Risk of recurrence and death in patients with breast cancer after delayed deep inferior epigastric perforator flap reconstruction

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Background: Postmastectomy reconstruction using a deep inferior epigastric perforator (DIEP) flap is increasingly being performed in patients with breast cancer. The procedure induces extensive tissue trauma, and it has been hypothesized that the release of growth factors, angiogenic agonists and immunomodulating factors may reactivate dormant micrometastasis. The aim of the present study was to estimate the risk of breast cancer recurrence in patients undergoing DIEP flap reconstruction compared with that in patients treated with mastectomy alone.

Methods: Each patient who underwent delayed DIEP flap reconstruction at Karolinska University Hospital, Sweden, between 1999 and 2013, was compared with up to four controls with breast cancer who did not receive a DIEP flap. The control patients were selected using incidence density matching with respect to age, tumour and nodal status, neoadjuvant therapy and year of mastectomy. The primary endpoint was breast cancer-specific survival. Survival analysis was carried out using Kaplan–Meier survival estimates and Cox proportional hazard regression analysis.

Results: The analysis included 250 patients who had 254 DIEP flap reconstructions and 729 control patients. Median follow-up was 89 and 75 months respectively ($P = 0.053$). Breast cancer recurrence developed in 50 patients (19.7 per cent) in the DIEP group and 174 (23.9 per cent) in the control group ($P = 0.171$). The 5-year breast cancer-specific survival rate was 92.0 per cent for patients with a DIEP flap and 87.9 per cent in controls ($P = 0.032$). Corresponding values for 5-year overall survival were 91.6 and 84.7 per cent ($P < 0.001$). After adjustment for tumour and patient characteristics and treatment, patients without DIEP flap reconstruction had significantly lower overall but not breast cancer-specific survival.

Conclusion: The present findings do not support the hypothesis that patients with breast cancer undergoing DIEP flap reconstruction have a higher rate of breast cancer recurrence than those who have mastectomy alone.

Introduction

Immediate or delayed breast reconstruction may be performed following mastectomy[1]. Breast reconstruction has been shown to improve body image and quality of life[2,3], and the timing of the procedure does not seem to influence the results[1]. The most common methods are implant-based and autologous, or a combination of the two. Following postmastectomy radiotherapy, delayed reconstruction using a deep inferior epigastric perforator (DIEP) flap is increasingly being performed[4,5]. DIEP flap reconstruction is also undertaken as an immediate breast reconstruction (IBR)[4,6–8]. DIEP flap reconstruction, first described in 1994[9], involves the transposition of adipose tissue and skin from the abdomen to the mastectomy site as a free microsurgical transplant in order to rebuild the breast[10].

Severe physical trauma, including major surgery, has been suggested to trigger tumour progression in patients with breast cancer[11,12]. The concept of tumour dormancy has been proposed as a possible explanation. Circulating tumour cells, derived from subclinical micrometastases and detected in the blood of patients without recurrence of breast cancer up to 25 years after primary diagnosis[13–15], may remain dormant until they are either reactivated or eliminated[14]. Reactivation may be initiated through an inflammatory response with subsequent production of cytokines and growth factors caused by surgical trauma[16,17]. Other mechanisms could be new mutations, scattering of secondary micrometastases[18], lack of vasculature surveillance[12,19–24] or inefficient immunosurveillance.

Breast reconstruction using autologous flaps may be considered a major tissue trauma as it involves extensive and prolonged surgery with exposure of large wound surfaces. The question arises whether breast reconstruction reactivates dormant micrometastases, and thereby increases the risk of breast cancer relapse and death. Evidence is conflicting[25–29], probably owing to inclusion of heterogeneous reconstructive methods and, in some instances, a lack of matched control groups for comparison.

As DIEP flap surgery is an extensive autologous reconstructive technique in increasing use today, the aim of this study was to assess whether the risk of breast cancer recurrence in a homogeneous group of women undergoing DIEP flap reconstruction was increased compared with that among women undergoing mastectomy alone.

Methods

This retrospective matched cohort study included all patients with breast cancer who underwent delayed DIEP flap breast reconstruction (DIEP group) after a previous breast cancer at the Department of Reconstructive Plastic Surgery, Karolinska University Hospital, Stockholm, Sweden, between January 1999 and December 2013 (*Fig. 1*). The study was approved by the ethical review board at Karolinska Institute in October 2014 (2014/1555-31).

Patients were identified from the microvascular registry at Karolinska University Hospital. Women undergoing reconstruction after prophylactic risk-reducing mastectomy were excluded. Surgical reports were reviewed for each patient, and only those with a verified DIEP flap reconstruction were included in a database. In the event of bilateral procedures in the same patient, each reconstruction was considered as a separate case for disease-free survival (DFS), but the individual was considered as a single entity for calculation of breast cancer-specific survival (BCSS) and overall survival (OS).

