

ORIGINAL ARTICLE

Puberty and Genetic Susceptibility to Breast Cancer in a Case–Control Study in Twins

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ABSTRACT

BACKGROUND

Breast cancer is thought to result from excessive cumulative exposure to ovarian hormones. Different predictors of hereditary and sporadic breast cancer suggest different pathogenic mechanisms. Affected twin pairs may help to illustrate such differences.

METHODS

We obtained information from 1811 pairs of female twins, one or both of whom had breast cancer. The pairs were stratified according to concordance or discordance for breast cancer, zygosity, the presence or absence of a family history of breast cancer, and the presence of bilateral or unilateral disease. Disease-concordant monozygotic pairs were assumed to have a higher genetic susceptibility than other subgroups of pairs. Paired twins were compared with respect to age at puberty and other factors. We calculated adjusted odds ratios for the diagnosis of breast cancer when only one twin was affected and for the first of the two diagnoses when both were affected.

RESULTS

Within disease-discordant monozygotic pairs, the twin with an earlier onset of puberty did not have an increased risk of breast cancer (adjusted odds ratio, 0.8; 95 percent confidence interval, 0.6 to 1.2). Within disease-concordant monozygotic pairs, the twin with earlier puberty was much more likely to receive the diagnosis first (adjusted odds ratio, 5.4; 95 percent confidence interval, 2.0 to 14.5). In contrast, a later first pregnancy, lower parity, and later menopause within the pair were associated with an increased risk of breast cancer when one twin was affected but did not predict an earlier diagnosis when both were affected.

CONCLUSIONS

Within the most genetically susceptible subgroup of twin pairs, the strong influence of earlier puberty on the age at the diagnosis of breast cancer and the absence of linkage to hormonal milestones later in life suggest that most cases of hereditary breast cancer are not related to cumulative hormone exposure and that they may instead result from an unusual sensitivity to pubertal hormones. Associations between breast cancer and early menarche and those with reproductive milestones in adulthood may reflect different genotypes.

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BREAST CANCER CAN RESULT FROM THE actions of ovarian hormones¹ that stimulate cell proliferation² and that may increase the rate of genetic errors in ductal cells. This view is based on hormonal risk factors, a “breast-age” (hormonal) index that predicts age-specific incidence,^{3,4} and differences in plasma estrogen levels between patients with cancer or their family members and controls.^{5,6} Even perinatal⁷⁻⁹ and environmental¹⁰⁻¹² risk factors have been attributed to hormonal differences. Genetic risk factors include those that regulate the production, transport, and metabolism of estrogens¹³; determine the hormonal sensitivity of cells¹⁴; or repair errors of replication.¹⁵

Observation of affected pairs of twins¹⁶ followed prospectively for new diagnoses showed a constant and much higher age-specific incidence of breast cancer throughout adulthood in the identical twins of women with cancer than in similar women in the general population.¹⁷ Moreover, the overall level of risk was more than twice that conferred by disease in a first-degree relative, constituting a much greater increase than would be produced by single dominant alleles.¹⁸ We postulated that genetically determined breast cancer accounts for a larger proportion of the total number of cases than previously thought and that most such cancers result from two or more individually low-penetrance allelic variants coexisting in a highly penetrant combination. We interpreted the constant, age-specific pattern of risk in identical twins of patients with breast cancer to be inconsistent with causation by cumulative exposure to hormones.

On the basis of the very high relative and cumulative risk to a woman who is genomically identical to a woman with cancer, disease in monozygotic twins who are both affected is considered largely to represent hereditary cancer, whereas disease in only one twin of a pair is believed to represent sporadic, or less heritable, disease. Cases among disease-discordant dizygotic pairs represent the same mixture of heritable and sporadic cases as those seen in ordinary case-control studies. The current analysis is based on a previously described population¹⁷ and includes all twins in affected pairs who completed a risk-factor questionnaire. To determine whether risk factors differed according to genetic susceptibility, we stratified pairs on the basis of zygosity, concordance or discordance of disease, the presence of bilateral or unilateral disease, and the presence or absence of a family history of breast cancer.

In contrast to a conventional analysis of case-control pairs, an analysis of pairs concordant for disease may seem unusual, since few differences in exposure might be expected. We hypothesized that an earlier exposure to hormones or exposure to a higher level of hormones might be linked to an earlier diagnosis of breast cancer.

METHODS

From 1980 to 1991, 17,245 twin pairs responded to advertisements in North American periodicals seeking “twins with cancer and other chronic diseases.”¹⁶ Among the 6325 female twin pairs were 2718 women with breast cancer, among them women in 200 monozygotic and 109 dizygotic disease-concordant pairs (i.e., pairs in which both twins were affected). The affected pairs were followed at regular intervals until February 1993 to identify additional cancer diagnoses in the women with a previous diagnosis and new diagnoses in the unaffected twins. By then, an additional 77 monozygotic and 22 dizygotic disease-concordant pairs had been identified. Assessment of ascertainment bias, diagnostic validation, and assignment of zygosity has been reported elsewhere.^{16,18}

At ascertainment, questionnaires concerning risk factors for breast cancer were sent to the 4241 living members of 2475 affected female twin pairs. Women from 1944 of these pairs (78.5 percent) replied. Responses from 1811 pairs (759 dizygotic and 1052 monozygotic) were considered sufficient for analysis. Each woman was asked about her twin as well as about herself, an approach that permitted assessment of pairs even when only one of the twins responded. Proxy responses were found to be biased only with respect to events occurring late in life.¹⁹

Standard case-control questions (e.g., about the age at menarche) were posed, as were questions unique to twin studies, calling for a comparative response with ranking of the relative magnitude or sequence of an exposure within the pair. Odds ratios were computed for each variable after the exclusion of pairs of twins who disagreed on the ranking of that variable and, in the context of menopausal variables, pairs in which only one of the twins responded.

