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Polygenic predisposition to breast cancer and the risk of coronary artery disease

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ABSTRACT

Background: Whether the increased risk of coronary artery disease (CAD) in patients with breast cancer may be linked to shared genetics is unknown. Our objective was to investigate the association of genetic predisposition to breast cancer with CAD risk via 1) a polygenic risk score 2) a nationwide case-control study.

Methods and results: We studied the associations of a polygenic risk score based on 91 single nucleotide polymorphisms previously associated with breast cancer in genome-wide association studies with the risk of CAD in a sample of patients undergoing coronary angiography. Secondary outcomes were prevalent atrial fibrillation, heart failure and breast cancer. Logistic regression models were used to analyze the associations. The risk of CAD associated with having a mother with breast cancer was analyzed with conditional logistic regression in the case-control study.

Among 4985 patients undergoing coronary angiography (median age 66 years (Quartile (Q) 1-Q3 57–73), 65% male) 3724 (75%) had CAD. Increasing polygenic risk score was not associated with risks of CAD (odds ratio (OR) 1.01, 95% confidence interval (CI) 0.94–1.08), atrial fibrillation (OR 1.03, CI 0.94–1.12), or heart failure (OR 0.97, CI 0.90–1.05). In women, increasing polygenic risk score was associated with the risk of breast cancer (OR 1.40, CI 1.14–1.73). The risk of CAD was not significantly increased in children with vs. without mothers with breast cancer (Hazard ratio 0.89 95% CI 0.83–0.96, p = 0.002).

Conclusions: Our study found no evidence of a shared genetic predisposition of breast cancer with CAD, atrial fibrillation, or heart failure.

1. Introduction

Extensive research has documented an increased risk of cardiovascular disease in patients with prior breast cancer, which partly appears to be linked to breast cancer treatments [1–4] and modifiable lifestyle-related risk factors [5–13]. Additionally, common signaling pathways may also be important for the development of breast cancer and cardiovascular disease [14]. Many of the genetic variants previously discovered in breast cancer, and cancer in general, represent broader molecular signaling pathways that

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; GWAS, genome wide association studies; ICD, International Statistical Classification of Diseases and Related Health Problems; HF, heart failure; HR, hazard ratio; OR, odds ratio; PCI, percutaneous intervention; Q, quartile; SD, standard deviations.

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are also of importance for myocardial and vascular signaling (e.g. vascular endothelial growth factor, transforming growth factor beta 1 and BRCA mutations) [15–19]. However, if shared genetic pathways underlie some of the epidemiological relation between breast cancer and coronary artery disease (CAD) remains unknown. The question merits further investigations in order to understand the overlap of the two disease entities. Ultimately, insight to the shared genetic predisposition could influence future individually tailored treatment and decrease the cardiovascular disease burden in breast cancer survivors. This study investigated the importance of genetic predisposition to breast cancer for the risk of CAD in two steps. First, we defined a polygenic risk score based on breast cancer loci identified in genome wide association studies (GWAS) [20] and estimated the associated risk of coronary artery disease (CAD). In sensitivity analyses risks of atrial fibrillation (AF) and heart failure (HF) were analyzed as well. Second, to estimate the risk associated with potentially undiscovered genetic variants, we investigated the risk of CAD in children who had a mother with breast cancer in a Danish nationwide population-based sample.