Patients in the DIEP group were matched with patients who underwent mastectomy alone (control group) using incidence density matching. Matching criteria were year of and age at mastectomy, tumour category and lymph node status. Patients in the DIEP group who received neoadjuvant therapy were matched with those in the control group who received such treatment in order to adjust for the absence of unaffected histopathological tumour size. Instead, radiological tumour size before neoadjuvant therapy was used to determine tumour category. A reference interval was assigned each patient in the DIEP group, corresponding to the interval between the date of mastectomy and the date of DIEP flap reconstruction (index date). Each matched patient in the control group who developed recurrence, died or underwent other reconstructive breast surgery during this reference interval was excluded. Immediate implant-based reconstruction was allowed in both groups. Up to four controls who did not undergo DIEP flap reconstruction were selected randomly for each case.
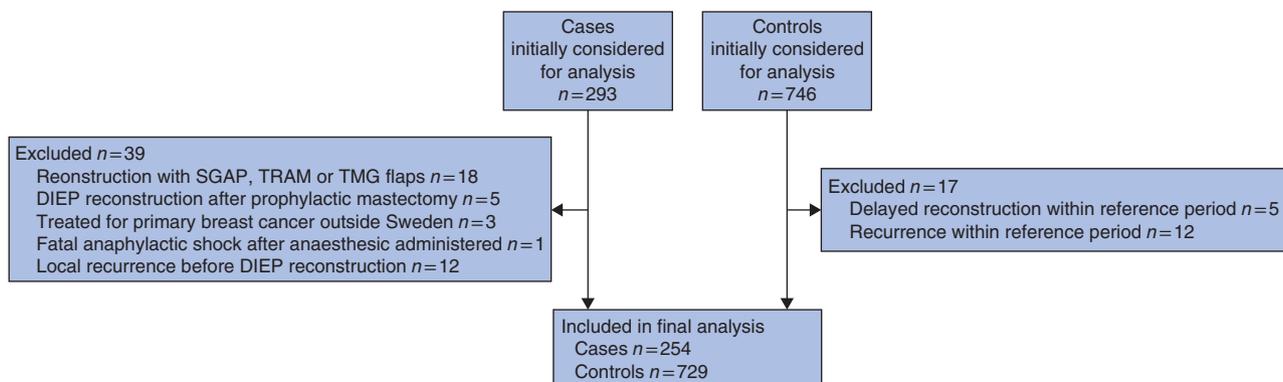

Fig. 1 Flow chart for the study. SGAP, superior gluteal artery perforator; TRAM, transverse rectus abdominis myocutaneous; TMG, transverse musculocutaneous gracilis

At Karolinska University Hospital, preoperative screening for distant metastasis (mammography, chest X-ray and bone scintigraphy) in patients considered for autologous reconstruction with DIEP flap surgery was initiated in 2008. Patients with distant metastasis were not offered DIEP flap reconstruction. To compensate for potential selection bias, patients in the DIEP group were divided into two groups, according to whether they underwent breast reconstruction before 2008, or from 2008 onwards.

Data on TNM stage, axillary lymph node status, oestrogen receptor (ER) status, progesterone receptor status and human epidermal growth factor receptor 2 (HER2) amplification status (registered from 2005) were extracted from the Swedish Breast Cancer Register, held by the Regional Cancer Centre in Stockholm, for all included patients. These data were then completed and validated by review of individual medical charts for each patient, and data on oncological treatments, recurrences (including sites), death and cause of death were updated. Information on tobacco use and BMI, when available, was also registered. For patients receiving a DIEP flap, the duration of reconstructive surgery, postoperative medical and surgical complications, and data on revisional surgery after reconstruction were registered. Electronic medical records in Sweden are linked to the population registry with continuous automatic updating of survival data. Therefore, information on vital status and date of death could be obtained directly by review of medical records.

Local recurrence was defined as histologically confirmed breast cancer recurrence in the ipsilateral skin, chest wall, or adjacent to or within the transposed abdominal tissue. Recurrence in the ipsilateral or contralateral axillary, infraclavicular or supraclavicular, interpectoral or internal mammary lymph nodes was considered as regional recurrence. Distant recurrence was defined as a breast cancer recurrence at any other site. The date of first diagnosis of each type of recurrence, confirmed either by radiology, cytology or histopathology, was recorded.

Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables as mean(s.d.) or median (range). The normality of distribution of all continuous variables was tested using the Shapiro–Wilks test, and parametric (Student's t test) or non-parametric (Mann–Whitney U test) tests used for statistical analysis, as appropriate. Pearson's χ^2 test and Fisher's exact test were used to analyse the distribution of categorical variables between the cohorts.

