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The Heritability of Breast Cancer among women in the Nordic Twin Study of Cancer

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Declaration of interests

None of the authors declares competing interests.

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ABSTRACT

Background

Family history is an established risk factor for breast cancer. Although some important genetic factors have been identified, the extent to which familial risk can be attributed to genetic factors versus common environment remains unclear.

Methods

We estimated the familial concordance and heritability of breast cancer among 21,054 monozygotic and 30,939 dizygotic female twin pairs from the Nordic Twin Study of Cancer, the largest twin study of cancer in the world. We accounted for left-censoring, right-censoring, as well as the competing risk of death.

Results

From 1943 through 2010, 3,933 twins were diagnosed with breast cancer. The cumulative lifetime incidence of breast cancer taking competing risk of death into account was 8.1% for both zygositys, while the cumulative risk for twins whose co-twins had breast cancer was 28% among monozygotic and 20% among dizygotic twins. The heritability of liability to breast cancer was 31% (95% CI 10% - 51%) and the common environmental component was 16% (95% CI 10% - 32%). For premenopausal breast cancer these estimates were 27% and 12%, respectively and for postmenopausal breast cancer 22% and 16%, respectively. The relative contributions of genetic and environmental factors were constant between ages 50 and 96. Our results are compatible with the Peto-Mack hypothesis.

Conclusion

Our findings indicate that familial factors explain almost half of the variation in liability to develop breast cancer, and results were similar for pre- and post-menopausal breast cancer

Impact

We estimate heritability of breast cancer, taking until now ignored sources of bias into account.

INTRODUCTION

Although much is known about the causes of breast cancer, the role of genetic factors remains incompletely understood(1, 2). In 2000 Lichtenstein and colleagues reported that 27% of the variation underlying breast cancer liability in a Nordic twin cohort could be explained by genetic factors(3). Today a number of specific genes have been identified that account for approximately 30% of the familial risk(4). The largest specific gene effects are associated with the BRCA1/2 which accounts for about 16% of the total familial risk(5).

Traditional twin studies to date have largely ignored issues of censoring and competing risk of death in estimating the genetic contribution to risk(3, 6). This can lead to severe bias in the estimates for incidence, risk concordance and heritability. In our analysis of the Nordic Twin Study of Cancer (NorTwinCan) data, we handle these issues by utilizing recently developed statistical methods(7). The purpose of this study is to conduct a refined investigation of the familial risk of breast cancer using the world's largest twin study of cancer. Our data have been expanded beyond those analyzed by Lichtenstein and colleagues(3) through the addition of the Norwegian twin cohorts and the inclusion of 14 to 16 additional years of follow-up for the Danish, Finnish and Swedish twin cohorts. Besides estimating the familial risk of breast cancer in monozygotic and dizygotic twin pairs by determining the cumulative incidence and casewise concordance, we also estimate the heritability of risk and of liability for breast cancer, and examine age differences in the familial risk of developing breast cancer. Peto and Mack hypothesized a pattern of constant incidence over age for cotwins of twins diagnosed with breast cancer(1), which we investigate. Additionally, we estimate heritability for pre- and post-menopausal cancer separately. These results provide a useful reference for genome wide association studies as well as for further studies on the etiology of breast cancer.

MATERIALS AND METHODS

The twin cohorts

This study is based on the population-based NorTwinCan database, consisting of the Danish(8), Finnish(9), Norwegian(10) and Swedish(11, 12) twin registries combined with data from the national cancer and mortality registries. In this database each twin has a personal identity code, which includes information on sex and birth date, and enables combination of twin, cancer and mortality information. Characteristics of the four twin cohorts are summarized in Table 1. Zygosity in the twin registries was determined by validated questionnaires, which are known to classify more than 95% of pairs of twins correctly(13). We restrict genetic analyses in the present study to same-sexed female twin pairs with known zygosity(9-13) as opposite-sex twin pairs require different methods and have been studied specifically in a recent study(14). The ethical committees for each country approved the study.

