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Report

Heritable aspects of dysplastic breast glandular tissue (DY)

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Summary

Breast parenchymal patterns, as visible on mammograms, are determined by the relative amount of radio-dense, glandular dysplastic tissue (DY). High percentages of DY are related to higher breast cancer risk. Previous studies reported heritable influences on DY of 32–67%, depending on the family relationship that was studied.

We assessed heritability in 466 sister-, 25 dizygotic twin- and 26 monozygotic twin-pairs participating in a population-based breast cancer screening program; the DOM project (Diagnostic Investigation Mamma Carcinoma).

The heritability was estimated for non-twin sisters, dizygotic and monozygotic twins seperately by computing correlations between siblings from the dichotomous DY-score (high risk versus low risk). This was done using methods based on the number of shared genes per sibtype.

Heritability estimates were 38, 34 and 88% for sisters, dizygotic twins and monozygotic twins respectively. Heritability estimates from models that combine monozygotic twins with dizygotic twins or sisters indicated that dominant gene effects, genetic interactions or gene–environment effects could be involved. Parity appeared to have an effect on the heritabile influence with estimates ranging from 90% in sisters that were both nulliparous, to 2% in sisterpairs discordant for nulliparity. These result indicate a substantial genetic influence on DY, but with a possible modifying ability of other factors, such as parity.

Introduction

Breast dysplasia (DY) has been the topic of much research over the last decades. It has been related to proliferated connective and stromal tissue and [1, 2] the relative amount of DY in the breast determines the breast parenchymal pattern, as visible on a mammogram because of the relatively high radio-density of DY [3].

Since the first classification of parenchymal patterns by Wolfe [4], DY has been identified as a risk factor for breast cancer and has been proposed as an intermediate endpoint for breast cancer studies [5, 6]. Several factors have been established to affect breast density, including age, weight, body mass index (BMI), parity, age at fist childbirth, menopausal status, causation of menopause (natural versus induced), use of hormone replacement therapy (HRT) and nutrition [7–13]. Nonetheless, these factors explain only a limited fraction of the variance in DY among women and much is still unclear about the origin of DY, the underlying mechanisms by which it is influenced and the direct pathway by which DY affects breast cancer risk.

Genetic factors may also play a role, as was previously reported by Pankow et al. [14] in a study in breast cancer cases and their relatives. They estimated a heritability, which is defined as the amount of variance in a trait that can be ascribed to genetic variation, of DY in sisters of 32–54%. Recently, Boyd et al. [15] reported the heritability of breast dysplasia in a population of recruited monozygotic and dizygotic twins from Canada and Australia. This study estimated the heritability of DY at 60–67%.

The aim of the present study was to determine the heritable influence on mammographic high risk

patterns from a general population. This population was represented in the cohort of the DOM (an acronym translated as 'Diagnostic Investigation Mammacancer') breast cancer screening program from Utrecht, The Netherlands [16]. Contrary to the study by Boyd, in which self-selected twin pairs were enrolled in the study and in contrast to Pankow, who specifically selected relatives of breast cancer cases, we included both sisters and twin pairs from a population-based cohort.

Materials and methods

Subjects

The DOM project was initiated in Utrecht, The Netherlands, in 1974 as a population-based breast cancer screening program with a scientific orientation [16]. Between 1974 and 1986 55,519 women, aged 39–68 at recruitment, attended one or more screening rounds. At each round, mammograms were made of both breasts, anthropometric indices were measured and an extensive questionnaire was administered. Through these questionnaires, data have been collected on, among others, demography, family history of breast cancer and reproductive and menstrual history. In the course of the project, women were invited to the screening in 4 sub-cohorts (DOM I–IV). Between these sub-cohorts, age at recruitment differed and varying questionnaires were used to collect baseline characteristics. This resulted in a varying availability of information and subsequently missing data for some characteristics for some participants.