2. Material and methods

2.1. Nationwide registers and the Copenhagen Cardiovascular Genetics (COGEN) biobank

The data utilized in this study came from the nationwide Danish administrative registries. Information from the different registers was crosslinked via the unique and permanent person registration numbers that all persons in Denmark have [21]. We combined data from 5 of the registers: 1) The Danish Civil Registration System holds information on the individual registration numbers, emigration/immigration status and date of birth [21], 2) The Danish National Patient Register, which has information on diagnosis and dates from all admissions and outpatient contacts in Danish Hospitals since 1978 [22], 3) The Danish Register of Medicinal Products holds data on all redeemed prescriptions from Danish Pharmacies [23], 4) The Danish Register of Causes of Death has information on vital status and date and cause of death [24], and 5) The Danish Fertility Register holds information on the mother and father of Danish children since 1954. Additionally, we combined the databases above with data from the Copenhagen Cardiovascular Genetics (COGEN) biobank, which is based on superfluous blood from patients admitted to cardiology departments in the capital region of Denmark. At present, the COGEN cohort consists of ~5900 consecutive, genotyped patients referred for coronary angiography in Eastern Denmark in the period 2010–2014. The database has been described in more detail recently [25,26]. Data from the COGEN cohort was linked with the Eastern Danish Heart Register, which holds information on consecutive patients referred for coronary angiography, percutaneous coronary interventions (PCI) or coronary artery bypass surgery (CABG) in Eastern Denmark since 2006 [27].

2.2. Study populations

For the genetic association analyses, the study population comprised all patients who had been genotyped in the COGEN cohort. We excluded individuals of non-European ancestry (based on principal components analysis, n = 560) and individuals without information on coronary angiography results (n = 62). Index was the date of the coronary angiography.

For the nested case-control study we evaluated the entire Danish population between 1978 and 2015 and included individuals who were registered with information on their biological mother. We identified as cases all patients diagnosed with CAD in the period 1997–2015. For each case we sampled at random one age and sex matched control from the risk set at the case date which contains all individuals alive without CAD. Exposure was defined as having a mother with breast cancer prior to the diagnosis of CAD.

2.3. Genotyping and the polygenic risk score

The Illumina Infinium Human CoreExome Beadchip-24v1.0 (Illumina, San Diego, CA, USA) was used for genotyping. The reference genome was Hg19 and imputation was done to the Haplotype Reference Consortium panel version 1.1 [28]. Standard quality controls were applied to the dataset before imputation. The quality control including exclusion of mislabeled sex and kinship control has been described more in detail recently [25]. Additionally, variants with call-rates <95% or variants that were not in Hardy-Weinberg equilibrium ($p < 10^{-4}$) were removed. Variants with imputation quality <0.3 were excluded.

We constructed a polygenic risk score based on 91 independent single nucleotide polymorphisms (SNPs) that had previously been associated with breast cancer in recent GWAS with individual p-values <5e-8 in the first GWAS results (Supplementary Tables 1.1 and 1.2). We ensured that the included SNPs were not in linkage disequilibrium prior to risk score aggregation (in pairwise linkage disequilibrium controls we found D < 0.8 for all relevant SNP combinations in a Northern European referent cohort) [29]. We used the beta-estimates from the a meta-analysis of the breast cancer GWAS results to compile an additive, weighted polygenic risk score (Supplementary Table 1.1 shows the SNPs comprising the polygenic risk score, references to the GWAS studies and the beta-estimates used in the polygenic risk score) [20]. The score was standardized to have mean = 0 and standard deviation (SD) = 1. As an explorative analysis, we created a risk score that comprised a subset of SNPs from the polygenic risk score comprised of 14 SNPs that were statistically significantly associated with coronary artery disease at p < 0.05 in the publically available results of the pooled analyses Cardiogram+C4D and UK biobank (Supplementary Table 1.2) [30,31].

2.4. Outcomes

For the genetic association study the outcome CAD was defined as having diffuse coronary artery disease or stenosis of at least a major artery on the coronary angiography. The registration of the coronary angiography findings has been validated previously with a high completeness (> 90%) [27]. Different definitions of the outcome were tested in sensitivity analyses. We analyzed 3 vessel disease vs. no 3 vessel disease and an ordinal outcome (0, diffuse coronary disease, 1, 2, 3 vessel disease). The outcomes in the sensitivity analyses, prevalent AF and HF at the time of the coronary angiography, were based on admissions and outpatient contacts with relevant International Statistical Classification of Diseases and Related Health Problems (ICD)-10-codes as the primary diagnosis.

For the nested case-control study we defined a breast cancer diagnosis as an admission or outpatient contact with breast cancer (ICD-10: C50). The outcome CAD used in the nested case-control study was based on admission or outpatient contact with ischemic heart disease (ICD-10 codes: I20–25).

