

# Survival Differences in Women with and without Autologous Breast Reconstruction after Mastectomy for Breast Cancer

John L. Semple, MD\*  
 Kelly Metcalfe, RN, PhD†‡  
 Farah Shoukat, MBBS†  
 Ping Sun, PhD‡  
 Steven Narod, MD‡

**Background:** Breast reconstruction (BR) is an option for women who are treated with mastectomy; however, there has been concern regarding the oncologic safety of BR. In this study, we evaluated recurrences and mortality in women treated with mastectomy and compared outcomes in those treated with mastectomy alone to those with mastectomy plus transverse rectus abdominis (TRAM) flap BR.

**Methods:** The prospective cohort study included women treated with mastectomy at Women's College Hospital from 1987 to 1997. Women with TRAM flap BR were matched to controls based on age and year of diagnosis, stage, and nodal status. Patients were followed from the date of diagnosis until death or date of last follow-up. Hazard ratios were generated to compare cases and controls for outcome variables using Cox's proportional hazards models.

**Results:** Of 443 women with invasive breast cancer, 85 subjects had TRAM flap BR. Sixty-five of these women were matched to 115 controls. The mean follow-up was 11.2 (0.4–26.3) years. There were no significant differences between those with and without BR with weight, height, or smoking status. Women with TRAM flap were less likely to experience a distant recurrence compared to women without a TRAM flap (relative risk, 0.42;  $P = 0.0009$ ) and were more likely to be alive (relative risk, 0.54;  $P = 0.03$ ).

**Conclusions:** Women who elect for TRAM flap BR after an invasive breast cancer diagnosis do have lower rates of recurrences and mortality than women treated with mastectomy alone. This cannot be explained by differences in various clinical or lifestyle factors. (*Plast Reconstr Surg Glob Open* 2017;5:e1281; doi: 10.1097/GOX.0000000000001281; Published online 3 April 2017.)

**B**reast cancer is the most common cancer in women.<sup>1</sup> Surgical treatment for women with invasive breast cancer includes either breast-conserving surgery or mastectomy. Recent trends suggest that the rates of mastectomy are rising.<sup>2,3</sup> For these women, postmastectomy breast reconstruction (BR) is an option that can be performed immediately (at the same time as mastectomy) or delayed (anytime after mastectomy). In the United States, the uptake of immediate breast reconstruction (IBR) ranges from 25% to 35% in women treated with

mastectomy.<sup>4,5</sup> In Canada, the uptake of IBR is considerably lower, with only 16% of women having IBR.<sup>6,7</sup> For women who do not have IBR, delayed BR is an option anytime after mastectomy. Postmastectomy BR can include either implant reconstruction or autologous tissue reconstruction.

Concerns have been raised that recurrences may not be detected in women with BR, and this may have had an impact on the use of reconstruction.<sup>8,9</sup> However, recent evidence suggests that postmastectomy BR does not impair detection of recurrences.<sup>10</sup> Furthermore, there has been concern that the use of postmastectomy BR could negatively affect survival rates in women with invasive breast cancer. However, there are now short- and long-term follow-up data that suggest that there is no impact of postmastectomy BR on survival.<sup>11,12</sup> Recently, it has been reported that postmastectomy BR may offer improved survival compared with mastectomy alone.<sup>13</sup> In a large cohort

From the \*Department of Surgery, Women's College Hospital, Toronto, Canada; †Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Canada; and ‡Breast Cancer Research, Women's College Research Institute, Toronto, Canada.

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of women with invasive breast cancer in Ontario, Canada, followed for over 20 years after diagnosis, BR was associated with a 17% reduced risk of death and a 19% reduced risk of breast cancer death.<sup>13</sup> This analysis included all types of BR, and it is unclear whether there are differences by type of BR. It has been suggested that the survival benefit may be due to “patient selection” issues by the surgeon or “lifestyle” characteristics of the patient. The objective of this study was to compare overall and breast cancer-specific survival in women treated with mastectomy for invasive breast cancer with and without autologous BR, taking into consideration lifestyle factors such as body mass index and smoking.