We identified sister- and twin-pairs, of which both siblings participated in DOM, using probabilistic matching [17]. All data used for matching had been collected at the time of recruitment in DOM. Sister pairs were identified by matching participants for family-name, mothers date of birth and number of siblings. Additionally, the resulting linked participants were checked for agreement in other available family-based variables, such as age of death of mother, number of sisters and/or number of brothers, date of birth within natural range and date of birth in accordance with birth-rank. Sister pairs that were fully concordant for the matching variables and not conflicting in any other family-based variable (for which a value was available for both siblings) were selected. This resulted in a total of 466 sister pairs that were considered eligible for analyses.

Twin pairs were identified by first selecting women for self reported twin-ship and self reported type of twin-ship. The women in the resulting group were subsequently matched for family-name and date of birth. Additionally, the remaining linked twin pairs were checked for accordance in other family-based variables such as date of birth of mother, number of sisters and/or brothers and age of death of mother. Twin pairs that were fully concordant for the matching variables and not conflicting in any other family-based variable were selected, which resulted in a total of 26 dizygotic twin pairs and 25 monozygotic twin pairs that were considered eligible for analyses.

Scoring of parenchymal patterns

As part of the original screening examination, mammograms were evaluated by a trained radiologist and the parenchymal pattern of each breast was classified [18]. All siblings were evaluated completely independent since no attention was paid to familial relations at this time. During the first screening rounds, the evaluation was done according to the Wolfe-classification, which distinguishes four categories; N for normal, non-dysplastic breasts (<25% DY), P1 for low-dysplastic breast (25–50% DY), P2 for breast with prominent ductal patterns and medium-dysplastic breast (50–75% DY) and DY for highly dysplastic breast (>75% DY) [4]. In later rounds, this scoring was reduced to a two level score for low and high risk patterns, which relate to combinations of N/P1 and P2/DY respectively. Therefore, the classification scores in our study were all collapsed into a dichotomous score of DY- versus DY+, which also relate to N/P1 and P2/DY respectively. DY values were available for all the identified siblings.

Data analysis

The dichotomous DY scores were cross-tabulated for concordance or discordance in DY between the two siblings within a pair ($DY_1 \pm$ versus $DY_2 \pm$). This was done separately for sisters, monozygotic twins and dizygotic twins. For each of the three populations, a correlation coefficient was calculated that is based on a comparison of the expected

and observed number of concordant and discordant pairs (tetrachoric correlation, SAS version 8).

As is described and utilised extensively in genetic epidemiology, the heritability (H2) of a factor is the percentage of variance in a trait that can be ascribed to variation in genetics. Heritability is usually estimated through several Mendalian-based approaches [19, 20], depending on the family relationship that is being studied.

(a) for monozygotic twins, the heritability equals the correlation;
(b) for dizygotic twins, the heritability equals two times the correlation;
(c) for sisters, the heritability equals two times the correlation;
(d) two times the difference between monozygotic twins and dizygotic twins;
(e) two times the difference between monozygotic twins and sister.

These methods are based on the assumption that monozygotic twins share 100% and dyzygotic twins and sisters on average share 50% of their genes. Consequently, if genetic effects are completely additive, then the correlation in monozygotic twins will be twice as high as the correlation between dizygotic twins or sisters. All five approaches we used to estimate the heritability (a–e) will then yield equal result and the combined models (d, e) are then limited to 100%. A result in the combined models (d, e) which exceeds 100% indicates that the data does not fit the additive model and that more complex genetic effects are present.

To evaluate whether non-genetic determinants of breast patterns were distributed equally according to DY-concordance, we compared the average within-pair difference for a number of characteristics between DY-concordant sister pairs and DY-discordant sister pairs. Differences in means were tested by ANOVA or a Chi-square test. In case of significant differences ($p_{2\text{-sided}} < 0.05$), heritability-estimates were calculated for a homogeneous sub-set of pairs. For example; DY-concordant and DY-discordant sibpairs may differ in the prevalence of nulliparity. Nulliparity is known to be related to a higher frequency of DY. So if one member of a sibpair is nulliparous and the other is parous, heritability could be masked due to the influence of parity on the DY patterns. We therefore estimated the heritability in DY in sub-sets of sister pairs in which either both sisters were parous or were both nulliparous.

