Ten-Year Multi-Institutional Results of Breast-Conserving Surgery and Radiotherapy in BRCA1/2-Associated Stage I/II Breast Cancer


ABSTRACT

Purpose
We compared the outcome of breast-conserving surgery and radiotherapy in BRCA1/2 mutation carriers with breast cancer versus that of matched sporadic controls.

Methods
A total of 160 BRCA1/2 mutation carriers with breast cancer were matched with 445 controls with sporadic breast cancer. Primary end points were rates of in-breast tumor recurrence (IBTR) and contralateral breast cancers (CBCs). Median follow-up was 7.9 years for mutation carriers and 6.7 years for controls.

Results
There was no significant difference in IBTR overall between carriers and controls; 10- and 15-year estimates were 12% and 24% for carriers and 9% and 17% for controls, respectively (hazard ratio [HR], 1.37; P = .19). Multivariate analyses for IBTR found BRCA1/2 mutation status to be an independent predictor of IBTR when carriers who had undergone oophorectomy were removed from analysis (HR, 1.99; P = .04); the incidence of IBTR in carriers who had undergone oophorectomy was not significantly different from that in sporadic controls (P = .37). CBCs were significantly greater in carriers versus controls, with 10- and 15-year estimates of 26% and 39% for carriers and 3% and 7% for controls, respectively (HR, 10.43; P < .0001). Tamoxifen use significantly reduced risk of CBCs in mutation carriers (HR, 0.31; P = .05).

Conclusion
IBTR risk at 10 years is similar in BRCA1/2 carriers treated with breast conservation surgery who undergo oophorectomy versus sporadic controls. As expected, CBCs are significantly increased in carriers. Although the incidence of CBCs was significantly reduced in mutation carriers who received tamoxifen, this rate remained significantly greater than in controls. Additional strategies are needed to reduce contralateral cancers in these high-risk women.

INTRODUCTION

Women with germline BRCA1/2 mutations have a 55% to 85% cumulative lifetime risk of breast cancer by age 70.1,3 Among BRCA1/2 mutation carriers who are at risk for breast cancer, preventive strategies that may significantly reduce this risk include bilateral prophylactic mastectomy4,6 or hormonal interventions such as bilateral oophorectomy and tamoxifen.7,9 For mutation carriers diagnosed with breast cancer, questions remain regarding the choice of best local therapy. In patients with sporadic breast cancer, conservative surgery and radiotherapy (RT) results in survival equivalent to that achieved with mastectomy and is widely used in the management of early-stage disease.10,11 Conflicting reports exist, however, regarding the success of a conservative approach in known BRCA1/2 mutation carriers, with some series reporting comparable outcomes to those achieved in sporadic breast cancer patients, whereas others suggest higher rates of in-breast tumor recurrence (IBTR) among BRCA1/2 carriers.12-16 Therefore, we evaluated the outcomes of BRCA1/2 mutation carriers with breast cancer treated with breast conservation therapy compared with matched sporadic controls with less than a 5% prior probability of having a detectable mutation in either gene. We also examined
the potential impact of oophorectomy and tamoxifen on rates of IBTR and the development of contralateral breast cancers (CBCs) in BRCA1/2 mutation carriers.

**METHODS**

**Study Design**

Investigators from 11 institutions in the United States (University of Pennsylvania, Philadelphia, PA; University of Utah, Salt Lake City, UT; Yale University, New Haven, CT; University of Chicago, Chicago, IL; Georgetown University, Washington, DC; University of Michigan, Ann Arbor, MI; Dana-Farber Cancer Institute, Boston, MA), Canada (University of Toronto, Toronto, ON; British Columbia Cancer Agency, Victoria, BC; Hamilton Regional Cancer Center, Hamilton, ON), and Israel (Sheba Medical Center, Ramat Gan) identified in their databases those women with stage I/II breast cancer and deleterious BRCA1/2 mutations treated with breast conservation therapy who consented to institutional review board (IRB) approved longitudinal studies at each institution. Patients were included if the breast cancer diagnosis was before or after inclusion in these longitudinal institutional studies. All patients were ascertained regardless of recurrence or survival status. Clinical data were abstracted through record review according to IRB guidelines at each collaborating institution and were then entered in a centralized database at the University of Michigan. Unique identifiers were assigned to maximize confidentiality per IRB compliance guidelines.