## METHODOLOGY

### Sample

We studied a cohort of women diagnosed with invasive breast cancer between the years 1987 and 1997 at the Henrietta Banting Breast Centre (HBBC). This database contains information on all women diagnosed with and treated for invasive breast cancer at Women’s College Hospital (WCH), Toronto, Canada. It was established to systematically collect data on clinical presentation, treatment, and outcomes in women who received primary breast surgery at WCH. Women whose information entered into the database are followed every 2 years to assess for new cancers, cancer recurrence, and vital status.

For this study, women were selected from the database if they had undergone mastectomy for an invasive breast cancer diagnosis (stages 1–3). Cases were identified as women who had a TRAM flap BR after mastectomy. Cases were matched to controls based on age of breast cancer diagnosis ( $\pm 2$  y), year of diagnosis ( $\pm 2$  y), stage, and lymph node status (positive/negative).

### Analysis

Cases and controls were compared for demographic and clinical characteristics using the *t* test for continuous variables and the chi-square test for categorical variables. Cox’s proportional hazards models were used to evaluate the relative risk (RR) of TRAM flap on breast cancer recurrence and death. Statistical analyses were done by SAS (9.4).

## RESULTS

Four hundred forty-three women with invasive breast cancer were treated with mastectomy, of which 85 subjects had TRAM flap BR. We were able to match 65 cases with 115 controls based on matching criteria (defined above). The mean age of the women at breast cancer diagnosis was 45.6 years (SD, 7.8), and for those with TRAM flap BR, the mean age at time of reconstruction was 46.9 years (SD, 8.2). Of the women with BR, 41.5% had IBR. There was a mean of 11.2 (0.4–26.3) years of follow-up available on the cohort and did not differ between cases and controls [10.4 y (0.4–26.2) for controls and 12.5 y (1.0–23.4) for cases with TRAM flap BR]. Cases and controls were similar with respect to demographic and clinical variables (Table 1).

There were no significant differences in weight ( $P = 0.89$ ), height ( $P = 0.30$ ), or smoking status ( $P = 0.20$ ) between women with and without BR.

In the multivariate analysis, women with TRAM flap were less likely to experience distant recurrence compared to women without TRAM (RR, 0.42;  $P = 0.009$ ) and more likely to be alive (RR, 0.54;  $P = 0.03$ ; Table 2). In the cases with TRAM flap, there were 18 deaths overall (27.7%) and 17 breast cancer-specific deaths (26.2%), and in controls, there were 49 deaths overall (42.6%) and 40 breast cancer-specific deaths (34.8%) ( $P = 0.05$  for breast cancer-specific death). The Kaplan–Meier overall survival estimates 25 years after invasive breast cancer diagnosis were 66.9% for women with TRAM flap [95% confidence interval (CI): 51.5%–78.4%] and 38.8% for women with mastectomy alone (95% CI: 19.5%–57.8%;  $P = 0.04$ ) (Fig. 1). The breast cancer-specific survival estimates at 25 years after invasive breast cancer diagnosis were 68.3% for cases with TRAM flap (95% CI: 57.2%–79.7%) and 56.8% for controls (95% CI: 41.9%–69.3%;  $P = 0.13$ ) (Fig. 2).

## DISCUSSION

For women treated with mastectomy, BR is an option to restore the breast mound. In this matched cohort study of women with invasive breast cancer treated with mastectomy over a 10-year period, postmastectomy TRAM flap BR was not associated with a worse prognosis. In fact, women with BR were significantly less likely to be diagnosed with a distant recurrence and were more likely to be alive at follow-up, compared to women with mastectomy alone. This could not be explained by differences in lifestyle or clinical factors between women with and without breast cancer.