The definitions are described in Supplementary Table 2 and have been validated previously with positive predictive values of 93% [32] (AF), 100% [22] (HF admissions) and 98% [22] (acute CAD admissions).

2.5. Comorbidity, drug therapy and socio-economy

The definition of outcomes and comorbidities were based on admissions and outpatient contacts with relevant ICD-10-codes as the primary diagnosis. Drug therapy was defined based on claimed prescriptions. Income levels were based on a 5-year period before the index date. Educational levels were defined as the longest education completed (Definitions are found in Supplementary Table 2).

2.6. Statistical analyses

To test for differences in baseline characteristics Kruskal-Wallis tests were used for continuous variables and the Chi^2 tests for categorical variables. Means were reported with standard deviations (SD) and medians with quartile 1-quartile 3 (Q1-Q3).

Association of CAD with presence of the individual SNPs from the polygenic risk score were analyzed with univariate logistic regression models. We analyzed the association of the polygenic risk score with CAD using logistic regression models. The main analysis was based on a logistic regression model adjusted for age at coronary angiography, sex and principal components 1 and 2. The polygenic risk score was analyzed as a continuous variable with linear effect on log odds scale. Interactions between the polygenic risk score and sex, age, smoking status and hypertension on the risk of CAD were tested by analyses of deviance on a model with and a nested model without the interaction term.

In the case control study, we modelled the effect of having a mother with breast cancer on the hazard rate of CAD using a conditional logistic regression model. To test if income and educational levels interacted with the risk of CAD associated with having a mother with breast cancer, we conducted additional analyses adjusted for income and educational level and including interaction terms, respectively.

The level of statistical significance was defined at 5%.The statistical analyses were performed using SAS Software version 9.4 (SAS Institute Inc.) and R: A language and environment for statistical computing [33].

2.7. Sensitivity analyses

We tested the association of the polygenic risk score with the secondary outcomes; prevalent breast cancer (in women only), AF and HF, using logistic regression models as described for the main analyses. Additionally, the polygenic risk score was analyzed as a categorical variable according to the quartiles of the score in analyses similar to the main analyses. As a sensitivity analysis we restrained the genetic association analyses to patients referred for coronary angiography on the suspicion of CAD (acute coronary syndrome or known ischemia).

2.8. Ethics

The project was approved by the local ethics committee of Region North Jutland, Denmark (Project number N-20140048). All patients included had a written informed consent. The Danish Data Protection Agency approved the COGEN

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Table 1
Baseline characteristics of the COGEN cohort according to quartiles of the genetic risk score at the time of coronary angiography.

