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Letter to *Blood*

TO THE EDITOR:

Increased prevalence of *BRCA1/2* mutations in women with macrotextured breast implants and anaplastic large cell lymphoma of the breast

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Women with a germline mutation in the *BRCA1* or *BRCA2* genes have high cumulative risks of developing breast cancer before the age of 80 years (ie, ~72% and 69%, respectively).[1] To reduce risk, an increasing proportion of *BRCA1/2* mutation carriers opt for preventive mastectomy and reconstruction with breast implants. However, breast implants are associated with a strongly increased relative risk (odds ratio = 400) of anaplastic large-cell lymphoma (BIA-ALCL), with a low absolute risk of 1/7000 at age 75 years.[2-4] Host susceptibility factors for BIA-ALCL are largely unknown. As we observed several women with *BRCA1/2* mutations, implants and BIA-ALCL, we examined whether *BRCA1/2* mutation carriership increases the risk of BIA-ALCL in women with implants.

In December 2018, we identified 49 confirmed cases of BIA-ALCL (median age, 55 years; range, 29-75) via the Dutch nationwide Pathology Database; methods were detailed previously.[2] Reasons for breast implants were cosmetic (n = 32), reconstruction after breast cancer surgery (n = 15), or prophylactic mastectomy (n = 2). All BIA-ALCL cases with reconstruction after breast cancer received macrotextured implants, whereas cosmetic cases received other implant types (Table 1). Median interval between insertion of implants to development of BIA-ALCL was 11 years (range, 3-39). Based on medical records of all BIA-ALCL cases, 6 women had *BRCA1/2* mutations (*BRCA1*, n = 4; *BRCA2*, n = 2). Of the 15 BIA-ALCL cases following breast cancer reconstruction, 4 (26.7%; 95% confidence interval [95% CI], 7.8-55.1) carried *BRCA1/2* mutations (median age at breast cancer diagnosis, 51; range, 26-60) (Table 1). To further examine the prevalence of *BRCA1/2* mutation carriers in our cohort, we analyzed germline DNA from 18/49 women with BIA-ALCL (supplemental Methods, available on the *Blood* Web site). Biopsy material of 1 of 6 known *BRCA1/2* mutation carriers was included and the mutation confirmed. No germline mutations were observed in the remaining women. Therefore, the prevalence of *BRCA1/2* mutations in our entire BIA-ALCL series is at least 12.2% (6/49; 95% CI, 4.6-24.8).

We compared the 26.7% prevalence of *BRCA1/2* mutations in BIA-ALCL cases after reconstruction for breast cancer (~30% of our cohort) with the expected prevalence, based on recently published age-specific prevalence rates of *BRCA1/2* mutations in an unselected Dutch breast cancer cohort diagnosed before 50 years.[5] However, 8/15 women in our cohort were diagnosed with breast cancer after age 49 (median age, 54; range, 50-60). Because no literature is available on *BRCA1/2* prevalence for this age group, we chose to apply the estimate for women aged 45 to 49 years as the best available approximation (Table 2).[5] Based on these data, 5.1% (95% CI 4.6-5.7) of BIA-ALCL cases with breast implants after breast cancer surgery would be expected to carry a *BRCA1/2* mutation.[5] This is significantly lower than our observed estimate of 26.7% (P = .006). Because the prevalence of *BRCA1/2* mutations decreases with older age at breast cancer diagnosis,[5,6] the calculated expected 5.1% prevalence overestimates the true expected *BRCA1/2* prevalence in breast cancer patients in our cohort of women with BIA-ALCL, rendering the true difference with our observed prevalence an underestimation.

Subsequently, to determine the risk of BIA-ALCL in *BRCA1/2* mutation carriers and noncarriers, we calculated the expected proportion of *BRCA1/2* mutations in women with breast implants in the general population (supplemental Methods). For women with implants for cosmetic reasons (~70% of the cohort), we assumed the prevalence to be similar to the general population, for which we used a recently reported estimate of 0.5% (95% CI, 0.5-0.6) based on 50,726 women of predominantly European ancestry[6] with *BRCA1/2* mutations, as classified in ClinVar.[7] This estimate is in line with other similar studies.[8-10] By combining the expected *BRCA1/2* prevalence rates for cosmetic and reconstructive cases with our previously reported overall cumulative risk of BIA-ALCL of 1/7000 at the age of 75 years,[2] we estimated the number of women with breast implants with and without *BRCA1/2* mutations. Based on (at least) 4 *BRCA1/2* mutation carriers with BIA-ALCL and 43 noncarrier BIA-ALCL cases, we then determined the absolute risk of developing BIA-ALCL in *BRCA1/2*

Table 1. Clinical characteristics of 17 women with BIA-ALCL after breast reconstruction for breast cancer and/or bilateral or contralateral prophylactic mastectomy because of breast cancer risk