Results

The characteristics of the study population, with regard to a number of factors that are known to influence the breast parenchymal pattern and/or

Table 1. Characteristics of sisters, dizygotic (DZ) twins and monozygotic (MZ) twins

Characteristic	Sisters		DZ Twins		MZ Twins	
	N[a]	Mean ± SE	N[a]	Mean ± SE	N[a]	Mean ± SE
Age at examination (year)	932	50.0 ± 0.21	52	51.7 ± 0.56	50	52.9 ± 0.72
Height (m)	932	1.63 ± 0.002	52	1.62 ± 0.009	50	1.61 ± 0.007
Weight (kg)	932	67.4 ± 0.35	52	66.7 ± 1.55	50	64.9 ± 1.43
Body mass index (kg/m^2)	932	25.1 ± 0.12	52	25.5 ±0.53	50	25.1 ± 0.59
Age at menarche (year)	927	13.8 ± 0.05	35	13.5 ± 0.23	29	13.7 ± 0.27
Age at natural menopause (year)	274	49.4 ± 0.25	16	48.1 ± 0.81	21	50.1 ± 0.78
Time since natural menopause (year)	274	7.2 ± 0.32	16	7.1 ± 1.06	21	4.8 ± 0.53
Children (average number)[b]	761	3.5 ± 0.06	46	3.3 ± 0.21	33	3.4 ± 0.33
Age at first childbirth[b] (year)	761	26.0 ± 0.15	46	27.0 ± 0.55	33	26.2 ± 0.87
Parity (% nulliparous)	932	18%	52	12%	50	34%
Menopause (% natural)	353	78%	29	55%	31	68%

[a] Number of subjects for which data was available. Values were not available for all women due to the use of different questionnaires in the course of the screening program.
[b] Only parous women included.

the breast cancer risk, are shown in Table 1. A total of 466 sister pairs; 932 subjects, 26 dizygotic twin-pairs; 52 subjects and 25 monozygotic twin-pairs; 50 subjects, were available for the study.

Due to the use of different questionnaires during the screening program, information was not available for all subjects for all characteristics. Nonetheless, the characteristics of the study-population as they were found are representative for the cohort from which the population was drawn.

Of 466 sister pairs, 61% (285 pairs) was concordant as to their DY pattern score. For dizygotic and monozygotic twins, these percentages were 58% (15 of 26) and 88% (22 of 25) respectively (Table 2).

The estimated heritability of dysplastic pattern was 38% ($r = 0.19$, 95%CI 0.04–0.034) for sisters ($2 \times r_{sisters}$), 34% ($r = 0.17$, 95%CI −0.45–0.79) for dizygotic twins ($2 \times r_{dizygotic\ twins}$) and 88% ($r = 0.88$, 95%CI 0.63–1.00) for monozygotic twins ($r_{monozygotic\ twins}$).

Through model d, which combines the estimates of monozygotic twins and dizygotic twins, the overall heritability of the breast dysplastic pattern is estimated at 142% ($2 \times (r_{t,monozygotic\ twins} - r_{t,dizygotic\ twins})$). When using sisters as a proxy for dizygotic twins (model e), this estimate is 138% ($2 \times (r_{t,monozygotic\ twins} - r_{t,sisters})$). These values over 100% show that the additive models are not sufficient to fit the data and are indicative of additional, non-additive effects.

Table 3 shows the distribution of within-pair differences of known determinants of DY patterns in the sister population. DY-concordant sister pairs and DY-discordant sister pairs differed significantly ($p_{2\text{-sided}} < 0.05$) in the average amount of within-pair difference in height, BMI and parity status.

All sister pairs were subsequently stratified into quartiles of the within pair difference for height and BMI seperately. For both variables, pairs in the first quartile were considered homogeneous. When we repeated the calculation of the heritability, including only sister pairs that were homogeneous for BMI or height the estimated heritability rates were 60 and 68% respectively (Table 4).

