Short Communication

Breast Cancer Risk in Monozygotic and Dizygotic Female Twins: A 20-Year Population-based Cohort Study in Finland from 1976 to 1995

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Abstract

This population-based study investigated the occurrence of breast cancer over a 20-year period in a cohort of monozygotic (MZ) and dizygotic (DZ) twins in Finland. Altogether, 13,176 female twins of known zygosity who were living in Finland at the end of 1975 were identified from the Finnish Twin Cohort Study and followed-up for cancer through the Finnish Cancer Registry for the years 1976–1995. Standardized incidence ratios (SIRs) were calculated, based on national cancer incidence rates. The relative risk of breast cancer for MZ twins compared to DZ twins was decreased [SIR_MZ/SIR_DZ ratio = 0.78; 95% confidence interval (CI), 0.58–1.0]; the decreased risk for MZ twins (SIR = 0.76; 95% CI, 0.58–1.0) accounted for this result, whereas the risk for DZ twins did not differ from the general population risk (SIR = 0.98; 95% CI, 0.84–1.1). There was no risk decrease among MZ twins in other cancers related to reproductive behavior; i.e., number of children and age at first birth seem not to explain the decreased risk of breast cancer. Our results, which are in line with earlier studies on the same topic, suggest that prenatal influences or postnatal behavioral factors may protect MZ female twins from breast cancer.

Introduction

Over the past decade, raised concentrations of estrogens in the mothers of twins have been repeatedly suggested to increase the risk of breast cancer among their offspring (1). The epidemiological evidence comes mostly from a very small number of studies on the occurrence of breast cancer in twins (2–6). In 1992, Hsieh et al. (2) reported an apparent 40% increase in the risk of breast cancer among twins compared to singletons. This observation was repeated recently in another case-control study in the United States (3), whereas two Nordic population-based studies with considerably larger numbers of breast cancers in twins (4, 5) found no material increase in the risk of breast cancer among twin subjects at any age. The Swedish study (4), however, showed an increase in breast cancer risk among young (<30 years old) DZ twins compared to MZ female twins. A parallel observation was recently made in Britain (6). To extend and place the few earlier results suggesting differences in breast cancer risk between twins and singletons, or between DZ and MZ twins, in a population context, we investigated whether there is such a twin/general population difference, or a MZ/DZ difference, in breast cancer risk and, if so, whether it is due to an excess DZ risk or a diminished MZ risk.

Materials and Methods

The data for the present study were obtained from two nationwide datasets: the Finnish Twin Cohort Study and the Finnish Cancer Registry. In 1974, the cohort of potential adult twins was compiled from the national central population register using selection procedures described elsewhere (7–9). An extensive health questionnaire was mailed to all persons who were aged 18 or older and for whom we had an adequate address (overall response rate = 89%). Twin zygosity was determined by examining the responses of both members of each twin pair to two questions on the similarity of appearance at school age. A set of decision rules was used to classify the twin pairs as MZ, DZ, or undetermined zygosity; 93% of all respondent pairs could be classified as MZ or DZ by this scheme. The validity of the questionnaire method of zygosity was studied in a subsample of 104 MZ and DZ twins using 11 polymorphic blood markers (10). The two approaches classified these pairs identically, and the probability of misclassification for the genetic marker system was computed to be 0.017 (10). Two-thirds of pairs were DZ, which reflects the high DZ twinning rate in Finland earlier in this century. This study includes all of the female-female twin pairs with known zygosity in which both cotwins were living in Finland on December 31, 1975.

The cancer cases diagnosed between 1976 and 1995 among the subjects were identified by record linkage to the Finnish Cancer Registry data using personal identification codes. The Finnish Cancer Registry is a nationwide database with information on all cases of cancer diagnosed in Finland since 1953 (11, 12). The reporting of cancer has been compulsory since 1961. Notifications on cancer patients are received independently from several sources such as hospitals, private...
physicians, pathological laboratories, and death certificates. In 1995, diagnoses were based on cytological confirmation in over 90% of the cases. In addition, the study cohort and the Finnish Cancer Registry data were linked to the files of the central population register to obtain data on death and emigration.

