Uptake of Risk-Reducing Surgery in Unaffected Women at High Risk of Breast and Ovarian Cancer Is Risk, Age, and Time Dependent

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Abstract

Purpose: **The uptake of risk-reducing surgery in women at increased risk of breast and ovarian cancer is highly variable between countries and centers within countries. We have investigated the rate, timing, and age of uptake of surgery in the northwest of England to report the results after up to 7 years in a Regional Genetics center.**

Methods: **Uptake was documented in 211 known unaffected *BRCA1/2* mutation carriers from 509 families and in 3,515 women at >25% lifetime risk of breast cancer without known mutations.**

Results: **Of the 211 mutation carriers, 40% opted for bilateral risk-reducing mastectomy (BRRM) and 45% underwent bilateral risk-reducing salpingo-oophorectomy (BRRSPO). Uptake of BRRM was significantly related to lifetime risk and age but continued over several years. In women not known to carry a BRCA mutation, 6.4% of women at 40% to 45% lifetime risk, 2.5% of women at 33% to 39% lifetime risk, and 1.8% of women at 25% to 32% lifetime risk underwent BRRM ($P < 0.005$). BRRSPO uptake was greater in *BRCA1* (52%) than *BRCA2* (28%) carriers but in both groups tended to occur within the first 2 years after gene test (except in the youngest age group) and in women between the ages of 35 and 45.**

Conclusion: **To truly assess the uptake of risk-reducing surgery, longer-term follow-up is necessary particularly in younger women who are likely to delay BRRSPO. Careful risk counseling does seem to influence women's decisions for surgery, although the effect is not immediate.** (Cancer Epidemiol Biomarkers Prev 2009;18(8): 2318–24)

Introduction

Management options available for women at high lifetime risk of breast and/or ovarian cancer due to their family history or for those women known to be carrying a mutation in *BRCA1/2* are limited. Screening for breast cancer with mammography and/or with magnetic resonance imaging is one option. This may be combined with chemopreventative agents, such as tamoxifen and raloxifene, and with advice on diet and lifestyle as well as the known endocrine risk factors. Although screening for ovarian cancer using transvaginal ultrasound and CA125 estimation is offered, there is not any strong evidence of the efficacy of this approach (1). Many women with *BRCA1* or *BRCA2* mutations now seriously consider undergoing bilateral risk-reducing mastectomy (BRRM) and/or bilateral risk-reducing salpingo-oophorectomy (BRRSPO). The efficacy of surgical procedures for reducing the risk of breast and ovarian cancer is now beyond dispute (2-6). However, uptake rates vary enormously with a much lower uptake in Israel and southern Europe compared with northern Europe (7-9). A recent study in women with *BRCA1/2* mutations from nine countries, including North America, examined differences in uptake according to country (9). Among 2,677 women with a *BRCA1/2* mutation, a 57.2% had undergone BRRSPO and 18% of unaffected women had had BRRM. There were large differences in the uptake of the different preventive options by country of residence with only 2.7% of Polish unaffected women undergoing BRRM compared with 36% of U.S. women (9). Nonetheless, rates even in North America also vary considerably between centers from single-figure percentages to uptake of ~50% (8-10). Most studies have assessed uptake in *BRCA1/2* mutation carriers alone, but these estimations have been after short-term follow-up and have not been adjusted to account for delays in decision making. We have investigated the uptake of risk-reducing mastectomy and oophorectomy in high-risk women in medium-term to long-term follow-up, particularly timing and age of uptake of surgery and the influence of breast biopsy and genetic testing on uptake in the northwest of England. This is to report the results after up to 7 years of follow-up in a Regional Genetics center.

Materials and Methods

A breast cancer family history clinic (FHC) was established in Manchester in 1987. The regional genetics

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Table 1. Uptake of BRRM and BRRSPO surgery by risk and BRCA mutation