For pairs homogeneous for parity (stratified for general parity-status as well as regarding the number of children), the estimated heritability rates were 46% for pairs with a similar parity status and 2% for pairs for who the two sisters differed in their parity status. Pairs with two nulliparous sisters had an estimated heritability of 90% and pairs with two parous sisters lead to an estimate of 26%, ranging from 30% in the substratum of pairs with an equal number of children to 24% in the sub-strata of pairs with an unequal number of children).

Discussion

The results of this study show a substantial influence of genes on the parenchymal pattern of the female breast. The estimates of the heritable effect range from 34 to 88% in different types of sibs. This study also shows that complex genetic effects, such as dominant genes or gene–environment interaction may be involved. Analyses of a number

Table 2. Distribution of concordant pairs, correlation coefficients and heritability estimates of dysplastic glandular tissue patterns in sisters, dizygotic (DZ) twins and monozygotic (MZ) twins

	N	DY-conc./DY-disc.[a]	r_t (95% CI)[b]	Heritability (H^2)[c]
Sister pairs	466	285/181	0.19 (0.04 – 0.34)	$2 \times r_{sisters} \times 100\% = 38\%$
DZ Twin pairs	26	15/11	0.17 (−0.45 – 0.79)	$2 \times r_{DZ\ twins} \times 100\% = 34\%$
MZ Twin pairs	25	22/3	0.88 (0.63 – 1.00)	$r_{MZ\ twins} \times 100\% = 88\%$
Combined estimate from MZ and DZ twins				$2 \times (r_{MZ} - r_{DZ}) \times 100\% = 142\%$
Combined estimate from MZ twins and sisters				$2 \times (r_{MZ} - r_{Sister}) \times 100\% = 138\%$

[a] Dichotimised DY patterns according to Wolfe [4].
[b] Correlation coeficient.
[c] Formula to compute heritability based on literature [19, 20].

Table 3. Mean difference in characteristic between sisters within a pair, according to pairs concordant and discordant for their DY score.

Characteristic	Within-pair differences				*p*
	DY-concordant sister pairs		DY-discordant sister pairs		
	N[a]	Mean Δ	*N*[a]	Mean Δ	
Age at examination (year)	285	3.39	181	3.30	0.70
Height (m)	285	0.04	181	0.05	0.03*
Weight (kg)	285	9.96	181	9.08	0.29
Body mass index (kg/m^2)	285	3.60	181	3.03	0.04*
Age at menarche (year)	283	1.45	180	1.50	0.64
Age at natural menopause (year)	86	4.42	52	4.54	0.59
Time since natural menopause (year)	86	5.12	52	5.66	0.59
Children[b] (average number)	211	1.41	118	1.23	0.26
Age at first childbirth (year)	211	3.63	118	3.81	0.62
Parity[c] (discordant pairs)[d]	285	52	181	50	0.02*
Natural menopause[c] (discordant pairs)[e]	86	28	52	10	0.12

[a] Only pairs with a valid result for both siblings were included.
[b] Only parous women included.
[c] Chi-square test. All other variables compared by ANOVA.
[d] 52 of 285 DY-concordant and 50 of 181 DY-discordant sibpairs include one women who has had at least one child, while her sister has not.
[e] 28 of 86 DY-concordant and 10 of 52 DY-discordant sibpairs include one women who has had a natural menopause, while her sister has not.
* Significant difference between groups; $p_{2\text{-sided}} < 0.05$.

