetimes. Using the age-specific distribution of family history in the National Health Interview Survey and associated risk levels observed in the Collaborative Breast Cancer Study (CBCS)(23), breast cancer risk was adjusted accordingly in the models.(Table 1)

Polygenic risk

Stratification based on polygenic risk used a polygenic risk score based on 77 SNPs, as defined by Mavaddat et al.(24) As a sensitivity analysis, we considered a PRS that included a larger number of common genetic variants (167 SNPs).(7) The polygenic risk scores are based on a multiplicative relative risk model for the joint effects of the SNPs, and are hence defined as the sum of risk alleles weighted by their effect size as estimated in the combined European ancestry Genome Wide Association Studies (GWAS) data.(7, 24) We established seven PRS groups spanning risk levels from 0 to 10 times the U.S. population average. (Table 1) Risk group prevalence was calculated by simulating the distribution of risk as a function of the PRS to match that of Mavaddat et al. Using the cut-off risk levels of the seven groups, we calculated the number of women in each group, for details see Appendix 2.

Table 1 Prevalence and relative risk (RR) according to polygenic risk score and family history of breast cancer.

Family history (FH) age groups **	**Risk relative to population average**	**% of all women**
FH positive between 30 and 39	2.19	4.7%
FH positive between 40 and 49	1.73	4.2%
FH positive between 50 and 64	1.39	5.9%
FH positive at age 65 or older	1.34	2.3%
No positive FH in life	0.79	82.9%
Polygenic risk groups *	**Risk relative to population average**	**% of all women**
Polygenic risk group 1	0.0 < RR ≤ 0.5	9.5%
Polygenic risk group 2	0.5 < RR ≤ 1.0	49.4%
Polygenic risk group 3	1.0 < RR ≤ 1.5	27.7%
Polygenic risk group 4	1.5 < RR ≤ 2.0	9.4%
Polygenic risk group 5	2.0 < RR ≤ 3.0	3.5%
Polygenic risk group 6	3.0 < RR ≤ 5.0	0.4%
Polygenic risk group 7	5.0 < RR ≤ 10.0	0.0 % *

* Based on the 77-SNP polygenic risk score (23), very few women would have 5 to 10-fold increased breast cancer risk.
**A positive first-degree family history was modeled as an increase in risk at the first age-year of each age-group.

Analysis

In total we examined 47 potential risk-groups; five family history, seven polygenic risk, and 35 combinations of both. We first used model projections on the harms (overdiagnoses and false-positives), and benefits (life-years gained and breast cancer deaths averted) of biennial screening *average-risk* women aged 50-74 as the benchmark for the outcomes of current screening guidelines. Overdiagnosis was defined as screen-detected cases (invasive + in situ) that would not have been diagnosed in the absence of screening. Next, we estimated the harms and benefits of the 19 screening strategies (described above) in each risk group. Among these comparisons, we selected the set of strategies that maximized the overall number of life-years gained, while maintaining a similar, or better, ratio of screens to life-years gained as seen with the baseline approach of biennial screening all women from 50-74. This methodology insured that risk-based screening would only increase the number of screens if the associated life-years gained increased at least proportionally. The overall population impact was quantified by accumulating the harms and benefits of the individual risk groups.

Sensitivity Analyses

To test the impact of improved polygenic risk scores on the harms and benefits of risk-based screening, we conducted sensitivity analyses of a PRS derived from 167 independent SNPs from the largest breast cancer GWAS to date.(7) In addition, since part of

the additional benefits of risk-based screening may accrue from an increased number of screens, we analyzed what the impact of polygenic risk-based screening could be if the total number of screens was fixed to the number performed with guideline screening (13 screens per woman with biennial 50-74).

RESULTS

Age-based guidelines

If all women among the 1985 US birth cohort undergo age-based biennial screening from ages 50 to 74, the models project an average of 11,157 screens and 124 life-years gained (range across models: (103 – 146) and 7 (6.4 – 7.6) breast cancer deaths averted for 1.000 women screened over their lifetimes vs. no-screening. These results provide a benchmark of 90 screens per life year gained of current screening guidelines. This threshold was used to select risk-based strategies with equal or better trade-off between screens and life-years gained.

Risk-based screening: family history

Women with a known family history of breast cancer before they reach age 50 (8.9% of all women) were screened biennially starting at either age 30 or at 40, depending on the age at which they first learned about breast cancer in a first-degree relative.(Table 2) This was estimated to lead to 44% more life-years gained and 24% reduction in breast cancer deaths relative to current screening guidelines. However, overdiagnoses increased by 26% and the number of false-positives doubled. The overall impact of a family history-based screening approach was modest due to the low prevalence of breast cancer family history in the population: 0.2 fewer cancer deaths and 7 additional life-years per 1,000 women screened over a lifetime.

Risk-based screening: polygenic risk

Next, we considered screening strategies targeted to polygenic risk. The optimal strategy that was selected for each polygenic risk group is given in Table 3 and Figure 1. Overall, polygenic risk-based screening was estimated to increase the number of screens by 17%, life-years gained by 19% and reduced breast cancer deaths by 11% compared to screening all women biennially from ages 50 to 74. The harms of screening such as overdiagnoses and false positives increased by 10% and 26%. In absolute numbers, using polygenic risk to personalize screening strategies was estimated to lead to 0.7 fewer cancer deaths and 24 additional life-years per 1,000 women screened.(Table 3)

Table 2 Benefits and harms of mammography screening based on breast cancer family history. Outcomes presented as average of two models per 1,000 women screened.

