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Editoral Comment

Is breast-conserving therapy in the genetically predisposed breast cancer patient a reasonable and appropriate option?

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We will begin by answering the question posed in the title of this commentary regarding the appropriateness of breast-conserving therapy in a genetically predisposed patient with a definitive 'yes'. We continue to offer breast-conserving therapy to genetically predisposed breast cancer patients and will present in this commentary the rationale for this position based on the available data.

The issue of breast-conserving therapy in women diagnosed with breast cancer who have a genetic predisposition to the disease is a complicated issue. Even prior to a diagnosis of breast cancer, the genetically predisposed patient may often be considering prophylactic mastectomy and/or prophylactic oophorectomy as risk-reducing strategies [1–3]. Although the impact of these prophylactic measures on survival remains debatable, it is clear that prophylactic bilateral mastectomy substantially reduces the risk of subsequent breast cancers. It would therefore appear that when a patient with a genetic predisposition is faced with a new diagnosis of breast cancer, ipsilateral therapeutic mastectomy as well as contralateral prophylactic mastectomy would be strongly considered. In addition, *BRCA1* and *BRCA2* are known to be involved in DNA repair. Hypothetically the administration of radiation, with its known damaging effects on DNA, may be associated with adverse normal tissue reactions, and increased rates of radiation-induced second malignancies [4–10]. Based on these considerations the issue of breast-conserving therapy followed by radiation therapy in the genetically predisposed patient is obviously approached with some trepidation.

In this issue of the *European Journal of Cancer*, Seynaeve and colleagues report on a series of conservatively managed breast cancer patients with a genetic predisposition [11]. In this series they observed a higher rate of ipsilateral breast tumour relapse (30% at 10 years) in the genetically predisposed cohort compared to a rate of 16% at 10 years in an age-matched 'sporadic' control group. As expected, contralateral events were also more frequent in the genetic cohort. On the surface these rates of relapse are high, and one might assume from these data that breast-conserving therapy should be avoided in the genetically predisposed patient. First, a few caveats regarding the Seynaeve study should be highlighted. As they acknowledge, not all patients in their series underwent full genetic testing. A majority of the hereditary group was 'unspecified hereditary breast cancer', based on very strong family histories. Similarly, the sporadic controls were presumed to be negative for a genetic predisposition based on family history. The lack of specific sequencing data on all patients weakens the impact of the findings. Another limitation of their study is the relatively short, 6-year median follow up. Despite these limitations, their ipsilateral and contralateral event rates were remarkably similar to those in a recently published study from our institution, where both the sporadic and genetic groups underwent complete sequencing of both *BRCA1* and *BRCA2* genes, and follow up exceeded 12 years [12]. The 12-year rates of ipsilateral and contralateral events in our genetic cohort with known mutations in *BRCA1* or *BRCA2* were 49% and 42%, respectively, compared to an ipsilateral relapse rate of 21% and contralateral relapse rate of 9% in sporadic patients (who were sequenced and tested negative for *BRCA1* and *BRCA2*). Selection criteria for our study were conservatively managed patients who were less than 42 years of age at diagnosis.

The observations of a higher rate of late local relapse are also consistent with the recent series by Robson, who reported a 10-year local relapse rate of 22% in hereditary patients compared to 6.9% in sporadic controls [13]. Although the difference in local control

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between sporadic and genetic patients in Robson's series was not statistically significant, the trends from these studies are quite similar. A large series by Pierce and colleagues of 71 genetic cases and 213 matched sporadic controls, all treated with lumpectomy and radiation, did not demonstrate a difference in local control between genetic and sporadic patients at relatively short follow up [14]. However, a recent report by Pierce and colleagues, with longer follow up and larger patient numbers, presented in abstract form at the San Antonio breast cancer meeting, did demonstrate with 8-year follow up a higher, though statistically insignificant, rate of ipsilateral events in genetically predisposed patients [15]. Recent series, reported in abstract form at ASCO by Bremer and colleagues [16] and Delaloge and colleagues [17], also demonstrate higher long-term rates of ipsilateral relapse in genetically predisposed patients. These studies are summarised in Table 1.

Despite different selection criteria, methodology and follow up in all of these series, there are some similar trends that are noteworthy. In our own series, as in the Seynaeve cohort, rates of local relapse in genetic and sporadic patients appear similar in the earlier years. With longer follow up, however, the genetic group continues to develop events in the conservatively treated breast. This is presumably due to the development of new primary tumours in the residual breast tissue. The assumption that these ipsilateral events represent new primary tumours is circumstantially supported by frequently noted changes in histology and/or location of the secondary event. It is therefore not surprising that series with shorter follow-up times, where the patients have not been at risk long enough to develop these secondary events, will fail to show a difference between sporadic and genetic cohorts of patients. An overview of all of these studies suggests that in the short term (within the first 5 years), true local relapse rates in *BRCA* carriers and genetically predisposed patients appear to be similar to those in to age-matched sporadic breast cancer patients. With longer follow up, genetically predisposed patients continue to develop second malignancies in both the ipsilateral and contralateral breast, with long-term event rates in each breast exceeding 30%.

