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J Med Genet 2009 46: 254-258 originally published online November 7, 2008
doi: 10.1136/jmg.2008.062232

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Risk reducing mastectomy: outcomes in 10 European centres

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Received 30 July 2008
Revised 11 October 2008
Accepted 16 October 2008
Published Online First
7 November 2008

ABSTRACT

Background: Increasingly women at high risk of breast cancer are opting for risk reducing surgery. The aim of this study was to assess the effectiveness of this approach in women at high risk in both carriers and non-carriers of *BRCA1/2*.

Methods: Data from 10 European centres that offer a genetic counselling and screening service to women at risk were obtained prospectively from 1995. Breast cancer risks were estimated from life tables and a control group of women at risk who did not undergo surgery.

Results: The combined centres have data on 550 women who have undergone risk reducing mastectomy with greater than 3334 women years of follow-up. Operations were carried out on women with lifetime risks of 25–80%, with an average expected incidence rate of 1% per year. No breast cancers have occurred in this cohort in the "at risk" unaffected breast, whereas >34 would have been expected. A high rate (2–3.6%) of occult disease was identified in the at risk breast at the time of surgery.

Interpretation: We conclude that risk reducing surgery is highly effective.

Management options for women at high lifetime risk of breast cancer are limited irrespective of their *BRCA1/2* status.^{1–3} There is doubt concerning the effectiveness of mammographic screening in these women particularly in *BRCA1* carriers.⁴ Screening by magnetic resonance imaging (MRI), while very sensitive, has yet to be shown to be associated with improved breast cancer survival.^{5–8} The efficacy of surgical procedures to reduce the risk of breast cancer appears clear, but is based on only three studies.^{9–11} While these have produced important information concerning the efficacy of risk reducing surgery, only one of these reported outcomes in high risk women not known to carry mutation in either *BRCA1* or *BRCA2*. Here we summarise the effectiveness of risk reducing surgery in a large cohort of women at high lifetime risk of breast cancer, whether mutation carriers or not, from eight European centres.

METHODS

Family history clinics were established at the eight participating centres (table 1) between 1987 and 1992. The clinics are run by consultants in medical oncology, clinical genetics or breast surgery often using a multidisciplinary approach, with close involvement of radiologists, and psychiatrist/psychologists.^{12 13} Women were considered eligible for

bilateral risk reducing mastectomy (RRM) if their lifetime risk of breast cancer was in excess of 25% or unilateral RRM if they already had a diagnosis of in situ or invasive breast cancer in the contralateral breast. In one centre (Paris) RRM was offered to *BRCA1/2* carriers only. Surgery was considered only after detailed counselling usually involving at least two sessions with a geneticist or oncologist, a psychological assessment and two surgical consultations. In non-mutation carriers family history was verified through cancer registries in order to avoid inappropriate surgery.^{14–16}

The possibility of genetic testing was also discussed in relation to the availability of a living affected member of the family and the basic underlying structure of the family. Time scales for genetic testing were discussed, and the woman asked to consider the potential impact of undergoing surgery, and finding subsequently that she is a non-carrier of her family mutation. Centres also emphasised that the genetic risks of breast cancer decrease with age and that remaining breast cancer risk is lower than lifetime risk in older women.

After a psychological assessment, detailed surgical consultations discussed the most appropriate surgical approach and whether a one or two stage procedure was preferable. Usually three options were discussed: (1) total bilateral mastectomy; (2) bilateral mastectomy with reconstruction using abdominal or latissimus dorsi flaps; or (3) the use of implants. The potential complications of each procedure along with the expected cosmetic result were discussed in detail.

Data collection

Information on breast cancer risk from family history and/or mutation status was obtained for each woman. The date and type of surgery as well as date of last follow-up was obtained on an annual basis from each centre. A person years at risk analysis was used to predict the number of expected cancers. Life tables were used based on breast cancer rates predicted either from mutation status or family history derived risk as previously described and validated.^{17 18} These estimations were largely based on breast only families from the CASH dataset¹⁹ and, for mutation carriers, from the Breast Cancer Linkage Consortium datasets.^{1–3} In Manchester a control group was obtained from the family history screening and follow-up service. Two controls at similar breast cancer risk and a date of birth within 2 years were obtained for

Table 1 Number and type of prophylactic mastectomies carried out by centre with women years of follow-up and expected cancers