Within each zygosity group, three strata were defined according to the probable level of genetic susceptibility: twins discordant for breast cancer, with no evidence of genetic or familial risk; twins discordant for cancer but with bilateral disease in

the affected twin or a history of breast cancer in another (nontwin) first-degree relative; and twins concordant for breast cancer. Pairs were analyzed as matched sets with the use of conditional logistic regression (PROC PHREG program, SAS Institute), with adjustment of odds ratios for potentially confounding variables. Heterogeneity between strata was assessed by determining (with use of the Wald test) whether the ratio of frequencies constituting the two odds ratios was statistically compatible with unity.

RESULTS

As we have previously reported,¹⁸ more monozygotic pairs than dizygotic pairs were concordant for breast cancer (20 percent vs. 12 percent) (Table 1). Among disease-concordant pairs, monozygotic and dizygotic pairs had a similar prevalence of factors associated with an increased genetic risk of breast cancer. Among disease-discordant monozygotic and dizygotic pairs, 20.9 percent and 24.3 percent, respectively, reported at least one such factor. Although a young age at diagnosis and Jewish ethnicity have been linked to BRCA1 and BRCA2 mutations, neither of these factors was significantly more prevalent among pairs with evidence of genetic risk (data not shown).

Within concordant pairs, the mean interval between the twins' diagnoses varied little according to zygosity (8.6 years in dizygotic pairs and 7.4 years in monozygotic pairs). No significant overall differences between twins within the groups stratified according to zygosity or disease concordance were seen with respect to mean parity or with respect to age at menarche, at the onset of breast development or menstrual regularity, at the time of the first full-term pregnancy, or at menopause (Table 2).

ONSET OF PUBERTY

Both direct measures and comparative measures (i.e., those referring to the within-pair rank order of events) with respect to age at menarche were obtained. In more than two thirds of the monozygotic and dizygotic pairs, the twins agreed that puberty had come later in one of the twins than in the other (more than one year later in 47.7 percent of the monozygotic pairs and 71.3 percent of the dizygotic pairs).

Most indicators of earlier puberty in one of the two twins were strongly and significantly associated with breast cancer in the discordant dizygotic

| Variable | Dizygotic | Monozygotic |
|--|-------------------|-------------|
| | Twins | Twins |
| | no. of pairs (%)† | |
| Concordance for breast cancer | | |
| Discordant | 670 (88.3) | 843 (80.1) |
| Concordant | 89 (11.7) | 209 (19.9) |
| Total | 759 | 1052 |
| Level of genetic risk | | |
| Discordant for breast cancer | | |
| Bilateral disease (GR+) | 40 (6.0) | 34 (4.0) |
| Breast cancer in another first-degree (nontwin) relative (GR+) | 109 (16.3) | 129 (15.3) |
| Both of the above (GR+) | 14 (2.1) | 13 (1.5) |
| Neither of the above (GR-) | 507 (75.7) | 667 (79.1) |
| Total | 670 | 843 |
| Concordant for breast cancer (all GR++) | | |
| Bilateral disease in one or both twins | 15 (16.8) | 41 (19.6) |
| Breast cancer in another first-degree (nontwin) relative | 15 (16.8) | 40 (19.1) |
| Both of the above | 9 (10.1) | 16 (7.7) |
| Neither of the above | 50 (56.2) | 112 (53.6) |
| Total | 89 | 209 |

* The genetic risk of breast cancer was assessed according to predefined terms at the outset of the study. GR- indicates no evidence of genetic risk (i.e., twins discordant for cancer, without bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), GR+ a possible increase in genetic risk (i.e., twins discordant for cancer but with bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), and GR++ a probable increase in genetic risk (i.e., twins concordant for cancer).

† Because of rounding, not all percentages total 100.

pairs with some evidence of genetic risk (Table 3). Among those without evidence of genetic risk, the same associations were weaker and were confined to pairs in which the affected twin received the diagnosis before the age of 50 years. The same measures predicted the earlier diagnosis within concordant, dizygotic pairs; earlier menarche was a significant factor when the first diagnosis came before the age of 50 years (Table 3).

When discordant monozygotic pairs were assessed, no link with earlier puberty was apparent in the pairs with no evidence of genetic risk, and only