FHC				
≥25% lifetime risk			3,515	
BRRM	Further advice		No request	
	211 (6%)		3,304 (94%)	
Nonmutation carriers	Surgery		No surgery	*P*
	112 (53%)			
Very high (40%+)	51 (6.4%)		747 (93.6%)	
High (33-39%)	45 (2.5%)		1,770 (97.5%)	<0.005
High moderate (25-32%)	16 (1.8%)		886 (98.2%)	
Mutation carriers	Tested positive		Tested negative	
	211 (35%)		392 (65%)	
BRCA1/2 carriers	Surgery	No surgery	Predicted uptake at 7 y (95% CI)	
	84 (40%)	127 (60%)		
BRCA1	39 (43%)	52	60% (47-74%)	0.07 (χ^2)
Before genetic testing	7			
BRCA2	35 (32%)	75	43% (30-58%)	0.494 (Kaplan-Meier)
Before genetic testing	3			
BRCA1/2 (<35 y)	32	37	86% (59-99%)	0.015
BRCA1/2 (35-45 y)	35	50	57% (37-67%)	
BRCA1/2 (46+ y)	8	39	19% (9-36%)	
BRRSPO	BRCA tested			
	211			
BRCA1/2 carriers	Surgery	No surgery	Predicted uptake at 7 y (95% CI)	
	96 (45%)	115 (55%)		
BRCA1	43 (52%)	39	66% (53-80%)	0.009 (χ^2)
Before genetic testing	16			
BRCA2	29 (28%)	76	42% (29-59%)	<0.005 (Kaplan-Meier)
Before genetic testing	8			
BRCA1/2 (<35 y)	8	59	23% (11-44%)	
BRCA1/2 (35-45 y)	50	34	76% (62-87%)	
BRCA1/2 (46+ y)	14	36	50% (32-71%)	

Abbreviation: 95% CI, 95% confidence interval.

service in the northwest region of England around Manchester covering ~4.5 million people established a cancer genetics service in 1990. Since 1987, more than 25,000 women have been referred to this regional combined service with a family history of breast and/or ovarian cancer. Women's lifetime risk of breast cancer is calculated, and screening and preventive measures are discussed. Women with a high risk of breast cancer (lifetime breast cancer risk, ≥25%) have been offered a discussion about BRRM since 1994. Genetic testing for *BRCA1/2* in the family is also discussed, and testing of affected family members is carried out if the family wishes. Women (even those from families without a proven BRCA1/2 mutation) wishing to discuss BRRM further are given a second genetics appointment followed by a psychological assessment. Women in whose family a *BRCA1/2* mutation is identified will go through a further protocol of genetic testing at which the option of BRRM is raised. Women testing positive for a family BRCA1/2 mutation are quoted lifetime risks of breast cancer of 50% to 85%. If, after a further two consultations with the appropriate surgeon (A.D.B. or A.B.) and a meeting with a breast care nurse, a woman wishes to proceed, arrangements are made for surgery as long as the risk has been confirmed by the genetics service. This is in accordance with our long-standing guidelines and those of the UK National Institute for Health and Clinical Excellence (NICE; refs. 11,12). NICE produces evidence-based national guidance on several health issues, including management of unaffected women at risk of familial breast cancer (12).

Mutation testing for *BRCA1/2* has been available since 1996, and to date, 509 families with pathogenic mutations have been identified in the catchment area of the Manchester regional genetics service. Women attending the specialist genetic clinics with a family history of breast/ovarian cancer have a detailed three-generation pedigree taken. If a *BRCA1/2* mutation is identified in an affected family member, further attempts are made to ensure that all individuals relevant to discussions on risk are represented on the pedigree. Once a family-specific pathogenic *BRCA1/2* mutation is identified, predictive testing is offered to all blood relatives. Mutation carriers and their close relatives are offered regular follow-up through the genetic register service and for regular breast screening.

The date of last follow-up of each individual was obtained from genetic clinic notes. Individuals at 50% risk of a mutation and ages 18 y or older were considered eligible for genetic testing from the time that the index case was informed of the family mutation. The index case and all relatives who had previously contacted the department were directly informed of the availability of testing and asked to pass on this information to all eligible relatives.

Women from *BRCA1/2* families are offered the option of BRRSPO either as a laparoscopic technique or as an open hysterectomy once they have completed their family. They are advised that undertaking this procedure before 50 y of age will also reduce their risk of breast cancer and that this risk reduction is not substantially abrogated by taking hormone replacement therapy (6).