Centre	No.	Age (years)	Mean	SM	MM	Bilateral	Contra-lateral	BRCA1/2	Women years f/u	Expected cancers	Sequential series	Information on RRO <50 years	Median follow-up (years) (completeness)
Manchester	245	21–60	41	27	218	179	66	87	1670.2	16.82	Yes	58/245 (24%)	7.3 (C)
Edinburgh	121	24–72	45	67	53	30	91	18	464.2	3.84	Yes	11/121 (9%)	4.7 (no follow-up on 9)
Aberdeen	22	33–57	43.8	6	16	12	10	4	74	0.6	Yes	7/22 (32%)	8.3 (one lost)
Leiden	35	20–53	38.5	23	12	31	4	24	267	3.17	Yes	Not available	9.2 (C)
Dusseldorf	8	29–46	37.5	3	5	7	1	2	85.3	0.59	Yes	2/8 (25%)	9.6 (C)
Oslo	28	27–59	40	11	17	24	4	13	299.5	3.18	Yes	Yes 6/28 (21%)	11.7 (C)
Southampton	33	32–57	43.8	16	16	9	24	14	165.7	1.94	Yes	Not complete	7.3 (one lost)
Belfast	22	28–57	41.5	22	0	9	13	11	99	1.25	Yes	3/22 (13%)	7.2 (C)
Guy's	32	26–56	40	23	5	12	20	25	179.9	2.5	Yes	10/32 (31%)	7.1 (C)
Paris	4	28–51	40.5	2	2	1	3	4	40.9	0.71	Yes	3/4 (75%)	10.2 (C)
Total	550	21–72		200	346	314	236	202	3334	34.44	Yes	100/492 (20%)	7.5

C, complete follow-up; f/u, follow-up; MM, modified mastectomy (includes subcutaneous, and skin sparing); SM, simple mastectomy.

women not known to be mutation carriers and one for each proven *BRCA1/2* carrier. Women were matched for cancer status at the time of surgery of the case and follow-up was censored at breast cancer diagnosis, last follow-up or death, whichever was the sooner. A final analysis included an adjustment for oophorectomy. We assumed that oophorectomy carried out before 50 years of age would reduce breast cancer incidence by 50%.²⁰

RESULTS

In all centres a concerted effort was made to ensure that all sequential surgeries were identified, with as up to date follow-up as possible. Follow-up in Manchester was ensured by annual questionnaire and invitation to a multidisciplinary follow-up clinic. Date of last follow-up was taken as last clinical review at all other centres unless there was certainty of patients having not developed cancer and still being alive. There was no information on follow-up on 11/550 (2%) of women.

Manchester

In Manchester 245 risk reducing mastectomies were performed (179 bilateral in unaffected women). The great majority of surgeries were modified skin sparing mastectomies (218/245 (89%)) with only 12 old style subcutaneous mastectomies, with all 206 other modified mastectomies using a skin sparing approach (tables 1 and 2). Nipple conservation was carried out in 65/218 (30%) modified mastectomies. There were 1672.87 women years of follow-up and no cancers were observed post-surgery, whereas 16.82 were expected from life table analysis.

There were 367 controls with 2438.44 years follow-up; 20.8 breast cancers were expected from life tables and 21 cancers were diagnosed.

At the time of surgery nine occult tumours were identified in the “at risk”, but ostensibly unaffected breast. These include two invasive lobular cancers in the contralateral breast of previously diagnosed (lobular carcinoma in situ (LCIS)). Three women with invasive ductal breast cancer undergoing contralateral mastectomy had an invasive occult cancer identified (one *BRCA1* and one *BRCA2* carrier). A further *BRCA2* carrier identified on mammography with ductal carcinoma in situ (DCIS) also had occult DCIS in the contralateral breast. One *BRCA1* carrier who had recently undergone normal breast MRI had bilateral 4 mm high grade DCIS lesions. A high risk patient with four breast cancers <60 years in relatives, who had tested negative along with her family for *BRCA1/2*, had a 4 mm invasive ductal cancer identified. Finally, a high risk patient undergoing bilateral mastectomy had a 1 mm invasive ductal cancer identified. Despite chemotherapy she developed local then distant metastasis 14 and 20 months later and died 40 months following surgery. Full *BRCA1/2* screening did not identify a mutation, but the family history of breast and ovarian cancer was still suggestive of a missed mutation. In total 9/245 (3.7%) of the patients in Manchester had significant pathology identified at surgery.