Table 4. Heritability rates for homogeneous sister pairs

	N	DY-conc./DY-disc.	r_t (95%CI)	H^2 (%)
BMI[a]	116	70/46	0.30 (0.02–0.57)	60
Height[b]	116	75/41	0.34 (0.07–0.62)	68
Parity				
Concordant parity within pair	363	233/130	0.23 (0.05–0.40)	46
Both sisters nulliparous	34	22/12	0.45 (−0.01–0.91)	90
Both sisters parous	329	211/118	0.13 (−0.06–0.32)	26
Equal number of children	104	65/39	0.15 (−0.18–0.49)	30
Unequal number of children	225	146/79	0.12 (−0.12–0.36)	24
Discordant parity within pair	103	52/51	0.01 (−0.30–0.31)	2

[a] Homogeneous pairs: pairs with a within pair BMI difference belonging to the lowest quartile of within pair BMI differences. The mean within pair BMI difference was 0.51 kg/m2; range 0.01–1.08 kg/m2
[b] Homogeneous pairs: pairs with a within pair height difference belonging to the lowest quartile of within pair height differences. The mean within pair height difference was 0.81 cm; range 0–1.70 cm.

of non-genetic factors indicate that some of these factors, especially parity, have a substantial influence on the heritability estimates.

Our study allowed for the analyses of sisters as well as dizygotic and monozygotic twins from the same population. The results enable a high

generalisation since they are based on a population- based screening cohort that was selected independent of breast cancer predisposition with a participation rate of over 80%. The estimates in our study differed only slightly from those previously reported and are of a similar direction and magnitude.

Since this study was begun in the early days of mammography where mammographic resolution may have been poor and breast density high, particularly in premenopausal women, we analysed the data in this regard. We obtained heritability from sisters with mammography in the 1970s (first portion of the recruitment period) and compared this to the estimate obtained from sisters screened in the 1980s. These estimates were 42% ($r = 0.21$, 95%CI −0.05–0.47) and 24% ($r = 0.12$, 95%CI −0.07–0.31) respectively and do not significantly differ from each other or the grouped estimate.

In a previous study, Wolfe et al. [21] included 122 sister pairs of which both sisters had been referred for diagnostic work-up in a breast clinic [21]. Although the original paper had a different set-up, their data can be restructured into a fourfold table of DY-scores, consisting of 88 DY-concordant pairs (63 DY+/DY+ and 25 DY-/DY-) and 34 DY-discordant pairs. This results in an estimated heritability of 78%, which is even substantially higher that our estimate in sisters.

However, since the women in that study were selected on the basis of their presence in the hospital files and had been referred because of breast symptoms, this may have caused an artificially high prevalence of DY positive scores. Women with a high DY score are known to have a higher risk of developing breast cancer and are also more often referred to the clinic because of a mammogram that is more difficult to interpret. In the population of Wolfe, 553 of 928 women (60%) had a P2 or DY score. This corresponds to DY+ in our population, which was found in 333 of 1034 women (32%). This high prevalence of DY+ scores in the study by Wolfe may have lead to a higher prevalence of DY-concordant sister pairs and thereby an overestimation of the heritability, if interpreted to reflect the general population. Recently, Boyd et al. (2002) reported an estimated heritability of 63% in a cohort of monozygotic and dizygotic twins, based on continuously measured percent DY scores adjusted for age, BMI, age at menarche, cessation of menstruation, parity and (in parous women) number of live births and age at first birth [22]. Prior to this, in a study in sisters belonging to breast cancer families, Pankow et al. [14] also reported a statistically significant heritability (32–54%) in continuously measured percent breast density adjusted for several factors [14].

As it is known that certain determinants influence the dysplastic appearance of the breast, we determined the within-pair difference in these determinants in our population of sisters. The average within-pair difference in these determinants between the sister-pairs with a concordant DY score and those with a discordant DY score was compared with ANOVA or a chi-square test. This indicated that the sister-pairs with a discordant DY score, on average, had a significantly ($p_{2\text{-sided}} < 0.05$) higher difference in BMI, height and parity-status.

In sister pairs that were homogeneous for BMI (116 pairs in the lowest quartile of within pair difference), the estimated heritability was 60% ($r = 0.30$, 95%CI 0.02–0.57). For sisters homogeneous for their height (116 pairs), the estimated heritability was 68% ($r = 0.34$, 95% CI 0.07–0.62).

