Letter to the Editor

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The *BRCA1/2* Parent-of-Origin Effect on Breast Cancer Risk—Letter

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We were interested to read the recent article in *Cancer Epidemiology, Biomarkers & Prevention* throwing doubt on a parent-of-origin effect in the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers (1). Previous research has suggested that there is a greater risk of breast cancer if the *BRCA1/2* mutation is inherited from the father (2–4). The authors showed that breast cancer was about 1.5-fold more prevalent in women with paternal inherited mutations (1). However, when they adjusted for referral bias by personal history of cancer, the effects disappeared. Ideally, prospective follow-up should provide the most robust data. We analyzed the North-West England BRCA database containing 659 *BRCA1* and 641 *BRCA2* families. We assessed breast cancer incidence in proven female mutation carriers from these families after the date the family was referred. Women were censored at the date of breast cancer, risk reducing mastectomy, death, or last follow-up if still alive. Breast cancer was twice as prevalent in non-index women with paternal inheritance, with 88 of 217 (40.6%) having breast cancer compared with only 199 of 813 (24.5%) of maternal origin. Rates of breast cancer from birth were also nearly twice as high at 9.0 per 1,000 [95% confidence interval (CI), 7.2–11.1] as opposed to 5.7 per 1,000 (95% CI, 4.9–6.6) annually, respectively. Kaplan–Meier analysis showed a significantly higher cumulative breast cancer penetrance ($P = 0.006$). However, when only those unaffected at family ascertainment were included, 75 breast cancers occurred in 649 women of maternal origin in 2,861.5 years (rate = 26/1,000; 95% CI, 20.6–32.8) compared with 28 of 153 of paternal origin in 755.8 years (rate = 37/1,000; 95% CI, 24.6–53.5); however, Kaplan–Meier lost significance ($P = 0.25$). Moreover, when women were only followed up from the date of presymptomatic testing, only 8 breast cancers occurred in 123 of paternal origin in 612.0 years compared with 41 in 593 in maternal-origin in 2,654.8 years. The rates were now nonsignificantly higher in maternal origin at 15/1,000 (95% CI, 11.1–21.0) compared with 13/1,000 (95% CI, 5.6–25.7) in paternal origin ($P = 0.47$). As stated by Vos and colleagues (1), the higher breast cancer rates reported previously are likely due to referral bias, with women with breast cancer being more likely to come forward for testing for the family mutation than unaffected females. The far lower number of women in the paternal origin group may also reflect that unaffected women are less likely to think they are at risk due to family communication issues (5) than those who are at risk on the maternal side. We concur that women should not receive any different advice regarding their breast cancer risk regarding the parental origin of their mutation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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