Table 2. Age at the Time of Occurrence of Selected Variables and Parity before the Diagnosis of Breast Cancer, According to Zygosity and Concordance for Breast Cancer.*

| Variable | Dizygotic, Pairs Discordant for Cancer | | Dizygotic, Pairs Concordant for Cancer | Monozygotic, Pairs Discordant for Cancer | | Monozygotic, Pairs Concordant for Cancer |
|---------------------------|---|----------------------|--|---|----------------------|--|
| | Unaffected Women | Women with Cancer | | Unaffected Women | Women with Cancer | |
| Breast development | | | | | | |
| Age — yr | 12.3 (12.2–12.4) | 12.2 (12.0–12.3) | 12.1 (11.9–12.3) | 12.2 (12.1–12.3) | 12.2 (12.1–12.3) | 12.2 (12.0–12.4) |
| No. of women | 557 | 541 | 137 | 741 | 714 | 337 |
| Menarche | | | | | | |
| Age — yr | 12.8 (12.7–12.9) | 12.7 (12.6–12.8) | 12.7 (12.4–12.9) | 12.8 (12.6–12.8) | 12.8 (12.7–12.8) | 12.8 (12.6–12.9) |
| No. of women | 625 | 591 | 154 | 804 | 768 | 379 |
| Menstrual regularity | | | | | | |
| Age — yr | 13.2 (13.0–13.3) | 13.0 (12.9–13.2) | 12.8 (12.4–13.1) | 13.1 (12.9–13.2) | 13.1 (13.0–13.2) | 13.2 (13.0–13.4) |
| No. of women | 546 | 490 | 128 | 678 | 636 | 321 |
| First full-term pregnancy | | | | | | |
| Age — yr | 24.2 (23.8–24.5) | 24.3 (24.0–24.8) | 24.9 (24.0–25.8) | 24.5 (24.2–24.9) | 24.8 (24.5–25.2) | 25.4 (24.9–26.0) |
| No. of women | 500 | 485 | 129 | 630 | 623 | 301 |
| Parity | | | | | | |
| Value | 2.3 (2.2–2.4) | 2.2 (2.1–2.4) | 2.1 (1.9–2.4) | 2.3 (2.2–2.4) | 2.2 (2.1–2.3) | 2.0 (1.9–2.2) |
| No. of women | 660 | 657 | 176 | 834 | 831 | 412 |
| Menopause† | | | | | | |
| Age — yr | 43.6 (42.7–44.4) | 43.5 (42.6–44.4) | 42.8 (40.9–44.8) | 44.6 (43.7–45.3) | 44.7 (43.9–45.5) | 44.4 (43.2–45.5) |
| No. of women | 306 | 266 | 74 | 365 | 357 | 164 |

* The values for age and parity are means, with 95 percent confidence intervals given in parentheses.

† Only women in whom menopause occurred before their diagnosis of breast cancer (or the diagnosis in their twins, for unaffected women) were included in this analysis. Women who had had a hysterectomy without oophorectomy were excluded.

moderate associations were seen within pairs with some degree of genetic risk (Table 3). However, within concordant monozygotic pairs, every indicator of earlier puberty in one twin than in the other strongly, consistently, and significantly predicted the first diagnosis of breast cancer. These indicators included earlier development of breasts (about six months before menarche, as also reported elsewhere²⁰) (Table 2), earlier menarche (whether according to a comparative or a direct response on the questionnaire), menarche before the age of 12 years, and earlier menstrual regularity (on average, six months after menarche). When we constructed a summary index of earlier puberty according to the concurrence of at least two of these indicators, the twin with earlier puberty was 5.4 times as likely to receive the first diagnosis of breast cancer (95 percent confidence interval, 2.0 to 14.5).

The interval between the twins' age at menarche did not influence the strength of the link between earlier puberty and an earlier breast-cancer diagnosis (Table 3), but when the first menarche in the

pair occurred before the age of 12 years, the association between earlier puberty and an earlier diagnosis was more than three times as strong as it was when puberty occurred at the age of 12 years or later (adjusted odds ratio, 3.1; 95 percent confidence interval, 1.3 to 7.6) (Table 4). In that circumstance, the association between an early-puberty index that was greater than 1 and an earlier diagnosis reached 9.1 (95 percent confidence interval, 1.1 to 77.1).

DEVELOPMENTAL AND OTHER REPRODUCTIVE VARIABLES

Within concordant monozygotic pairs, greater height and weight during childhood (known predictors of early puberty) in one twin than in the other were associated with an earlier diagnosis of breast cancer (Table 5). A history of more medical problems at birth or during infancy in one twin than in the other was related to an increased risk of breast cancer within discordant pairs and to an earlier diagnosis within concordant dizygotic (but not monozygotic) pairs. Within discordant monozygotic pairs

Table 3. Puberty-Related Risk Factors and Adjusted Odds Ratios for Breast Cancer or First Breast Cancer among Twins, According to Zygosity, Concordance for Breast Cancer, and Level of Genetic Risk.*

