Mammographic Density and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers


Abstract

High breast density as measured on mammograms is a strong risk factor for breast cancer in the general population, but its effect in carriers of germline BRCA1 and BRCA2 mutations is unclear. We obtained mammograms from 206 female carriers of BRCA1 or BRCA2 mutations, 96 of whom were subsequently diagnosed with breast cancer and 136 relatives of carriers who were themselves noncarriers. We compared the mammographic densities of affected carriers (cases) and unaffected carriers (controls), and of mutation carriers and noncarriers, using a computer-assisted method of measurement and visual assessment by two observers. Analyses were adjusted for age, parity, body mass index, menopausal status, and hormone replacement therapy use. There was no difference in the mean percent density between noncarriers and carriers. Among carriers, increasing mammographic density was associated with an increased risk of breast cancer ($P_{\text{trend}} = 0.024$). The odds ratio (OR; 95% confidence interval) for breast cancer associated with a density of $\geq 50\%$ was 2.29 (1.23-4.26; $P = 0.009$). The OR did not differ between BRCA1 and BRCA2 carriers or between premenopausal and postmenopausal carriers. The results suggest that the distribution of breast density in BRCA1 and BRCA2 carriers is similar to that in noncarriers. High breast density in carriers is associated with an increased risk of breast cancer, with the relative risk being similar to that observed in the general population. Use of mammographic density could improve individual risk prediction in carriers. (Cancer Res 2006; 66(3): 1866-72)

Introduction

Numerous epidemiological studies have shown that breast density as measured on mammograms is a risk factor for breast cancer. The risk of breast cancer associated with the highest category of density has been estimated to be two to six times greater than in the lowest density category (1–8). Increasing density is associated with increasing breast cancer risk in both premenopausal and postmenopausal women, with the effect persisting for $\geq 10$ years after mammography (9).

Mammographic density has also been shown to be a risk factor for breast cancer in women with family history of the disease (10). This raises the question of whether mammographic density is also a risk factor in carriers of germline mutations in the major breast cancer susceptibility genes BRCA1 and BRCA2. These mutations confer high lifetime risks of breast cancer (11). If mammographic density were a risk factor for breast cancer in carriers, it would therefore have important implications for the counseling and management of such women.

In addition, analysis of twin data has indicated that mammographic density is strongly determined by genetic factors (12). This raises the question of whether BRCA1 or BRCA2 carrier status itself
Materials and Methods

Patients were recruited through the Epidemiological Study of BRCA1 and BRCA2 mutation carriers (EMBRACE). This ongoing epidemiological study of BRCA1 and BRCA2 mutation families in the United Kingdom and Ireland (http://www.srl.cam.ac.uk/genepri/embraceindex.htm). Women and men can participate in EMBRACE if (a) they are carriers or noncarriers from known BRCA1 and BRCA2 mutation-positive families, (b) they have undergone or are undergoing testing for BRCA1 and BRCA2 mutations, or (c) they have declined BRCA genetic testing but have been counseled at a genetic clinic. Both affected and unaffected individuals are eligible to participate in the study. All participants must be >18 years old and must give written informed consent. They are requested to complete a baseline questionnaire, which includes questions on lifestyle factors, menstrual history, pregnancies, and past medical history. Individuals are followed prospectively and further questionnaires are administered at 2 and 5 years after baseline. Subsequent cancer occurrence is notified through the Office of National Statistics. The study was approved by the Eastern Multicentre Ethics Committee.

For the present study, we identified female carriers and noncarriers from the seven largest EMBRACE recruiting centers: Manchester Regional Genetics Service; Department of Cancer Genetics; Royal Marsden NHS Hospital; Wessex Clinical Genetics Service; Northern Clinical Genetics Service; East Anglian Regional Genetics Service; South East Thames Regional Genetics Service; and West Midlands Regional Clinical Genetics Service. All individuals had undergone a specific test for the mutation segregating within their family, so that their carrier status was known. We attempted to obtain mammograms from all individuals in the study regardless of disease status.