Statistical analyses

We followed the approaches used by Scheike and colleagues(15, 16) which extend classical methods of twin data analysis to correct for censoring and competing risk of death during follow-up, when studying breast cancer risk in a twin, given breast cancer in the co-twin. We have previously described these methods in a study of prostate cancer(17). If neither censoring nor competing risk of death were present then our results would agree with those obtained from the standard quantitative genetic models of twin data(18, 19). Our modelling distinguished three possible outcomes. A twin could either be (a) diagnosed with cancer, (b) die before end of follow up, without being diagnosed with breast cancer, or (c) be censored by either being lost to follow up, mostly due to emigration (<2%) or surviving without breast cancer until end of follow-up. Times of entry and end of follow-up were defined for each country (Table 1). Both twins in a pair are

followed up the same time, and can hence be assumed censored at the same time except if one twin emigrated, in which case we artificially censored the cotwin.

We estimated the casewise concordances in MZ and DZ pairs, both overall and by age. This provides a measure of the risk of developing breast cancer conditional on the cotwin being diagnosed with breast cancer. As we have almost full ascertainment in this study, the casewise concordance will equal the probandwise concordance used in some other studies. Moreover, we calculated the multilocus index as a measure of non-additive effects of multiple risk loci(20, 21), To investigate pre-menopausal cancer we only considered as cases those with a diagnosis before age 50, while for investigating post-menopausal cancer, we only considered as cases those with a diagnosis after or at age 53, considering diagnosis at an earlier age as competing risk. Those ages were chosen as the median age of menopause has been estimated to be around 51 years, with some variation(22).

The biometric ACE model was used to estimate additive genetic (A), common environment (C) and unique individual effects (E) explaining the variation in liability of breast cancer(18, 19). MZ twins are genetically identical at the sequence level, therefore A effects are perfectly correlated in MZ pairs. In contrast, DZ twins are genetically as similar as siblings, which corresponds to a correlation of 0.5 for A effects. Common environmental effects (C) are assumed to be equal and correlate 1.0 in all pairs regardless of zygosity. Hence a higher concordance between MZ twins compared to DZ twins indicates a genetic effect. If the C effects that influence variance in the liability to develop breast cancer are more correlated among members of MZ than DZ pairs this would lead to an overestimation of A, and if they were less correlated among members of MZ than DZ pairs this would lead to an underestimation of A. The E component is assumed to be independent within twin pairs. In addition, using the Akaike information criterion, we checked whether alternative models that included a dominant genetic effect (D) instead of the additive

genetic or common environment effect, improved the fit of the model. Doing this we took into account that models containing a D component, without an A component would be biologically implausible, hence mainly checking the fit of an ADE model.

We used a liability threshold model to estimate the variance components, as well as the cumulative incidence and casewise concordance, both overall and by age. We tested for equal cumulative risk of cancer between MZ and DZ twins, and compared this risk with risk estimates calculated by the non-parametric Aalen-Johansen estimator(23). For these estimates we used the maximum age in the dataset (slightly above 100 years) as the endpoint of the lifetime risk. We investigated if country or birth year should be added as covariates. As the age at diagnosis was used as the time scale in the time to event models, it was automatically taken into account in the non-parametric baseline hazard.

Furthermore, we investigated the pattern suggested by Peto and Mack of breast cancer incidence in patients' relatives(1), by plotting cumulative hazard of breast cancer diagnosis stratified by age of onset in the cotwin, taking account for censoring and competing risk of deaths.

The statistical software R(24) was used with the package mets(16, 25), etm(23), mvna(26) and prodlim(27) for all analyses.

RESULTS

The NorTwinCan cohort comprises 104,539 women from same-sexed twin pairs of known zygosity of whom 3,933 were diagnosed with breast cancer through 2010 at the latest (Table 1). Restricting to complete pairs, there were 3,911 cases of breast cancer diagnosed among 42,110 MZ and 61,880 DZ twins, i.e. among 51,995 pairs. Of these 124 MZ and 141 DZ pairs were concordant for breast cancer.