The primary endpoint was BCSS. Secondary endpoints were OS and DFS. Survival was always calculated from the date of DIEP flap reconstruction for patients in the DIEP group, and from the index date in the control group (date of DIEP flap reconstruction in the corresponding case), until the date of any first local, regional or distant recurrence (DFS), date of death from breast cancer (BCSS), or date of death from any cause (OS). For OS, patients were censored at the date of last medical chart review, whereas for BCSS and DFS they were censored at the date of last follow-up. Five-year survival rates were calculated by the Kaplan–Meier method, and the log rank test was used to compare groups. To assess the impact of different factors on BCSS, OS and DFS, univariable and multivariable Cox regression analyses were carried out. Results are presented as hazard ratios (HR) with 95 per cent confidence intervals. Recurrence patterns were evaluated by estimation of the HR for recurrence using the life-table method.

All reported P values are two-tailed with $P < 0.050$ considered significant. Statistical analyses were performed using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

A total of 254 DIEP flap reconstructions were undertaken in 250 patients. In all, 729 control patients were matched with DIEP cases: 29 cases had four controls, 213 had three controls, 20 had two controls and 21 had one control. Demographic and histopathological data for each group, and information on oncological treatments including neoadjuvant and adjuvant therapy are shown in *Tables 1* and *2* respectively, and indicate that the matching procedure was successful. However, there were significant differences between the two groups in some variables. The rate of IBR was higher in the control group. A nipple-sparing procedure was performed in only two patients who had IBR. A higher proportion of patients in the DIEP group received adjuvant radiotherapy and chemotherapy; all radiotherapy was administered after the initial mastectomy and never after the DIEP flap reconstruction.

The median age at mastectomy was 48 (range 28–67) years in the DIEP group and 48 (25–67) years in the control group. Median invasive tumour diameter was 28·5 (1–100) and 30 (1–170) mm respectively ($P = 0.540$).

The median operating theatre time for DIEP flap reconstruction was 510 (range 265–1009) min. Theatre time was significantly shortened in the DIEP group operated from 2008 onwards (460 (265–1009) min *versus* 610 (347–847) min before 2008; $P < 0.001$).

Follow-up

The median interval from mastectomy to DIEP flap reconstruction was 36 (range 12–314) months, with a median age

Table 1 Comparison of patient and tumour characteristics for patients who did or did not have deep inferior epigastric perforator flap reconstruction

	DIEP cohort (*n* = 254)	Control cohort (*n* = 729)	*P*¶
Year of mastectomy†			0·941
1980–1999	73 (28·7)	208 (28·5)	
2000–2005	85 (33·5)	237 (32·5)	
2006–2012	96 (37·8)	284 (39·0)	
Age (years)†			0·968
< 40	56 (22·0)	162 (22·2)	
41–50	94 (37·0)	275 (37·7)	
> 51	104 (40·9)	292 (40·1)	
Tumour invasiveness			0·907
Invasive	245 (96·5)	702 (96·3)	
In situ	9 (3·5)	27 (3·7)	
Invasive tumour type‡			0·801
Ductal	174 (71·0)	461 (65·7)	
Lobular	38 (15·5)	114 (16·2)	
Mixed	7 (2·9)	13 (1·9)	
Other	7 (2·9)	19 (2·7)	
Missing	19 (7·8)	95 (13·5)	
Tumour stage†§			0·189
Tis	9 (3·5)	27 (3·7)	
T1	65 (25·6)	178 (24·4)	
T2	140 (55·1)	365 (50·1)	
T3	40 (15·7)	159 (21·8)	
Invasive tumour size (mm)*	28·5 (1–100)	30 (1–170)	0·540#
In situ tumour type			0·511**
DCIS	8 (89)	25 (93)	
LCIS	1 (11)	2 (7)	
Lymph node status			0·786
Node positive	134 (52·8)	400 (54·9)	
Node negative	113 (44·5)	324 (44·4)	
Missing	7 (2·8)	5 (0·7)	
No. of positive lymph nodes*	1 (0–21)	1 (0–31)	0·119#
Oestrogen receptor status			0·428
Negative	61 (24·0)	162 (22·2)	
Positive	176 (69·3)	534 (73·3)	
Missing	17 (6·7)	33 (4·5)	
Progesterone receptor status			0·285
Negative	75 (29·5)	231 (31·7)	
Positive	148 (58·3)	419 (57·5)	
Missing	31 (12·2)	79 (10·8)	
HER2 status			0·279
Not amplified	89 (35·0)	215 (29·5)	
Amplified	31 (12·2)	81 (11·1)	
Missing	134 (52·8)	433 (59·4)	
Nottingham Histological Grade (invasive tumours)			0·525
1	12 (4·9)	37 (5·3)	
2	88 (35·9)	220 (31·3)	
3	72 (29·4)	215 (30·6)	
Missing	73 (29·8)	230 (32·8)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Matching variables. ‡Reported as invasive if invasiveness was diagnosed, with no acknowledgement of associated *in situ* disease; the *in situ* type is reported only for patients with purely *in situ* disease. §Preoperative clinical tumour size if neoadjuvant therapy administered; postoperative histopathological tumour size if no neoadjuvant therapy received. DIEP, deep inferior epigastric perforator; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; HER2, human epidermal growth factor receptor 2. ¶χ^2 test, except #Mann–Whitney U test and **Fisher's exact test.

