Short Communication

Effect of Mammography on Breast Cancer Risk in Women with Mutations in *BRCA1* or *BRCA2*

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Abstract

Women who carry mutations in either the *BRCA1* or *BRCA2* genes are at risk for early-onset breast cancer and are recommended to begin screening mammography at age 25 to 30 years. Results of *in vitro* and animal studies suggest that BRCA1/BRCA2 mutation carriers are hypersensitive to ionizing radiation and possibly to radiation-induced breast cancer. This study was undertaken to investigate the association of low-dose radiation exposure from mammograms with breast cancer status in *BRCA* mutation carriers. One hundred sixty-two female mutation carriers provided information at time of genetic testing about exposure to mammograms before enrollment. Using unconditional logistic regression, breast cancer status was not associated with number of mammograms received before diagnosis (affected women) or ascertainment [unaffected women; adjusted odds ratio (OR), 0.94; *P* = not significant]. A larger group of 213 women provided information about lifetime number of mammograms. There was no association between mammogram exposure and risk in the group as a whole (adjusted OR, 1.04; *P* = not significant), although there was a modest association in *BRCA1* carriers (adjusted OR, 1.08; *P* = 0.03). These findings indicate that screening mammography is unlikely to be associated with a large increase in breast cancer risk in this population. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2311–3)

Introduction

Women carrying germ-line mutations in *BRCA1* or *BRCA2* are at risk for early-onset breast cancer (1). Such women currently receive annual mammograms beginning at age 25 to 30 years (2, 3). However, the benefits of mammography in very young women at hereditary risk are not defined and there are concerns that early mammography could increase the risk of cancer. Exposure to radiation has been shown to increase the risk of breast cancer in female atomic bomb survivors as well as in women receiving various forms of diagnostic and therapeutic X-ray exposure (4). *BRCA1* and *BRCA2* gene products are involved in the normal repair of DNA damage of the type caused by ionizing radiation, and *BRCA*-deficient cells are hypersensitive to radiation (5). Some studies have noted abnormalities in the DNA damage response in cells harboring a single mutated copy of *BRCA1* or *BRCA2* (1, 6-8), suggesting that radiation sensitivity may not require loss of both alleles. Other studies have not shown a phenotype associated with haploinsufficiency (9-11), and a clear connection between *in vitro* radiosensitivity and a clinical predisposition to breast cancer from low-dose radiation exposure has not been established. To evaluate the possibility of such a connection, we examined the risk of breast cancer associated with mammogram exposure before genetic testing in women with deleterious *BRCA* mutations.

Materials and Methods

The subjects of this study are 213 *BRCA* mutation carriers identified at Memorial Sloan-Kettering Cancer Center (New York, NY) and at Hospital Sant Pau (Barcelona, Spain). All women received appropriate pretest genetic counseling and provided informed consent for testing. Before undergoing testing, women completed a baseline questionnaire, which included questions describing their participation in mammogram screening before enrollment. At Memorial Sloan-Kettering Cancer Center, the questionnaire was administered as part of Institutional Review Board–approved follow-up studies of women at hereditary risk conducted between January 1995 and December 2004. It included questions pertaining to the age at first mammogram, lifetime number of mammograms, and number of mammograms received in the preceding 12 months. Exposure before the diagnosis of breast cancer was calculated by subtracting the reported number of mammograms received in the year before enrollment from the lifetime total number of mammograms. This calculation was only done for women who completed the baseline questionnaire within 1 year of their breast cancer diagnosis. In Barcelona, the questionnaire was completed as part of the baseline clinical assessment between January 1996 and December 2004. Women directly reported the number of mammograms that they had received before diagnosis (if affected) or before enrollment (if unaffected). Postdiagnosis mammograms were not reported in Barcelona.