The cumulative incidence of breast cancer over the life span was 8.1% and did not differ between MZ and DZ twins. Table 2 presents the lifetime risk of disease, casewise concordances for disease risk by zygosity, and the genetic and common environmental variance components underlying variation in breast cancer liability. These results reveal a considerably increased risk of breast cancer among women whose co-twin had breast cancer. This familial effect is substantially greater among MZ than DZ pairs.

Figure 1 shows the casewise concordance of breast cancer. At every age, breast cancer risk among DZ twins whose co-twin had breast cancer was higher compared to the overall cumulative incidence. Moreover, the breast cancer risk for a MZ twin given that her co-twin was already diagnosed was 1.5 times higher than the corresponding concordance risk for DZ pairs. The relative recurrence risk was higher in MZ than in DZ pairs (Table 3). The multilocus index provided no clear indication of genetic heterogeneity for breast cancer, with estimates non-significantly different from 2. The relative recurrence risk for both MZ and DZ twins was higher at younger ages, while the multilocus index was relatively stable by age.

Fitting the biometric models adjusting for censoring and competing risk, the ACE model fitted best; neither the A nor the C could be dropped without significantly worsening the fit. The ACE model indicated about 31% heritability and 16% common environment effect. Adding the year of birth or country as covariate did not change the ACE-heritability estimates.

Figure 2 shows the magnitude of the additive genetic and common environmental variance components of breast cancer liability by age at diagnosis derived from the biometric ACE modelling. It appears that the size of those components does not differ between 60 and almost 100 years of age.

Among concordant twin pairs, there were slight and non-significant zygosity differences in the time between the diagnosis of breast cancer in the first and second twin. The mean difference was 11.8 years (SE 0.80) for concordant MZ pairs and 11.7 years (SE 0.83) for concordant DZ pairs (*p*-value 0.92). Figure 3 shows the cumulative hazard of breast cancer dependent on the cotwin's age at diagnosis, stratified by zygosity. A later cancer occurrence in a twin, if the cotwin was diagnosed at a higher age is visible in the figure, both for MZ and DZ twins. Although this pattern is present for MZ as well as DZ twins, it is much stronger for MZ, with an early diagnosis in the cotwin being associated with earlier and higher hazard for the twin. The Peto-Mack hypothesis(1) would predict parallel curves for higher ages in Figure 3, a pattern which is not violated in this study.

We investigated post-menopausal breast cancer separately and observed casewise concordances of 21% in MZ and 16% in DZ pairs. Moreover, the common environment component was estimated to be 16% while the heritability was 22% (Table 2). For pre-menopausal breast cancer we observed a concordance of 10% in MZ and 6% in DZ pairs resulting in a common environment estimate of 12% and heritability of 27% (Table 2). Hence, pre-menopausal breast cancer seems to have a slightly higher genetic contribution than post-menopausal breast cancer, and slightly lower common environment contributions.

We also looked into metachronous bilateral breast cancer as described by Hartmann et al.(28), defined as two diagnoses of breast cancer in the same woman at least 3 months apart. In the NorTwinCan cohort there were 5 MZ twins with bilateral breast cancer, four of these concordant with a cotwin who had only one breast cancer diagnosis. There were 3 DZ twins with bilateral breast cancer, all from pairs discordant for any breast cancer.

Finally, the NorTwinCan cohort contains 98,841 men with known zygosity from same-sex twin pairs. Of those 17 were diagnosed with breast cancer during follow-up, consisting of 7 MZ and 10

DZ twins. None of those were concordant for breast cancer with their cotwin, and we have not conducted further analyses on the data from the male twins.

DISCUSSION

Results from this large, population-based and virtually complete cohort of Nordic twins provide evidence that genetic differences between women explain a substantial portion of the variation (31%) in liability to develop breast cancer. Moreover, among DZ twins who are as genetically similar as siblings, the lifetime probability of developing breast cancer if the co-twin had cancer is around 20% which is twice the lifetime risk in the general population. Our study also provides new insights regarding the importance of genetic effects across age of diagnosis. Specifically, the relative contribution of genetic factors was similar across the age groups, while the effect of common environment drops slightly in the older group.