Table 2 Comparison of oncological treatments in patients who did or did not have deep inferior epigastric perforator flap reconstruction

	DIEP cohort (n = 254)	Control cohort (n = 729)	P*
Implant-based IBR			< 0·001
Yes	21 (8·3)	149 (20·4)	
No	162 (63·8)	259 (35·5)	
Missing	71 (28·0)	321 (44·0)	
Neoadjuvant treatment			0·389
Yes	94 (37·0)	248 (34·0)	
No	160 (63·0)	481 (66·0)	
Neoadjuvant endocrine therapy			0·483†
Yes	1 (0·4)	6 (0·8)	
No	253 (99·6)	723 (99·2)	
Neoadjuvant chemotherapy			0·270
Yes	94 (37·0)	242 (33·2)	
No	160 (63·0)	487 (66·8)	
Neoadjuvant targeted HER2 therapy			0·069
Yes	8 (3·1)	10 (1·4)	
No	246 (96·9)	719 (98·6)	
Adjuvant treatment			< 0·001
Yes	246 (96·9)	651 (89·3)	
No	7 (2·8)	75 (10·3)	
Missing	1 (0·4)	3 (0·4)	
Adjuvant radiotherapy			< 0·001
Yes	209 (82·3)	445 (61·0)	
No	44 (17·3)	281 (38·5)	
Missing	1 (0·4)	3 (0·4)	
Adjuvant chemotherapy			0·029
Yes	157 (61·8)	393 (53·9)	
No	96 (37·8)	333 (45·7)	
Missing	1 (0·4)	3 (0·4)	
Adjuvant endocrine therapy			0·413
Yes	190 (74·8)	526 (72·2)	
No	63 (24·8)	200 (27·4)	
Missing	1 (0·4)	3 (0·4)	
Adjuvant targeted HER2 therapy			0·499
Yes	30 (11·8)	75 (10·3)	
No	223 (87·8)	651 (89·3)	
Missing	1 (0·4)	3 (0·4)	

Values in parentheses are percentages. DIEP, deep inferior epigastric perforator; IBR, immediate breast reconstruction; HER2, human epidermal growth factor receptor 2. *χ^2 test, except †Fisher's exact test.

at reconstruction of 52 (30–69) years. Median follow-up was 89 (range 4–214) months following reconstruction. In the control group, median follow-up, calculated from the date of DIEP flap reconstruction in the corresponding case (index date), was 75 (0–367) months (P = 0·053). Median follow-up after the date of mastectomy was 134 (range 28–375) months in the DIEP group and 122 (25–421) months in the control group (P = 0·004).

Recurrence and survival

A total of 224 recurrences were recorded: 50 among patients who had DIEP flap reconstruction (19·7 per cent) and 174 controls (23·9 per cent) (P = 0·171). Median time to any first breast cancer recurrence was 74·5 and 60·5 months respectively (P = 0·339). Local recurrences developed in 11 patients (4·3 per cent) in the DIEP group

and 31 (4·3 per cent) in the control group (P = 0·958), and regional relapse in eight (3·1 per cent) and 33 (4·5 per cent) respectively (P = 0·344). Forty-three patients (16·9 per cent) in the DIEP group and 149 controls (20·4 per cent) developed distant recurrence (P = 0·224). Five-year DFS rates were 83·3 and 77·7 per cent respectively (P = 0·143) (*Fig. 2a*).

Thirty-three patients (13·0 per cent) in the DIEP group and 132 (18·1 per cent) in the control group died from breast cancer (P = 0·060), resulting in a 5-year BCSS rate of 92·0 and 87·9 per cent respectively (P = 0·032) (*Fig. 3a*). There were 37 non-breast cancer deaths (14·6 per cent) among patients who had DIEP flap reconstruction and 188 (25·8 per cent) among control patients (P < 0·001), with 5-year OS rates of 91·6 and 84·7 per cent respectively (P < 0·001) (*Fig. 4a*).