With respect to normal tissue reactions it should be noted that there is no evidence from any of these studies that *BRCA* carriers have more severe normal tissue reactions or higher rates of radiation-induced second malignancies than their sporadic counterparts treated with conservative surgery and radiation [12,14,15,18]. Larger numbers of patients with even longer follow up are, however, needed to evaluate these issues more thoroughly.

Given these observations of a high rate of late second tumours in the conservatively managed breast as well as the contralateral breast, in genetically predisposed women, one might ask how we could conclude that breast-conserving therapy is an acceptable option. It should be noted that none of the patients in the Yale series with *BRCA* mutations underwent prophylactic oophorectomy or was on tamoxifen. The use of tamoxifen was also very limited in the genetic cohort in Seynaeve's study. Several recent studies have clearly demonstrated that both tamoxifen and prophylactic oophorectomy substantially reduce the risk of subsequent breast malignancies [19–23]. Specifically, recent studies by Rebbeck, Kauf and Narod suggest that prophylactic oophorectomy, tamoxifen, or both will significantly reduce the risk of subsequent breast cancers in *BRCA*-mutation carriers. If indeed these late secondary events observed in the genetic cohorts are new primary tumours, the use of prophylactic measures such as oophorectomy, tamoxifen and other available hormonal agents may substantially reduce these secondary events. Additional data on conservatively managed *BRCA* breast cancer patients treated prophylactically with oophorectomy and hormonal agents will be required to assess the magnitude of this effect in this particular population.

An important question is what effect a higher local recurrence rate might have on patient mortality. A recent analysis of the randomised NSABP B06 trial for genetically uncharacterised women showed that a group with a 39% incidence of local recurrence due to lack of radiation therapy had a probability of death from

Table 1
Breast-conservation therapy in genetically predisposed patients

Study	No. of patients	No. of *BRCA* patients	Follow up (years)	Local relapse (%)			Contralateral relapse (%)		
				Genetic	Sporadic	*P*	Genetic	Sporadic	*P*
Robson [13]	305	28	10	22	6.9	0.25	27.0	9.5	0.002
Seynaeve [11]	261	87	6.1	30	16	0.05	13.8	6.3	0.06
Pierce [15]	469	170	10	125	8.6	0.55	25	4	<0.001
Haffty [12]	127	22	12.7	49	21	0.007	42	9	0.001
Bremer [16]	110	9	5	29	6	0.022	NA	NA	
Delaloge [17]	96	37 *BR_1* 16 *BR_2*	10	9 37	12 12	0.07	NA	NA	

NA, not available.

breast cancer about 20% greater than a comparable group in which the local recurrence rate was only 14% due to radiation therapy [24]. However, several studies have shown that the association between local recurrence and worse survival is largely confined to those cases where the recurrence is relatively early and represents return of the original primary tumour, whereas the later recurrences, such as are seen in the population with *BRCA* mutations, are more likely to be new primary tumours and do not have as great an impact on survival [25,26]. Based on these data, it appears unlikely that treating patients with *BRCA* mutations with breast-conserving therapy would result in a significant worsening of survival.

What, then, are reasonable options for the newly diagnosed breast cancer patient with a genetic predisposition who tests positive for *BRCA1* or *BRCA2*? Clearly, therapeutic mastectomy of the affected breast and prophylactic contralateral mastectomy is one option that should be considered. Although unilateral therapeutic mastectomy might be considered, the contralateral breast is at nearly equal risk for failure and bilateral mastectomy would clearly make the most sense with respect to risk reduction. Once hormonal status and issues of child bearing have been addressed, prophylactic oophorectomy to reduce the risk of ovarian cancer should also be considered.

Acknowledging the limitations of available data, patients desiring breast conservation should be offered breast-conserving therapy. They should be counselled about the relatively high risks of subsequent second primary tumours in the ipsilateral and contralateral breast, as well as the risks of ovarian cancer. We should advise patients that available data suggests that prophylactic oophorectomy, once hormonal status and childbearing issues have been addressed, substantially reduces the risks of subsequent ovarian cancers as well as subsequent breast cancers. The added risk reduction of hormonal agents such as tamoxifen should also be discussed. Although definitive clinical data are limited, breast-conserving therapy, with added prophylactic measures to reduce the risk of secondary malignancies of the ovaries and breast, remains a reasonable option for those genetically predisposed breast cancer patients desiring breast conservation.

Ultimately, the decision about lumpectomy or mastectomy is a very personal one and comes down to patient preference. Each woman must consider her own lifestyle and value systems and make this decision individually. At the present time, women routinely choose lumpectomy despite the known 15% chance of local recurrence. The question really is how many women will accept a higher chance of local recurrence at 10 years in order to retain their own breasts. Clearly, the data now emerging will help women make a more informed decision.

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