The study was designed as a retrospective cohort study of women diagnosed with a first primary breast cancer. Mutation carriers were women with a known deleterious BRCA1 or BRCA2 mutation and breast cancer treated with breast conservation therapy. They were matched by age (within 2 years) and date of diagnosis (within 6 months) in a 1:1 ratio with sporadic controls, defined as women with breast cancer treated with breast conservation therapy with less than a 5% prior probability of having a BRCA1/2 mutation. Controls were selected randomly from the radiation oncology databases within the same institution to control for variation in institutional treatment policies.

**Patient Cohorts**

**Genetic mutation carrier cohort.** Women with deleterious germline BRCA1/2 mutations treated with breast conservation therapy for stage I/II breast cancer diagnosed by April 2001, who had previously consented to longitudinal follow-up studies, were identified in the databases of the high-risk clinics of the collaborating institutions. All patients in the genetic mutation carrier cohort were tested for BRCA1/2 germline mutations and were known to be mutation carriers with the exception of three patients who were dead at time of the analysis but were affected members of families with known deleterious germline mutations. Methods used for mutation testing included protein-truncation testing, conformation-sensitive gel electrophoresis, allelic discrimination assay, and direct sequencing of DNA. All mutations were known to result in a truncated protein and were considered deleterious mutations. Women with sequence variants of uncertain significance were excluded from the data set.

**Sporadic controls.** Controls were women with stage I/II breast cancer treated with breast conservation therapy, with no more than one postmenopausal relative with breast cancer and no family history of ovarian cancer. Using these criteria for control selection, no more than 5% of controls would be expected to have BRCA1/2 mutations. For IBTR rates between nonsurgical genetic and sporadic participants using the Cox proportional hazards model. Rates of IBTR were then compared between nonsurgical sporadic participants and surgical genetic patients, under the assumption that all bilateral oophorectomies in the genetic mutation carrier cohort were performed at the time of their initial diagnosis of breast cancer. These expected rate estimates for the genetic oophorectomy group were computed from the Cox model from the first analysis and compared with the observed rates from the nonsurgical sporadic participants using a log-rank test.

**RESULTS**

**Study Populations**

A total of 160 patients, all with a deleterious BRCA1/2 mutation, were identified in the databases of the collaborating institutions. All known patients with genetic mutations who met the study criteria were included in the analyses. Of the 160 carriers, 123 had BRCA1 mutations and 37 were BRCA2 mutation carriers. Because of the limited number of BRCA2 mutation carriers, analyses of mutation carriers were performed combining all carriers into one genetic mutation carrier cohort. These 160 patients were matched to 445 controls. One hundred thirty-two patients were matched 1:3 to controls; because of the limited numbers of controls of comparable young age and follow-up, 21 patients were matched 1:2 and seven were matched 1:1. Median observation time for mutation carriers was 7.9 years (range, 0.5 to 23.4 years) and 6.7 years (range, 0.3 to 21.7 years) for controls. Median age at diagnosis was 40.1 years (range, 21.9 to 74.3 years) for carriers and 41.0 years (range, 22.6 to 75.1 years) for controls.