| Risk Factor | Dizygotic, Discordant for Cancer | | Dizygotic, Concordant for Cancer | Monozygotic, Discordant for Cancer | | Monozygotic, Concordant for Cancer |
|--|-------------------------------------|---------------|-------------------------------------|---------------------------------------|---------------|--|
| | GR- | GR+ | GR++ | GR- | GR+ | GR++ |
| Diagnosis at any age | | | | | | |
| No. of pairs | 508 | 163 | 88 | 667 | 176 | 209 |
| First menarche (comparative response) | 1.1 (0.9–1.3) | 1.4 (0.9–2.0) | 1.4 (0.9–2.4) | 1.0 (0.8–1.2) | 0.8 (0.5–1.1) | 1.6 (1.2–2.3)† |
| First menarche (direct response) | | | | | | |
| By 1 yr | 1.1 (0.8–1.5) | 1.6 (0.9–2.9) | 1.6 (0.7–3.5) | 1.1 (0.8–1.4) | 1.2 (0.7–2.2) | 1.4 (0.8–2.3) |
| By ≥2 yr | 1.2 (0.8–1.6) | 1.5 (0.9–2.7) | 1.6 (0.6–4.3) | 0.6 (0.4–1.1) | 0.8 (0.3–2.2) | 1.4 (0.6–3.3) |
| By any interval | 1.1 (0.9–1.4) | 1.6 (1.0–2.4) | 1.6 (0.8–3.0) | 1.0 (0.8–1.2) | 1.1 (0.7–1.8) | 1.4 (0.9–2.2) |
| Age at menarche <12 yr | 1.1 (0.7–1.6) | 2.2 (1.1–4.4) | 2.3 (0.8–6.6) | 0.8 (0.5–1.3) | 0.6 (0.2–1.7) | 3.0 (1.2–7.8)† |
| First breast development | 1.0 (0.8–1.3) | 1.7 (1.1–2.6) | 1.8 (0.9–3.3) | 0.8 (0.6–1.1) | 0.8 (0.4–1.6) | 3.6 (1.7–7.7)† |
| First menstrual regularity | 1.1 (0.8–1.4) | 1.3 (0.8–1.9) | 1.2 (0.6–2.1) | 1.0 (0.8–1.3) | 1.0 (0.6–1.6) | 2.4 (1.5–3.7)† |
| Early-puberty index >1‡ | 1.0 (0.7–1.3) | 1.4 (0.8–2.3) | 1.4 (0.7–3.0) | 0.8 (0.6–1.2) | 0.8 (0.3–1.9) | 5.4 (2.0–14.5)† |
| Age at diagnosis | | | | | | |
| No. of pairs with first diagnosis <50 yr | 262 | 87 | 52 | 324 | 89 | 115 |
| No. of pairs with first diagnosis ≥50 yr | 244 | 75 | 34 | 341 | 87 | 93 |
| First menarche (comparative response) | | | | | | |
| <50 yr | 1.3 (0.9–1.8) | 1.3 (0.8–2.1) | 1.3 (0.7–2.4) | 1.0 (0.7–1.2) | 0.9 (0.5–1.5) | 1.4 (0.9–2.2) |
| ≥50 yr | 0.9 (0.6–1.2) | 1.4 (0.8–2.6) | 1.9 (0.8–4.5) | 1.1 (0.8–1.4) | 0.6 (0.3–1.1) | 2.1 (1.2–3.6)† |
| First menarche (direct response) | | | | | | |
| <50 yr | 1.3 (0.9–1.8) | 1.2 (0.7–2.1) | 3.0 (1.2–7.0) | 1.0 (0.7–1.4) | 1.5 (0.8–2.9) | 1.1 (0.6–2.0) |
| ≥50 yr | 1.0 (0.7–1.4) | 2.2 (1.1–4.4) | 0.6 (0.2–1.9) | 0.9 (0.7–1.3) | 0.8 (0.4–1.7) | 1.8 (0.9–3.5) |
| Age at menarche <12 yr | | | | | | |
| <50 yr | 1.2 (0.7–2.0) | 2.4 (0.9–5.9) | 3.4 (0.9–12.7) | 0.8 (0.4–1.6) | 0.7 (0.2–2.3) | 4.3 (1.2–15.6)† |
| ≥50 yr | 0.9 (0.5–1.8) | 2.0 (0.7–5.8) | 0.5 (0.1–6.5) | 0.7 (0.3–1.6) | 0.6 (0.1–4.0) | 1.7 (0.4–7.3) |
| First breast development | | | | | | |
| <50 yr | 1.2 (0.9–1.7) | 1.6 (0.9–2.8) | 1.4 (0.7–3.1) | 0.7 (0.5–1.1) | 1.2 (0.5–3.0) | 2.6 (1.1–6.4)† |
| ≥50 yr | 0.8 (0.6–1.2) | 1.9 (0.8–4.2) | 2.4 (0.7–7.9) | 0.9 (0.6–1.5) | 0.4 (0.1–1.2) | 7.9 (1.7–36.2)† |
| First menstrual regularity | | | | | | |
| <50 yr | 1.3 (0.9–1.7) | 1.1 (0.7–1.9) | 1.0 (0.5–2.0) | 0.9 (0.6–1.2) | 1.3 (0.7–2.5) | 1.8 (1.1–3.2) |
| ≥50 yr | 0.9 (0.6–1.3) | 1.5 (0.8–2.9) | 1.8 (0.5–6.2) | 1.1 (0.8–1.6) | 0.6 (0.3–1.4) | 3.5 (1.7–7.4)† |
| Early-puberty index >1‡ | | | | | | |
| <50 yr | 1.2 (0.8–1.8) | 1.4 (0.7–2.6) | 1.1 (0.4–2.6) | 0.8 (0.5–1.4) | 1.3 (0.4–4.4) | 5.2 (1.4–18.6)† |
| ≥50 yr | 0.7 (0.4–1.1) | 1.4 (0.6–3.3) | 3.1 (0.6–15.9) | 0.8 (0.4–1.6) | 0.3 (0.1–1.4) | 5.8 (1.2–27.4)† |

* All variables were adjusted for nulliparity and age at first full-term pregnancy (age, ≤25 yr vs. >25 yr) and variables other than those related to first menarche, first breast development, and first menstrual regularity were also adjusted for first menarche. Numbers in parentheses are 95 percent confidence intervals. GR- indicates no evidence of genetic risk (i.e., twins discordant for cancer, without bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), GR+ a possible increase in genetic risk (i.e., twins discordant for cancer but with bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), and GR++ a probable increase in genetic risk (i.e., twins concordant for cancer).