Case	*BRCA* mutation information	Age at breast cancer, y	Reason for breast implant insertion	Age at breast implant insertion, y	Breast implant type and location	Other breast cancer treatment	Interval to BIA-ALCL	BIA-ALCL lymphoma sites
1	*BRCA 1* mutation, details not disclosed	NA	Bilateral prophylactic mastectomy	46	Bilateral, Allergan, macrotextured, silicone	NA	10	Left breast
2	*BRCA1* gene 5396 + 1G ->A	NA	Bilateral prophylactic mastectomy	44	Bilateral, Allergan, macrotextured, silicone	NA	12	Right breast
3	*BRCA2* gene 8295T ->A (cys2689end, exon18	35	Right-sided mastectomy for breast cancer; 6 years later left-sided prophylactic mastectomy	35 and 40	Bilateral, McGhan, macrotextured, silicone	Chemotherapy and radiotherapy	8	Left breast
4	*BRCA1* exon [11]C.4097-1G>A splicing (49%) at Alamut/NCBI (confirmed mutation in MLPA/ NGS analysis in this study)	60	Left-sided mastectomy for breast cancer and right-sided prophylactic mastectomy	60	Bilateral, Allergan, macrotextured, silicone	None	4 and 6	Left breast
5	Heterozygous c.5722_5723delCT p.(Leu1908Argfs*2) exon 11 v *BRCA2*	37	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy	47	Bilateral, Allergan, macrotextured, silicone	Radiotherapy	13	Left breast, axillary lymph node
6	c.66dupA p.Glu23fs *BRCA1*, exon 2	40	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy	40	Bilateral, Allergan, macrotextured, silicone	Chemotherapy	9	Left breast
7	NA	26	Right-sided mastectomy for breast cancer (reconstruction 3 y later)	29	Right, McGhan, macrotextured, silicone	Chemotherapy and radiotherapy	26	Right breast and axilla, right lung
8	NA	49	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy (familial cancer, no proven mutation)	49	Bilateral, McGhan, macrotextured, silicone	None	7	Right breast
9	NA	56	Right-sided mastectomy for breast cancer, left-sided prophylactic mastectomy (familial cancer, no proven mutation)	56	Bilateral, McGhan, macrotextured, silicone	Chemotherapy	5	Left breast

Implant type in the remaining 32 BIA-ALCL cases who received breast implants for cosmetics purposes was Allergan/Inamed/McGhan (n = 15), Eurosilicone (n = 3), Rofill PIP (n = 1), Monobloc (n = 1), Sebbin (n = 1), Mentor (n = 1), Nagor (n = 1), and unknown (n = 9). Other detailed information on these cases can be found in the supplements of de Boer et al.[2]

Table 1. (continued)

Case	*BRCA* mutation information	Age at breast cancer, y	Reason for breast implant insertion	Age at breast implant insertion, y	Breast implant type and location	Other breast cancer treatment	Interval to BIA-ALCL	BIA-ALCL lymphoma sites
10	NA	51	Right-sided mastectomy for breast cancer, 6 y later left-sided mastectomy for breast cancer	51	Bilateral, Allergan, macrotextured, silicone	None	6	Right breast
11	NA	46	Left-sided mastectomy for breast cancer	46	Left, Inamed, macrotextured, silicone	None	13	Left breast
12	NA	48	Right-sided breast cancer, 1 y later left-sided prophylactic mastectomy left with subsequent reconstruction	49	Bilateral, Allergan, macrotextured, silicone	Chemotherapy and hormonal therapy	9	Left breast
13	NA	51	Left-sided mastectomy for breast cancer, reconstruction 2 y later	53	Left, McGhan, macrotextured, silicone	Chemotherapy and hormonal therapy	7	Left breast
14	NA	51	Left-sided mastectomy for breast cancer, reconstruction in 2009	53	Left, Allergan, macrotextured, silicone,	None	8	Left breast
15	NA	52	Left-sided mastectomy for mammary carcinoma of the breast, right-sided mastectomy for pain/ mastopathy	52	Bilateral, McGhan, macrotextured, silicone	None	12	Left breast
16	NA	59	Right-sided mastectomy for breast cancer	61	Right, McGhan, macrotextured, silicone	Hormonal therapy	12	Right breast
17	NA	57	Right-sided mastectomy for breast cancer, contralateral side augmentation	61	Bilateral McGhan, macrotextured, silicone	Hormonal therapy	14	Right breast

Implant type in the remaining 32 BIA-ALCL cases who received breast implants for cosmetics purposes was Allergan/Inamed/McGhan (n = 15), Eurosilicone (n = 3), Rofill PIP (n = 1), Monobloc (n = 1), Sebbin (n = 1), Mentor (n = 1), Nagor (n = 1), and unknown (n = 9). Other detailed information on these cases can be found in the supplements of de Boer et al.[2]

mutation carriers to be ~1/1551 (95% CI, 1/5692−1/606) before the age of 75 years, compared with 1/7507 (95% CI, 1/10,373 - 1/5573) in noncarriers with a breast implant (odds ratio = 4.8; 95% CI. 1.7-13.5; $P = .012$). The BIA-ALCL risk of 1/1551 for women with a *BRCA1/2* mutation may be underestimated because (1) the expected age-specific *BRCA1/2* mutation prevalence in women with breast cancer aged 50 to 60 was overestimated and (2) we could only determine *BRCA1/2* mutation status in 18/49 BIA-ALCL cases.