The clinical and pathologic characteristics of the mutation carriers and sporadic controls are compared in Table 1. Treatment factors were comparable between groups, however negative/close margins were more commonly observed among mutation carriers ($P = .06$). Mean RT dose to the breast was comparable between cohorts (47.5
In-Breast Tumor Recurrence

There was no significant difference in overall rates of IBTR between the two cohorts (Fig 1A). Ten- and 15-year IBTR rates were 12% (95% CI, 9% to 15%) and 24% (95% CI, 17% to 33%) in mutation carriers versus 9% (95% CI, 7% to 10%) and 17% (95% CI, 12% to 21%) in sporadic controls, respectively (P = .19). Among patients who experienced local recurrence, the median time to IBTR was 8.7 years for mutation carriers and 4.7 years in the controls (P = .01). Information from clinical records regarding the quadrant of the original lesion and the recurrence was available in 15 of 19 (79%) isolated recurrences in the carriers and in 31 of 35 (89%) controls. Recurrent lesions in carriers were located more commonly in quadrants other than the quadrant of the primary lesion versus controls (ie, 60% v 29%; P = .04). With 3.3-year median follow-up time after IBTR in the mutation carriers and 2.9-year median follow-up time in the sporadic controls, recurrence at any site occurred in 29% (10 of 35) of controls experiencing an IBTR compared with 0% (0 of 19) in mutation carriers (P = .01).

IBTR was assessed within the genetic mutation carrier cohort by bilateral oophorectomy status. A statistically nonsignificant reduction in IBTR after oophorectomy was observed in mutation carriers who underwent oophorectomy compared with those who did not (hazard ratio [HR], 0.55; P = .44). However, when IBTR was compared among mutation carriers and sporadic controls who did not undergo bilateral oophorectomy, IBTR was significantly higher in mutation carriers, as shown in Figure 1B (HR, 1.9; P = .03). To determine whether the more favorable results in the oophorectomy patients, in part, could be due to an excess of estrogen receptor (ER)–positive tumors in patients who underwent oophorectomy, ER status was compared between mutation carriers who did and did not undergo bilateral oophorectomy; 26% of cancers in patients who underwent oophorectomy were ER positive versus 20% in patients who did not undergo oophorectomy (P = .43).

IBTR was compared by tamoxifen use. The effect of tamoxifen was found to be independent of mutation status (interaction P = .52), therefore outcome after tamoxifen was assessed in the combined genetic mutation carriers and sporadic cohorts. Tamoxifen use was associated with a 58% reduction in IBTR (HR, 0.42; P = .07). When the analysis was performed in the combined cohort, only in those patients who did not undergo bilateral oophorectomy was a 63% reduction in IBTR observed (HR, 0.37; P = .06). When similar analyses were performed within the genetic mutation carriers cohort only, a nonsignificant reduction in IBTR was observed in mutation carriers who received tamoxifen, with 5-, 10-, and 15-year estimates of IBTR of 0%, 0%, and 22% in mutation carriers versus 5%, 14%, and 25% in mutation carriers without tamoxifen, respectively (HR, 0.29; P = .22). When tamoxifen use was analyzed specifically in patients with genetic mutations who had not undergone oophorectomy, no subsequent IBTRs were observed in the group taking tamoxifen versus 5-, 10-, and 15- year IBTR rates of 8%, 17%, and 31% without tamoxifen, respectively (P = .1).

Multivariate analyses for IBTR were then performed for all patients in the genetic and sporadic cohorts, and then between only those mutation carriers and sporadic controls who did not undergo bilateral oophorectomy (Table 2). Although mutation status was not an independent predictor of IBTR in the overall data set, it was a significant predictor when all patients who underwent bilateral oophorectomy were removed from the analysis (P = .04).

CBCs

Similar analyses were performed for the development of CBCs. Patients in the genetic mutation carrier cohort had a significantly greater risk of developing CBCs compared with controls. Ten- and
15-year rates of CBCs were 26% (95% CI, 22% to 30%) and 39% (95% CI, 31% to 47%) in mutation carriers compared with 3% (95% CI, 2% to 4%) and 7% (95% CI, 5% to 10%), respectively, in sporadic controls (HR, 9.57; \( P < .0001 \); Fig 2). Differences in CBC rates between the cohorts with genetic mutations and sporadic controls were greater among mutation carriers who had not undergone oophorectomy compared with controls, with 5-, 10-, and 15-year estimates of CBC in mutation carriers of 16%, 34%, and 45% v 1%, 4%, and 9% in controls, respectively (HR, 10.47; \( P < .0001 \)).