Row	Risk group based on family history (FH) of breast cancer		Screening strategy	Number of screens	Life years gained *	Breast cancer deaths averted *	Over diagnoses	False positives	Screens / life year gained	Life years gained / overdiagnoses
1	*Average risk population*		Biennial 50-74	11157	124	7.0	14.5	917	90	8.6
2	Positive FH ages 30-39	Guideline	Biennial 50-74	10815	168	9.3	16.5	892	64	10.2
3		Risk-based strategy	Biennial 30-74	20528	254	11.9	21.7	2079	81	11.7
4			*% change (3) vs. (2)*	*90%*	*51%*	*28%*	*31%*	*133%*	*25%*	*16%*
5	Positive FH ages 40-49	Guideline	Biennial 50-74	10904	168	9.3	16.7	901	65	10.1
6		Risk-based strategy	Biennial 40-74	15713	228	11.3	20.3	1468	69	11.3
7			*% change (6) vs. (5)*	*44%*	*36%*	*20%*	*21%*	*63%*	*6%*	*12%*
8	Positive FH < age 50	Guideline	Biennial 50-74	10857	168	9.3	16.6	896	65	10.1
9		Risk-based strategies (rows 3,6)	Biennial 30/40-74	18256	242	11.6	21.0	1791	75	11.5
10			*change (9) vs. (8)*	*68%*	*44%*	*24%*	*26%*	*100%*	*17%*	*14%*
11	Positive FH 50-64	Guideline/risk-based	Biennial 50-74	11054	162	9.0	16.8	908	68	9.6
12	Positive FH 65+	Guideline/risk-based	Biennial 50-74	11185	129	7.5	16.8	915	87	7.7
13	No FH during life	Guideline/risk-based	Biennial 50-74	11236	105	5.8	15.7	919	107	6.7
14	**FH groups aggregated (rows 3,6,11,12,13)**			11813	131	7.2	14.9	997	90	8.8
15			*% change (14) vs. (1)*	*6%*	*6%*	*3%*	*3%*	*9%*	*0%*	*3%*

*The life-years gained and breast cancer deaths averted are relative to the life-years and breast cancer deaths of women at the same level of risk who are not screened.

Risk-based screening: polygenic risk and family history

Finally, we considered risk stratification by polygenic risk and family history simultaneously, defining 35 risk groups. (Table 4, optimal strategies given in Appendix 3) At the population level, risk-based screening using polygenic risk and family history was estimated to lead to 31 additional life years gained, 1 fewer breast cancer death and 1.8 additional overdiagnoses per 1,000 women screened.

Sensitivity Analyses

We also considered the effect of using an enhanced polygenic risk score of 167 SNPs instead of 77 SNPs. The percentage of women undergoing a different screening strategy based on the 167-SNP PRS distribution was small: 7.6%.(Appendix 2) The estimated number of mammograms decreased by approximately 1%, the number of overdiagnoses,

false positives, breast cancer deaths and life years gained remained virtually unchanged. (Table 4) Without increasing the number of mammograms of guideline (biennial 50-74) screening, a PRS screening approach based on 77 SNPs still gained 9% additional life years and 3% more breast cancer deaths averted.

Table 3 Benefits and harms of mammography screening based on polygenic risk. Outcomes presented as average of two models per 1,000 women screened.

Row	Risk group based on polygenic risk score (PRS)		Screening strategy	Number of screens	Life years gained *	Breast cancer deaths averted *	Over diagnoses	False positives	Screens / life year gained	Life years gained / overdiagnoses
1	*Average risk population*		Biennial 50-74	11157	124	7.0	14.5	917	90	8.6
2	PRS7 (5.0 < RR < 10.0)	Guideline	Biennial 50-74	8886	512	27.5	28.0	726	17	18.3
3	Risk-based strategy		Annual 30-74	35214	959	42.8	53.3	3648	37	18.0
4			*% change (3) vs. (2)*	*296%*	*87%*	*56%*	*90%*	*403%*	*112%*	*-2%*
5	PRS6 (3.0 < RR < 5.0)	Guideline	Biennial 50-74	9897	352	19.3	24.8	811	28	14.2
6	Risk-based strategy		Annual 35-74	32835	616	28.8	42.5	3253	53	14.5
7			*% change (6) vs. (5)*	*232%*	*75%*	*50%*	*72%*	*301%*	*89%*	*2%*
8	PRS5 (2.0 < RR < 3.0)	Guideline	Biennial 50-74	10469	252	13.9	21.0	859	42	12.0
9	Risk-based strategy		an40-50,bi50-74	19574	358	17.2	26.2	1954	55	13.7
10			*% change (9) vs. (8)*	*87%*	*42%*	*23%*	*25%*	*127%*	*31%*	*14%*
11	PRS4 (1.5 < RR < 2.0)	Guideline	Biennial 50-74	10844	183	10.2	17.7	891	59	10.3
12	Risk-based strategy		Biennial 40-74	15646	242	12.1	21.2	1462	65	11.4
13			*% change (12) vs. (11)*	*44%*	*32%*	*18%*	*20%*	*64%*	*9%*	*10%*
14	PRS3 (1.0 < RR < 1.5)	Guideline	Biennial 50-74	11091	137	7.6	15.2	912	81	9.0
15	Risk-based strategy		Biennial 40-74	15923	180	9.0	18.1	1487	89	9.9
16			*% change (15) vs. (14)*	*44%*	*32%*	*18%*	*19%*	*63%*	*9%*	*10%*
17	PRS2 (0.5 < RR < 1.0)	Guideline	Biennial 50-74	11332	90	5.1	12.4	932	126	7.3
18	Risk-based strategy		Biennial 50-74	11332	90	5.1	12.4	932	126	7.3
19			*% change (18) vs. (17)*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0%*
20	PRS1 (0.0 < RR < 0.5)	Guideline	Biennial 50-74	11588	40	2.3	9.0	953	290	4.4
21	Risk-based strategy		Triennial 50-74	8020	34	1.9	8.3	705	238	4.1
22			*% change (21) vs (20)*	*-31%*	*-16%*	*-15%*	*-8%*	*-26%*	*-18%*	*-8%*
23	**PRS groups aggregated (rows 3,6,9,12,15,18,21)**			13011	148	7.7	15.9	1154	88	9.3
24			*% change (23) vs. (1)*	*17%*	*19%*	*11%*	*10%*	*26%*	*-2%*	*9%*

*The life-years gained and breast cancer deaths averted are relative to the life-years and breast cancer deaths of women at the same level of risk who are never screened.

Table 4 Benefits and harms comparison of mammography screening based on breast cancer family history, polygenic risk score, and family history combined with polygenic risk – for both the primary analysis and the sensitivity analyses. Outcomes presented as average of two models per 1,000 women screened.