There are several strengths of the current study which extend the work by Lichtenstein and colleagues(3). Our study includes more than twice the number of pairs and breast cancer events, one additional country, new birth cohorts and more than 10 years of additional follow-up. We accounted for varying follow-up time, problems of censoring, and competing causes of death(3). We estimated the genetic component of variation in liability to develop breast cancer to be 31% (95% CI 10%-52%), which is similar to that reported by Lichtenstein and colleagues of 27% (95% CI 4%-41%)(3). However, our study provides novel insight into the variation across age for measures of risk and liability of breast cancer diagnosis. Namely, although the heritability estimates are similar, our incorporation of competing risk of death and censoring revealed that the lifetime cumulative incidence of breast cancer is lower (8.1%) as compared to the 75 year incidences of 13% for MZ and 9% in DZ as reported earlier(3).

Our analyses assume that the probability of screening among co-twins is independent of zygosity. However, if an MZ co-twin is more likely to be screened than a DZ co-twin of a diagnosed twin, the genetic component might be inflated due to overdiagnosis(29), but in that case we would have observed a higher incidence of breast cancer in the MZ than the DZ twins. However, MZ twins had only a 0.3% higher incidence than DZ twins in all countries, and therefore differential screening seems unlikely. The lack of difference in incidence between MZ and DZ twins is consistent with the assumption that the causes (genetic and environmental) of breast cancer do not differ by twin type. Other uncontrolled co-factors as education or health behavior could also influence the results, if they would differ by zygosity, but earlier studies indicate no large differences between MZ and DZ twins(30-33).

It has been reported previously that casewise concordance in DZ twins may increase with age(1), As expected we detect a similar pattern in our data, but taking prevalence by age into account, the relative recurrence risk is greatest among younger women and decreases slightly with age in MZ and DZ pairs while the corresponding multilocus index appears to be stable across age.

Moreover, our investigation of the age of diagnosis, depending on the cotwin's age at diagnosis shows an association, both for MZ and DZ twins, with an earlier diagnosis in the cotwin being associated with an earlier diagnosis and higher incidence in the twin. This pattern is, consistent with heritable risks, much stronger in MZ than in DZ twins. Our results are consistent with the hypothesis of constant hazard at higher ages by Peto and Mack(1) although they only predicted the dependency on age of diagnosis of the cotwin for DZ twins, while we find evidence of it for MZ twins as well.

Twin studies provide context for genome wide association studies, which have identified multiple risk loci for breast cancer incidence(4). The multilocus index, being less than two and

stable across age, suggests an additive effect of multiple genes. The index in breast cancer is lower than that observed in prostate cancer(17). Our estimates of total heritability make it possible to determine the extent to which breast cancer variability is explained by risk loci known today. The concept of missing heritability has been proposed to describe the discrepancy between the variance in cancer associated with identified genetic loci and total heritability(34, 35) and as only 30% of the familial risk can be explained by known genes(4) a large amount of the heritable risk found in this study remains unexplained by known genetic risk factors . A recent study on height and BMI indicates that much of the missing heritability in those cases can be explained by a large number of small genetic effects not detected as significant in current genome-wide association studies (GWAS)(36), a similar pattern could explain the missing heritability of breast cancer.

In summary, heritability does not provide an estimate directly translatable to public health policy(37). It does, however, provide insight into individual differences in susceptibility to develop breast cancer, framing results from genome wide association studies and missing heritability. Estimates of the shared risk of breast cancer between MZ twins, who have identical genomes, provide an upper limit of the potential for genotyping and whole-genome sequencing to classify individuals' risk(35, 37, 38). Finally, casewise concordance among DZ twins can help us to assess the cancer risk of first degree relatives in families affected by breast cancer.