In the combined genetic and sporadic cohorts, tamoxifen use was associated with a significant reduction in the rate of CBCs (HR, 0.25; \( P < .005 \)). In the combined cohort of patients who did not undergo oophorectomy, an additional reduction in CBCs was observed with tamoxifen use (HR, 0.11; \( P = .001 \)). A significant reduction in the rates of CBCs was observed within the mutation carriers by tamoxifen use, with an approximate 69% reduction in CBC among mutation carriers who received tamoxifen versus mutation carriers not treated with tamoxifen (HR, 0.13; \( P = .02 \)). When rates of CBCs were then compared among mutation carriers by whether they underwent oophorectomy, the risk reduction with tamoxifen was even greater, with 5-, 10-, and 15-year estimates with and without tamoxifen of 6% v 19%, 6% v 41%, and 6% v 54%, respectively (HR, 0.13; \( P = .02 \)). When rates of CBCs were then compared among mutation carriers by whether they underwent oophorectomy, the risk reduction with tamoxifen was even greater, with 5-, 10-, and 15-year estimates with and without tamoxifen of 6% v 19%, 6% v 41%, and 6% v 54%, respectively (HR, 0.13; \( P = .02 \)).

### Table 2. Multivariate Analysis for Ipsilateral and Contralateral Breast Tumor Failure

<table>
<thead>
<tr>
<th></th>
<th>Category†</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
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<td>Mutation status</td>
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<td>1.37</td>
<td>0.77 to 2.42</td>
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<td>1.99</td>
<td>1.04 to 3.79</td>
<td>.04</td>
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<td>Tamoxifen</td>
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<td>0.39</td>
<td>0.09 to 1.69</td>
<td>.21</td>
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<td>0.25 to 0.95</td>
<td>.03</td>
<td>0.52</td>
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<td>Margins</td>
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<td>0.18 to 3.19</td>
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<td>1.41</td>
<td>0.32 to 6.30</td>
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<tr>
<td>Stage</td>
<td>II v I</td>
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<td>0.36 to 1.33</td>
<td>.27</td>
<td>0.71</td>
<td>0.33 to 1.53</td>
<td>.38</td>
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<tr>
<td>Age§</td>
<td></td>
<td>0.96</td>
<td>0.92 to 0.99</td>
<td>.01</td>
<td>0.96</td>
<td>0.92 to 0.99</td>
<td>.02</td>
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<tr>
<td>Mutation status</td>
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<td>&lt; .0001</td>
<td>11.73</td>
<td>5.76 to 23.87</td>
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<td>.33</td>
<td>1.00</td>
<td>0.97 to 1.04</td>
<td>.99</td>
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</tbody>
</table>

Abbreviation: HR, hazard ratio.
†Ipsilateral/contralateral tumor failure for patients with genetic mutations and sporadic controls overall.
†Ipsilateral/contralateral tumor failure for patients with genetic mutations and sporadic controls who did not undergo bilateral oophorectomy.
‡The referent group is always the second of the two categories.
§The HR for age refers to the risk associated with a 1-year increase in age.
oophorectomy, a nonsignificant reduction in CBCs was observed after oophorectomy (HR, 0.46; $P = .15$).

Multivariate analyses for CBCs were performed first for all patients in the genetic and sporadic cohorts, and second, only in mutation carriers and controls who had not undergone oophorectomy (Table 2). As expected, mutation status was a highly significant predictor for the development of CBCs in both analyses, with an approximately 10-fold increase in BRCA1/2 mutation carriers in the overall analysis, and a 12-fold increase when patients who had undergone oophorectomy were excluded.