Other centres

Data from the other centres regarding type of surgery, follow-up and expected cancers is shown in table 1. The breakdown for contralateral versus bilateral RRM is shown in table 2. Two ipsilateral invasive apparent new primaries have occurred in the affected breast. One patient had bilateral RRM for DCIS, the other for invasive ductal cancer. Again there was a relatively high frequency of occult cancer found at surgery with 6/305

Table 2 Breakdown of risk reducing mastectomy by contralateral and bilateral surgery by centre with women years of follow-up and expected cancers

	Bilateral			Unilateral			Combined		
	Years	Expected cancer	Number	Years	Expected cancer	Number	Years	Expected cancer	Number
Aberdeen	46.83	0.34	11	27.36	0.26	10	74.19	0.60	21
Belfast	39.70	0.39	9	59.34	0.86	13	99.04	1.25	22
Dusseldorf	79.35	0.53	7	5.95	0.06	1	24.91	0.59	8
Edinburgh	108.88	0.99	25	355.35	2.85	87	464.23	3.84	112
Guys	77.47	0.99	12	89.15	1.35	20	166.62	2.34	32
Curie Paris	15.87	0.32	1	25.12	0.39	3	40.99	0.71	4
Leiden	233.73	2.76	31	33.38	0.42	4	267.11	3.18	35
Oslo	231.33	2.14	24	68.18	1.04	4	299.51	3.18	28
Southampton	48.51	0.72	8	117.16	1.22	24	165.66	1.94	32
Manchester	1273.48	12.12	179	399.39	4.70	66	1672.87	16.82	245
Total	2155.15	21.30	307.00	1178.58	13.15	232.00	3333.73	34.45	539

11 risk reducing mastectomies did not have information on follow-up.

(2%) non-Manchester cases having either invasive or in situ disease.

Combined analysis

There were 314 bilateral RRM in unaffected women and 236 contralateral mastectomies, making 550 women in total. Follow-up was available on 539 women as there was no follow-up time on 11. The 16 women with tumour in the at risk breast at time of surgery were censored at surgery for further follow-up. No breast cancers post-surgery have occurred in 2155.15 years of follow-up, with 21.30 expected from life tables. In women undergoing contralateral mastectomy 236 women have had 1178.58 years follow-up with 13.15 cancers expected. Again no cancer has occurred in the "at risk" unaffected breast.

We observed 0 events after RRM, and the 95% confidence interval (CI) for breast cancer incidence for this figure was 0 to 3.7. There were 3334 observation years. Median combined follow-up was 7.5 years with a mean of 6.1 years. The point estimate observed for annual incidence rate was 0 in 3334 women years of follow-up (95% CI 0 to 3.7/3334) or 0.001 cases annually, equivalent to at least a 90% reduction in breast cancer risk. If date of last follow-up for living patients was taken as 1 October 2008 when all centres were last contacted, then total expected cancers would have been 49 and still none have been reported.

Adjustment for oophorectomy

Increasingly women are opting for early oophorectomy as a combined measure to reduce both breast and ovarian risk. Of the 245 women in the Manchester dataset, 28 had undergone risk reducing oophorectomy before and 30 after RRM. The adjusted rates are shown in table 3. Thus oophorectomy reduced the expected cancers from 16.82 to 14.63. Although information on oophorectomy was available from most of the

centres, the dataset in other centres was not complete enough to analyse separately. If a similar proportion had undergone early oophorectomy in the other centres (only 42/247 (17%) were notified to us, table 1) this would have reduced the expected cancers in at risk breast tissue to 29.87 from 34.44.

DISCUSSION

We report the long term prospective follow-up of both bilateral and contralateral RRM in a multicentre EU collaborative study which provides further evidence for the efficacy of RRM in both proven mutation carriers and in the high risk non-carriers. Our data concerning the efficacy of RRM support previously reported data for bilateral RRM in mutation carriers and non-carriers from a large single centre study⁹ and in relation to carriers from a further single centre¹⁰ and one multicentre study.¹¹ Our study provides robust support for the reproducibility of the 90–95% reported reduction in risk produced by RRM. No cancers have been detected in follow-up after initial surgery when >20 were expected.