For each individual, we aimed to collect the earliest available mammograms together with the latest available mammograms before any breast cancer diagnosis. Where no other mammogram was available, a mammogram taken at the time of breast cancer diagnosis was used, but only the breast contralateral to that with the tumor was used. The mammogram from the affected breast was also excluded from density scoring for any mammographic procedure done within 6 months of diagnosis. No mammograms after breast cancer diagnosis were included. Mammograms were located using information from the questionnaire together with records in the clinical genetics departments. Usually, two films were available of each breast from two different angles (i.e., cranio-caudal and mediolateral oblique). Films were requested from the relevant radiology department, which forwarded the mammograms to the study and were digitized on a Vidar digitizer at the Cambridge Breast Unit, Addenbrookes Hospital.

Measuring mammographic density. Mammographic density was scored using three methods. Two observers (any two of R.W., R.D., and G.M.) scored all available mammograms (early and late, right and left breast sides, and cranio-caudal and mediolateral oblique) using the four-category Wolfe scoring system (17) and the Boyd six-point quantitative scale (18). Density was also assessed by two readers (J.B. and R.W.) using a computer-assisted method, CUMULUS (1, 19). In this method, digitized images were displayed on screen and thresholds were set to define the edge of breast and the edge of the dense area. The software then computes the total area and the area of dense tissue. Analyses were based on the estimate of the percentage of breast area that is dense tissue. Because oblique views (mediolateral oblique) are consistently available in the United Kingdom but cranio-caudal views are sometimes not available, these analyses were based on mediolateral oblique views. The readers were blinded as to the carrier and affection status of the individual to whom the mammogram belonged. All readings were also made independently for each breast side. For the purpose of this report, the computerized continuous scores were regarded as the primary analysis because it is widely used and provides a fully quantitative measure of density. The Wolfe scores were also used because they have also been widely used in other studies and provide a different classification based on parenchymal patterns. The six-point visual Boyd scores have not been reported here.

The present analyses were based on a total sample of 426 individuals for whom mammographic data were available. Two hundred fifty-one of these were carriers of deleterious mutations in BRCA1 or BRCA2 (157 BRCA1, 93 BRCA2, and 1 carrier of both mutations) and 175 noncarriers. Mutations were regarded as deleterious if they would be predicted to lead to a truncated protein or were missense variants classified as deleterious by the Breast Cancer Information Core (http://research.nhgri.nih.gov/projects/bic). Epidemiological data were not available for 20 subjects and these were excluded, leaving 406 individuals for analysis.

Definition of disease status. Individuals were considered to be affected (cases) if they had developed cancer and no other cancer or breast cancer before any other cancer. These were censored at the date of the first breast cancer (106 in total). Individuals with no personal history of cancer were assumed to be unaffected (controls) and were censored at the questionnaire date (n = 250). If the individuals had developed breast cancer after another type of cancer, they were censored at the first cancer and were assumed to be unaffected (7 in total). For 6 of these, however, no mammogram was available before the first cancer and these did not contribute to the analyses. Individuals who had not developed breast cancer but had developed another type of cancer were censored at the date of the first cancer and were treated as unaffected (n = 40). Individuals with no information from medical records on the first type of cancer (other than breast) were censored at the self-reported age of the first cancer and were also assumed to be unaffected (3). Thirty-three individuals for whom the mammographic screening took place after the occurrence of cancer (any type) were excluded from the analyses because cancer treatment might alter breast density. In total, there were 221 BRCA1 and BRCA2 mutation carriers (118 unaffected and 103 affected) and 152 noncarriers (149 unaffected and 3 affected). Note that few affected noncarriers were included in this study because most affected individuals in families in which a mutation has been identified are themselves carriers.

For the computerized score analyses, a particular reading was included in the analysis only if the digitized image had been scored by both readers. This was not possible for all mammograms because the “edge” of the breast area could not be defined due to poor quality of the image. After these exclusions, 206 carriers (110 unaffected and 96 affected; 93 with invasive breast cancer and 3 with ductal carcinoma in situ) and 136 noncarriers (133 unaffected and 3 affected, all invasive) contributed in the analyses of the computer-assisted scores. These individuals had at least one mammographic reading using the computerized method for at least one breast side. One hundred sixty-three of those individuals (92 carriers and 71 noncarriers) had also further computerized readings at a later age, which were eligible for inclusion in the analyses.