† P<0.05 for the comparison between the concordant pairs (GR++) and discordant pairs (GR-).

‡ An early-puberty index of greater than 1 was defined as the presence of two or more of the following: first menarche, first breast development, or first menstrual regularity.

Table 4. Menarche-Related Risk Factors and Adjusted Odds Ratios for Breast Cancer or First Breast Cancer among Twins, According to Zygosity, Concordance for Breast Cancer, and Level of Genetic Risk.*

| Risk Factor | Dizygotic, Discordant for Cancer | | Dizygotic, Concordant for Cancer | Monozygotic, Discordant for Cancer | | Monozygotic, Concordant for Cancer |
|--|-------------------------------------|---------------|--|---------------------------------------|---------------|--|
| | GR- | GR+ | GR++ | GR- | GR+ | GR++ |
| No. of pairs | 421 | 135 | 68 | 574 | 164 | 171 |
| First menarche in pair and age at first menarche | | | | | | |
| <12 yr | 1.1 (0.8–1.7) | 1.9 (0.9–3.7) | 2.0 (0.7–5.6) | 1.0 (0.6–1.5) | 0.6 (0.2–1.6) | 3.1 (1.3–7.6)† |
| ≥12 yr | 1.1 (0.8–1.5) | 1.3 (0.7–2.2) | 1.3 (0.6–3.0) | 1.0 (0.7–1.3) | 1.6 (0.9–2.8) | 1.0 (0.6–1.6) |
| ≥13 yr | 1.2 (0.8–1.8) | 1.8 (0.8–3.9) | 1.1 (0.3–3.8) | 1.3 (0.8–2.1) | 1.6 (0.7–3.5) | 1.1 (0.5–2.6) |
| Early-puberty index >1 and age at first menarche‡ | | | | | | |
| <12 yr | 1.0 (0.6–1.7) | 1.6 (0.7–3.4) | 2.2 (0.6–8.6) | 0.7 (0.3–1.5) | 1.0 (0.2–5.2) | 9.1 (1.1–77.1)† |
| ≥12 yr | 1.0 (0.7–1.6) | 1.3 (0.6–2.7) | 1.0 (0.3–3.0) | 1.0 (0.6–1.5) | 0.7 (0.2–2.1) | 4.6 (1.3–17.0) |
| ≥13 yr | 0.9 (0.5–1.7) | 1.9 (0.7–5.4) | 0.2 (0.1–1.4) | 0.9 (0.4–1.8) | 0.7 (0.2–2.5) | 2.8 (0.5–14.8) |

* All variables were adjusted for nulliparity and age at first full-term pregnancy (≤ 25 yr vs. > 25 yr). Numbers in parentheses are 95 percent confidence intervals. GR- indicates no evidence of genetic risk (i.e., twins discordant for cancer, without bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), GR+ a possible increase in genetic risk (i.e., twins discordant for cancer but with bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), and GR++ a probable increase in genetic risk (i.e., twins concordant for cancer).

† $P < 0.05$ for the comparison between concordant pairs (GR++) and discordant pairs (GR-).

‡ An early puberty index of greater than 1 was defined as the presence of two or more of the following: first menarche, first breast development, or first menstrual regularity.

of twins, but not within other pairs, earlier first full-term pregnancy and higher parity in one twin were significantly associated with a reduced risk of breast cancer (adjusted odds ratio for each of these factors, 0.7; 95 percent confidence interval, 0.5 to 0.9).

Within each subgroup of discordant pairs of dizygotic twins, earlier menopause (either by natural causes or by bilateral oophorectomy) and fewer reproductive years conferred the expected protection against breast cancer (Table 6). No such effects were seen within concordant monozygotic pairs. Use of estrogen-replacement therapy had no effect in any subgroup, but use of such therapy was of short duration in most of the participants.

DISCUSSION

Our findings support the hypothesis that the risk of breast cancer for a genetically susceptible woman is determined not by cumulative exposure to ovarian hormones but rather by exposure to the flood of hormones present at puberty. Among monozygotic twins, breast cancer that occurred within disease-concordant pairs was more likely than not to be heritable, and breast cancer that occurred within

disease-discordant pairs was more likely than not to represent the sporadic form. Within genetically susceptible twin pairs, the first twin to experience puberty, especially if she did so before the age of 12, was much more likely to be the first twin to receive a diagnosis of breast cancer at a later date. If these disease-concordant monozygotic pairs had been interviewed just after the first diagnosis (permitting a comparison between the initial case and the as yet unaffected twin control), evidence of earlier puberty would have ranked among the strongest predictors of breast cancer. Within these pairs, the factors usually found to be the strongest predictors — age at first full-term pregnancy, parity, and age at menopause — were completely unrelated to the sequence of diagnoses.

In contrast, within the discordant monozygotic pairs, composed of twins with sporadic cases and controls, the pattern of risk was reversed. By any measure, relative age at puberty was unrelated to the risk of breast cancer. Moreover, sporadic breast cancer was linked to each reproductive factor during adulthood, suggesting that these cancers may be caused by higher cumulative exposure to ovarian hormones over a lifetime.