a DIEP *versus* control
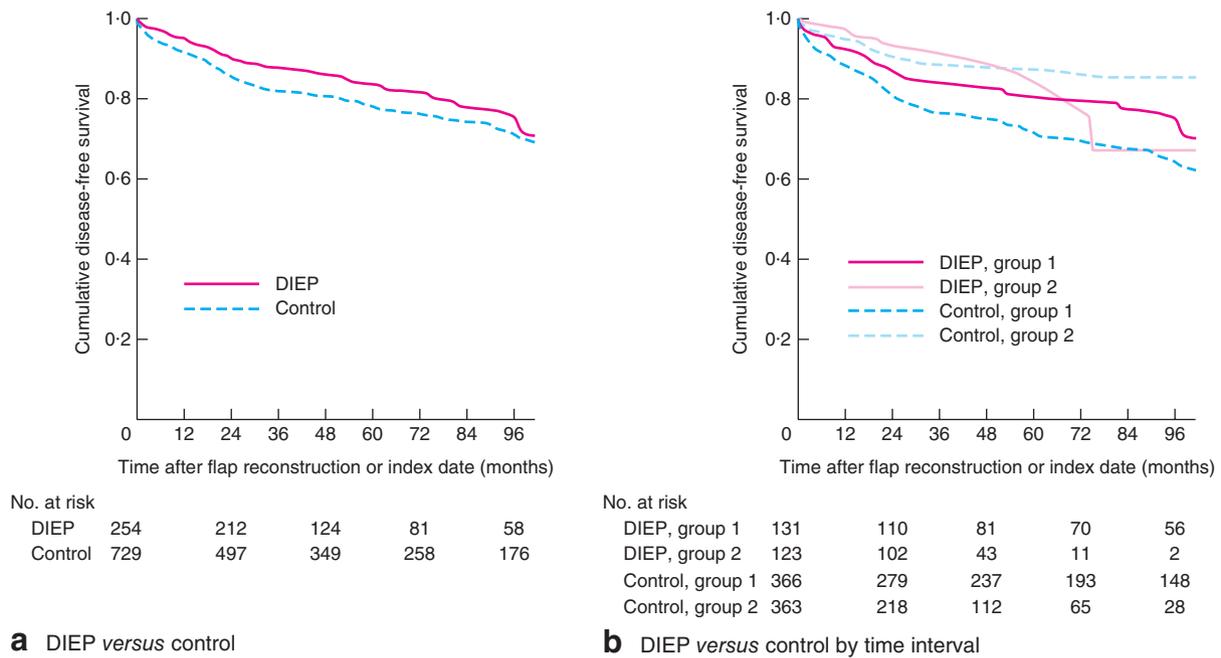
b DIEP *versus* control by time interval

Fig. 2 Kaplan–Meier curves for disease-free survival: **a** deep inferior epigastric perforator (DIEP) *versus* control cohorts, and **b** according to whether reconstruction (DIEP cohort) or index date (control cohort) was before 2008 (group 1) or from 2008 onwards (group 2). **a** $P = 0.143$, **b** $P < 0.001$ (log rank test). [Correction added on 17 May 2018, after first online publication: in Fig. 2b, DIEP control group 1 and group 2 have been correctly transposed]
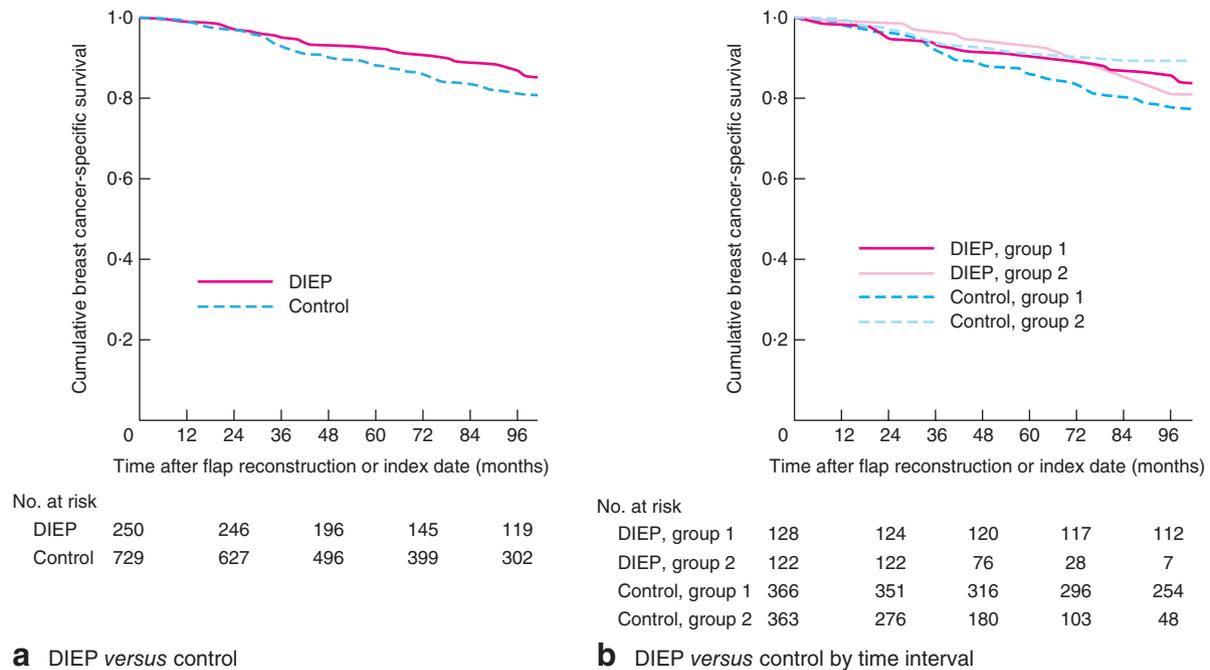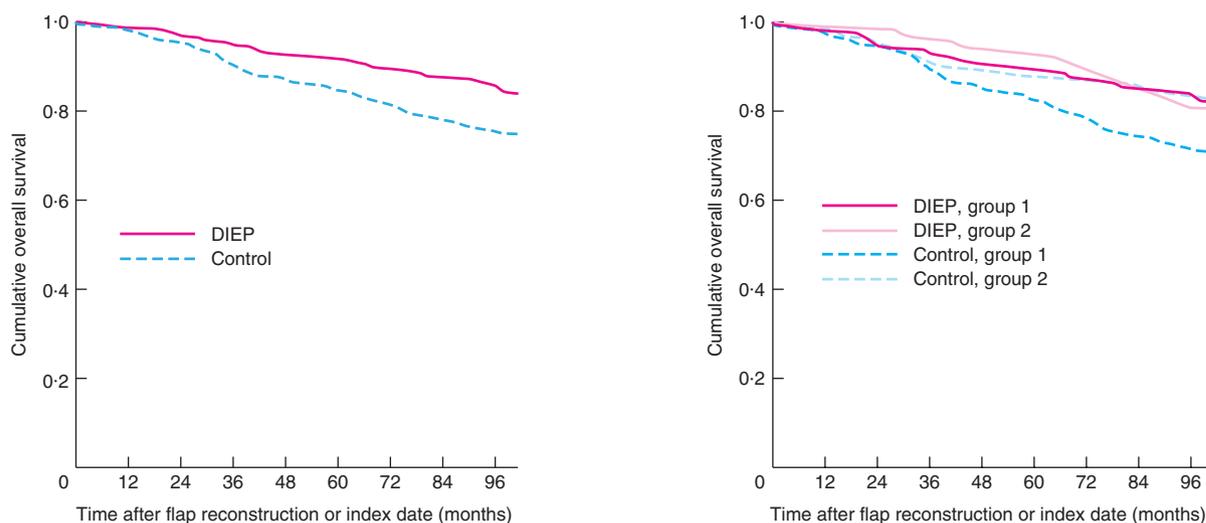