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Table 1. Description of female twins from same-sexed pairs in the Nordic Twin Studies of Cancer (NorTwinCan) Cohorts

	Denmark	Finland	Norway	Sweden	Total
Birth cohorts	1870-2004	1880-1957	1895-1979	1886-2008	
Cancer registration since	1943	1953	1953	1958	
Initiation of Follow-Up	1943	1975	1964	1961	
End of Follow-up	2009-12-31	2010-12-31	2008-12-31	2009-12-31	
N female twins	33,339	12,507	12,824	45,869	104,539
N MZ/DZ complete pairs	6,235/10,430	2,026/4,179	2,935/3,439	9,859/12,892	21,055/30,940
N MZ/DZ complete uncensored pairs	1,251/2,332	403/792	195/232	1,781/3,238	3,630/6,594
N breast cancer cases	1,229	635	358	1,711	3,933
N breast cancer in complete pairs	1,229	630	352	1,700	3,911
N breast cancer in complete uncensored pairs	695	221	91	907	1,914
N concordant uncensored MZ/DZ pairs	44/48	15/23	13/5	52/65	124/141
N discordant uncensored MZ/DZ pairs	170/341	39/106	18/37	243/430	470/914
N unaffected uncensored MZ/DZ pairs	1,037/1,943	349/663	164/190	1,486/2,743	3,036/5,539

Table 2. Cumulative risk, casewise concordance risk and heritability of liability to breast cancer diagnosis in the NorTwinCan database. Bias-correction due to censoring by the inverse probability weighting technique. Lifetime risk for premenopausal cancer is up to 50 years while lifetime risk for post-menopausal cancer is conditional on survival to age 53 years.

Age at diagnosis	Lifetime risk and 95% CI	Casewise concordance and 95% CI		Estimates and 95% CIs from twin modeling	
		MZ	DZ	Common env. c^2	Heritability h^2
Any ages	8.1% (7.8%, 8.5%)	28% (23%, 33%)	20% (17%, 24%)	16% (10%, 32%)	31% (10%, 52%)
<50 years	1.5% (1.2%, 1.7%)	10% (5%, 17%)	6% (3%, 10%)	12% (0%, 39%)	27% (0%, 62%)
≥53 years	7.2% (6.6%, 7.8%)	21% (16%, 27%)	16% (13%, 20%)	16% (0%, 34%)	22% (0%, 46%)

Table 3. Relative recurrence risk and multilocus index of breast cancer by decades of age of diagnosis of breast cancer for female MZ and DZ pairs. Bias-correction due to censoring and competing risk of death.

Age	Relative recurrence risk for MZ (95% CI)	Relative recurrence risk for DZ (95% CI)	Multilocus index (95% CI)
All	2.16 (1.77, 2.55)	1.70 (1.41, 1.99)	1.64 (0.78, 2.50)
<50	5.91 (1.75, 10.07)	3.51 (1.02, 6.00)	1.96 (-0.59, 4.51)
50-60	4.93 (3.36, 6.50)	2.77 (1.83, 3.71)	2.21 (0.74, 3.68)
60-70	2.98 (2.27, 3.69)	2.24 (1.73, 2.75)	1.60 (0.74, 2.46)
70-80	2.50 (2.01, 2.99)	1.80 (1.45, 2.15)	1.87 (0.87, 2.87)
80-90	2.15 (1.76, 2.54)	1.67 (1.38, 1.96)	1.71 (0.77, 2.65)
90+	2.04 (1.65, 2.43)	1.68 (1.39, 1.97)	1.53 (0.65, 2.41)

Figure legends:

Fig 1: Casewise concordance of breast cancer risk by age at diagnosis for MZ pairs and DZ pairs, and the marginal risk of breast cancer. The risks are adjusted for censoring and competing risk of death. Transparent areas show 95% confidence.

Fig 2: Additive genetic and common environment component of liability to breast cancer by age at diagnosis. Bias-correction due to censoring and competing risk of death by the inverse probability weighting technique. Transparent areas show 95% confidence.

Fig 3: Pattern of cumulative breast cancer hazard in monozygotic (left) and dizygotic (right) twins with respect to age of diagnosis of the cotwin. Bias-correcting due to censoring and competing risk.