Comparisons of uptake of risk-reducing surgery between *BRCA1* and *BRCA2* mutation carriers and based on age at testing (patients were divided into groups based on age at testing) were assessed using Kaplan-Meier curves and χ^2 tests. Kaplan-Meier curves were commenced from time of first assessment for non-mutation carriers and date of genetic test result for mutation carriers. Follow-up was censored at date of last assessment. All risk-reducing surgery was carried out by our experienced team, and all appointments, including dates of

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surgery, were logged on a dedicated database. Women undertaking risk-reducing surgery before assessment/genetic testing were excluded from the main analyses but are included in the tables for completeness.

Women from families without known *BRCA1/2* mutations were considered eligible for surgery if at >25% lifetime risk at time of risk assessment. Breast cancer risks were assessed using a manual risk assessment and using the Tyrer-Cuzick model as previously described (13, 14). Three cut points for risk were based on NICE guidance thresholds and include the more usual risk categories discussed with women (1 in 4, 1 in 3; 40%). Age categories for mutation carriers were devised to roughly divide the number of carriers into three equal tertiles. Point prevalence and uptake rates at 7 y were assessed. Ovarian cancer risks were not systematically available on nonmutation carriers as these were largely carried out in a different clinic in Manchester. Uptake of BRRSPO is not therefore reported in non-mutation carriers. All procedure, including genetic testing and risk-reducing surgery, is covered by the UK healthcare system.

Results

Since starting to offer presymptomatic testing for *BRCA1/2* in 1994, 603 of 1,250 women unaffected by breast or ovarian cancer have undertaken a predictive test for a known mutation in 509 families. Thirty-five percent (211 of 603) of tested individuals were positive for the family mutation: 98 in *BRCA1* and 113 in *BRCA2*. The median length of time from positive predictive test result to last follow-up was 4.19 years. Ten women (7 with *BRCA1* mutations) had previously undergone a BRRM and 24 women (16 *BRCA1* and 8 *BRCA2*) had undergone BRRSPO (Table 1). Overall uptake of surgery in women with either *BRCA1* or *BRCA2* mutations is shown in Table 1 along with predicted uptake at 7 years from Kaplan-Meier analysis.

Bilateral Risk-Reducing Mastectomy. BRRM uptake was proportional to risk ($P < 0.005$); uptake was highest in carriers of mutations in either *BRCA1* or *BRCA2* (43% and 32% uptake, respectively) and lowest in the group of women at high-moderate risk (between 25% and 32% lifetime risk). In the high-moderate risk group, only 16 of 886 (1.8%) women offered surgery undertook BRRM, with 2.5% and 6.4% in the high-risk and very high-risk (non-*BRCA1/2* carriers), respectively, undertaking BRRM (Fig. 1; Table 1).

BRRM uptake varied with time with the majority of *BRCA1/2* carriers (59% and 83%) undertaking BRRM within 2 years of receiving a genetic test result, whereas most high-moderate and high-risk women had surgery later than 2 years after initial discussion and many beyond 4 years. Very high-risk noncarriers, although not having such a high uptake for BRRM, were similar to mutation carriers with 43% uptake within the first 2 years ($P < 0.005$; Fig. 1B). Although the uptake of carriers tended to be early, there was a continued increase in uptake so that by 7 years the actuarial predicted uptake for BRRM for *BRCA1* carriers was 60% and 43% for *BRCA2* carriers (Fig. 2A). BRRM uptake is age dependent because the majority of women opted for surgery between the ages of 35 and 45 years (Figs. 1 and 2C). There was also a nonsignificant significant trend for high-risk women to have surgery before 35 and lower risk to have surgery after the age of 45 ($P = 0.47$).

Uptake of BRRM in Women at Risk of Breast Cancer but not Known to Carry a *BRCA1/2* Mutation. Data from the FHC in Manchester on women ages <60 years show that 6% of women at 25% lifetime risk or above seek further advice about BRRM. Among women at ≥25% risk, the age at first assessment ranged from 16.85 to 70.8 years (median, 38.8 years) and 95% are white Caucasian. The median follow-up among 3,515 women from first assessment was 8.1 years. Of these, 3.3% (112) finally decided to undergo BRRM. The uptake of surgery depends on the estimates of their lifetime risk of breast cancer. Of women