Row	Risk group	Screening strategy	Number of screens	Life years gained *	Breast cancer deaths averted *	Over diagnoses	False positives	Screens / life year gained	Life years gained / overdiagnoses
1	*Average risk population*	Biennial 50-74	11157	124	7.0	14.5	917	90	8.6
2	*FH groups aggregated*	Risk-based strategies	11813	131	7.2	14.9	997	90	8.8
3		*% change (2) vs. (1)*	*6%*	*6%*	*3%*	*3%*	*9%*	*0%*	*3%*
4	PRS groups *aggregated*	Risk-based strategies	13011	148	7.7	15.9	1154	88	9.3
5		*% change (4) vs. (1)*	*17%*	*19%*	*11%*	*10%*	*26%*	*-2%*	*9%*
6	*PRS + FH groups aggregated*	Risk-based strategies	13032	155	8.0	16.3	1157	84	9.5
7		*% change (6) vs. (1)*	*17%*	*24%*	*14%*	*14%*	*26%*	*-6%*	*10%*
8	***Sensitivity Analyses***								
9	PRS groups *aggr. (167 SNPs)*	Risk-based strategies	12948	149	7.7	15.9	1150	87	9.4
10		*% change (9) vs. (1)*	*16%*	*20%*	*11%*	*10%*	*25%*	*-3%*	*9%*
11	*PRS + FH aggr. (167 SNPs)*	Risk-based strategies	12722	154	7.9	16.2	1128	83	9.5
12		*% change (11) vs. (1)*	*14%*	*24%*	*14%*	*12%*	*23%*	*-8%*	*11%*
13	*Redistributing screens* **	Risk-based strategies	11172	135	7.2	14.2	968	85.7	10.3
14		*% change (13) vs. (1)*	*0%*	*9%*	*3%*	*-2%*	*6%*	*-7%*	*13%*

**The life-years gained* and breast cancer deaths averted are relative to the life-years and breast cancer deaths of women at the same level of risk who are never screened.

** The redistributing screens scenario represents a scenario where the number of screens of current screening guidelines (in row 1) is not *increased, rather redistributed across the population based on the polygenic risk scores. The selection of screening strategies in this scenario are given in Appendix 2.*

DISCUSSION

This is the first modeling study to quantify the harms and benefits of breast cancer screening based on polygenic risk and family history. Using two tumor type-specific natural history models including sensitivity and specificity of digital mammography, we show that risk-based screening has greater projected benefits when based on polygenic risk scores than family history. The screening approach combining polygenic risk scores and family history resulted in the maximal improvement in outcomes compared to current

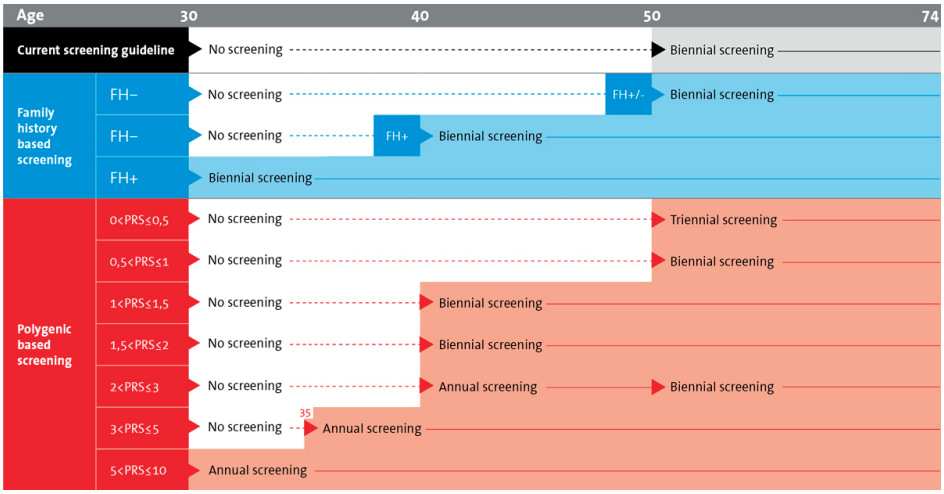

Figure 1 Selected screening strategies in the family history (blue), and polygenic risk (red) screening approaches. Starting age and interval of screening, as well as family history status may change by age (top row).
The screening strategies selected for the 35 risk-groups in the polygenic risk combined with breast cancer family history screening approach can be found in Appendix 3.

age-based screening guidelines. The risk group-specific outcomes suggest that high risk women could initiate screening at an earlier age, and that women with below-average risk could consider screening at longer intervals than current age-based guidelines. Inclusion of additional, more recently identified SNP into the models only modestly improved the benefits and harms. With the inclusion of more SNPs in the future, there is still potential for a PRS to further improve the discriminatory performance. Notably, polygenic risk used in combination with breast density, and reproductive, lifestyle, and hormonal factors is likely to improve risk prediction and the harm-benefit ratio for stratified screening.(25)

Current age-based guidelines recommend that women should discuss screening with healthcare providers to select the best approach for their individual risk.(2, 21) Our analysis extends this advice by providing specific screening strategies that could be considered in practice based on genetic risk factors. Our data suggest that among higher than average-risk women (i.e., twice the average population risk), initiating screening at an earlier age (<50) is likely to provide greater benefits than harm.

Our results are consistent with our previous work on risk-based screening based on more common classical risk factors (26, 27) and prior research in other countries. In Spain, Vilaprinyo and colleagues performed an analysis using four risk-groups based on breast density, family history, and personal history of breast biopsy to guide screening for women aged 40-85.(28) Recently, Pashayan used a life-table model to assess risk-based screening for women 50-85 in the United Kingdom based on polygenic risk profile.(11)

Like our results, both studies concluded that risk-based screening strategies were more efficient and had lower harm-benefit ratios than age-based screening.