Figure 1:
Casewise Concordance of Breast Cancer in Nordic Twins

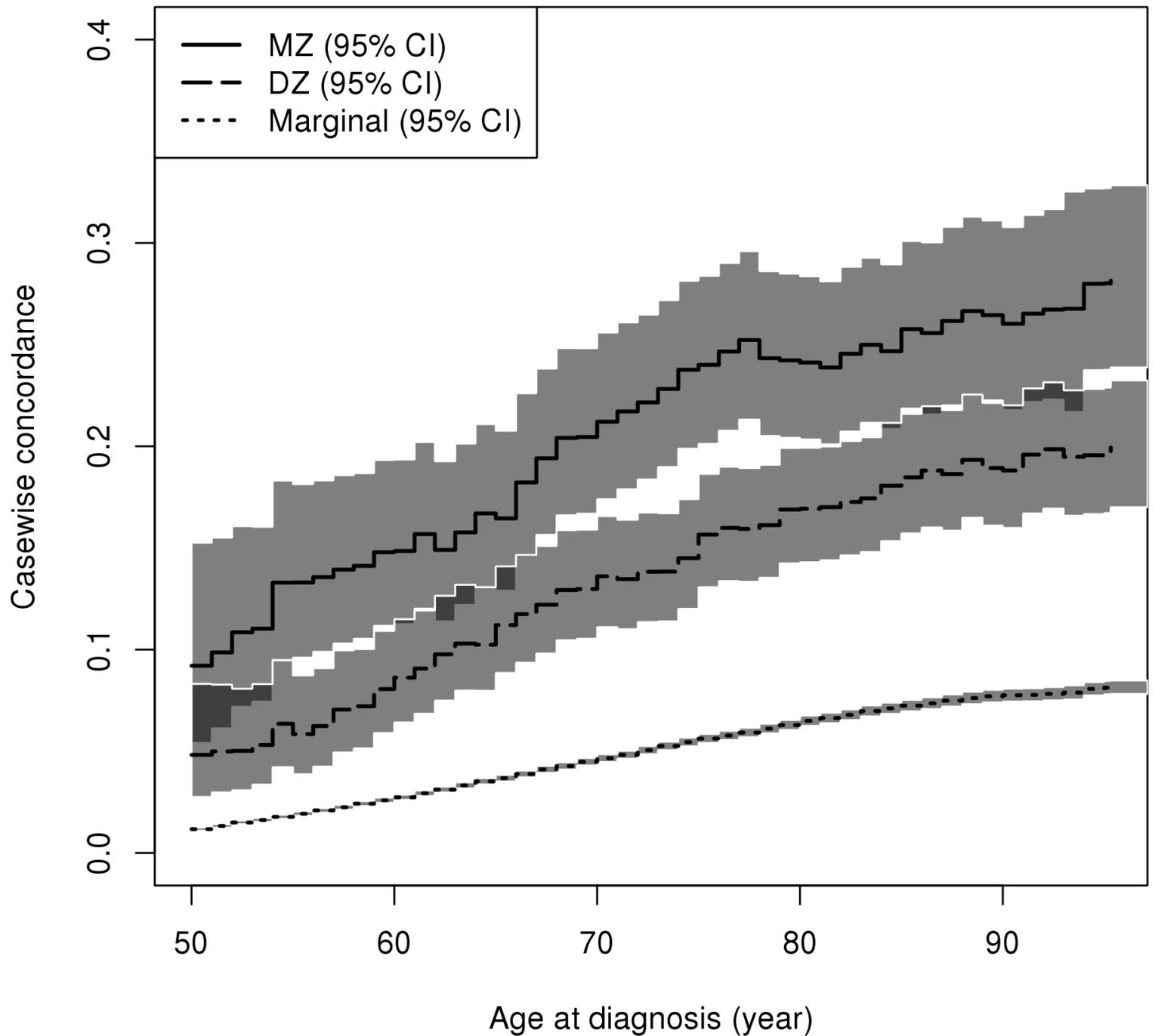


Figure 2:
Heritability of Liability of Breast Cancer in Nordic Twins