For all sister pairs with a similar parity-status (both sisters parous or both sisters nulliparous), the estimated heritability was 46% ($r = 0.23$, 95% CI 0.05–0.40). Estimates in parous pairs were similar and not affected by a difference in the number of children. In nulliparous pairs, however, the estimated heritability was 90% ($r = 0.45$, 95% CI −0.01–0.91). Although this estimate is based on only 34 observations, it is in sharp contrast to the estimated heritability in sister pairs with a dissimilar parity status, which was only 2% ($r = 0.01$, 95% CI −0.30–0.31).

These results indicate that there may be a very strong, genetically determined tendency for siblings to develop a similar parenchymal pattern, but that this heritability may be obscured in a heterogeneous population. As it appears, changes in a women's parenchymal pattern, caused by a first childbirth, are so pronounced that they can completely mask the heritable influence. The similarity apparently partially returns if both sibs are parous, while it is only marginally affected by the additional number of children. In addition to an important role for genes, this clearly shows important roles for non-genetic factors (in this case we assume that nulliparity is not genetically

determined). Although the confidence intervals of the estimates in the various strata are wide and are overlapping, these result indicate that non-genetic influences, especially parity, may have a strong influence on the heritability of parenchymal patterns.

In our study, heritability in the various types of sibs was highest in the monozygotic twins and lower in dizygotic twins and sisters. The heritability in monozygotic twins is thought to be overestimated due to a higher concordance in other, non-genetic, circumstances. This influence of other factors is indicated by the analysis in selected homogeneous sister pairs. An assumption that is made in twin studies is that environmental factors are the only cause of phenotypic variance in monozygotic twins. In the estimation of heritability, shared environmental influences can, however, not be fully excluded.

This argument is supported by our estimation of the heritability from the combined approaches. In these approaches, the heritability is estimated by two times the difference between the correlation in monozygotic twins minus the correlation in dizygotic twins or sisters ($H^2 = 2 \times (r_{\text{monozygotic}} - r_{\text{dizygotic}})$ or $H^2 = 2 \times (r_{\text{monozygotic}} - r_{\text{sisters}})$). It is based on the number of genes that is shared by the different types of sibling. In the case of a purely additive genetic affect, the estimated heritability from monozygotic twins, who share 100% of their genes, should be double the effect found in dizygotic twins or sisters who only share half of their genes. This would result in outcomes from the combined approaches which are equal to the outcome in monozygotic twins alone [19, 20].

In our case, the combined approach results in an estimated heritability of 142% when using the dizygotic-estimate and 138% when using the sister-estimate. These estimates exceed 100% and thus indicate that the 'simple' additive model does not fit the data. With regard to the small number of mono- and dizygotic twins and the indication that environmental effects have had a certain influence on the heritability estimates in sibs, these high estimates may be due to random variation. They may, however, also be an indication that the factors that affect parenchymal patterns are more than merely genetically additive and that a dominant genetic influence, shared environmental factors, genetic interaction (epistasis) or gene–environment interaction also play a role.

The heritability of DY and the mechanisms underlying it are important, because they may point to the influence of genes in relation to the occurrence of breast cancer. A study in Scandinavian twins revealed a heritability of breast cancer of 27% (95% CI 4–41%) [23]. Known genes involved in breast cancer, such as BRCA1, BRCA2 and ATM, however account for only a small proportion of this effect, leaving sufficient room for other, less penetrating genes, gene–gene interaction and/or gene–environment interaction [24]. Vachon et al. reported the identification of a region on chromosome 6 that appeared to be linked to breast density, which strengthens the evidence towards an independent genetic influence on breast density [25]. In a more recent publication, the predictive value of polymorphisms in genes involved in steroid hormone biosynthesis and metabolism were studied, but a consistent relation could not be found [26]. To our knowledge, further advances have not been reported so far.

In conclusion, genetic factors may play a substantial role in breast density, but modifying effects by other (non-genetic) factors such as parity are just as important. In view of the established relation between high risk parenchymal patterns and breast cancer risk, the identification of genes that are involved in breast density could be an important step in breast cancer reserach.

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