While our results, and the results of others lend support to risk-based screening, our approach was unique in evaluating whether the associated increases in benefits were merely attributed to the increase in the number of screening examinations. In the sensitivity analyses, we demonstrated that, redistributing the guideline-concordant number of screens across all women, increased life-years gained and breast cancer deaths averted more than overdiagnoses and false-positives would increase. However, this also showed that a large part of the projected benefit-increase was explained by the greater number of mammograms as screening increases cancer detection.

Implementing breast cancer screening based on polygenic risk and family history status would require a one-time saliva sample to establish a polygenic risk profile. The result, together with a questionnaire about family history could assist women in making choices about more personalized screening options. Knowledge of genetic susceptibility to breast cancer could guide early detection strategies. However, ethical aspects of genetic testing such as patient autonomy, accessibility, possible (unknown) differential effects across ancestries, should be considered before the implementation or recommendation of polygenic risk-based screening. Overall, it will be essential to develop and evaluate polygenic risk models for non-European ancestry women.

This study has several important strengths including consistent results across two well-established simulation models, use of U.S. national data, and evaluation of polygenic risk and family history information to personalize breast cancer screening. There are also several caveats that should be considered in evaluating the results. First, we did not explicitly model the effects of rare but higher risk variants in genes such as BRCA1, BRCA2, PALB2, CHEK2 or ATM that could be used to tailor screening strategies. Mutations in genes BRCA1 and BRCA2 confer exceptionally high risk, and carriers of mutations in these genes are typically advised to undergo annual screening with both MRI and mammography, starting at an early age.(29) MRI has higher sensitivity than mammography but is associated with a higher false-positive rate. We anticipate that if MRI were to be used as screening modality in the setting of higher than average polygenic risk, projected benefits would be larger but false-positives and possibly overdiagnoses would increase as well. Second, while we account for differing tumor natural history by ER/HER2 tumor status, the models assumed that polygenic risk did not affect tumor type and tumor progression since there are insufficient data to inform modeling of variation in natural history. However, an increasing number of SNP associations are known to differ by tumor subtype, particularly ER-status (30, 31), and there is some data showing that the PRS has differential effects by mode of detection (32). It is possible in due course that a separate PRS consisting of SNPs associated with faster or slower growing tumors may inform screening intensity. Third, we did not explicitly consider second degree family members

with breast cancer, nor the use of breast density or other risk factors which may have potential value for risk-based screening.(26) Fourth, to test the efficacy of risk-based screening, we assumed 100% uptake of genetic testing, screening, and treatment. Fifth, the effectiveness of screening in combination with treatment in women under age 40 has been assessed in case-control studies, but not in a randomized controlled trial. Finally, the PRS used in this study was developed using data primarily from Caucasian women of European ancestry. Screening strategies should be re-assessed for minority groups as genetic databases evolve.

Overall, this research showed that more breast cancer deaths could be prevented and lives extended for select, but identifiable, groups of women at high risk due to their family history of breast cancer and polygenic risk. These results are intended to inform continued debates about optimal breast cancer screening strategies and could begin to guide patient-provider discussions in routine clinical practice.

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APPENDIX

1. **Model descriptions**
2. **Prevalence and relative risk calculations for the polygenic risk score groups**
3. **Strategies in the combined polygenic risk score and family history screening approach**
4. **Individual model predictions**

APPENDIX 1

Model Descriptions

The Institutional Review Board at Georgetown University approved the study as exempt based on the use of de-identified data. Detailed descriptions of model inputs and model validation have been described in detail elsewhere.(11, 17-19)

Model Erasmus University Medical Center (Model E)

Model E, also known as MISCAN-Fadia which is an acronym for Microsimulation Screening Analysis – Fatal Diameter is a breast cancer simulation model that uses continuous tumor growth to simulate the natural history of breast cancer. The model simulates individual life histories from birth to death, with and without breast cancer, in the presence and in the absence of screening and treatment. Life histories are simulated according to discrete events such as birth, tumor inception, metastasis, and death from breast cancer or death from other causes. Model E consists of four main components: demography, natural history of breast cancer, screening, and treatment. Screening impact on the natural history of breast cancer is assessed by simulating continuous tumor growth and the "fatal diameter" concept. This concept implies that tumors diagnosed at a size that is between the screen detection threshold and the fatal diameter are cured, while tumors diagnosed at a diameter larger than the fatal tumor diameter metastasize and lead to breast cancer death. MISCAN-Fadia includes different natural histories for molecular subtypes based on a tumor's ER status and HER-2 status.

Model Georgetown University-Albert Einstein College of Medicine (Model GE)

Model GE is a continuous-time, event-driven microsimulation of single-life histories of women utilizing a parallel universes approach. The parallel universes approach starts with the generation of a basic life history for each simulated woman in the absence of any screening or adjuvant treatment. The effects of each screening and adjuvant treatment strategy under study are then simulated starting using the exact same basic life

history. In this manner, the outputs for the different screening and adjuvant treatment strategies are matched pairs. The approach for simulating breast cancer natural history is phenomenological, relying on dates, stage, and age of clinical and screen detection for a tumor molecular subtype without explicitly modeling tumor growth. The model accommodates differences in natural history associated with estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) biomarkers, as well as conventional breast cancer risk factors. Breast cancer incidence depends on age, time period, and birth cohort, and is modified based on risk. The incidence includes a subset of ductal carcinoma in situ (DCIS) tumors that never surface clinically and eventually regress.

APPENDIX 2

Prevalence and relative risk calculation for polygenic risk score groups (77-SNPs PRS)

We modeled the distribution of risk relative to the average woman without a family history (RR*) as a function of polygenic risk and family history:

$$RR^* = Lognormal\left(FH\chi\left(\mu_i + \frac{\sigma_i}{2}\right) - \left(\frac{\sigma_i}{2}\right)^2 , \sigma_i\right)$$

Where FHx is an indicator for first degree family history of breast cancer (yes=1, no=0), γ is the log relative risk of family history (adjusted for polygenic effects), and σ_i is the log relative risk associated with a one standard deviation change in the polygenic risk score in age group i.

We used the following parameter values for μ_i and σ_i from Table 3 in Mavaddat (2015) JNCI.