a DIEP *versus* control

b DIEP *versus* control by time interval

Fig. 3 Kaplan–Meier curves for breast cancer-specific survival: **a** deep inferior epigastric perforator (DIEP) *versus* control cohorts, and **b** according to whether reconstruction (DIEP cohort) or index date (control cohort) was before 2008 (group 1) or from 2008 onwards (group 2). **a** $P = 0.032$, **b** $P = 0.002$ (log rank test). [Correction added on 17 May 2018, after first online publication: in Fig. 3b, DIEP control group 1 and group 2 have been correctly transposed]

Fig. 4 Kaplan–Meier curves for overall survival: **a** deep inferior epigastric perforator (DIEP) *versus* control cohorts, and **b** according to whether reconstruction (DIEP cohort) or index date (control cohort) was before 2008 (group 1) or from 2008 onwards (group 2). **a** $P < 0.001$, **b** $P < 0.001$ (log rank test). [Correction added on 17 May 2018, after first online publication: in Fig. 4b, DIEP control group 1 and group 2 have been correctly transposed]

Taking into consideration metastasis screening initiated in January 2008, survival was calculated for patients who underwent DIEP flap reconstruction before and after that date (DIEP groups 1 and 2), with their individually matched control patients separated into corresponding groups (control groups 1 and 2). The 5-year OS rate was highest for patients who had DIEP flap reconstruction from 2008 onwards (92·4 per cent) followed by those who had reconstruction before this time (89·3 per cent), matched control patients with an index date from 2008 onwards (87·4 per cent) and, finally, matched control patients with an index date earlier than 2008 (82·6 per cent) ($P < 0.001$) (*Fig. 4b*). A similar pattern was seen for 5-year BCSS (92·4, 90·1, 90·4 and 85·9 per cent respectively; $P = 0.002$) (*Fig. 3b*).

Risk factors for breast cancer death are reported in *Table 3*; HER2 amplification and targeted therapy were excluded from the analysis owing to a high frequency of missing data (*Tables 1* and *2*). Interestingly, ER positivity was significantly associated with a higher risk of breast cancer death after DIEP flap reconstruction (index date in controls), most probably because ER-negative disease tends to recur earlier than ER-positive disease, leading to selection of patients with ER-negative disease who are already past

the peak of recurrence risk once they are offered breast reconstruction. After adjustment for all tumour and patient characteristics and treatments listed in *Table 3*, control patients still had a significantly lower OS, but not BCSS, rate. Adding local and regional recurrence separately into the multivariable analysis resulted in a HR of 2·11 (95 per cent c.i. 1·03 to 4·32) for local recurrence and 4·62 (2·30 to 9·27) for regional recurrence. Operating theatre time, and interval between mastectomy and DIEP reconstruction had no significant impact on any of the endpoints analysed.