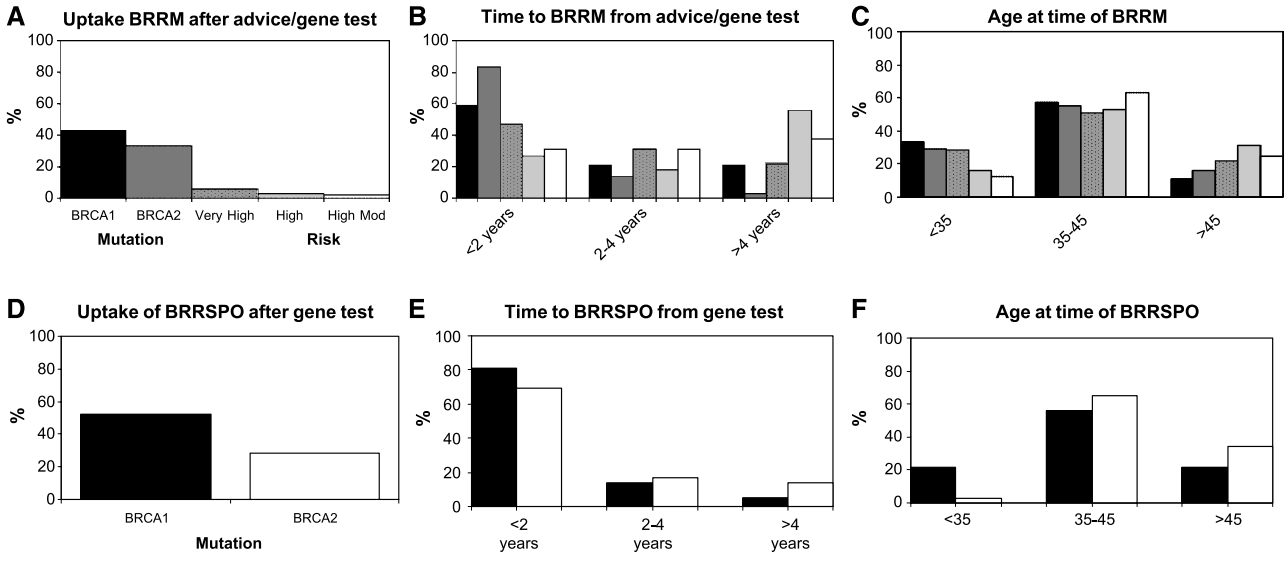

Figure 1. Uptake, time to surgery, and age at surgery for a >25% risk of developing breast cancer and to BRRSPO for mutation carriers.