The choice between autologous and implant-based postmastectomy BR is based on multiple factors, including treatment factors (including radiation therapy) and patient-specific factors and preferences. The majority of research that has been done examining oncologic safety of BR has not examined type of reconstruction separately (autologous vs implant)<sup>13–16</sup> or has focused solely on implant-based reconstruction.<sup>10,17,18</sup> In this study, we have examined oncologic outcomes in women with TRAM flap postmastectomy BR.

We observed that women with TRAM flap BR had significantly lower rates of distant recurrence than women with mastectomy alone (20.0% vs 34.8%;  $P = 0.02$ ). We also observed that women with TRAM flap were significantly less likely to be diagnosed with any type of recurrence compared to women with mastectomy alone ( $P = 0.02$ ). This has also been observed in women with implant-based BR. Hölmich et al. (2008)<sup>10</sup> reported that disease-free survival was significantly higher for women with implant-based reconstruction than for women with mastectomy alone.

With implant-based BR, there have been hypotheses raised regarding the potentially beneficial biologic effect. This includes the foreign body reaction induced by the implant that may cause the increase in natural killer cell activity against tumor cells.<sup>19</sup> An additional hypothesis is

**Table 1. Comparison of Cases and Controls in the 65 Matched Sets**

	No. Reconstruction, N = 115 (in 65 Matched Sets)	TRAM Reconstruction, N = 65	P (t test)
Year of birth (SD)	1949.0 (8.6) (1931–70)	1947.2 (8.7) (1930–68)	0.94
Year of first surgery (SD) (range)	1994.7 (3.2) (1987–99)	1994.6 (3.5) (1987–00)	0.99
Age of first surgery (SD) (range)	45.6 (7.8) (28–62)	45.5 (7.8) (28–61)	0.93
Height (SD) (cm)	163.1 (5.6) (150–178)	164.3 (6.6) (147–180)	0.30
Missing	9		
Weight (SD) (kg)	62.7 (10.2) (43.3–90.9)	64.9 (12.4) (47.7–102.2)	0.89
Missing	17	9	
Current smoker (%)	16.6	11.1	0.22
Missing	4	2	
Lymph node status			Matched
Negative	47 (40.9%)	28 (43.1%)	
Positive	68 (59.2%)	37 (56.9%)	
Stage			Matched
1	37 (32.2%)	22 (33.9%)	
2	62 (53.9%)	35 (53.9%)	
3	16 (13.9%)	8 (12.3%)	
Grade			0.63
1	9 (9.2%)	6 (12.0%)	
2	42 (42.9%)	24 (48.0%)	
3	47 (48.0%)	20 (40.0%)	
Missing	17	15	
Chemotherapy			0.98
No	40 (35.1%)	22 (34.9%)	
Yes	74 (64.9%)	41 (65.2%)	
Missing	1	2	
Radiation therapy			0.92
No	89 (78.8%)	50 (78.1%)	
Yes	24 (21.2%)	14 (21.9%)	
Missing	2	1	
Age of TRAM surgery (SD) (range)	NA	46.9 (8.2) (28–63)	NA
Tumor size (mm)	28.5 (0–90)	28.6 (0–130)	0.98
Vital status			
Alive	66 (57.4%)	47 (72.3%)	0.23
Dead	49 (42.6%)	18 (27.7%)	0.05
Dead of breast cancer	40 (34.8%)	17 (26.2%)	

\*Mean value of the means of each set.  
NA, not available.

**Table 2. RR of TRAM Flap BR on Breast Cancer Recurrences and Death**

	Univariate, RR (95% CI), P	Multivariate, RR (95% CI), P*
Local recurrence		
No	1	1
Yes	0 (0–NA)	0 (0–NA)
Regional recurrence		
No	1	1
Yes	0.38 (0.13–1.13), 0.08	0.35 (0.11–1.06), 0.06
Distant recurrence		
No	1	1
Yes	0.50 (0.27–0.93), 0.03	0.42 (0.22–0.80), 0.009
Any recurrence		
No	1	1
Yes	0.58 (0.33–1.04), 0.07	0.50 (0.27–0.91), 0.02
Status		
Alive	1	1
Dead (all-cause death)	0.57 (0.33–0.97), 0.04	0.54 (0.31–0.94), 0.03
Dead of breast cancer	0.65 (0.37–1.15), 0.14	0.60 (0.33–1.08), 0.09