	Sigma (σ)		
Age	**All cancers**	**ER+**	**ER-**
< 40	0.46 (0.38 – 0.53)	0.56 (0.47 – 0.65)	0.48 (0.36 – 0.59)
40-49	0.46 (0.42 – 0.50)	0.53 (0.48 – 0.57)	0.36 (0.29 – 0.43)
50-59	0.48 (0.45 – 0.51)	0.54 (0.50 – 0.57)	0.37 (0.32 – 0.43)
≥60	0.41 (0.38 – 0.43)	0.44 (0.41 – 0.47)	0.36 (0.31 – 0.42)
All ages	*0.44 (0.42 – 0.46)*	*0.49 (0.47 - 0.51)*	*0.37 (0.34 – 0.40)*

To model the distribution of risk relative to the population average, we consider RR = RR*/mean(RR*), where the mean of RR* is taken over the joint distribution of family history and polygenic risk in the population. The distributions of risk relative to the population average for various subgroups are displayed in the following figures:

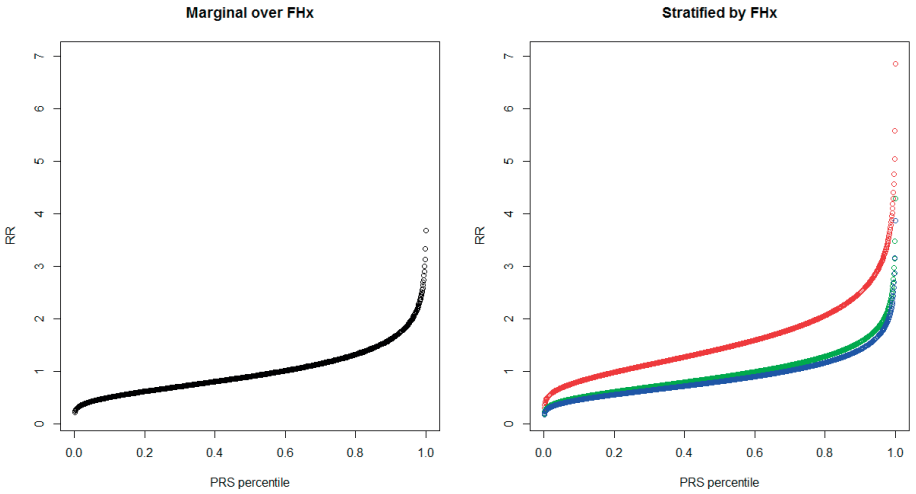

Figure 1: Distribution of breast cancer relative risk as a function of PRS (left) and family history + PRS (right). Red represents FH+ < age 40 women, green: FH+ between ages 40 and 65, blue: no FH in life.

In the screening approach based on a polygenic risk score **(77-SNPs)** combined with family history of breast cancer, the prevalence distribution of women among the risk-groups is as follows:

	Polygenic risk score groups (low to high polygenic risk)						
FH group	**0.0-0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**2.0-3.0**	**3.0-5.0**	**5.0-10.0**
30 < FH+ < 40	0.9%	20.2%	33.5%	23.4%	17.6%	4.2%	0.3%
40 < FH+ < 49	0.9%	20.3%	33.5%	23.3%	17.5%	4.3%	0.3%
50 < FH+ < 64	9.6%	51.0%	27.7%	8.4%	3.0%	0.3%	0.0%
65 < FH+ < 100	9.7%	50.9%	27.7%	8.4%	3.0%	0.3%	0.0%
No FH in life	14.0%	54.8%	23.3%	5.9%	1.8%	0.2%	0.0%

Sensitivity analyses

In the sensitivity analyses screening based on a polygenic risk score consisting of 167 SNPs instead of 77 SNPs, we used a sigma (σ) of 0.48 instead of 0.44. The prevalence distribution of women among the polygenic risk groups based on the 77-SNP and 167-SNP polygenic risk score is as follows. The total percentage of women who end up in a different risk group based on the 167-SNP PRS compared to the 77-SNP PRS is 7.6%.

Polygenic risk group	77-SNPs	167-SNPs	Screening strategy
Polygenic risk group 1 (0.0 < Relative Risk < 0.5)	9.5%	12.3%	Triennial 50-74
Polygenic risk group 2 (0.5 < Relative Risk < 1.0)	49.4%	47.3%	Biennial 50-74
Polygenic risk group 3 (1.0 < Relative Risk < 1.5)	27.7%	26.0%	Biennial 40-74
Polygenic risk group 4 (1.5 < Relative Risk < 2.0)	9.4%	9.4%	Biennial 40-74
Polygenic risk group 5 (2.0 < Relative Risk < 3.0)	3.5%	4.3%	Hybrid 40-74
Polygenic risk group 6 (3.0 < Relative Risk < 5.0)	0.4%	0.6%	Annual 35-74
Polygenic risk group 7 (5.0 < Relative Risk < 10.0)	0.0 % *	0.0 % *	Annual 30-74

* Based on the 77-SNP and 167-SNP polygenic risk score [21], practically zero women would have 5 to 10-fold increased breast cancer risk.

In the screening approach based on a polygenic risk score **(167-SNPs)** combined with family history of breast cancer, the prevalence distribution of women among the risk-groups is as follows:

	Polygenic risk score groups (low to high polygenic risk)						
FH group	**0.0-0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**2.0-3.0**	**3.0-5.0**	**5.0-10.0**
30 < FH+ < 40	1.6%	22.1%	31.3%	21.6%	17.6%	5.4%	0.5%
40 < FH+ < 49	1.6%	22.1%	31.4%	21.6%	17.5%	5.4%	0.5%
50 < FH+ < 64	12.0%	48.5%	26.2%	9.0%	3.8%	0.5%	0.1%
65 < FH+ < 100	12.0%	48.6%	26.1%	9.0%	3.8%	0.6%	0.0%
No FH in life	17.5%	51.9%	21.8%	6.3%	2.3%	0.3%	0.0%

In the screening approach that redistributed the number of screens of biennial 50-74 across the different polygenic risk groups, the following screening strategies were selected:

Polygenic risk group	Screening strategy
Polygenic risk group 1 (0.0 < Relative Risk < 0.5)	No screening
Polygenic risk group 2 (0.5 < Relative Risk < 1.0)	Biennial 50-74
Polygenic risk group 3 (1.0 < Relative Risk < 1.5)	Biennial 45-74
Polygenic risk group 4 (1.5 < Relative Risk < 2.0)	Biennial 45-74
Polygenic risk group 5 (2.0 < Relative Risk < 3.0)	Hybrid 40-74
Polygenic risk group 6 (3.0 < Relative Risk < 5.0)	Hybrid 40-74
Polygenic risk group 7 (5.0 < Relative Risk < 10.0)	Annual 30-74

APPENDIX 3

Selected screening strategies in the approach combining polygenic risk scores (PRS) with family history (FH) of breast cancer.