	Q1 (n = 1241)	Q2 (n = 1247)	Q3 (n = 1246)	Q4 (n = 1251)	p-Value
Polygenic risk score, mean (sd)	−1.3 (0.5)	−0.3 (0.2)	0.3 (0.2)	1.3 (0.5)	NA
Male, n (%)	806 (64.9)	801 (64.2)	818 (65.7)	803 (64.2)	0.854
Age, median [Q1,Q3]	66 [58, 73]	65 [57, 73]	66 [58, 74]	66 [57, 74]	0.231
Smoker, n (%)	553 (44.6)	588 (47.2)	585 (47.0)	593 (47.4)	0.458
Body mass index, median [Q1,Q3]	27 [24, 31]	27 [24, 30]	27 [24, 30]	27 [24, 30]	0.005
Medical history, n (%)					
Diabetes mellitus	241 (19.4)	225 (18.0)	248 (19.9)	232 (18.5)	0.634
Prior stroke	98 (7.9)	97 (7.8)	99 (8.0)	88 (7.1)	0.807
Peripheral embolism	5 (0.4)	6 (0.5)	3 (0.2)	6 (0.5)	0.754
Peripheral artery disease	60 (4.8)	58 (4.7)	53 (4.3)	55 (4.4)	0.901
Hypertension	608 (49.0)	582 (46.7)	616 (49.4)	575 (46.0)	0.224
Alcohol abuse	34 (2.7)	41 (3.3)	34 (2.7)	27 (2.2)	0.391
Chronic liver disease	14 (1.1)	15 (1.2)	11 (0.9)	15 (1.2)	0.854
Chronic kidney disease	52 (4.2)	37 (3.0)	38 (3.0)	36 (2.9)	0.214
Chronic obstructive pulmonary disease	102 (8.2)	96 (7.7)	82 (6.6)	90 (7.2)	0.447
Prior cancer	177 (14.3)	172 (13.8)	180 (14.4)	185 (14.8)	0.913
Drug therapy, n (%)					
Digoxin	72 (5.8)	65 (5.2)	82 (6.6)	58 (4.6)	0.177
Calcium channel blockers	318 (25.6)	287 (23.0)	292 (23.4)	272 (21.7)	0.143
Beta blockers	514 (41.4)	510 (40.9)	547 (43.9)	494 (39.5)	0.156
Non loop diuretics	375 (30.2)	359 (28.8)	356 (28.6)	351 (28.1)	0.67
Loop diuretics	214 (17.2)	198 (15.9)	208 (16.7)	181 (14.5)	0.257
RAS-inhibitors	577 (46.5)	536 (43.0)	592 (47.5)	526 (42.0)	0.014
Vitamin K antagonists	134 (10.8)	102 (8.2)	119 (9.6)	112 (9.0)	0.147
Aspirin	572 (46.1)	560 (44.9)	596 (47.8)	565 (45.2)	0.45
NOAC	36 (2.9)	30 (2.4)	33 (2.6)	51 (4.1)	0.07
Income level					
Q1	311 (25.1)	300 (24.1)	342 (27.4)	293 (23.4)	NA
Q2	313 (25.2)	308 (24.7)	310 (24.9)	315 (25.2)	NA
Q3	319 (25.7)	303 (24.3)	292 (23.4)	333 (26.6)	NA
Q4	298 (24.0)	336 (26.9)	302 (24.2)	310 (24.8)	0.313
Educational level, n (%)					
Basic school	370 (29.8)	352 (28.2)	381 (30.6)	377 (30.1)	NA
High school education	35 (2.8)	36 (2.9)	23 (1.8)	43 (3.4)	NA
Vocational education	532 (42.9)	476 (38.2)	518 (41.6)	488 (39.0)	NA
Short/medium length higher education	187 (15.1)	242 (19.4)	214 (17.2)	205 (16.4)	NA
Long higher education	82 (6.6)	105 (8.4)	78 (6.3)	103 (8.2)	NA
Unknown	35 (2.8)	36 (2.9)	32 (2.6)	35 (2.8)	0.045
LVEF < 45%, n (%)	216 (27.2)	196 (25.7)	195 (25.7)	208 (26.1)	0.881
Indication for coronary angiography, n (%)					
Unknown	24 (1.9)	22 (1.8)	24 (1.9)	29 (2.3)	NA
Arrhythmia	36 (2.9)	41 (3.3)	33 (2.6)	42 (3.4)	NA
CAG after PCI/CABG	<3	8 (0.6)	5 (0.4)	8 (0.6)	NA
Acute coronary syndrome	472 (38.0)	478 (38.3)	490 (39.3)	484 (38.7)	NA
Cardiomyopathy	98 (7.9)	86 (6.9)	85 (6.8)	76 (6.1)	NA
Valvular pathology	92 (7.4)	88 (7.1)	92 (7.4)	86 (6.9)	NA
Known ischemia	517 (41.7)	524 (42.0)	517 (41.5)	526 (42.0)	0.918
Consequence of coronary angiography, n (%)					
Unknown	62 (5.0)	84 (6.7)	76 (6.1)	61 (4.9)	NA
None	113 (9.1)	108 (8.7)	93 (7.5)	105 (8.4)	NA
Medical treatment	456 (36.7)	460 (36.9)	479 (38.4)	496 (39.6)	NA
PCI	432 (34.8)	416 (33.4)	406 (32.6)	410 (32.8)	NA
CABG	39 (3.1)	40 (3.2)	39 (3.1)	47 (3.8)	NA
Thorax conference	139 (11.2)	139 (11.1)	153 (12.3)	132 (10.6)	0.589

SD: standard deviation. Q: Quartile. BMI: body mass index. RAS: Renin-angiotensin system. NOAC: non-vitamin K oral anticoagulation. LVEF: left ventricular ejection fraction estimated with echocardiography. PCI: Percutaneous coronary intervention. CABG: coronary artery bypass grafting.

biobank (Project number 00916 GEH-2010-001) and the case-control study (Project number 2007-58-0015).