Statistical methods. The primary analyses involved the quantitative measure of density derived using the computer-assisted method. As described above, the study included mammograms taken at one or two different time points for each participant. For each age, a single measure of density was derived representing the average percentage of the area that is dense over the available breast sides (right and left) and over the two readers (R.W. and J.B.). A categorical variable with five levels was also derived from the “average density” variable, representing different categories of breast density: 0 to <10%, 10% to <25%, 25% to <50%, 50%
for this, mutation carriers were assigned weights such that the observed incidence rates among the carriers in the study sample are consistent with established breast cancer risk estimates for BRCA1 and BRCA2 carriers(11). A weighted linear regression was therefore carried out, assuming the computed weights for mutation carriers and a weight of 1 for all noncarriers. This approach is described in detail elsewhere (22). Probability plots were used to assess the normality assumption for the residuals and the residuals were plotted against the predicted values to investigate any systematic trends.

All the analyses were adjusted for gene, age at mammographic screening, body mass index (BMI), parity at screening, menopausal status at screening, and hormone replacement therapy (HRT) use, because these factors are associated with both breast cancer risk and mammographic density. Use of tamoxifen was not included because only three women were known to have been participants in a tamoxifen prevention trial (International Breast Cancer Intervention Study) before the date of a mammogram scored in the analysis. Age at mammographic screening was coded as a categorical variable with the following levels: <30, 30-34, 35-39, 40-44, 45-49, 50-54, and ≥55. BMI was assumed to be a continuous covariate and was based on the height and weight reported by the study participants at the baseline questionnaire. Parity at screening was coded as a binary variable, indicating whether the individual had had a live birth by that age. Menopausal status was coded as a covariate with four levels representing the menopausal status in relation to the age at mammographic screening: (a) premenopausal; (b) natural menopause or menopause due to bilateral oophorectomy; (c) menopause for other reasons, including radiotherapy, medication, or reason not given; and (d) unknown menopausal status because of hysterectomy without bilateral oophorectomy or because the menopausal status had not been reported. However, for the analyses, categories a and c were grouped, and individuals with unknown menopausal status were considered menopausal if they were ≥55 years old at screening and premenopausal otherwise. Finally, HRT use was coded as a binary variable representing whether an individual had ever used HRT by the age at mammographic screening. BMI, parity, menopausal status, and HRT use were based on information provided at the baseline questionnaire. Although the information did not correspond to the age at mammographic screening, it was the only available information on other risk factors. Analysis of the

### Table 1. Characteristics of the women used in the main analyses of the computerized scores for mammographic density

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BRCA1/BRCA2 carriers</th>
<th>Noncarriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unaffected</td>
<td>Breast cancer cases</td>
</tr>
<tr>
<td>Individuals</td>
<td>110</td>
<td>96</td>
</tr>
<tr>
<td>Observations</td>
<td>175</td>
<td>123</td>
</tr>
<tr>
<td>Age at censoring, mean (SD)</td>
<td>43.9 (10.0)</td>
<td>42.8 (7.9)</td>
</tr>
<tr>
<td>Age at screening, mean (SD)*</td>
<td>43.0 (9.7)</td>
<td>42.3 (7.5)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.8 (5.6)</td>
<td>26.3 (4.5)</td>
</tr>
<tr>
<td>Parous at screening,* n (%)</td>
<td>36 (20.6)</td>
<td>18 (14.6)</td>
</tr>
<tr>
<td>No</td>
<td>36 (20.6)</td>
<td>18 (14.6)</td>
</tr>
<tr>
<td>Menopause at screening,* n (%)</td>
<td>139 (79.4)</td>
<td>105 (85.4)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>111 (63.4)</td>
<td>92 (74.8)</td>
</tr>
<tr>
<td>Menopausal 1 †</td>
<td>42 (24.0)</td>
<td>19 (15.4)</td>
</tr>
<tr>
<td>Menopause 2 ‡</td>
<td>7 (4)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (8.6)</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>HRT use at screening,* n (%)</td>
<td>142 (81.1)</td>
<td>104 (84.6)</td>
</tr>
<tr>
<td>Never</td>
<td>142 (81.1)</td>
<td>104 (84.6)</td>
</tr>
<tr>
<td>Ever</td>
<td>33 (18.9)</td>
<td>19 (15.4)</td>
</tr>
</tbody>
</table>