Risk group		Screening strategy
PRS group 1 (0.0 < RR < 0.5)	FH positive between 30 and 39	Triennial 30-74
	FH positive between 40 and 49	Triennial 40-74
	FH positive between 50 and 64	Triennial 50-74
	FH positive at age 65 or older	Triennial 50-74
	No positive FH in life	Triennial 50-74
PRS group 2 (0.5 < RR < 1.0)	FH positive between 30 and 39	Biennial 35-74
	FH positive between 40 and 49	Biennial 40-74
	FH positive between 50 and 64	Biennial 50-74
	FH positive at age 65 or older	Biennial 50-74
	No positive FH in life	Biennial 50-74
PRS group 3 (1.0 < RR < 1.5)	FH positive between 30 and 39	Biennial 30-74
	FH positive between 40 and 49	Biennial 40-74
	FH positive between 50 and 64	Biennial 45-74
	FH positive at age 65 or older	Biennial 45-74
	No positive FH in life	Biennial 45-74
PRS group 4 (1.5 < RR < 2.0)	FH positive between 30 and 39	Annual 30-50 + Biennial 50-74
	FH positive between 40 and 49	Annual 40-50 + Biennial 50-74
	FH positive between 50 and 64	Biennial 40-74
	FH positive at age 65 or older	Biennial 40-74
	No positive FH in life	Biennial 40-74
PRS group 5 (2.0 < RR < 3.0)	FH positive between 30 and 39	Annual 30-74
	FH positive between 40 and 49	Annual 40-74
	FH positive between 50 and 64	Annual 40-50 + Biennial 50-74
	FH positive at age 65 or older	Annual 40-50 + Biennial 50-74
	No positive FH in life	Annual 40-50 + Biennial 50-74
PRS group 6 (3.0 < RR < 5.0)	FH positive between 30 and 39	Annual 30-74
	FH positive between 40 and 49	Annual 35-74
	FH positive between 50 and 64	Annual 35-74
	FH positive at age 65 or older	Annual 35-74
	No positive FH in life	Annual 35-74
PRS group 7 (5.0 < RR < 10.0)	FH positive between 30 and 39	Annual 30-74
	FH positive between 40 and 49	Annual 30-74
	FH positive between 50 and 64	Annual 30-74
	FH positive at age 65 or older	Annual 30-74
	No positive FH in life	Annual 30-74

APPENDIX 4

Benefits and harms projections of mammography screening based on breast cancer family history. Outcomes for model E (Erasmus) per 1,000 women screened.

Risk group based on family history (FH) of breast cancer	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
Positive FH ages 30-39	Biennial 50-74	10754	141.5	8.6	21.2	889
Risk-based strategy	Biennial 30-74	20466	212.1	10.9	28.5	2083
Positive FH ages 40-49	Biennial 50-74	10859	141.3	8.6	21.4	897
Risk-based strategy	Biennial 40-74	15670	182.7	10.0	26.4	1472
Positive FH ages 50-64	Biennial 50-74 (risk-based)	11025	126.0	7.9	21.6	911
Risk-based strategy	Biennial 40-74 (risk-based)	11143	104.3	6.6	21.6	911
Positive FH ages 65+	Biennial 50-74 (risk-based)	11197	88.3	5.4	19.3	920

Benefits and harms projections of mammography screening based on breast cancer family history. Outcomes for model GE (Georgetown-Einstein) per 1,000 women screened.

Risk group based on family history (FH) of breast cancer	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
Positive FH ages 30-39	Biennial 50-74	10875	194.7	10.0	11.9	895
Risk-based strategy	Biennial 30-74	20590	296.6	13.0	14.9	2076
Positive FH ages 40-49	Biennial 50-74	10949	195.2	10.1	12.1	906
Risk-based strategy	Biennial 40-74	15755	274.3	12.5	14.1	1464
Positive FH ages 50-64	Biennial 50-74 (risk-based)	11084	197.2	10.2	12.1	906
Risk-based strategy	Biennial 40-74 (risk-based)	11227	154.2	8.4	12.1	919
Positive FH ages 65+	Biennial 50-74 (risk-based)	11275	121.6	6.2	12.1	919

Benefits and harms projections of mammography screening based on polygenic risk scores. Outcomes for model E (Erasmus) per 1,000 women screened.

Risk group based on polygenic risk score (PRS)	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS7 (5.0 < RR < 10.0)	Biennial 50-74	9009	361	21.3	44.4	750
Risk-based strategy	Annual 30-74	35105	763	36.1	91.9	3668
PRS6 (3.0 < RR < 5.0)	Biennial 50-74	9889	267	16.2	37.9	820
Risk-based strategy	Annual 35-74	32616	517	26.0	70.4	3255
PRS5 (2.0 < RR < 3.0)	Biennial 50-74	10429	200	12.2	30.2	863
Risk-based strategy	An40-50,bi50-74	19165	281	14.6	38.6	1930
PRS4 (1.5 < RR < 2.0)	Biennial 50-74	10799	148	9.1	23.5	892
Risk-based strategy	Biennial 40-74	15604	191	10.6	28.3	1467
PRS3 (1.0 < RR < 1.5)	Biennial 50-74	11048	113	7.0	18.4	912
Risk-based strategy	Biennial 40-74	15889	145	8.1	21.9	1490
PRS2 (0.5 < RR < 1.0)	Biennial 50-74	11298	75	4.7	12.6	932
Risk-based strategy	Biennial 50-74	11298	75	4.7	12.6	932
PRS1 (0.0 < RR < 0.5)	Biennial 50-74	11567	34	2.1	5.8	953
Risk-based strategy	Triennial 50-74	8005	27	1.7	4.5	758

Benefits and harms projections of mammography screening based on polygenic risk scores. Outcomes for model GE (Georgetown-Einstein) per 1,000 women screened.