\*Adjusted by age of surgery, tumor size, nodes (positive/negative), chemotherapy (yes/no), and radiotherapy (yes/no).  
NA, not available.

that the implant causes tissue compression that results in a decrease in blood flow leading to decreased cell turnover.<sup>20</sup> There is also the idea of a possible cooling effect of the implants that may decrease the metabolic activity of remaining cancer cells in the surrounding tissue.<sup>20–22</sup> These hypotheses may help explain the oncologic benefits of implant-based reconstruction, but we have also now observed benefits associated with autologous BR that could not be explained by these hypotheses.

Several studies suggest that BR may offer a survival advantage when compared to women who are treated with mastectomy alone, although no randomized controlled trials have been conducted because of ethical issues.<sup>11,13,14</sup> In a population-based matched cohort study of women with invasive breast cancer in Ontario, Canada, followed for over 20 years after diagnosis, BR was associated with a 17% reduced risk of death and a 19% reduced risk of breast cancer death.<sup>13</sup> A Danish population-based study<sup>10</sup> also suggests that

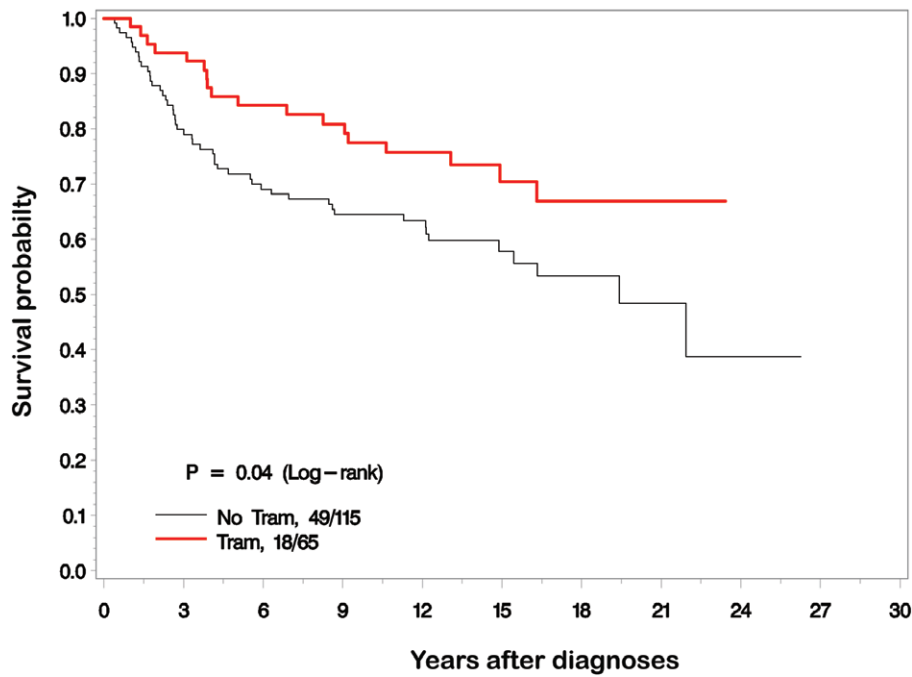


Fig. 1. Survival of overall death in subjects with or without TRAM surgery.