*Corresponds to all observations.
† Natural or bilateral oophorectomy.
‡ Other reasons, including radiotherapy, medication, or reason not given.
Table 2. Distribution of percent breast density among mutation carriers diagnosed with breast cancer and unaffected carriers

<table>
<thead>
<tr>
<th>% Dense breast area</th>
<th>Unaffected*</th>
<th>Affected*</th>
<th>OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;50</td>
<td>110</td>
<td>53</td>
<td>1.00</td>
</tr>
<tr>
<td>≥50</td>
<td>65</td>
<td>70</td>
<td>2.29 (1.23-4.26)</td>
</tr>
<tr>
<td>0 to &lt;10</td>
<td>20</td>
<td>10</td>
<td>1.00</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>31</td>
<td>16</td>
<td>1.17 (0.35-3.93)</td>
</tr>
<tr>
<td>25 to &lt;50</td>
<td>59</td>
<td>27</td>
<td>0.92 (0.30-2.89)</td>
</tr>
<tr>
<td>50 to &lt;75</td>
<td>64</td>
<td>66</td>
<td>2.27 (0.70-7.39)</td>
</tr>
<tr>
<td>≥75</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Number of observations, including repeated measurements on the same individual.
†Categories 50 to <75 and ≥75 grouped together. All analyses adjusted for age at mammography, BMI, parity at mammography, menopausal status at mammography, HRT use by the age at mammography, and gene.

Wolfe scores was additionally adjusted for the radiologist to correct for any systematic differences in scoring the mammograms. All statistical tests were two sided.

Agreement in the scoring between readers was assessed through correlation coefficients for the computerized method and via weighted κ coefficients for the Wolfe scoring system. All analyses were carried out using the Statistical Package Stata version 8 (Stata Corp., College Station, TX).

Results

The number of women used in the main analyses of the computerized mammographic density scores and a summary of their characteristics are shown in Table 1. In total, there were 110 unaffected (control) carriers (72 BRCA1 and 38 BRCA2) and 96 carriers (52 BRCA1 and 44 BRCA2) who had developed breast cancer (cases). Sixty-five of the unaffected carriers, 27 of the breast cancer patients, and 71 of the noncarriers had mammograms at two different time points. Both the mean age at censoring and the mean age at scored mammogram were significantly higher in noncarriers than in carriers (mean difference, 3.80, P = 0.001 and 3.17, P < 0.001, respectively). However, there were no significant differences in these ages between affected and unaffected mutation carriers. There were no significant differences in BMI, parity, menopausal status, or HRT use between carriers and noncarriers or between affected and unaffected mutation carriers. The 206 mutation carriers came from 177 distinct families and the total number of 342 carriers and noncarriers came from 263 distinct families. Analyses allowing for familial clustering of mammographic density produced results that were virtually identical to the results when no such allowance was made and are therefore not reported.

The correlation in the percentage of mammographically dense tissue between left and right breasts was estimated to be 0.83 and 0.87 for readers J.B. and R.W., respectively. The correlation between J.B. and R.W. for the average percentage of dense tissue (over the left and right breasts) was 0.88, indicating very good agreement in the scores between the two readers. For the subsequent analyses, we used the average percentage of dense area over the scores of the two readers.

Mammographic density and breast cancer risk in carriers. Table 2 shows the distribution of average mammographic density among unaffected carriers and BRCA1/BRCA2 mutation carriers who have developed breast cancer. When analyzed as a continuous covariate, a 1% increase in mammographic density in carriers was estimated to increase the OR [95% confidence interval (95% CI)] for breast cancer risk by 2.0% (0.3-3.8%; P trend = 0.024). The OR (95% CI) for the risk of breast cancer in BRCA1 and BRCA2 carriers with density ≥50% compared with carriers with density <50% was 2.29 (1.23-4.26; P = 0.009). There was no evidence of a difference in risk between women with <25% versus 25% to 50% density.