The observed numbers of cancers and person-years at risk were calculated by zygosity, age (5-year age groups), and calendar period of diagnosis (1976–1980, 1981–1985, 1986–1990, and 1991–1995). Calculation of person-years began on January 1, 1976, and ended at emigration, at death, or on December 31, 1995, whichever occurred first. The expected numbers were calculated by multiplying the stratum-specific number of person-years by the corresponding cancer incidence in Finland. The SIRs for MZ and DZ twins were computed by dividing the observed number of cases by the expected number, and the relative SIR for MZ compared to DZ twins (SIRMZ / SIRDZ) was computed by dividing the SIR for MZ twins by that for DZ twins. The 95% CIs were derived under the Poisson assumption.

Data on other potential confounders were available only at the cohort level, not at the population level. The further adjusted RRs were obtained from logistic regression models (SAS Version 6.12, proc logistic function) that included terms for zygosity, age, education (primary or less/secondary or more), and marital status (single/other) to compare breast cancer risk among MZ twins to that among DZ twins.

### Results

The study cohort consisted of, in total, 13,176 female twins (Table 1). As of January 1, 1976, >40% of the subjects belonged to the youngest age group (18–29 years), whereas only 10% were 60 years old or older. The age distributions of the twins did not differ by zygosity.

A total of 245 breast cancers, 51 ovarian cancers, 51 cancers of the uterine corpus, and 485 other cancers were diagnosed among the subjects between 1976 and 1995 (Table 2). The SIR for breast cancer among MZ twins was 0.76 (95% CI, 0.59–0.97), whereas the SIR among DZ twins was 0.98 (95% CI, 0.84–1.1; Table 2). The risk of breast cancer among MZ twins was lower than that in DZ twins (SIRMZ / SIRDZ = 0.78; 95% CI, 0.58–1.0). The logistic model with additional adjustment for marital status and education provided an almost identical risk estimate (RR = 0.75; 95% CI, 0.56–1.0). The SIRs for ovarian cancer, cancer of the uterine corpus, and other cancers did not differ from the general population risk for either MZs or DZs.

### Discussion

The cancer registration system in Finland is virtually complete (12), and the computerized record linkage procedure using unique identification numbers is precise (13). It should be noted that cancers occurring among the cohort members as well as those among general population were both registered using the same procedures. Thus, there was no additional case ascertainment for cohort members, which might, in theory, bias (which here means increase) the SIRs. The follow-up of cohort members as well as that of all cancers during the period covered for death and emigration was completed for the period of this study. Therefore, it was very unlikely that the technical incompleteness would cause bias in the results.

Together with the findings of all four previous studies on breast cancer in twins compared to singletons or the general population (2–5), our results suggest that breast cancer risk for adult twins in general is close to that for the general population. The combined RR, computed for the earlier studies as well as our study, was 1.05 (95% CI, 0.99–1.10; Fig. 1). Exclusion of the two small case-control studies (2, 3) from the joint analysis did not materially change the combined risk estimate (RR = 1.04; 95% CI, 0.98–1.10). It should be noted, however, that these populations differ in the distributions of breast cancer risk factors and the overall incidence of breast cancer, the incidence being the lowest in Finland (14).

In our study, the risk of breast cancer in adult MZ female twins was decreased compared to DZ twins and decreased compared to the general population in Finland during 1976–1995. All three previous European population-based studies also showed corresponding risk estimates around 0.9 (Fig. 2; Refs. 4–6). The combined RR for breast cancer in MZ compared with DZ twins was 0.88 (95% CI, 0.79–0.99; Fig. 2).