3. Results

3.1. Polygenic risk score analyses

In total, 4985 patients undergoing coronary angiography and with available genetic data were included. The study population had a median age of 66 years (Q1-Q3 57–73) and 65% were men. Age, sex, comorbidities, drug therapy, and income and educational levels were equally distributed across the quartiles of the polygenic risk score at the time of coronary angiography (Table 1). In total 92 women (2% of the sample) had prevalent breast cancer and 3724 (75%) had CAD verified on the coronary angiography.

Analyses of the association of the individual SNPs comprising the score with CAD are supplied in Supplementary Table 3. There was no significant association between the polygenic risk score and the risk of CAD in the logistic regression analyses (OR 1.01 95% CI 0.94–1.08, p = 0.783) (Fig. 1 and Fig. 2). Sensitivity analyses of CAD as a categorical variable and 3 vs. no 3 vessel disease yielded similar results. The polygenic risk score was not associated with the outcomes in the sensitivity analyses; AF (1.03 95% CI 0.94–1.12, p = 0.539) or HF (OR 0.97 95% CI 0.90–1.05, p = 0.470). Increasing polygenic risk score was associated with increased risk of breast cancer in women (OR 1.40 95% CI 1.14–1.73, p = 0.002) (Fig. 2). We found no evidence of interaction between the

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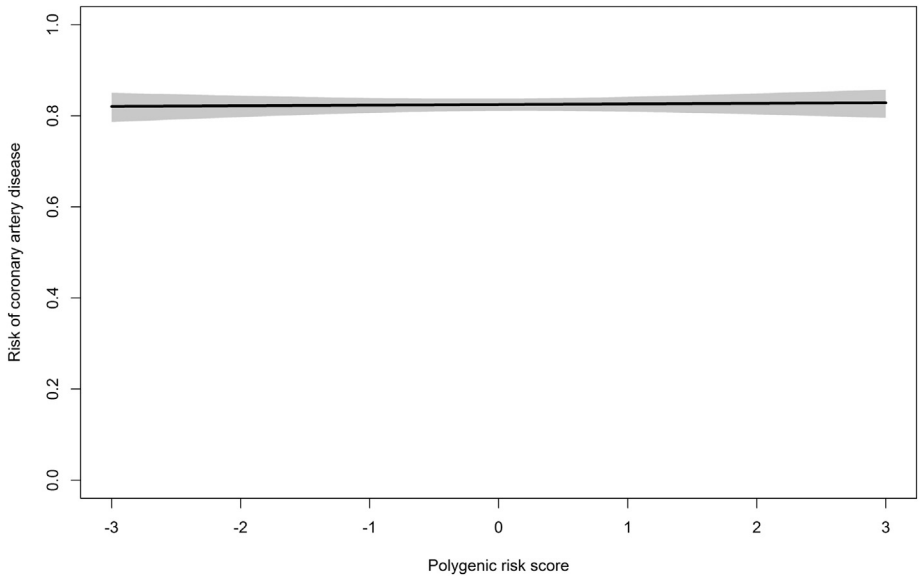

Fig. 1. Polygenic risk score and the risk of coronary artery disease. Fig. 1: Prediction of risk of coronary artery disease from the polygenic risk score. Results from the main logistic regression model adjusted for age, sex and principal component 1 and 2.

polygenic risk score and sex, age, smoking status, and hypertension on the risks of CAD (test for interaction, p = 0.42, p = 0.59, p = 0.28 and p = 0.41). When analyzing only patients referred for coronary angiography with suspicion of CAD, similar results were obtained. The polygenic risk score was not associated with CAD (OR 1.03, 95% CI 0.95–1.11, p = 0.5047), AF (OR 1.04, 95% CI 0.93–1.15, p = 0.4976) or HF (OR 0.99, 95% CI 0.89–1.10, p = 0.8748). The polygenic score was associated with breast cancer (OR 1.57, 95% CI 1.25–1.99, p = 0.0001), as in the main analysis.