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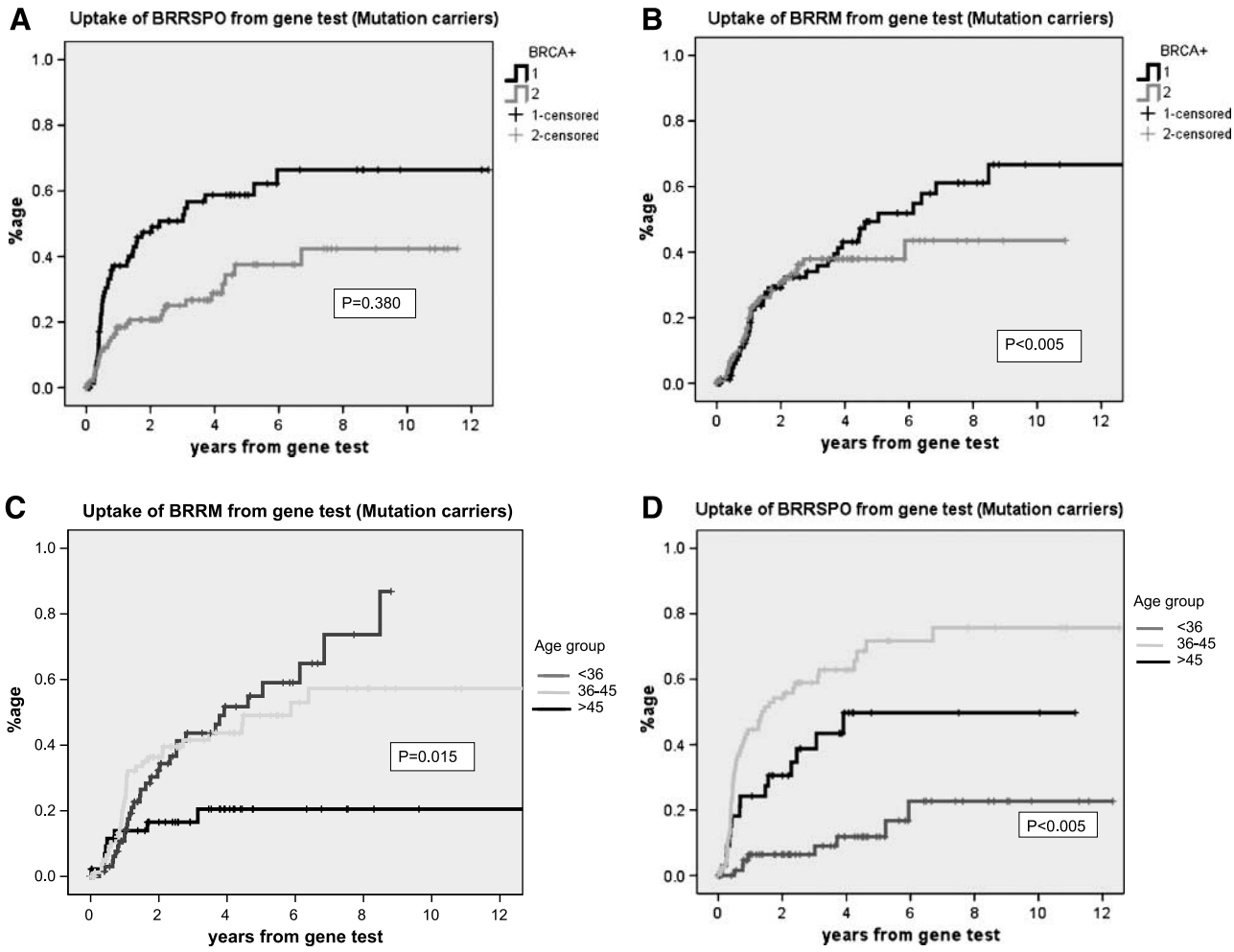

Figure 2. Comparison of cumulative percentage uptake of BRRM and BRRSPO in *BRCA1/2* carriers from time of genetic test result in previously unaffected women. **A.** BRRM stratified by gene. **B.** BRRSPO stratified by gene. **C.** BRRM stratified by age group. **D.** BRRSPO stratified by age group.

at 25% to 32% risk, 1.8% (16 of 902) have undergone surgery; the uptake increased to 2.5% (45 of 1,815) in women at 33% to 39% lifetime risk and 6.15% (49 of 798) in women at 40% to 45% lifetime risk (Table 1). Time to BRRM from testing/first assessment for all groups can be seen in Fig. 1.

Effect of Breast Biopsy. Of the 176 women who had attended the FHC for screening and subsequently undertook BRRM, 27 [15.3% (includes 5 of 64 *BRCA1/2* carriers)] had recently undergone a fine-needle aspiration of the breast, which proved benign. Of the remaining 3,523 women at ≥25% risk who had undergone screening at the FHC and who had not undertaken BRRM only, 270 [7.5% (includes 4 of 120 mutation carriers)] had received a benign fine-needle aspiration report at any time ($P < 0.01$).

Bilateral Risk-Reducing Salpingo-Oophorectomy. BRRSPO only applies to mutation carriers, for even very high risk of breast cancer non-mutation carriers does not substantially exceed the population risk for ovarian cancer (1 in 70 lifetime chance). The uptake of BRRSPO was greater for *BRCA1* carriers (52%) compared with 28% for *BRCA2* carriers (Fig. 2B). As with BRRM, uptake was usually within the first 2 years after gene test, although some waited beyond 4 years (especially those ages <35 years at genetic testing; Fig. 2D) so that the predicted uptake at 7 years was 65% for *BRCA1* and 40% for *BRCA2* (Fig. 2B), again statistically significant ($P < 0.005$). Most surgery, as with BRRM, occurred between the ages of 35 and 45 years, although *BRCA1* carriers had surgery at a lower age, reflecting the earlier onset of ovarian cancer in *BRCA1* carriers compared with *BRCA2* carriers.