Results

The subjects of this report were all carriers of clearly deleterious mutations (121 BRCA1 and 92 BRCA2). The median age at ascertainment was 43 years (range, 25-73)

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Table 1. Association between breast cancer status and number of mammograms before diagnosis (affected within 1 year of enrollment) or questionnaire (unaffected)

Gene	Affected carriers (*n*)	Unaffected carriers (*n*)	OR (95% CI)*	*P*
BRCA1 and *BRCA2* combined	34	128	0.94 (0.88-1.00)	0.06
BRCA1	17	69	0.99 (0.90-1.10)	0.84
BRCA2	17	59	0.91 (0.83-1.00)	0.06

*OR adjusted for age at diagnosis (affected) or questionnaire (unaffected).

among the 85 women with breast cancer and 45 years (range, 20-77 years) among the 128 women without breast cancer. The median age at diagnosis for the affected *BRCA1* carriers was 41 years (range, 24-72) and 42 years (range, 24-82) for the affected *BRCA2* carriers. Exposure to mammography before ascertainment was reported by 190 (89%) women. For both affected and unaffected women, the median age at first mammogram was 35 and the median number of mammograms before ascertainment was 8. The median time from first mammogram, for those who had received one before ascertainment, was 11 years (maximum, 36) in affected women and 12 years (maximum, 58) in unaffected women. The median number of mammograms received >5 years before ascertainment was only available for the New York cohort and was 2.0 in women with breast cancer and 3.5 in women without cancer.

Unconditional logistic regression, adjusted for age at ascertainment, was done to assess the association between breast cancer status and the number of mammograms received before diagnosis (affected women) or enrollment (unaffected women) in the 162 subjects for whom this information was available (Table 1). There was no significant association between cancer status and mammogram exposure [odds ratio (OR), 0.94; 95% confidence interval (95% CI), 0.88-1.00; two-sided $P = 0.06$]. No statistically significant association was noted when the analysis was stratified by mutation carrier status (*BRCA1* or *BRCA2*) or by age (>40 or <40 years at diagnosis or ascertainment). A second analysis was done to assess the association between breast cancer status and lifetime total number of mammograms. In this analysis, there was no significant association between cancer status and total mammogram exposure in the group as a whole (adjusted OR, 1.04; 95% CI, 0.99-1.09; P = not significant) or in *BRCA2* carriers (adjusted OR, 0.98; 95% CI, 0.89-1.07; P = not significant). A significant association was observed in *BRCA1* carriers (adjusted OR, 1.08; 95% CI, 1.01-1.16; $P = 0.03$).

Discussion

BRCA mutation carriers are recommended to begin breast cancer screening with annual mammography at age 25 to 30 years. The published literature is conflicting about the risk of developing breast cancer for BRCA mutation carriers associated with exposure to radiation from diagnostic X-rays, particularly mammograms. Diagnostic chest X-ray exposure was associated with increased breast cancer risk in one study (12). However, screening mammography was not associated with increased risk in another report (13). The present study provides some reassurance. Detailed information about mammogram exposure was obtained before genetic test results were known, minimizing possible recall bias. The primary analysis did not show an excess risk for carriers associated with mammogram exposure before diagnosis (for affected women) or enrollment (for unaffected women). Our method of estimating prediagnostic mammogram exposure was conservative and could underestimate the true exposure in affected women. We therefore also examined the association between cancer status and total lifetime exposure in an expanded cohort, which includes diagnostic and postdiagnostic mammograms. This would tend to overestimate an association with mammography (because the postdiagnostic exposures could not have contributed to the development of cancer). An association between cancer status and lifetime mammogram exposure was observed in *BRCA1* carriers but not in the group as a whole. As this association was not observed when diagnostic and postdiagnostic mammograms were excluded, this effect may be an artifact of including incremental exposures after cancer diagnosis and not a causal association with prediagnostic screening mammograms.

These data suggest that low-dose radiation exposure from screening mammography is unlikely to induce large numbers of breast cancers in women with *BRCA* mutations. A post hoc power calculation using a normal approximation method indicates that the analysis of the effect of mammogram exposure before ascertainment or diagnosis has an 80% power to detect an OR of 1.35. The combined analysis of risk associated with lifetime mammogram exposure has an 80% power to detect an OR of 1.2. Although the current sample size is sufficient to identify modest risks, larger confirmatory studies would allow assessment of potentially important covariates, such as year of ascertainment and specific mutation position within *BRCA1* or *BRCA2*.

Several studies have shown incremental cancer detection by mammography in programs based on breast magnetic resonance imaging (14, 15). Without affirmative evidence of a significant increase in radiation-induced cancer, this modality should continue to be part of a breast cancer surveillance program for women at hereditary risk.

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