Using prior GWAS data (Cardiogram+CD4 and UK biobank, downloaded from http://www.cardiogramplusc4d.org/) [30,31], we looked up the 91 breast cancer associated SNPs included in the polygenic risk score and observed that 14 out of 91 SNPs (~15%) had a p-value <0.05. In explorative analyses we constructed a score comprising these 14 SNPs (see Supplementary Tables 1.1 and 1.2) and tested this 14 SNP score similarly to the main analyses. The score was not statistically significantly associated with CAD (OR 0.95 95% CI 0.88–1.01, p = 0.09) or prevalent breast cancer (OR 1.06, 95% CI 0.86–1.32, p = 0.56).

3.2. Nationwide case-control study

For the case-control study we included 2,047,525 individuals, who were registered with a biological mother. Table 2 shows the baseline characteristics of the matched cohort of children to mothers with breast cancer and controls from the background population. Median age was 48 years (Q1-Q3 43–53). Among the children to mothers with breast

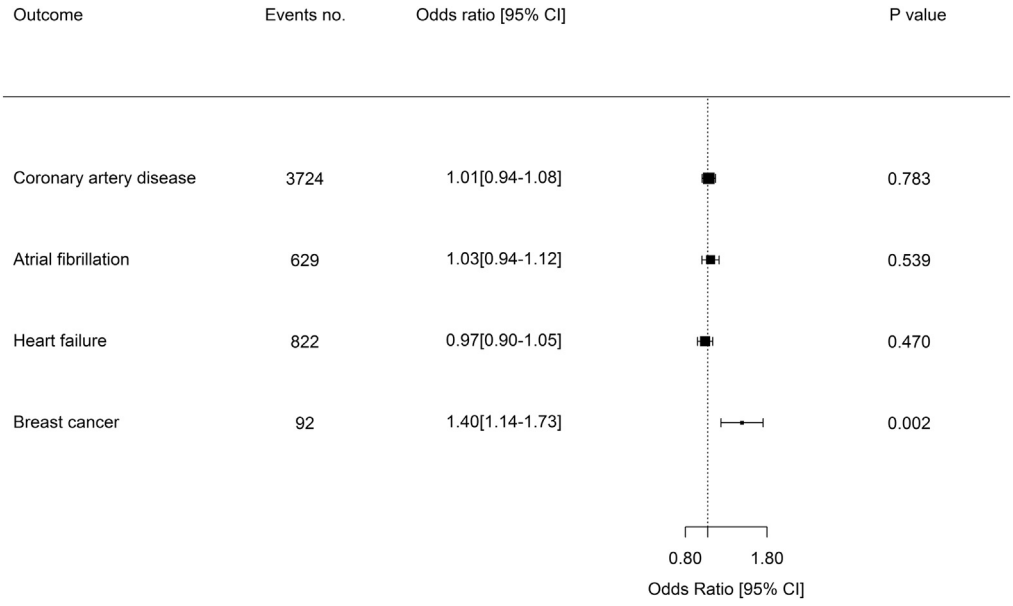

Fig. 2. Odds ratios of breast cancer, coronary artery disease, 3 vessel coronary artery disease, heart failure and atrial fibrillation associated with increasing polygenic risk score per score point (estimates from logistic regression models adjusted for age, sex and principal components 1 and 2).

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Table 2
Characteristics of children to mothers with breast cancer and matched controls at the time of coronary artery disease diagnosis.