As for the analyses of age-group specific risks, much attention has previously been paid to the possibility of breast cancer risk increase in young adult DZ twins. Our observation here of a SIR of 2.6 (95% CI, 0.31–9.4) in young adult DZ twins would, in theory, be compatible with the earlier risk estimates, although the power is too low for reliable conclusions. The Swedish study (4) reported a SIR of 6.7 (95% CI, 2.9–13.1), when DZ twins were compared to the general population, and the British study (6) reported a RR of 2.9 (95% CI, 0.8–10.4), when DZ twins were compared to MZ twins. Raised maternal estrogen concentration during pregnancy has been suggested to provide an explanation for these observations.

On the other hand, it remains unclear how the “maternal-estrogen etiology hypothesis” relates to the potential breast cancer risk difference among young MZ compared with DZ twins. This risk difference has been observed in all of the three epidemiological studies conducted thus far, based on our findings and the reanalysis of published data [Finland, RR = 0 and 95% CI, 0–10; Sweden (4), RR = 0 and 95% CI, 0–0.84; and Britain (6), RR = 0.34 and 95% CI, 0.10–1.3; the RRs were computed either as ratio of two SIRs based on the published figures given separately for MZ and DZ twins (4) or as reverse of the published risk estimates (6)]. The only report comparing biological estrogen concentrations among pregnant mothers of MZ with those of DZ twins showed, in fact, no differences in urinary estrogen concentrations by zygosity (15). In view of the
lack of further biological and epidemiological evidence, it can only be speculated that some pregnancy-related hormone, besides estrogen, to which MZ and DZ twins would be differentially exposed might be a more likely candidate for increasing breast cancer risk in young DZ twins.

According to another hypothesis, low birth weight would be preventive for breast cancer. For instance, a case-control study nested within the Nurses’ Health Study (16) showed breast cancer risk to be directly related to birth weight ($P_{\text{trend}} = 0.004$). Presuming this, one would expect twins and MZ twins, in particular, to have a reduced risk of breast cancer because birth weights of twins tend to be lower than those of singletons and those of MZ twins tend to be lower than those of DZ twins (17). In our study, only the MZ twins that had a reduced risk, whereas the risk for DZ twins was not reduced. Therefore, the “low birth weight” hypothesis appears to have the potential to provide only a partial explanation to our findings.

In addition to prenatal influences, it is also possible that direct genetic or postnatal biological or behavioral factors might explain the reduced risk in MZ twins. MZ and DZ twinning are apparently independent familial traits that are inherited both paternally and maternally (18, 19). If genetic factors were to account for the MZ/DZ difference in breast cancer risk, they would need to cosegregate together with some as yet unidentified genes that mediate the propensity to twinning.

As an example of postnatal biological factors, the age at menarche in Finland, reported by 16-year-old twin girls, is later for MZ than DZ twins (difference in means $= 0.3$ years, $P = 0.05$; Ref. 20). As for most other biological and behavioral factors, however, MZ and DZ twins have been found to be remarkably similar. On the other hand, if reproductive behavior among MZ twins would explain their reduced breast cancer risk, one would expect to see similarly low SIRs in cancers of the uterine corpus and ovary. This was not the case. Overall, it would be invaluable to investigate the prevalence of prenatal
and postnatal risk factors of breast cancer in a large-scale population-based twin study.

In conclusion, the risk of breast cancer in adult MZ female twins was decreased relative to DZ twins and relative to the general population in Finland during 1976–1995. The risk in DZ twins was not different from that for the general population. This finding was specific to breast cancer because there was no MZ/DZ difference for cancer at other sites. This observation suggests that MZ twin sisters may have characteristics that protect against breast cancer. These may be prenatal influences, such as factors leading into low birth weight or factors caused by maternal hormone levels during the pregnancy, but they may also be postnatal behavioral characteristics changing the risk factor profile in later life. Further identification of such risk factors and their differences between MZ and DZ twins with breast cancer may provide new clues to breast cancer etiology.

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References

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