Uptake of Predictive Testing among Women Having Previously Undertaken Risk-Reducing Surgery. We have assessed the uptake of genetic testing in women where the result became available after they had undertaken risk-reducing surgery. Mutations were detected in the families of 25 women after they had undergone BRRM and they thus became eligible for predictive genetic testing. Of these, 24 (96%) have proceeded to testing. Fifty women with previous BRRSPO became eligible for genetic testing. Of these, 33 (66%) have undertaken testing compared with only 393 of 930 (42%) of women who had not undergone previous surgery. Women who had previously undergone BRRM were statistically more

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likely to undertake predictive testing than both the BRRSPO group ($\chi^2 = 5.239$; $P = 0.022$) and the nonsurgery group ($\chi^2 = 22.44$; $P < 0.005$). The BRRSPO group was also more likely to undergo predictive testing than the nonsurgery group ($\chi^2 = 11.33$; $P = 0.005$).

Discussion

This large single-center study in women unaffected by breast cancer with and without *BRCA1/2* mutations has shown that uptake of risk-reducing surgery is risk, time, and age dependent. All women seen in a FHC since 1994 have received a personalized risk assessment, and those with an estimated lifetime risk of breast cancer between 25% and 85% were offered BRRM. The uptake and timing of surgery was directly related to the magnitude of the risk of breast cancer, and most women had BRRM between the ages of 35 and 45. This was similar for women with proven ovarian cancer risk, with most *BRCA1/2* carriers opting for BRRSPO in the same age group. It is not surprising that women at very high risk were more likely to undergo surgery, but we believe we are the first to report that uptake of risk-reducing surgery in unaffected women is dependent on risk level, especially with respect to families without proven mutations but at high familial risk of breast cancer. To our knowledge, this is the first study to describe actual uptake in women who have undertaken BRRM on risk alone. Although previous studies have reported outcomes of surgery in these women (2), no study has shown the effect of counseled risk; indeed, one study of 254 women showed that counseled risk did not influence intentions to undergo BRRM (15). We have shown a clear effect of counseled risk on actual uptake with this increasing from 1.8% at the lowest level of risk acceptable for preventive surgery (25-32%) to 6.4% of those at 40% to 45% risk. In *BRCA1/2* carriers where risk is even higher, uptake reached 40%. Even among *BRCA1/2* mutation carriers, there is evidence for lower uptake of BRRSPO among *BRCA2* carriers (9). This may reflect the lower incidence and marginally better prognosis of ovarian cancer in *BRCA2* mutation carriers (16).

Women continue to opt for surgery at least 7 years following their presymptomatic genetic test. This was also true for BRRM in those undertaking surgery on risk alone from time of first assessment. For BRRSPO, this may reflect a decision to defer surgery in a young woman who has not finished childbearing. However, for BRRM, this may reflect greater difficulty with the decision. Anecdotally, women undertaking BRRM later seemed to do so because of a further breast cancer morbidity or mortality in their family. Psychological factors may also affect women's decisions, including their subjective risk of breast cancer, cancer worry, previous breast biopsies, and educational level (17-21). Breast biopsies are potential trigger factors for uptake of BRRM. Clinical experience indicates that many women require a longer period of reflection, information gathering, and consultation before deciding to proceed to risk-reducing surgery. Life stage, occupation, and educational commitments may also lead to a deferment for some women. The results of this study show that it is inappropriate to assume that uptake after as little as 1 to 3 years of follow-up will be the definitive figure for all women (22-30). Previous studies show uptakes of between 0% to 54% for BRRM, in *BRCA1/2* mutation carriers, but do not discuss the likelihood of further women undergoing the procedure.

In an Australian study (22) of 142 unaffected female mutation carriers, 70 (49%) had elected to receive their mutation result. Of those who knew their mutation result, 11% underwent BRRM and 29% had bilateral BRRSPO. These figures are much lower than in the present study. However, the median follow-up was 2.9 years (22) compared with our 4.1 years. A large multicenter study in the United Kingdom, including our center, reported an uptake of 34% for BRRM and 43% for BRRO at the 3-year point among 193 unaffected women testing positive for *BRCA1*/2 (23). At 2.9-year follow-up time, only 82%/83% of our total BRRM/BRRSPO had been done. Fifty percent of women in the Australian study will not have reached even the 2.9-year point. The health service system in Australia is similar to the United Kingdom; it is likely, therefore, that their study will have underestimated uptake of surgery by at least 30%. The UK multicenter study is likely to give more realistic uptake figures beyond 3 years because of the greater number of cases. Our study suggests that women continue to opt for surgery beyond this point.