Table 3 shows the results when the BRCA1 and BRCA2 mutation carriers were considered separately. Among BRCA1 mutation carriers, the OR (95% CI) for risk of breast cancer in women with density ≥50% relative to women with density <50% was 2.77 (1.15-6.67; P = 0.023). A 1% increase in breast density among BRCA1 mutation carriers was estimated to increase the OR (95% CI) for breast cancer risk by 2.9% (0.5-5.3%; P = 0.016). Among BRCA2 mutation carriers, the OR (95% CI) for the ≥50% dense category relative to the <50% dense category was 2.24 (0.84-6.00; P = 0.11). A 1% increase in density among BRCA2 carriers was estimated to increase the OR (95% CI) for breast cancer risk by 0.9% (−1.7% to 3.6%).

The association between breast density and disease status according to their menopausal status at censoring is also shown in Table 3. Breast density ≥50% was associated with a similar OR in premenopausal women (OR, 2.58; 95% CI, 1.25-5.35) and postmenopausal women (OR, 2.49; 95% CI, 0.70-8.81). Similarly, there was no significant interaction between mammographic density and age at mammographic screening (data not shown).

To address the possibility that some of the association between density and breast cancer risk might be related to the development or diagnosis of the tumor, we further analyzed the data by excluding all mammograms that were taken within 1 year before the diagnosis

Table 3. Distribution of mammographic density by mutation type and menopausal status at censoring

<table>
<thead>
<tr>
<th>% Dense breast area</th>
<th>Unaffected*</th>
<th>Affected*</th>
<th>OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;50</td>
<td>69</td>
<td>27</td>
<td>1.00</td>
</tr>
<tr>
<td>≥50</td>
<td>44</td>
<td>36</td>
<td>2.77 (1.15-6.67)</td>
</tr>
<tr>
<td>BRCA2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;50</td>
<td>41</td>
<td>26</td>
<td>1.00</td>
</tr>
<tr>
<td>≥50</td>
<td>21</td>
<td>34</td>
<td>2.24 (0.84-6.00)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;50</td>
<td>58</td>
<td>28</td>
<td>1.00</td>
</tr>
<tr>
<td>≥50</td>
<td>45</td>
<td>53</td>
<td>2.58 (1.25-5.35)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;50</td>
<td>43</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>≥50</td>
<td>14</td>
<td>16</td>
<td>2.49 (0.70-8.81)</td>
</tr>
</tbody>
</table>

*Number of observations, including repeated measurements on the same individual.
†All analyses adjusted for age at mammography, BMI, parity at mammography, and HRT use by the age at mammography. Analyses by gene corrected for menopausal status. Analyses by menopausal status excluded carriers of unknown menopausal status and were corrected for gene.
of breast cancer. After these exclusions, there were 225 observations in 149 carriers. Carriers with mammographic density ≥50% had OR (95% CI) of 2.67 (1.20-5.94) of developing breast cancer compared with carriers with breast density <50% and an OR (95% CI) of 5.94 (0.98-35.98) compared with carriers with breast density <10%. A 1% increase in density was estimated to result in 3.4% increase in the OR (95% CI) for breast cancer (0.8-6.1%; P_trend = 0.010). Thus, the association between density and breast cancer risk was somewhat stronger than in the analysis of the complete data set.

**Wolfe scoring system.** Further analyses were done using the four-point Wolfe method for scoring parenchymal patterns. The majority (98%) of these readings were done by two radiologists (R.D. and R.W.). The weighted κ coefficient between these two readers was 0.70, indicating substantial agreement between the radiologists. Consistent with the computer-assisted analyses, higher density was associated with increased cancer risk (Table 4; P_trend = 0.035). The OR (95% CI) of breast cancer for individuals in the DY category relative to the N1 was 2.78 (1.00-7.72).

**Carrier status and mammographic density.** The results of the weighted and unweighted linear regression analyses for the effect of carrier status on mammographic density are shown in Table 5. A total of 505 mammographic readings from 342 individuals were used in the analyses. We found no significant association between BRCA1 or BRCA2 mutation carrier status and mammographic density. When the carrier status was the only variable included in the linear regression, mammographic density was estimated to be slightly but not significantly higher among BRCA1/BRCΑ2 mutation carriers than noncarriers. After adjustment for age at screen, BMI, parity, menopausal status, and HRT use, the mean density was slightly lower in carriers than noncarriers. This difference became slightly larger in the weighted analysis, but the difference was still small and nonsignificant. When stepwise backward estimation was carried out on the full model (all covariates included), only age at mammography, BMI, and menopausal status were significant at the 5% level (R² = 0.33, under weighted model). Similarly, no significant differences in mean density between carriers and noncarriers were observed when BRCA1 and BRCA2 carriers were considered separately (mean difference in percent density between noncarriers and carriers in adjusted weighted analysis, 2.9% and 0.3% for BRCA1 and BRCA2, respectively).