Surgical adjustments and complications after reconstruction

Ipsilateral adjustment surgery after DIEP flap reconstruction was performed in 175 patients (68·9 per cent) (median 1 (range 1–4) procedures per patient). This included shaping of the breast, liposuction, lipofilling and scar revision. Contralateral surgery was performed in 147 patients (57·9 per cent) (median 1 (range 1–4) procedures per patient), including mastopexy, breast reduction, implant-based augmentation, implant replacement or capsulectomy. Nipple reconstruction was undertaken in 212 patients (83·5 per cent) and flap revision owing to suspected surgical complications in 22 (8·7 per cent). Partial or total flap

Table 3 Univariable and multivariable Cox regression analysis with breast cancer-specific survival as the binary endpoint

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Cohort				
DIEP	1·00 (reference)		1·00 (reference)	
Control	1·52 (1·03, 2·22)	0·033	1·35 (0·80, 2·26)	0·263
Age at mastectomy				
≤ 40	1·00 (reference)		1·00 (reference)	
41–50	0·87 (0·58, 1·29)	0·484	0·66 (0·38, 1·16)	0·149
> 51	0·73 (0·48, 1·09)	0·127	0·85 (0·50, 1·45)	0·550
Year of mastectomy				
1980–1999	1·00 (reference)		1·00 (reference)	
2000–2005	0·78 (0·55, 1·10)	0·164	0·53 (0·30, 0·94)	0·029
2006–2012	0·59 (0·37, 0·96)	0·034	0·34 (0·18, 0·66)	0·001
Invasive tumour category				
T1	1·00 (reference)		1·00 (reference)	
T2	1·09 (0·74, 1·60)	0·665	1·52 (0·80, 2·91)	0·206
T3	1·98 (1·29, 3·03)	0·002	2·22 (1·07, 4·62)	0·032
Nottingham Histological Grade				
1	1·00 (reference)		1·00 (reference)	
2	1·69 (0·61, 4·72)	0·314	1·45 (0·44, 4·84)	0·543
3	1·98 (0·71, 5·51)	0·191	1·79 (0·53, 6·10)	0·353
Oestrogen receptor status				
Negative	1·00 (reference)		1·00 (reference)	
Positive	1·26 (0·87, 1·81)	0·229	3·58 (1·42, 9·00)	0·007
Progesterone receptor status				
Negative	1·00 (reference)		1·00 (reference)	
Positive	0·98 (0·70, 1·37)	0·905	1·12 (0·63, 2·02)	0·698
Lymph node status				
Node-negative	1·00 (reference)		1·00 (reference)	
Node-positive	2·48 (1·75, 3·52)	< 0·001	2·19 (1·21, 3·97)	0·010
Radiotherapy*				
Yes	1·00 (reference)		1·00 (reference)	
No	0·53 (0·38, 0·76)	0·001	0·74 (0·41, 1·35)	0·33
Chemotherapy*				
Yes	1·00 (reference)		1·00 (reference)	
No	0·59 (0·41, 0·87)	0·007	0·694 (0·33, 1·48)	0·345
Endocrine therapy*				
Yes	1·00 (reference)		1·00 (reference)	
No	1·06 (0·76, 1·47)	0·750	2·83 (1·18, 6·76)	0·019

Values in parentheses are 95 per cent confidence intervals. *Including both neaodjuvant and adjuvant therapy.

necrosis occurred in 16 (6·3 per cent) and two (0·8 per cent) patients respectively. Complications after DIEP flap reconstruction did not have a signficant effect on DFS, BCSS or OS rates.

Discussion

This matched cohort study did not find an increased risk of recurrence after DIEP flap breast reconstruction. On the contrary, unadjusted 5-year OS and BCSS rates were significantly higher among patients who had DIEP flap reconstruction than those in control patients. A similar trend was also seen for DFS, without reaching statistical significance.

These results conflict with some earlier publications on increased rates of breast cancer recurrence following large-flap breast reconstruction[25,26], although the results of most studies[27,28,30,31] are in line with the present findings. Lindford and colleagues[31] reported a lower rate of distant recurrence in 112 patients with delayed breast reconstruction, including autologous pedicle or microvascular flaps and implant-based reconstruction, compared with 391 patients undergoing mastectomy alone (12·5 *versus* 21·5 per cent; *P* = 0·034). More favourable rates of both OS and BCSS were noted in patients undergoing delayed breast reconstruction.