Another study in women with *BRCA1/2* mutations from nine countries, including North America, examined differences in uptake according to country (9). Information was recorded on BRRM and BRRSPO. In 2,677 women with a *BRCA1/2* mutation, a follow-up questionnaire was completed (mean, 3.9 years; range, 1.5-10.3 years) after genetic testing. One thousand five hundred thirty-one women (57.2%) had undergone BRRSPO. Of the 1,383 women without breast cancer, 248 (18.0%) had had BRRM. There were large differences in the uptake of the different preventive options by country of residence. This difference in uptake may be due to both the women themselves and their clinicians (7, 31, 32), reflecting important cultural differences. For instance, in a study of Israeli women, BRRSPO was perceived as more acceptable both from an attitudinal as well as practical aspect, reflected in large differences in uptake from BRRM. Greater trust in breast screening may also have contributed (32). From a psychological point of view, anticipation of regret that women would feel if they developed breast cancer having rejected the option of surgery together with fear of leaving young children motherless have also been found to be predictive of uptake of BRRM, signifying an emotional coping process in decision making (33). Differences in uptake have been widely reported (2, 8), but the great variation even within North America is remarkable (2, 8-10). Clearly, some of this variation is related to the attitudes of clinicians who may offer these options or not (9, 32). Our uptake of BRRM is high even for Northern Europe. This may reflect that BRRM, including skin-sparing mastectomy, is discussed as a realistic option for all women at high risk, and they have access to excellent oncoplastic surgical reconstruction (6, 11, 12, 34). Although the large study of uptake between countries (9) confirms the large differences in uptake, it did not explore the issue of time since testing. Uptake for BRRM by 7 years was 43% to 60% of *BRCA1/2* carriers in our study. The prevalence figures given in these studies may be misleading, as prevalence figures reflect the uptake in women at a range of follow-up times from assessment/genetic testing, which may include many women at <1 year who have not had time to make a decision for surgery (our prevalence figure is currently only 37%).

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Uptake rates in women with breast cancer for contralateral mastectomy are clearly related to risk. Several studies, including one from our own center, have shown that testing positive for a *BRCA1/2* mutation substantially increases uptake of risk-reducing contralateral surgery (35-37). This is particularly the case when testing is available at the time of diagnosis when uptake rates are even higher than unaffected BRRM rates. Rates also vary considerably between countries with 0% uptake in Norway and 49% in the United States (37). However, women finding out mutation status after completing their primary breast cancer treatment have a lower uptake of risk-reducing mastectomy than those who are identified before definitive surgery (35).

This study is the first to explore this new area of time since testing and showed that women are still likely to have risk-reducing surgery more than 7 years afterwards. This is particularly true for young women who, after completing their family, then opt for BRRSPO, but there is also a substantial deferment in uptake in some for BRRM.

There are important differences in age at testing. There is very little uptake of BRRM in women tested over 45 years, but the vast majority of *BRCA1* carriers over 35 years opt for BRRSPO. Uptake in younger women of BRRSPO is likely to be delayed until the family is complete, but uptake at <35 years is still significant in *BRCA1* (13).

We have also found that women who have undergone BRRM are more likely to come forward for predictive genetic testing than other women at risk. Lerman et al. previously reported their surprise that women in this group were not only keen to know their mutation status but also delighted when they tested negative (24). As women are continuing to opt for BRRM despite the absence of a genetic test in their family, it is reassuring that as long as they are well prepared, this is unlikely to lead to adverse consequences should they later test negative for the family breast cancer predisposing mutation.

Our study has found that uptake of risk-reducing surgery is age, risk, and time dependent and likely to be higher overall in long-term follow-up than previous estimates. Many women with *BRCA1/2* mutations are still opting for BRRM despite the offer of magnetic resonance imaging screening. It seems likely that it will need a greater prospect of nonsurgical prevention to provide a reasonable alternative to preventive surgery for many women. Unfortunately, uptake of chemoprevention trials remains disappointing in this high-risk group (38). Until such breakthroughs in prevention and improvements in screening are delivered, a large proportion of fully informed women will still opt for BRRSPO and BRRM as the only valid risk-reducing options.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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