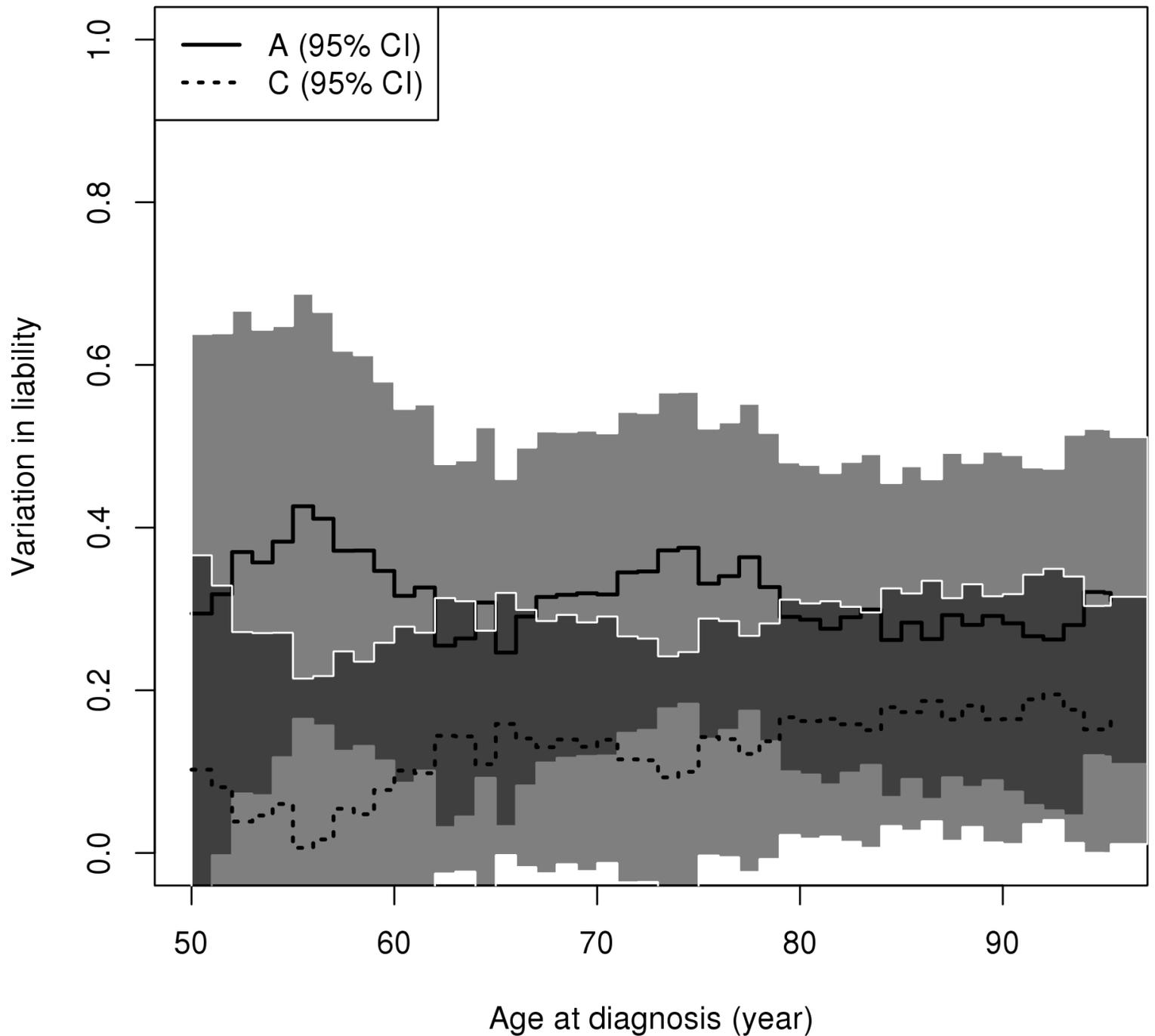
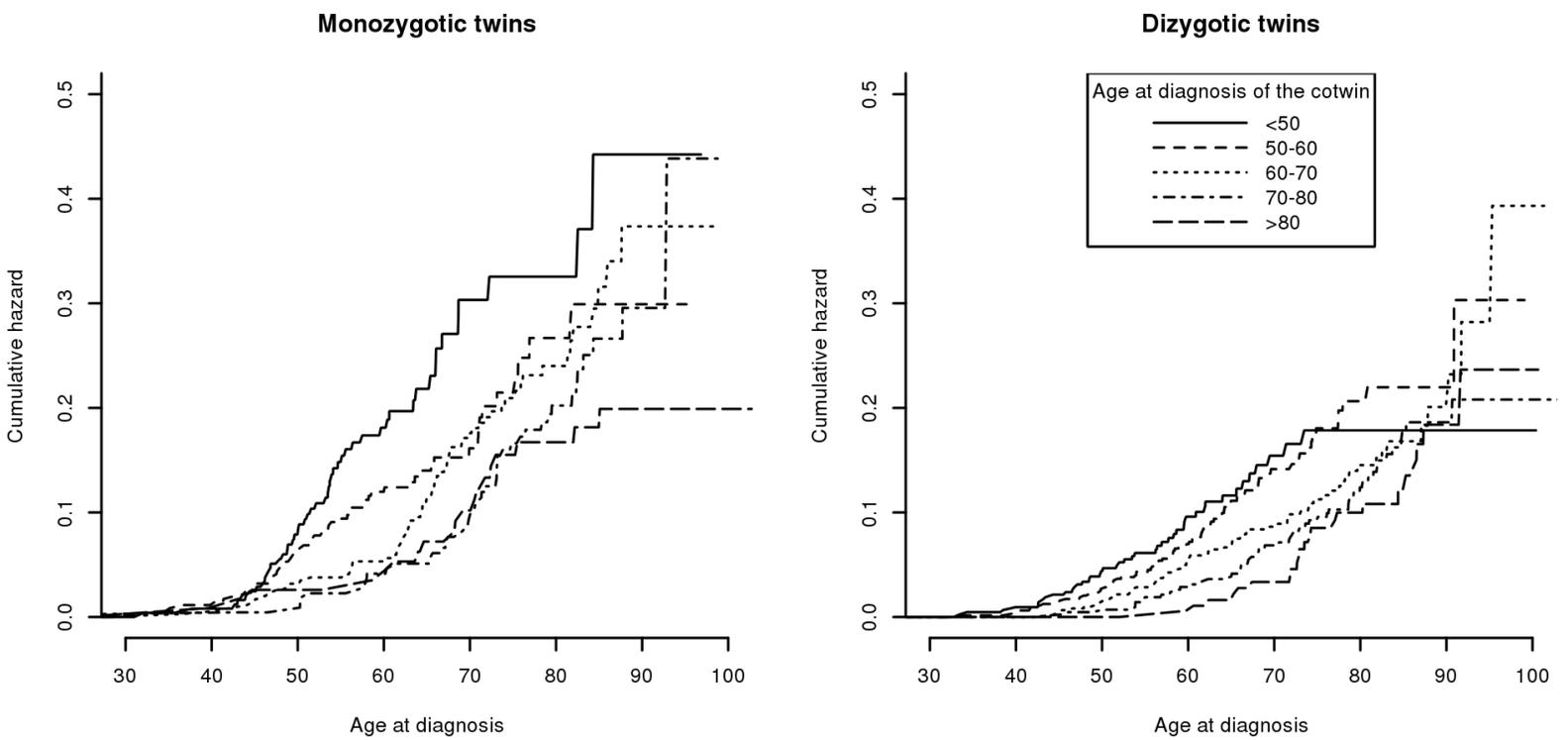


Figure 3



Cancer Epidemiology, Biomarkers & Prevention

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The Heritability of Breast Cancer among women in the Nordic Twin Study of Cancer

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