We excluded the 2 *BRCA1/2* cases with bilateral prophylactic mastectomy (BPM) from the risk calculation given previously because *BRCA1/2* mutation carriership was the a priori indication for BPM and subsequent breast reconstruction. Nationwide data from the Hereditary Breast and Ovarian Cancer Research Group Netherlands indicate that 1950 Dutch *BRCA1/2* mutation carriers underwent BPM, with ~75% having a reconstruction with implants.[11] Therefore, the observation of 2 women with BIA-ALCL in this population (~1/730) further

Table 2. Age-specific prevalence of *BRCA1/2* mutation carriers among breast cancer cases as observed in van den Broek[11] and number of BIA-ALCL cases with breast cancer by age

	Age at breast cancer diagnosis, y				
	<35	35-39	40-44	45-49	>50*
Expected prevalence of *BRCA1/2* mutations in breast cancer patients (%)[11]	10.7	6.1	4.3	2.4	2.4*
Observed BIA-ALCL patients per age category (n)	1	2	1	3	8

The prevalence of *BRCA1/2* mutation carriers among BIA-ALCL cases with breast cancer was estimated as the geometric mean of age-specific *BRCA1/2* prevalences among BIA-ALCL cases multiplied by 100/61 to correct for the incomplete mutation testing panel.[11]

Calculation: $(0.1069 \times 0.0612^2 \times 0.0432 \times 0.024^{11})^{(1/15)} = 0.0312$. After correction: $0.0312 \times 100/61 = 5.1$ (95% CI, 4.6-5.7).

*Prevalence for age 45-49 y was also used for the group aged >50 y to best approximate prevalence because specific data for this age group are unknown.[11]

supports our findings of increased risk of BIA-ALCL in *BRCA1/2* mutation carriers.

The currently estimated risk for BIA-ALCL in women with *BRCA1/2* mutations applies to the Dutch population; these findings need to be validated in other BIA-ALCL series. Recently, a prospective single institution study from Memorial Sloan-Kettering Cancer Center, NY, NY, presented an exceptionally high risk for BIA-ALCL in women with implants after breast cancer surgery (1/355).[12] At least 5 of 10 BIA-ALCL cases had a previous contralateral prophylactic mastectomy.[13] Possibly, this high risk is at least partly related to specific features, including genetic characteristics, of the patient population in the adherence area of this single institution.

Our study has several limitations. First, if *BRCA1/2* mutation carriers with breast cancer would more often undergo mastectomy (with reconstruction) than lumpectomy, we may have overestimated BIA-ALCL risk in carriers compared with noncarriers. However, a recent Dutch study shows that breast cancer recurrence rates in *BRCA1/2* mutation carriers (and noncarriers) do not differ between mastectomy and lumpectomy, suggesting that this bias may be small.[14] Second, we did not account for the number of implants per woman, although *BRCA1/2* mutation carriers with breast cancer likely have a higher rate of bilateral implants than non-*BRCA1/2* breast cancer patients because of increased rates of contralateral breast cancer and prophylactic contralateral mastectomy.[15] Higher bilateral implant prevalence may have led to some overestimation of our calculated BIA-ALCL risk in *BRCA1/2* mutation carriers. The extent of this bias is unclear, however, because we actually do not know whether bilateral implants increase risk of BIA-ALCL compared with unilateral implants. Third, *BRCA1/2* mutation testing could only be performed in 18/49 women; as a consequence, our risk estimates are conservative. Strengths of our study include the complete nationwide ascertainment of BIA-ALCL cases, histopathological confirmation of all cases, and the availability of complete clinical data, including implant type. Because all breast cancer patients in this study, both *BRCA1/2* carriers and noncarriers, had macrotextured breast implants, confounding by "high-risk" implant types can be excluded.[16-19]

This study has been performed in the context of a breast cancer population with macrotextured breast implants. If validated in larger international cohorts, the results of this study may have important implications for breast reconstruction options after breast cancer surgery and prophylactic mastectomy in women with established *BRCA1/2* mutations. Such implications would include personalized patient information for *BRCA1/2* mutation carriers opting for implants and promotion of alternative autologous breast reconstruction procedures.

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Authorship

Contribution: M.d.B. designed the research, performed research, collected data, contributed to analytical tools, analyzed data, performed statistical analysis, and wrote the paper; D.d.J. and F.E.v.L. designed the research, performed researched, contributed to analytical tools, analyzed data, and wrote the paper; M.H. designed the research, analyzed data, performed statistical analysis, and wrote the paper; and N.J.H., C.J.M.v.N., H.E.J.M.-H., J.P.d.B., H.A.R., and R.R.W.J.v.d.H. designed the research, analyzed data, and wrote the paper.

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Footnotes

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For original data, please contact the corresponding author.

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