**Ipsilateral and Contralateral Tumor Events After Bilateral Oophorectomy**

Given that the relative risk reduction associated with tamoxifen use was shown to be similar between mutation carriers and sporadic controls overall, outcome after oophorectomy in BRCA1/2 carriers was compared with that in the general sporadic population (sporadic breast cancer patients who had not undergone oophorectomy). IBTR rates were not significantly different between the two cohorts ($P = .39$, Fig 3A). An analysis for risk of CBC in carriers who had undergone oophorectomy versus controls without oophorectomy demonstrated a statistically significant increase in CBCs in mutation carriers who had undergone oophorectomy versus controls ($P = .007$; Fig 3B).

**DISCUSSION**

This study demonstrated similar rates of IBTR between women with BRCA1/2 mutations and sporadic controls treated with breast-conserving surgery and RT. However, rates of IBTR were twice as high among BRCA1/2 mutation carriers who did not

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**Fig 2.** Overall contralateral breast cancers in BRCA1/2(r) mutation carriers and sporadic controls. HR, hazard ratio.

**Fig 3.** (A) Ipsilateral breast tumor recurrence among BRCA1/2(r) mutation carriers who have undergone bilateral prophylactic oophorectomy (BO) versus sporadic controls who have not undergone oophorectomy. (B) Contralateral breast cancers among BRCA1/2 mutation carriers who have undergone BO versus sporadic controls who have not undergone oophorectomy. The number of events for the BO genetic mutation carrier groups is predicted based on the described respective time-dependent covariate models under the assumption that the BO occurred at the time of the breast cancer diagnosis for each patient.
undergo oophorectomy compared with controls (Fig 1B). However, when the outcome in only those mutation carriers who underwent bilateral oophorectomy was compared with that of sporadic controls, the risk of IBTR was similar (Fig 3A). Furthermore, when tamoxifen use was analyzed in mutation carriers who had not undergone oophorectomy, no local failures were observed in carriers after tamoxifen, compared with rates of 8%, 17%, and 31% at 5, 10, and 15 years, respectively, without tamoxifen. Collectively, these results suggest a benefit in in-breast tumor control in BRCA1/2 carriers from hormonal interventions.

Prior outcome studies of BRCA1/2 mutation carriers treated with breast conservation therapy generally have not considered the impact of tamoxifen and bilateral oophorectomy on rates of IBTR. Although some series have shown similar rates of IBTR between mutation carriers and sporadic controls, others have shown increased rates of IBTR among mutation carriers. Many of these studies have not commented specifically on the use of tamoxifen or whether patients have undergone prophylactic oophorectomy. One exception, however, was a series from Yale University, which demonstrated a highly significant increase in IBTR in mutation carriers compared with controls; no patients in this study underwent bilateral oophorectomy or received tamoxifen. Thus, our results suggest that either lack of consideration of the effect of bilateral oophorectomy and/or tamoxifen or the selection of patients who did receive either intervention may have contributed to the discordant rates of IBTR after breast-conserving surgery and RT in BRCA1/2 carriers versus controls in previously reported series.

Both the increased interval to local recurrence and the increased frequency of recurrences in quadrants other than the primary in mutation carriers compared with controls suggest that most of the IBTRs in mutation carriers are second primary cancers rather than true recurrences; this finding also was observed by others. Although the sample size in this study may have been too small for this difference to reach statistical significance, a trend suggesting a decreased IBTR risk was associated with both bilateral oophorectomy and tamoxifen use; these findings are consistent with previously published data from our group and others. We and others have demonstrated previously a significant reduction in breast cancer risk in mutation carriers after bilateral oophorectomy. In an analysis of 99 BRCA1/2 mutation carriers who underwent oophorectomy and 142 who did not, the risk of a subsequent breast cancer was reduced by 53% after oophorectomy. Similar to our results, tamoxifen use was also associated with a 41% reduction in breast cancer risk in BRCA1/2 mutation carriers previously. Thus, our findings are consistent with a prevention of new cancers with bilateral oophorectomy and tamoxifen.