Risk group based on polygenic risk score (PRS)	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS7 (5.0 < RR < 10.0)	Biennial 50-74	8763	664	33.6	11.6	702
Risk-based strategy	Annual 30-74	35323	1154	49.4	14.6	3628
PRS6 (3.0 < RR < 5.0)	Biennial 50-74	9905	436	22.4	11.7	802
Risk-based strategy	Annual 35-74	33054	715	31.7	14.7	3252
PRS5 (2.0 < RR < 3.0)	Biennial 50-74	10509	303	15.7	11.8	855
Risk-based strategy	An40-50,bi50-74	19982	436	19.8	13.8	1979
PRS4 (1.5 < RR < 2.0)	Biennial 50-74	10890	218	11.3	11.9	889
Risk-based strategy	Biennial 40-74	15688	292	13.6	14.1	1458
PRS3 (1.0 < RR < 1.5)	Biennial 50-74	11133	160	8.3	12.0	911
Risk-based strategy	Biennial 40-74	15957	215	10.0	14.4	1483
PRS2 (0.5 < RR < 1.0)	Biennial 50-74	11367	105	5.5	12.1	932
Risk-based strategy	Biennial 50-74	11367	105	5.5	12.1	932
PRS1 (0.0 < RR < 0.5)	Biennial 50-74	11609	46	2.4	12.3	953
Risk-based strategy	Triennial 50-74	8035	41	2.1	12.1	651

Benefits and harms projections of mammography screening based on polygenic risk scores and breast cancer family history combined. Outcomes for model E (Erasmus) per 1,000 women screened.

Risk group based on polygenic risk score (PRS) and breast cancer family history (FH)		Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS group 7 (5.0 < RR < 10.0)							
FH+ ages 30-39		Biennial 50-74	8093	313	18.2	37	675
	Risk-based strategy	Annual 30-74	32362	903	38.5	96	3419
FH+ ages 40-49		biennial 50-74	8413	335	19.4	41	701
	Risk-based strategy	Annual 30-74	33415	826	37.1	99	3522
FH+ ages 50-64		biennial 50-74	8876	327	19.4	47	740
	Risk-based strategy	Annual 30-74	34847	720	34.2	97	3650
FH+ ages 65+		biennial 50-74	9169	288	17.5	46	763
	Risk-based strategy	Annual 30-74	35564	659	31.5	93	3708
PRS group 6 (3.0 < RR < 5.0)							
FH+ ages 30-39		biennial 50-74	9117	258	15.4	37	758
	Risk-based strategy	Annual 30-74	35293	663	29.9	83	3678
FH+ ages 40-49		biennial 50-74	9365	268	15.9	40	778
	Risk-based strategy	Annual 35-74	31196	587	28.2	82	3135
FH+ ages 50-64		biennial 50-74	9744	250	15.3	43	809
	Risk-based strategy	Annual 35-74	32308	501	25.4	79	3233
FH+ ages 65+		biennial 50-74	9999	215	13.4	41	829
	Risk-based strategy	Annual 35-74	32925	444	22.7	73	3282
PRS group 5 (2.0 < RR < 3.0)							
FH+ ages 30-39		biennial 50-74	9812	204	12.4	33	814
	Risk-based strategy	Annual 30-74	37225	496	23.1	68	3845
FH+ ages 40-49		biennial 50-74	10005	207	12.6	34	829
	Risk-based strategy	Annual 40-74	28112	411	20.9	63	2671
FH+ ages 50-64		biennial 50-74	10301	191	11.8	36	854
	Risk-based strategy	an40-50,bi50-74	19055	269	14.2	44	1922
FH+ ages 65+		biennial 50-74	10507	161	10.2	33	870
	Risk-based strategy	an40-50,bi50-74	19275	235	12.4	40	1940
PRS group 4 (1.5 < RR < 2.0)							
FH+ ages 30-39		biennial 50-74	10319	158	9.7	27	854
	Risk-based strategy	an30-50,bi50-74	28744	309	14.1	42	3146
FH+ ages 40-49		biennial 50-74	10466	159	9.7	28	866
	Risk-based strategy	an40-50,bi50-74	19196	246	12.4	37	1933
FH+ ages 50-64		biennial 50-74	10694	145	9.0	29	885
	Risk-based strategy	Biennial 40-74	15501	184	10.4	34	1459

FH+ ages 65+		biennial 50-74	10855	121	7.7	26	897
	Risk-based strategy	Biennial 40-74	15672	159	9.0	30	1473
PRS group 3 (1.0 < RR < 1.5)							
FH+ ages 30-39		biennial 50-74	10319	158	9.7	27	854
	Risk-based strategy	Biennial 30-74	19926	263	13.0	38	2037
FH+ ages 40-49		biennial 50-74	10466	159	9.7	28	866
	Risk-based strategy	Biennial 40-74	15212	220	11.8	35	1435
FH+ ages 50-64		biennial 50-74	10694	145	9.0	29	885
	Risk-based strategy	Biennial 45-74	13370	171	10.2	33	1199
FH+ ages 65+		biennial 50-74	10855	121	7.7	26	897
	Risk-based strategy	Biennial 45-74	13551	145	8.8	30	1213
PRS group 2 (0.5 < RR < 1.0)							
FH+ ages 30-39		biennial 50-74	11041	85	5.2	16	911
	Risk-based strategy	Biennial 35-74	18652	132	6.9	21	1833
FH+ ages 40-49		biennial 50-74	11117	84	5.2	16	918
	Risk-based strategy	Biennial 40-74	15964	113	6.2	19	1496
FH+ ages 50-64		biennial 50-74	11238	75	4.7	16	927
	Risk-based strategy	biennial 50-74	11238	75	4.7	16	927
FH+ ages 65+		biennial 50-74	11325	62	4.0	14	934
	Risk-based strategy	biennial 50-74	11325	62	4.0	14	934
PRS group 1 (0.0 < RR < 0.5)							
FH+ ages 30-39		biennial 50-74	11447	39	2.4	8	944
	Risk-based strategy	Triennial 30-74	14742	47	2.5	8	1724
FH+ ages 40-49		biennial 50-74	11483	39	2.4	8	946
	Risk-based strategy	Triennial 40-74	10983	38	2.1	7	1218
FH+ ages 50-64		biennial 50-74	11538	35	2.2	7	951
	Risk-based strategy	Triennial 50-74	7987	26	1.7	6	756
FH+ ages 65+		biennial 50-74	11578	28	1.8	7	954
	Risk-based strategy	Triennial 50-74	8012	22	1.4	5	758