Table 5. Developmental and Reproductive Risk Factors and Adjusted Odds Ratios for Breast Cancer or First Breast Cancer among Twins, According to Zygosity, Concordance for Breast Cancer, and Level of Genetic Risk.*

| Risk Factor | Dizygotic, Discordant for Cancer | | Dizygotic, Concordant for Cancer | Monozygotic, Discordant for Cancer | | Monozygotic, Concordant for Cancer |
|---|-------------------------------------|---------------|--|---------------------------------------|---------------|--|
| | GR- | GR+ | GR++ | GR- | GR+ | GR++ |
| No. of pairs | 507 | 163 | 88 | 667 | 176 | 209 |
| Developmental factors | | | | | | |
| Greater weight at birth | 1.0 (0.8–1.3) | 0.9 (0.6–1.3) | 1.1 (0.7–1.9) | 0.8 (0.7–0.9) | 1.1 (0.8–1.6) | 1.1 (0.8–1.5) |
| First to walk | 1.1 (0.8–1.5) | 1.1 (0.6–1.8) | 0.8 (0.4–1.9) | 1.0 (0.7–1.5) | 0.8 (0.4–1.8) | 0.9 (0.5–1.9) |
| More medical problems than other twin | | | | | | |
| At birth | 1.0 (0.8–1.4) | 1.3 (0.8–2.1) | 2.5 (1.2–5.5) [†] | 1.6 (1.2–2.2) | 1.9 (1.1–3.3) | 1.1 (0.7–1.9) |
| During infancy | 1.3 (0.9–1.8) | 1.4 (0.8–2.3) | 1.7 (0.8–3.4) | 1.2 (0.8–1.6) | 2.0 (1.1–3.9) | 1.1 (0.6–2.0) |
| Greater height | | | | | | |
| At 10 yr | 1.3 (1.1–1.6) | 0.6 (0.4–0.9) | 1.3 (0.8–2.2) | 0.8 (0.6–0.9) | 1.3 (0.8–2.0) | 1.5 (0.9–2.3) [†] |
| At 20 yr | 1.2 (0.9–1.5) | 0.8 (0.5–1.1) | 1.1 (0.7–1.8) | 0.8 (0.6–1.0) | 1.2 (0.8–1.9) | 1.0 (0.7–1.6) |
| Greater weight | | | | | | |
| At 10 yr | 1.1 (0.9–1.4) | 0.8 (0.5–1.1) | 0.8 (0.5–1.5) | 0.7 (0.6–0.9) | 1.1 (0.7–1.8) | 1.5 (0.9–2.4) [†] |
| At 20 yr | 1.0 (0.8–1.2) | 1.0 (0.7–1.5) | 0.9 (0.6–1.6) | 0.8 (0.6–0.9) | 0.7 (0.5–1.1) | 1.1 (0.7–1.6) |
| Greater body-mass index | | | | | | |
| At 20 yr | 1.3 (1.0–1.7) | 1.4 (0.9–2.0) | 1.0 (0.5–2.1) | 0.9 (0.7–1.1) | 0.7 (0.4–1.1) | 0.9 (0.6–1.4) |
| At 40 yr | 1.3 (1.0–1.7) | 1.2 (0.7–1.9) | 0.7 (0.4–1.4) | 1.2 (0.9–1.5) | 0.7 (0.5–1.1) | 1.2 (0.8–1.9) |
| Reproductive factors | | | | | | |
| Age at first full-term pregnancy | | | | | | |
| ≤25 yr | 0.9 (0.7–1.3) | 0.8 (0.4–1.4) | 1.2 (0.5–2.8) | 0.7 (0.5–0.9) | 1.1 (0.6–2.0) | 1.2 (0.7–2.1) |
| >25 yr | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Nulliparity | 1.2 (0.8–1.8) | 1.6 (0.8–3.2) | 1.4 (0.6–3.2) | 1.0 (0.7–1.5) [‡] | 0.7 (0.4–1.3) | 1.9 (0.9–3.9) [‡] |
| Parity | | | | | | |
| Nulliparity | 1.2 (0.8–1.8) | 1.6 (0.8–3.3) | 1.3 (0.6–3.0) | 1.0 (0.7–1.5) | 0.6 (0.3–1.2) | 2.0 (0.9–4.0) |
| 1 or 2 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| ≥3 | 1.0 (0.7–1.4) | 0.8 (0.4–1.5) | 1.0 (0.5–2.1) | 0.7 (0.5–0.9) [‡] | 1.0 (0.6–1.6) | 1.3 (0.8–2.1) |
| Current or previous use of oral contraceptives | 1.0 (0.7–1.5) | 1.8 (0.8–3.8) | 2.2 (0.6–7.6) | 1.1 (0.8–1.5) | 0.9 (0.5–1.6) | 1.1 (0.6–2.1) |

* All variables were adjusted for nulliparity and age at first full-term pregnancy (≤25 yr vs. >25 yr); variables other than those related to first menarche, first breast appearance, and first menstrual regularity were also adjusted for first menarche. Numbers in parentheses are 95 percent confidence intervals. GR- indicates no evidence of genetic risk (i.e., twins discordant for cancer, without bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), GR+ a possible increase in genetic risk (i.e., twins discordant for cancer but with bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), and GR++ a probable increase in genetic risk (i.e., twins concordant for cancer).

[†] P<0.05 for the comparison between the concordant pairs (GR++) and the discordant pairs (GR-).

[‡] P<0.05 for trend.

Taken together, our findings suggest that the relatively minor increase in risk seen after early menarche in population-based studies reflects an average of risks derived from a minority with a strong, genetically determined susceptibility to the hormonal milieu of puberty and a majority without such susceptibility. If we had not stratified the twins in

our study according to genetic risk, the overall relative risk associated with the first menarche within the pair would have been 1.2 (95 percent confidence interval, 1.0 to 1.3), a risk similar to that found in many population-based studies.