In contrast to the present results and those of Lindford *et al.*[31], Isern and co-workers[25] reported a higher

recurrence rate after delayed reconstruction with different types of autologous free and pedicle flap reconstructions than after conventional mastectomy. As tumour stage was not matched for, however, the rate of lymph node metastasis was significantly higher for cases than controls (66·4 *versus* 53·8 per cent), possibly explaining the worrying conclusions. Other studies[32–34] have also investigated the recurrence risk following delayed implant-based breast reconstruction, and found no increased risk of recurrence.

Recently, Dillekås and colleagues[26] described a bimodal pattern of recurrence in a heterogeneous group of delayed breast reconstructions (after 18 months and 5–6 years) and their matched controls undergoing mastectomy alone (after 24 months and 5–6 years). Such a pattern was not found in the present study, either after DIEP flap reconstruction or after the corresponding date for controls; the present data do not therefore support the theory of activation of dormant micrometastases after reconstruction. Although Dillekås *et al.* suggested that HRs for more extensive surgical interventions were higher owing to the growth of clinically undetected micrometastases, autologous flap reconstruction comprised only 28 per cent of their study group, making it difficult to draw such conclusions.

With reference to the reactivation of dormant micrometastases, the so-called angiogenic switch implies that alteration of the microenvironment may enable dormant cancer cells to produce angiogenesis stimulators, making the tissue surrounding the micrometastasis proangiogenic and thereby promoting metastatic growth[24,35]. This might be a direct consequence of the imbalance between increased levels of angiogenic agonists such as vascular endothelial growth factor, as measured in surgical wound fluid collected within few hours of surgery[36], along with reduced levels of angiogenesis inhibitors such as thrombospondin 1[17,35]. Major surgery may also induce immunomodulation, leading to deterioration of cellular immune defences by a shift from a Th1- to a Th2-dominant cytokine profile, and the production of growth factors and immunomodulatory substances[11,19,37–39]. Allawi and colleagues[34] studied whether accidental trauma or surgery might activate dormant micrometastases leading to increased rates of breast cancer relapse, but did not find any association. Likewise, the present study did not provide evidence to support the clinical relevance of these hypotheses.

Breast cancer recurrence is most likely to develop within the first 2 years after index surgery[11,40,41], and so patients at the authors' institution commonly receive a DIEP flap reconstruction no earlier than 24 months after mastectomy. Thus, patients who have DIEP flap reconstruction are a selected group with a 'security margin' after the primary mastectomy; this was accounted for in the matching procedure of the present analysis. The additional requirement of a BMI under 35 kg/m^2 and no active smoking for a DIEP flap reconstruction, however, represents a selection bias that is more difficult to adjust for, and a higher rate of active smokers must be suspected among the control patients. Unfortunately, no group comparison regarding smoking habits was possible owing to a high rate of missing data in the control group. This was also true for information on BMI.

There are further potential selection mechanisms to be taken into account. The fact that a larger percentage of patients in the DIEP than the control group received adjuvant therapy may underline that these women represent a generally healthier group receiving or tolerating more oncological treatment. In addition, previously irradiated patients may be offered autologous reconstruction strategies more often than non-irradiated patients[42]. There are some indications that the timing of radiotherapy may affect risk of recurrence after breast reconstruction[43]; however, this could not be analysed in the present cohort in which all radiotherapy had been administered well before DIEP flap reconstruction. Co-morbidity is probably less common among patients selected for breast reconstruction, a selection bias supported by data reported by Offodile and colleagues[44]. Furthermore, women opting for breast reconstruction are likely to be of higher socioeconomic status[45,46], whereas low socioeconomic status is linked to worse breast cancer survival[47]. Although ethnicity alone does not seem to influence BCSS, survival differences have been reported among patients classified as African American, Hispanic, Asian/Pacific Islander, other/unknown and white[48,49]. Possible explanatory factors include the role of demographics, biology and disparities in quality of care[48,49]. All these factors could potentially explain the significantly better OS and BCSS in the DIEP group, and will be included in future investigations.

The initiation of metastasis screening in 2008 could have biased the survival analysis to the advantage of patients having DIEP flap reconstruction as women diagnosed with relapse were not offered reconstruction. Although there were few such patients, those with a worse prognosis would have been filtered out, possibly contributing to superior survival rates in the DIEP group. Subgroup analysis, however, showed lower survival rates for patients in both groups who had surgery in the earlier time period, rather suggesting an effect of improved breast cancer detection and treatment over time. Nevertheless, preoperative metastasis screening should contribute to increased oncological safety of DIEP flap reconstruction by improving patient selection.

Although a larger number of cases would have been desirable, this study nevertheless included a large homogeneous group of DIEP flap reconstructions. Control patients were specifically matched by major prognostic factors in order to bring the analysis as close as possible to the ideal design of an RCT. Such a prospective trial, however, is hardly possible owing to substantial ethical issues regarding the decision-making processes of both patient and surgeon.

The present study does not support the hypothesis that patients with breast cancer undergoing DIEP flap reconstruction have a higher rate of breast cancer recurrence than patients undergoing mastectomy alone.

Acknowledgements

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