Benefits and harms projections of mammography screening based on polygenic risk scores and breast cancer family history combined. Outcomes for model GE (Georgetown-Einstein) per 1,000 women screened.

Risk group based on polygenic risk score (PRS) and breast cancer family history (FH)		Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS group 7 (5.0 < RR < 10.0)							
FH+ ages 30-39		biennial 50-74	7417	774	38.6	11	589
	Risk-based strategy	Annual 30-74	31822	1550	62.5	14	3293
FH+ ages 40-49		biennial 50-74	7716	805	40.2	11	612
	Risk-based strategy	Annual 30-74	32912	1513	62.7	14	3407
FH+ ages 50-64		biennial 50-74	8289	865	43.2	12	658
	Risk-based strategy	Annual 30-74	34391	1381	60.4	15	3550
FH+ ages 65+		biennial 50-74	8904	702	37.2	13	713
	Risk-based strategy	Annual 30-74	35681	1155	52.1	16	3663
PRS group 6 (3.0 < RR < 5.0)							
FH+ ages 30-39		biennial 50-74	8979	545	27.6	11	723
	Risk-based strategy	Annual 30-74	35662	1030	42.8	14	3653
FH+ ages 40-49		biennial 50-74	9188	557	28.2	11	740
	Risk-based strategy	Annual 35-74	31419	975	41.9	14	3102
FH+ ages 50-64		biennial 50-74	9579	580	29.4	12	772
	Risk-based strategy	Annual 35-74	32409	875	39.7	15	3198
FH+ ages 65+		biennial 50-74	9996	462	24.9	12	809
	Risk-based strategy	Annual 35-74	33282	717	33.6	15	3274
PRS group 5 (2.0 < RR < 3.0)							
FH+ ages 30-39		biennial 50-74	9849	392	20.0	11	799
	Risk-based strategy	Annual 30-74	37764	722	30.4	15	3848
FH+ ages 40-49		biennial 50-74	9999	398	20.3	12	811
	Risk-based strategy	Annual 40-74	28395	647	28.9	14	2658
FH+ ages 50-64		biennial 50-74	10277	409	20.9	12	834
	Risk-based strategy	an40-50,bi50-74	19772	546	25.3	14	1959
FH+ ages 65+		biennial 50-74	10572	323	17.5	12	860
	Risk-based strategy	an40-50,bi50-74	20084	440	21.1	14	1988
PRS group 4 (1.5 < RR < 2.0)							
FH+ ages 30-39		biennial 50-74	10412	285	14.7	12	848
	Risk-based strategy	an30-50,bi50-74	29630	492	20.6	14	3196
FH+ ages 40-49		biennial 50-74	10521	288	14.8	12	857
	Risk-based strategy	an40-50,bi50-74	19997	438	19.4	14	1979
FH+ ages 50-64		biennial 50-74	10722	295	15.2	12	873
	Risk-based strategy	Biennial 40-74	15530	372	17.6	14	1443

FH+ ages 65+		biennial 50-74	10935	231	12.5	12	892
	Risk-based strategy	Biennial 40-74	15745	296	14.6	14	1463
PRS group 3 (1.0 < RR < 1.5)							
FH+ ages 30-39		biennial 50-74	10778	213	11.0	12	880
	Risk-based strategy	Biennial 30-74	20478	327	14.3	15	2065
FH+ ages 40-49		biennial 50-74	10859	216	11.1	12	887
	Risk-based strategy	Biennial 40-74	15656	304	13.8	14	1455
FH+ ages 50-64		biennial 50-74	11009	218	11.2	12	899
	Risk-based strategy	Biennial 45-74	13063	253	12.2	13	1167
FH+ ages 65+		biennial 50-74	11166	171	9.3	12	913
	Risk-based strategy	Biennial 45-74	13217	196	9.9	13	1181
PRS group 2 (0.5 < RR < 1.0)							
FH+ ages 30-39		biennial 50-74	11133	141	7.3	12	911
	Risk-based strategy	Biennial 35-74	18051	205	9.1	15	1777
FH+ ages 40-49		biennial 50-74	11187	141	7.3	12	916
	Risk-based strategy	Biennial 40-74	16017	198	9.0	14	1489
FH+ ages 50-64		biennial 50-74	11285	143	7.4	12	924
	Risk-based strategy	biennial 50-74	11285	143	7.4	12	924
FH+ ages 65+		biennial 50-74	11389	111	6.1	12	933
	Risk-based strategy	biennial 50-74	11389	111	6.1	12	933
PRS group 1 (0.0 < RR < 0.5)							
FH+ ages 30-39		biennial 50-74	11505	62	3.2	12	944
	Risk-based strategy	Triennial 30-74	14019	76	3.4	15	1431
FH+ ages 40-49		biennial 50-74	11529	62	3.2	12	946
	Risk-based strategy	Triennial 40-74	10986	74	3.4	14	1044
FH+ ages 50-64		biennial 50-74	11572	63	3.3	12	950
	Risk-based strategy	Triennial 50-74	8012	56	2.9	12	649
FH+ ages 65+		biennial 50-74	11618	49	2.7	12	954
	Risk-based strategy	Triennial 50-74	8042	43	2.4	12	652