If an onset of puberty that is 7.2 months earlier, on average, in one twin than in the other within a

Table 6. Menopause-Related Risk Factors and Adjusted Odds Ratios for Breast Cancer or First Breast Cancer among Twins, According to Zygosity, Concordance for Breast Cancer, and Level of Genetic Risk.*

| Risk Factor | Dizygotic, Discordant for Cancer† | | Monozygotic, Discordant for Cancer | | Monozygotic, Concordant for Cancer |
|---|--------------------------------------|---------------|---------------------------------------|---------------|--|
| | GR- | GR+ | GR- | GR+ | GR++ |
| No. of pairs | 170 | 66 | 301 | 82 | 90 |
| Menopausal status at diagnosis | | | | | |
| Before menopause | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| After natural menopause | 0.7 (0.3–1.9) | 0.5 (0.1–2.4) | 1.2 (0.5–2.6) | 1.1 (0.2–6.6) | 0.4 (0.1–2.0) |
| After bilateral oophorectomy | 0.6 (0.2–1.5) | 0.6 (0.1–2.7) | 0.7 (0.4–1.5) | 1.6 (0.3–8.8) | 1.5 (0.4–4.5) |
| Age at menopause‡ | | | | | |
| First group (youngest) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Second group | 1.3 (0.4–4.1) | 1.6 (0.3–9.1) | 1.3 (0.6–2.8) | 1.1 (0.1–8.9) | 0.3 (0.1–1.9) |
| Third group (oldest) | 4.8 (1.6–14)§ | 4.4 (0.8–26) | 1.1 (0.5–2.8) | 0.8 (0.1–5.4) | 0.2 (0.1–1.4) |
| Later menopause than other twin | | | | | |
| By 1 or 2 yr | 1.6 (0.9–2.5) | 1.1 (0.5–2.3) | 1.0 (0.7–1.4) | 0.6 (0.2–1.2) | 0.9 (0.4–1.7) |
| By 3–6 yr | 0.6 (0.2–1.3) | 0.3 (0.1–1.3) | 0.7 (0.4–1.2) | 0.5 (0.2–1.7) | 1.8 (0.6–5.1) |
| By ≥7 yr | 1.8 (0.8–3.9) | 2.2 (0.6–7.7) | 1.0 (0.5–1.8) | 0.3 (0.1–1.4) | 0.5 (0.1–2.2) |
| By ≥7 yr | 4.2 (1.5–11) | 1.9 (0.5–7.8) | 2.0 (0.9–4.4) | 1.3 (0.3–5.5) | 0.5 (0.1–1.7) |
| Reproductive period before diagnosis¶ | | | | | |
| First group (shortest) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Second group | 2.5 (0.9–6.2) | 1.0 (0.2–4.6) | 1.1 (0.5–2.4) | 0.6 (0.2–2.5) | 1.1 (0.3–4.4) |
| Third group (longest) | 3.9 (1.4–11)§ | 3.2 (0.7–13) | 1.3 (0.5–3.1) | 0.4 (0.1–2.0) | 0.4 (0.1–1.8) |
| Longer reproductive period than other twin | | | | | |
| Longer reproductive period than other twin | 1.8 (1.2–2.6) | 1.6 (0.8–3.1) | 0.9 (0.6–1.2) | 0.8 (0.5–1.5) | 0.9 (0.5–1.5) |
| Current or previous use of estrogen-replacement therapy | | | | | |
| Current or previous use of estrogen-replacement therapy | 1.0 (0.4–2.2) | 1.1 (0.4–3.1) | 1.1 (0.6–1.9) | 0.5 (0.1–2.4) | 0.9 (0.4–2.4) |

* All variables were adjusted for first menarche, nulliparity, and age at first full-term pregnancy (≤ 25 yr vs. > 25 yr). Numbers in parentheses are 95 percent confidence intervals. GR- indicates no evidence of genetic risk (i.e., twins discordant for cancer, without bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), GR+ a possible increase in genetic risk (i.e., twins discordant for cancer but with bilateral disease in the affected twin or a history of breast cancer in another [nontwin] first-degree relative), and GR++ a probable increase in genetic risk (i.e., twins concordant for cancer). Data shown include only double-respondent pairs in which each twin was premenopausal, had undergone natural menopause, or had undergone bilateral oophorectomy.

† Data for disease-concordant dizygotic pairs are not shown because the sample was too small.

‡ The three groups for age at menopause were defined on the basis of the controls' age distribution, as follows: discordant dizygotic, GR-: < 43 yr, 43–47 yr, and ≥ 48 yr; discordant dizygotic, GR+: < 42 yr, 42–46 yr, and ≥ 47 yr; discordant monozygotic, GR-: < 42 yr, 43–48 yr, and ≥ 49 yr; discordant monozygotic, GR+: < 43 yr, 43–49 yr, and ≥ 50 yr; concordant monozygotic: < 44 yr, 44–49 yr, and ≥ 50 yr.

§ $P < 0.05$ for trend.