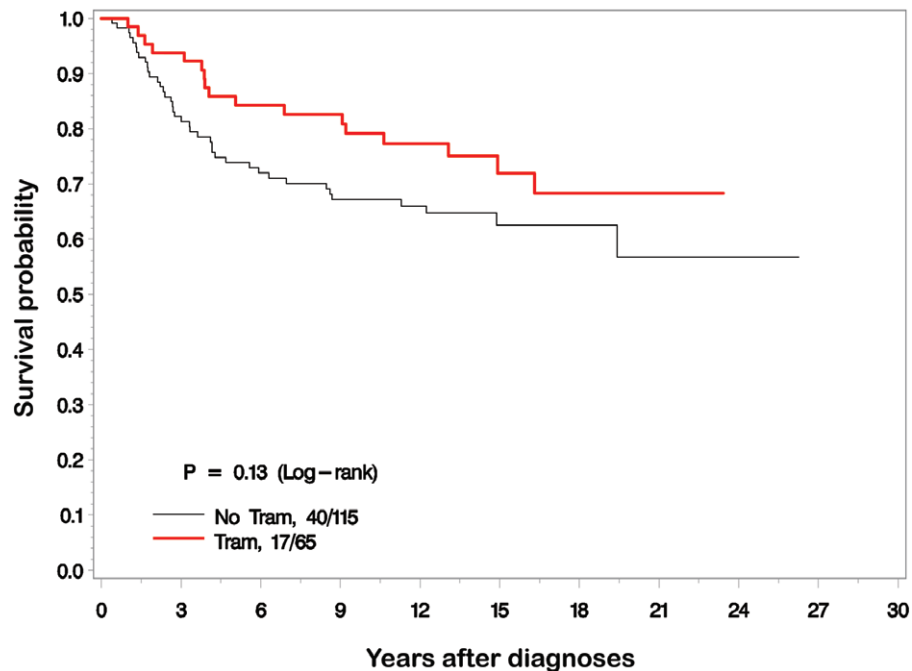


Fig. 2. Survival of breast cancer-specific death in subjects with or without TRAM surgery.

there may be long-term survival advantages associated with postmastectomy BR. Although we did not observe statistically significant differences in breast cancer-specific mortality (OR, 0.60; 95% CI: 0.33–1.08;  $P = 0.09$ ), we did observe a significant difference in all-cause mortality, with women with mastectomy alone being significantly less likely to be alive after breast cancer diagnosis compared to women with TRAM flap BR (OR, 0.54; 95% CI: 0.31–0.94;  $P = 0.03$ ).

An explanation that has been offered to explain differences in recurrences and mortality has been related to confounding factors and selection bias in terms of the patients who are offered BR (nonobese, nonsmokers). Much of the previous research examining outcomes associated with postmastectomy BR has utilized population-based registries with limited clinical and lifestyle data. In this study, we were able to examine factors known to in-

fluence breast cancer–specific survival including smoking and obesity.<sup>23,24</sup> There were no significant differences in smoking, weight, or height between women treated with mastectomy alone and those with postmastectomy BR. Therefore, we do not attribute the differences in prognosis to selection bias of patients.

There are several limitations to this study. The sample size able to be matched was small with 65 subjects with TRAM flap BR and 115 matched controls. This is smaller than previous studies that have examined oncologic outcomes associated with BR using large administrative databases. However, our study used data from a clinical database, and therefore we had access to demographic and lifestyle data that have not been available in prior studies. However, we did not have access to information on comorbidities that could have had an impact on survival. In addition, the women in this study were treated in Canada where we have universal health care, which includes the provision of BR at no cost to the patient. As a result, these research findings may not be generalizable to women in countries without universal health care.

In summary, women with autologous BR do not have worse oncologic outcomes compared to women with mastectomy alone. In fact, women with TRAM flap BR were found to have lower levels of distant recurrence and better overall survival than women treated with mastectomy alone. The differences could not be explained by differences in prognostic factors, treatments, demographic, or various lifestyle factors between women with and without BR. Women considering postmastectomy BR should be counseled that BR will not compromise oncologic outcomes.

**John L. Semple, MD, MSc, FRCSC, FACS**  
 Women's College Hospital  
 Chair, Surgical Research  
 Canadian Breast Cancer Foundation  
 Professor, Department of Surgery  
 University of Toronto  
 76 Grenville St, Toronto  
 ON, Canada M5S 1B2  
 E-mail: john.semple@wchospital.ca

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