**Discussion**

In the present study, we have evaluated the evidence for association between mammographic density and risk of developing breast cancer among BRCA1 and BRCA2 mutation carriers. We found significant evidence of increasing breast cancer risk with increasing density when this was assessed using a computerized method for estimating the percentage of breast area occupied by mammographically dense tissue. The OR for breast cancer among female carriers with ≥50% dense breasts compared with carriers with <50% dense breasts was estimated to be 2.29. The OR did not differ between BRCA1 and BRCA2 mutation carriers, although the association was slightly weaker and not significant in BRCA2 carriers. However, the number of BRCA2 mutation carriers in our sample was limited. Similarly, there was no difference in the OR between premenopausal and postmenopausal carriers. The association was not significant in postmenopausal carriers alone, but the number of postmenopausal women was small. To avoid the possibility that the association might be an artifact related to the development or diagnosis of the tumor, we repeated the analyses, excluding all mammograms within 1 year before diagnosis, but the estimated ORs increased. Exclusion of the single individual censored at the diagnosis of a cancer other than breast cancer, before a breast cancer diagnosis, also made no difference to the estimated ORs.

Our results indicate that the relative risk of breast cancer associated with high mammographic density in carriers is similar to that seen in studies in the general population (1, 5, 9, 23–26). Such studies have also estimated that women having breasts that are >75% dense have ORs of 5 to 6 of developing the disease compared with women with fatty breasts (1, 9, 27). We were not able to evaluate the risk difference between these two extreme categories in our data because of the small number of individuals with >75% dense breasts. We also found a significant trend in breast cancer risk associated with the Wolfe classification of mammographic patterns. The estimated OR associated with the DY pattern (2.78) was again similar to that seen in general population studies (5, 9, 23, 25, 28). To our knowledge, this is the first study that has investigated the variation in breast cancer risk by mammographic density in BRCA1 and BRCA2 mutation carriers.

We found no evidence of a difference in mammographic density between BRCA1 or BRCA2 mutation carriers and noncarriers—the 95% CI excluded a 6.5% difference in mean density. Our results agree with those from two smaller studies, which investigated this issue (14, 16). Two other studies reported that BRCA1/BRCΑ2 mutation carriers may be associated with higher mammographic densities than women from the general population (13, 15). Huo et al. (15) compared digitized mammograms of 30 carriers (among whom 16 had developed breast cancer) with the mammograms of a group of women at low risk of developing breast cancer using linear discriminant analysis. However, their results could be biased because there was no correction for the fact that the sample of carriers included women who developed breast cancer. Chang et al. (13) compared the preoperative mammograms for density between 9 BRCA1 affected carriers and 19 breast cancer cases without mutations. However, they did not correct for any other covariates (we observed a similar increased density in the unadjusted model).

A potential limitation of our study is the fact that the mammograms were obtained retrospectively in some cases several years before the baseline questionnaire. Therefore, some of the covariates used in our models might not correspond exactly to the age at mammographic screening, most notably BMI. However, our results have shown the association between BMI and density to be

<table>
<thead>
<tr>
<th>Density category</th>
<th>Unaffected*</th>
<th>Affected*</th>
<th>OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>199</td>
<td>84</td>
<td>1.00</td>
</tr>
<tr>
<td>P1</td>
<td>145</td>
<td>37</td>
<td>0.58 (0.25-1.34)</td>
</tr>
<tr>
<td>P2</td>
<td>542</td>
<td>244</td>
<td>1.01 (0.40-2.52)</td>
</tr>
<tr>
<td>DY</td>
<td>188</td>
<td>224</td>
<td>2.78 (1.00-7.72)</td>
</tr>
</tbody>
</table>

*Number of observations, including repeated measurements on the same individual. † All analyses adjusted for age at mammography, BMI, parity at mammography, menopausal status at mammography, and HRT use by the age at mammography and reader.
significant and similar to that observed previously (29). Moreover, BMI did not seem to be related to the disease status in our study. Adjustment for BMI or the other risk factors made little difference to the risk estimates.