¶ The three groups for length of reproductive period were defined on the basis of the controls' distribution, as follows: discordant dizygotic, GR-: < 30 yr, 30–34 yr, and ≥ 35 yr; discordant dizygotic, GR+: < 29 yr, 29–33 yr, and ≥ 34 yr; discordant monozygotic, GR-: < 29 yr, 29–35 yr, and ≥ 36 yr; discordant monozygotic, GR+: < 31 yr, 31–35 yr, and ≥ 36 yr; and concordant monozygotic: < 31 yr, 31–36 yr, and ≥ 37 yr.

genetically identical pair can lead after decades to a diagnosis of heritable breast cancer that is 7.4 years earlier, on average, very-long-term consequences depend on a genetic factor that acts no later than at puberty. This factor could affect only the hormonal milieu of puberty or the cellular response to it. Because puberty marks a brief period of great proliferation and differentiation in the epithelial and stromal cells of the breasts,²¹ a heritable factor related to cellular susceptibility provides the plausible ex-

planation. Increases in gonadal hormone production continue into adulthood,²² and any heritable alteration would not be likely to act at such an early age. Hormone levels could not be directly measured in our study, but empirical evidence of an unusual hormonal milieu, early or late, was not apparent. Although women with an earlier menarche tend to have higher estrogen levels than those with a later menarche,²³ in our study, the group of twins with hereditary breast cancer was similar to the group

with sporadic breast cancer in terms of parity, age at menarche, age at the time of breast development, age at the time of initial menstrual regularity, and age at menopause. Finally, no reproductive variable occurring in adulthood in the twins we studied predicted the earlier diagnosis. As a result, we favor the hypothesis that much of the genetic susceptibility to breast cancer derives from a pathologic cellular response to the physiologic increase in the production of hormones at puberty.

Although few of the women with hereditary breast cancer in our study were tested for the dominant mutations in *BRCA1* or *BRCA2*,¹⁸ these allelic variants probably do not explain their genetic susceptibility. Most received the diagnosis after the age of 40 years, and their tumors tended to be estrogen-receptor–positive rather than estrogen-receptor–negative.¹⁸ Moreover, the proportion of twins who were Jewish was not especially high (9.6 percent and 7.5 percent of concordant and discordant monozygotic pairs, respectively), and only 3.8 percent of concordant monozygotic pairs reported a twin or other first-degree relative with ovarian cancer — a proportion similar to that in other subgroups of twins.

We cannot identify a study artifact that might explain our results. The twins were ascertained as case–control pairs, matched according to the level of motivation to participate in the study and other unmeasurable confounding factors. When we included known, measurable confounding variables in the analysis (including the variables reported above, as well as height in childhood and adulthood, body-mass index and body weight at 20 and 40 years of age, change in body-mass index between these ages, and use or nonuse of alcohol and tobacco), the results did not change. Questionnaire responses within twin pairs were unrelated to their prior perceptions of the cause of their breast cancer. When the women were asked to speculate about the causes of breast cancer, “stress” was the most common response, and women from concordant monozygotic pairs were not more likely than others to mention “hormonal factors.” Because of concern about possible nonindependence of responses, we requested the women first to complete the questionnaire independently in black ink and then to use red pens (which were provided) if they wished to change an answer. Twins in less than 1 percent of all the pairs made changes with regard to age at menarche.

The inclusion of pairs in which diagnoses of

breast cancer were ascertained retrospectively could theoretically have resulted in the omission of women with a short survival, provided that the surviving twin preferentially chose not to participate in the study. Such omission appears to have been unlikely, however, since survivors were represented among the participants in expected proportions¹⁶ and, in any case, since women who had died were included by means of proxy information. Moreover, we compared the results from concordant monozygotic pairs identified prospectively with the results from pairs identified retrospectively. Of the 34 concordant monozygotic pairs in which the twins differed according to the early puberty index, 14 were identified before the second case was diagnosed. The adjusted odds ratio for early puberty derived solely from this prospective subgroup (4.9; 95 percent confidence interval, 1.1 to 22.4) is similar to that based solely on the subgroup of pairs identified retrospectively (6.7; 95 percent confidence interval, 1.8 to 25.2).

In a study of twin pairs in Scandinavia and Great Britain that were discordant for breast cancer, more rapid prepubertal growth and earlier breast development were predictive of breast cancer, although small numbers precluded stratification according to genetic risk.²⁴ Age at menarche has been found to predict breast cancer in some studies of women with breast cancer who have a family history of the disease^{25,26} but not in other such studies,^{27,28} and age at menopause has been found to be unrelated to breast cancer in the presence of a family history.²⁹ Even so, such results cannot be directly compared with our findings, since family history alone was used in those studies to identify women with cancer who were at high genetic risk; women with cancer associated with genes of low penetrance and combinations of alleles inherited from different parents would have been excluded.

Thus, a major form of hereditary breast cancer may be triggered by unusual sensitivity to the rush of hormones at puberty. Such a genetic sensitivity to hormone exposure has been observed in rats: estradiol treatment promotes breast cancer only in certain strains.³⁰ Modification of the risk of breast cancer according to age at the time of hormone exposure is also not an unprecedented finding. The carcinogenic action of ionizing radiation on the breast is magnified by early age at exposure,³¹ and the protection against induced breast cancer in rats given genistein, a soy isoflavonoid, is enhanced when it is given before puberty.³²

If a substantial subgroup of women in the general population is at higher risk for breast cancer than the rest of the population because of very early puberty, then as the age at puberty continues to decline in the population, this subgroup may become increasingly prominent. Only when the pertinent genotype or genotypes become known can methods of intervention and detection of hereditary breast cancer be devised. Genomic material from

identical twins who are concordant for disease should greatly facilitate that search.

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