Although the present results demonstrate a reduction in ipsilateral and contralateral breast cancer events associated with oophorectomy and tamoxifen use in BRCA1/2 carriers, the reductions are modest compared with the 90% or greater reductions observed after bilateral prophylactic mastectomy. Given that a randomized comparison between breast conservation therapy versus therapeutic and prophylactic mastectomy in BRCA1/2 carriers with early-stage breast cancer is not feasible, a meta-analysis may be needed to formulate treatment recommendations. Schwartz et al observed that approximately equal percentages of breast cancer patients with BRCA1/2 mutations chose bilateral mastectomy and breast-conserving surgery as their definitive surgery. Thus, considerable interest exists in breast conservation therapy among mutation carriers. Our results support consideration of tamoxifen use and bilateral oophorectomy in BRCA1/2 carriers interested in breast conservation for reduction in both ipsilateral and contralateral breast cancers. However, even with these strategies, a significantly higher risk of CBC remains in carriers compared with that observed in sporadic controls. Thus, additional risk reduction interventions are needed in BRCA1/2 carriers interested in breast conservation, particularly for long-term control of the contralateral (uninvolved) breast.

Although this study yielded clinically relevant information for BRCA1/2 mutation carriers, several limitations should be noted. This study was sufficiently powered to evaluate differences in the recurrence rates between mutation carriers and controls; however, assessment of tamoxifen use and bilateral oophorectomy as factors potentially influencing the risk of recurrence were not accounted for in the initial design of the study. Second, this is a retrospective cohort study. Ideally, the influence of oophorectomy on IBTR/new cancers and CBCs would be studied in a prospective clinical trial to eliminate the potential for lead-time bias. However, given the frequent practice of performing prophylactic bilateral oophorectomies in known BRCA1/2 carriers, it is unclear whether such a trial could be performed. It should be noted that we accounted for a potential lead-time bias by adjusting for the timing of oophorectomy by use of a time-dependent covariate analysis. We also acknowledge that differences in methods of entry into this study could have resulted in an unintentional selection bias. Specifically, patients in the sporadic cohort were obtained by randomly selecting patients from radiation oncology institutional databases who fulfilled the matching criteria. They were not constrained by consent to longitudinal follow-up as in the cohort with genetic mutations. As noted previously, prospective recruitment of patients onto the study would minimize the risk of bias, but it is unclear whether such a prospective trial would be feasible. Finally, we defined bilateral oophorectomy as a prophylactic procedure that occurred at least 3 months before a breast cancer recurrence to minimize inclusion of those patients in who, the oophorectomy might have been performed as part of the therapy for a breast cancer recurrence. Had the defined interval between time to oophorectomy and recurrence been greater than the 3 months, the protective effect of oophorectomy would likely have been more pronounced.

In summary, our results demonstrate comparable 10-year rates overall of IBTR among BRCA1/2 mutation carriers with those observed in matched sporadic controls after breast-conserving surgery and RT. These data also suggest that tamoxifen use and bilateral oophorectomy were associated with reduced IBTR/new primary cancer risk and fewer CBCs in mutation carriers. These findings are consistent with the reduction in new cancers after tamoxifen use and oophorectomy observed by others in BRCA1/2 carriers without a prior diagnosis of breast cancer. Thus, the potential impact of oophorectomy and tamoxifen use should be discussed with BRCA1/2 mutation carriers with breast cancer contemplating breast conservation therapy, and the effect of oophorectomy and tamoxifen use should be considered in future analyses of breast conservation in BRCA1/2-associated disease. Despite these interventions, mutation carriers had a significantly greater risk of developing CBCs when compared with sporadic controls. Thus, additional strategies are needed in BRCA1/2 mutation carriers interested in breast conservation primarily to reduce their CBC risk to levels observed in women with early-stage sporadic disease.
REFERENCES


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Additional authors involved in the design of the study, acquisition of patient data, and interpretation of the results are Sharon L. Kardia from the University of Michigan, School of Public Health, Ann Arbor, MI, and Kelly Metcalfe from the University of Toronto, Toronto, Ontario, Canada.

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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