	Children to mothers without breast cancer (n = 48,281)	Children to mothers with breast cancer (n = 3109)	Total (n = 51,390)	p-Value
Men, n (%)	37,806 (78.3)	2384 (76.7)	40,190 (78.2)	0.035
Age (years), median [Q1,Q3]	48 [43, 53]	48 [43, 53]	48 [43, 53]	NA
Medical history, n (%)				
Coronary artery disease	24,236 (50.2)	1470 (47.3)	25,706 (50.0)	0.002
Heart failure	2154 (4.5)	123 (4.0)	2277 (4.4)	0.2
Atrial fibrillation	1288 (2.7)	77 (2.5)	1365 (2.7)	0.559
Diabetes mellitus	4859 (10.1)	267 (8.6)	5126 (10.0)	0.009
Prior stroke	1429 (3.0)	68 (2.2)	1497 (2.9)	0.015
Peripheral embolism	201 (0.4)	7 (0.2)	208 (0.4)	0.138
Peripheral arterial disease	859 (1.8)	45 (1.4)	904 (1.8)	0.196
Hypertension	6165 (12.8)	366 (11.8)	6531 (12.7)	0.112
Alcohol abuse	1079 (2.2)	61 (2.0)	1140 (2.2)	0.348
Chronic liver disease	2340 (4.8)	154 (5.0)	2494 (4.9)	0.822
Chronic kidney disease	1606 (3.3)	86 (2.8)	1692 (3.3)	0.1
COPD	1947 (4.0)	100 (3.2)	2047 (4.0)	0.027
Prior cancer	3535 (7.3)	272 (8.7)	3807 (7.4)	0.004
Drug therapy, n (%)				
Digoxin	361 (0.7)	20 (0.6)	381 (0.7)	0.582
Calcium channel blockers	4432 (9.2)	264 (8.5)	4696 (9.1)	0.208
Non loop diuretics	4397 (9.1)	265 (8.5)	4662 (9.1)	0.287
Loop diuretics	2564 (5.3)	171 (5.5)	2735 (5.3)	0.678
RAS inhibitors	7650 (15.8)	459 (14.8)	8109 (15.8)	0.115
Vitamin K antagonists	809 (1.7)	60 (1.9)	869 (1.7)	0.32
Aspirin	6022 (12.5)	344 (11.1)	6366 (12.4)	0.022
NOAC	89 (0.2)	6 (0.2)	95 (0.2)	1
Income level, n (%)				
Q1	12,129 (25.1)	701 (22.5)	12,830 (25.0)	NA
Q2	12,107 (25.1)	748 (24.1)	12,855 (25.0)	NA
Q3	12,073 (25.0)	779 (25.1)	12,852 (25.0)	NA
Q4	11,972 (24.8)	881 (28.3)	12,853 (25.0)	NA
Educational level, n (%)				
Basic school	18,249 (37.8)	1021 (32.8)	19,270 (37.5)	NA
High school education	2119 (4.4)	155 (5.0)	2274 (4.4)	NA
Vocational education	18,990 (39.3)	1280 (41.2)	20,270 (39.4)	NA
Short/medium length higher education	5736 (11.9)	413 (13.3)	6149 (12.0)	NA
Long higher education	1660 (3.4)	157 (5.0)	1817 (3.5)	NA
Unknown	1527 (3.2)	83 (2.7)	1610 (3.1)	NA

COPD: chronic obstructive pulmonary disease. RAS: Renin-angiotensin system. NOAC: Non-vitamin K oral anticoagulation. Q: quartile.

cancer fewer were men (76.7% vs. 78.3%), had CAD (47.3% vs. 50.2%), diabetes (8.6% vs. 10.1%) or prior stroke (2.2% vs. 3.0%) compared with children to mothers without breast cancer. Prior cancer was more frequently observed in children to mothers with breast cancer compared to children to mothers without breast cancer (8.7% vs. 7.3%). Baseline pharmacotherapies were equally distributed. Higher levels of education and income were more frequent among children to mothers with breast cancer compared with children to mothers without breast cancer. In conditional logistic regression analysis the risk of CAD was significantly lower in children of mothers with breast cancer compared with children whose mothers did not have breast cancer (HR 0.89 95% CI 0.83–0.96, p = 0.002).

4. Discussion

In this study we investigated the association of polygenic predisposition to breast cancer with the risk of CAD. The study had two main findings. First, a polygenic predisposition to breast cancer, in terms of a polygenic risk score based SNPs previously associated with breast cancer, was not associated with increased risk of CAD among patients referred for coronary angiography. Second, having a mother with breast cancer was not associated with an increased risk of developing CAD.