Occult malignancy was detected in 15/550 (2.7%) mastectomy specimens, thus during counselling women need to be warned about the potential of detecting occult malignancy which may indicate the need for investigation of nodes in the axilla and adjuvant therapy. Given the additional sensitivity of MRI,^{5–9} this should ideally be carried out preoperatively in all women undergoing RRM. The Rotterdam group have now updated their follow-up on 358 women undergoing RRM (177 in unaffected bilateral cases) in BRCA1/2 carriers.²¹ Although no primary breast cancer occurred after RRM (after a median follow-up of 4.5 years), one previously unaffected woman presented with metastatic breast cancer 4 years after surgery, although a primary tumour was not found in the breast despite extensive review. This is in line with our case where a 1 mm tumour was detected at RRM and she later developed

Table 3 Effect of oophorectomy on expected cancers in Manchester

	Number of women	Years of follow-up	Expected cancers
No oophorectomy	187	1313.95	11.79
Oophorectomy pre-RRM	28	140.09	1.02
Oophorectomy post-RRM	30	68.16 (pre-oophorectomy)	0.93 (pre-oophorectomy)
		147.99 (post-oophorectomy)	0.89 (post-oophorectomy)
Total	245	1670.19	14.63

RRM, risk reducing mastectomy.

metastatic disease, suggesting metastases can arise from very small tumour foci in some cases.

There are now a number of studies which have investigated at the efficacy of contralateral RRM.^{21–24} Of the 745 women in the Mayo Clinic study, eight breast cancers occurred during follow-up whereas 156.7 were predicted, giving a 95% reduction in risk.²² Another study on contralateral RRM showed an estimated reduction in the occurrence of contralateral disease of 97% (95% CI 87% to 99%).²³ A further study showed one cancer in follow-up whereas 11 were expected, and reported that lobular histology was predictive of significant pathology in the contralateral breast.²⁴ This is supported by the two occult lobular cancers detected in our study. Finally, in a Dutch study concentrating on mutation carriers, one woman developed an invasive contralateral primary breast cancer after contralateral RRM, whereas six were observed in the surveillance group, equivalent to a 91% reduction in risk ($p < 0.001$).²⁵

Most studies have used life table analysis to calculate expected cancers. We have shown the accuracy of these estimations for our control group where 21 cancers occurred and 20.8 were expected. These data suggest that estimates for expected cancers from the present study are likely to be robust. Even when we adjust for the preventative effect of oophorectomy, there were no cancers in at risk tissue post-surgery with nearly 30 expected. In assessing the degree of prevention the nine occult invasive cancers detected at surgery need to be deducted from the expected cancers. Thus only 21 breast cancers can be said to have been truly “prevented”. As such, the percentage reduction in short to medium term follow-up is only 70% due to the occult cancers detected at surgery in our report. Previous reports have not accounted for this element in their percentage risk reductions. Nonetheless, if the absence of prospective breast cancers continues to a normal life expectancy of say 80 years, as many as 250 further breast cancers could be prevented in this patient group. Even allowing for a 90% reduction in risk, this would potentially still prevent 225 breast cancers. However, it is important to continue long term follow-up in all studies to determine the potential incidence of late occurrences.

A high proportion of the patients in our study underwent modified mastectomies with skin sparing. The absence of prospective cancers, especially in the Manchester group where the great majority of procedures were skin sparing, emphasises the need to advise women on all their options and not to exaggerate the “necessity” to undergo straightforward mastectomies which may result in lower patient uptake and greater dissatisfaction with appearance. These procedures should be carried out in centres with specific oncological expertise to ensure adequate clearing of breast tissue from the skin flaps.²⁶

Acknowledgements: Conception—Evans DG; Data collection—Evans DG, Shenton A, Vasen HFA, Howell A, Moller P, Baidam A, Anderson E, Brain A, Eccles D, Lucassen A, Pichert G, Hamed H, Maehle L, P Morrison, D Stoppat-Lyonnet, Gregory H, Smyth E, Niederacher D Nestle-Krämling C, Campbell J, Lalloo F; Data analysis—Evans DG, Shenton A; Manuscript writing—All; Approval of final version—All. We dedicate this paper to Andrew Shenton (statistician) who died tragically, at a young age, on 19 February 2008.

Competing interests: None declared.

Patient consent: Not required.

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