The etiological basis of mammographic density and its association with breast cancer remains poorly understood. Breast density reflects the proportion of breast tissue that is epithelial or stromal rather than fatty, and the association with breast cancer risk may partly reflect the amount of at-risk mitotically active tissue. The reduction in breast density at menopause and the association with HRT use indicate that hormonal exposure is an important determinant of breast density (30). However, although mammographic density reduces with age, the major determinants of density seem to be genetic; a recent study of MZ and DZ twins estimated that ~60% of the variation in density could be attributable to genetic factors (12). To date, no genes strongly related to mammographic density have been identified, although several associations have been suggested. Such genes would also be predicted to be associated with breast cancer risk; Boyd et al. (12) estimate that such genes might account for ~20% of the familial risk of breast cancer. A plausible model, therefore, is that these genes also modify the breast cancer risk in BRCA1 and BRCA2.

### Table 5. Linear regression results for the effect of BRCA1/BRCA2 mutation status on percentage dense tissue

<table>
<thead>
<tr>
<th>Variables included</th>
<th>Unweighted</th>
<th></th>
<th></th>
<th>Weighted</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate † (95% CI)</td>
<td>P</td>
<td>R²</td>
<td>Estimate † (95% CI)</td>
<td>P</td>
<td>R²</td>
</tr>
<tr>
<td>Carrier status</td>
<td>1.64 (-3.03 to 6.31)</td>
<td>0.490</td>
<td>0.002</td>
<td>0.78 (-4.23 to 5.79)</td>
<td>0.761</td>
<td>0.000</td>
</tr>
<tr>
<td>Full model †</td>
<td>-1.21 (-5.09 to 2.67)</td>
<td>0.541</td>
<td>0.327</td>
<td>-2.15 (-6.20 to 1.90)</td>
<td>0.298</td>
<td>0.336</td>
</tr>
</tbody>
</table>

*The variables included in the linear regression model.
† Coefficient associated with being a mutation carrier.
‡ Full model includes in addition to carrier status, age at mammographic screening, BMI, parity at screening, menopausal status at screening, and HRT use by screening.

**Figure 1.** Predicted cumulative risk of breast cancer within 10 years of mammography for an unaffected BRCA1 mutation carrier at ages 35, 45, and 55 years by mammographic density. These estimates are based on the following assumptions: (a) that the BRCA1 breast cancer risks reported by Antoniou et al. (11) represent the average risks over all density categories; (b) the distribution of density among carriers is equal to that observed in this study, weighted to adjust for oversampling of affected individuals (see text); and (c) that the estimated OR of 2.29 for mammographic density approximates the relative hazard over this 10-year period.
carriers to a similar relative extent as in the general population. Our results also indicate that these breast density genes do not include BRCA1 and BRCA2 themselves.

Breast density has also been suggested as an early marker of response in prevention trials. In particular, tamoxifen is known to reduce breast density, and exposure to dietary phytosterogens, which may be protective against breast cancer, is also associated with a reduction in breast density (30–33). Our results suggest that breast density may also be a useful marker of response in mutation carriers.

Although several other breast cancer risk factors are known, their effect on breast cancer in studies of carriers is modest and conflicting. In contrast, mammographic density provides a risk factor that is easy to measure and may have a marked influence on subsequent breast cancer risk. For example, consider an unaffected 35-year-old BRCA1 carrier. According to the risks estimated by Antoniou et al. (11) from population-based studies, the risk of breast cancer over the subsequent 10 years is ~20%. If we assume that our estimated OR of 2.29 for the effect of mammographic density approximates the relative hazard over this 10-year period, the estimated breast cancer risk by age 45 years would be 13% in women with <50% density and 27% for women with ≥50% density (Fig. 1). Such differences may be sufficient to influence clinical management. Moreover, given the associations observed in the general population, it is likely that larger differences in the risk estimates will be obtained for women with density measurements in the tails of the distribution. However, larger studies will be needed to determine the precise quantitative relationship with risk, and prospective studies of carriers will also be needed to examine the relationship between mammographic density and breast cancer risk longitudinally.

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**References**


Mammographic Density and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers


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