Our observation that polygenic predisposition to breast cancer was not associated with increased risk of CAD was in contrast to our main hypothesis. We hypothesized that the established increased risk of CAD in patients with breast cancer may be partly explained by common physiological pathways involved both in breast cancer development and cardiovascular biology, as suggested by data derived from animal models [19,34,35]. Additionally, of the SNPs associated with breast cancer in GWAS more than expected (14 out of 91–15%) were also associated with cardiovascular disease in prior GWAS of CAD. However, as we did not find significant association between the polygenic risk score and increased risk of CAD, AF or HF, our results support that modifiable risk factors for cardiovascular disease may be more important than genetics in patients with breast cancer regarding CAD risk [14]. In particular conventional adjuvant treatments such as anthracycline chemotherapy [1], trastuzumab [2], aromatase inhibitors [3], and radiotherapy [4] have been considered important risk factors for developing cardiovascular disease. Additionally, modifiable or lifestyle related factors involved in both breast cancer and cardiovascular disease such as alcohol [7,8], body mass index [9,11], physical activity [10,12,13], hormone replacement therapy [36], and smoking [5,6] have been suggested as drivers for the association. Notably, it has been reported that polygenic predisposition estimated as a polygenic risk score and modifiable risk factors predicted risk of breast cancer in a multipliable manner [37] and that taken together they comprised a useful risk stratification tool for the risk of breast cancer [38]. A similar relationship for genetic predisposition to breast cancer and risk of cardiovascular disease is plausible and warrants future studies. However, in the current study we did not find any interaction between the polygenic risk score and age, sex, smoking or hypertension, respectively, on the risks of CAD, AF or HF.

The non-increased risk of CAD in children to mothers with breast cancer compared with the background population was another main finding of this study. Importantly, the study population was comprised of relatively young patients, as the Danish Fertility Register was established in 1954. The young study population has probably

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influenced our results. Our results suggest that having a mother with breast cancer was not associated with a greater risk of developing CAD at a young age (median age 48 years). In the future it will be interesting to study the risk of developing CAD at an older age in this population. Most likely, our findings reflect the complexity of signaling pathways and their association with SNP variants. Potentially, the pathways induced by different genes can have inverse effects on risks of breast cancer and CAD under some physiological conditions. There are few reports in potential agreement with such theory; e.g. reports on p53 [34,39]. Moreover, an explanation for the lower risk in the children to mothers with breast cancer could be increased awareness of important risk factors for both cancer and cardiovascular disease.

4.1. Strengths and limitations

The complete follow-up and detailed and valid knowledge on the medical records and drug therapy of the study population were strengths of this study. The COGEN cohort is based on a selected sample, consisting of patients referred for coronary angiography, which may influence the obtained results. Specifically, we cannot make inferences on the association of the polygenic risk score with subclinical CAD. Thus, it remains to be determined whether the polygenic risk score may be associated with CAD in a non-referred population and if the polygenic risk score is associated with subclinical CAD. Additionally, as the COGEN cohort consists of coronary angiography referred patients, the patients with breast cancer suffering from early disease and death may not be included. However, this may not pose a major problem as the SNPs comprising the polygenic risk score are believed to be normally distributed in the general population and their overall impact on breast cancer risk to be modest to moderate.

The SNPs used in our study were carefully chosen based on association with breast cancer in recent GWAS. However, different combinations of SNPs in other risk scores will probably merit investigation in the future, as more associations are reported. The valid information on CAD from coronary angiography was a major asset to the study and ensured a high validity of this endpoint. Regarding the endpoints of AF, HF and CAD the positive predictive values have been estimated to be 93–100% [22,32]. The study populations were Danish, primarily Caucasian individuals and extrapolation beyond these populations may not be valid.

4.2. Conclusions

In conclusion polygenic predisposition to breast cancer was not associated with increased risks of developing CAD, AF or HF in this study. CAD was less frequent among children to mothers with breast cancer. The results suggest that CAD in patients with breast cancer is not due to shared genetics underlying the two diseases.

Declaration of Competing Interest

Nothing to disclose: All authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.051.

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