The Breast 59 (2021) 383–392

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Survival in breast cancer patients with a delayed DIEP flap breast reconstruction after adjustment for socioeconomic status and comorbidity

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ARTICLE INFO

Article history:
Received 3 January 2021
Received in revised form
15 June 2021
Accepted 3 July 2021
Available online 15 July 2021

Keywords:
Breast reconstruction
Socioeconomic status
Comorbidity
DIEP flap reconstruction

ABSTRACT

Purpose: Overall survival in breast cancer patients receiving a delayed deep inferior epigastric perforator (DIEP) flap breast reconstruction is better than in those without delayed breast reconstruction. This study aimed at determining the impact of socioeconomic status (SES) and comorbidity on these observations.
Materials and methods: This matched cohort study included all consecutive women undergoing a delayed DIEP flap reconstruction at Karolinska University Hospital, Sweden, between 1999 and 2013. Controls had not received any delayed breast reconstruction and were relapse-free after a corresponding follow-up interval. Matching was by year of and age at mastectomy, tumour stage and lymph node status. Charlson Comorbidity Index (CCI) and socioeconomic data were obtained from national registers. Associations with breast cancer-specific (BCSS) and overall survival (OS) were investigated by Kaplan-Meier survival estimates and Cox proportional hazard regression analysis.
Results: Women in the DIEP group (N = 254) more often continued education after primary school (88.6% versus 82.6%, P = 0.026), belonged to the high-income group (76.0% versus 63.1%, P < 0.001), were in a partnership (57.1% versus 55.7%, P = 0.024) and healthier (median CCI 1.00 (range 0–13) versus 2.00 (range 0–16), P = 0.021) than the control group (N = 729). After adjustment for tumour and treatment factors, SES and comorbidity, OS remained significantly better for the DIEP group than the control group (HR 2.27, 95% CI 1.44–3.55).
Conclusion: Women with a delayed DIEP flap reconstruction are a subgroup of higher socioeconomic status and better health. Higher survival estimates for the DIEP group persisted after adjusting for those differences, suggesting the presence of further unmeasured covariates.

1. Introduction

Surgery is an essential part of breast cancer treatment with curative intent and can be performed either as breast-conserving surgery or mastectomy. In case of mastectomy, breast reconstruction can be offered either as an immediate or a delayed procedure. For the latter, the deep inferior epigastric perforator (DIEP) flap, consisting of adipose tissue and skin from the abdomen that is transposed to the mastectomy site as a free microsurgical transplant, is commonly performed [1,2]. While some reports observed a worse survival for patients undergoing large reconstructive procedures, assumedly releasing growth factors that may reactivate dormant tumour cells, our group found a significantly better overall

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https://doi.org/10.1016/j.breast.2021.07.001

survival in DIEP patients than in matched controls without any delayed breast reconstruction [3]. The current analysis aimed to identify underlying differences between the groups that could explain these observations.

Socioeconomic status (SES) is a complex concept covering features such as income, level of education, occupation, family status, and housing. A lower SES is linked to worse breast cancer-specific survival [4–6], partly explained by the diagnosis being made at a later stage, lower figures of attendance in mammography screening [4–7] and decreased rates of chemotherapy [4,5,8,9]. Life style factors associated with cancer risk and lower survival, such as obesity and smoking, are more common in socioeconomically deprived groups, as is comorbidity [10]. Comorbidity is a mediator of overall death but also decreases cancer-specific survival by modulating adjuvant treatments strategies that in turn impact on survival [11–14]. In addition, significant comorbidities pose a clear contraindication for breast reconstruction.

In a systematic review, patients with indicators of lower SES were less likely to undergo any type of breast reconstruction [15]. While such observations may be due to income disparities in some countries [16], they have also been confirmed countries with national health services such as Canada and Denmark [15]. In Sweden, despite featuring a tax-funded public health service, immediate reconstruction rates are significantly affected by SES [17]. Thus far, a corresponding analysis regarding delayed breast reconstruction has not been performed.

2. Materials and methods

2.1. Data collection

This is a secondary analysis of the 1:3 matched cohort study previously published by Adam et al. [3]. The DIEP group, consisting of all women with a previous therapeutic mastectomy who underwent delayed DIEP flap reconstruction at the Department of Reconstructive Plastic Surgery, Karolinska University Hospital, Stockholm, Sweden, between January 1999 and December 2013, was identified from the microvascular registry at Karolinska University Hospital. No immediate DIEP flap reconstructions were included. All data were verified by individual review of medical charts. The control group, consisting of women with a therapeutic mastectomy but no delayed breast reconstruction, was matched with regard to year of and age at mastectomy, tumour stage and lymph node status as matching criteria. Each patient in the control group was assigned a reference date corresponding to the date of the DIEP reconstruction in the corresponding DIEP case. This was done in order to make the groups even more comparable as the progression along the cancer pathway was then made more similar in both groups. All included patients were recurrence free and free of any other disseminated malignancy between the date of mastectomy and the date of DIEP reconstruction or the corresponding reference date. Only women undergoing secondary DIEP reconstructions were included in the study group in order to achieve a highly homogeneous study group for comparison with the control group. We specifically chose the DIEP flap reconstruction since it is an autologous reconstruction method increasing in popularity and is one of the reconstructive strategies associated with large tissue trauma.

Data extracted from the Swedish National Breast Cancer Register included tumour stage, axillary lymph node status, oestrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) amplification status (registered from 2005 onwards) and Nottingham Histological Grade (NHG). Information on BMI, smoking, oncological treatment, recurrences, and date and cause of death were retrieved through medical chart review.

Of note, implant-based immediate breast reconstruction (IB-IBR) was not an exclusion criterion in the primary study since it does not affect survival [18]. IB-IBR cases were consequently also included in the current analysis. Sensitivity analyses were carried out in order to analyse the impact of IB-IBR on overall survival (OS) and breast cancer-specific survival (BCSS), respectively. The study was approved by the regional Ethical Review Board at Karolinska Institutet, Stockholm, in October 2014 (2014/1555–31). Since only existing data sources were used, no study-specific consent form was required.

2.2. Comorbidity

All Swedish citizens are given a unique 10-digit personal identification number at birth, which enables linkage to national registers. Data on comorbidity were obtained from the National Inpatient Register (IPR) that holds data on any diagnosis a patient is given at hospital discharge. Up to 30 International Statistical Classification of Diseases-10th Revision (ICD-10) codes were obtained per patient.

Subsequently, three-digit ICD-10 codes were used to calculate the Charlson Comorbidity Index (CCI), a tool to measure severity of comorbid disease [19,20]. The CCI provides an overall score for comorbidity weighted by level of severity in 19 selected conditions (age, myocardial infarction, congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular accidents, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, mild/severe liver disease, uncomplicated/end-organ damage diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease (CKD), solid tumour, leukemia, lymphoma and HIV). Scores per condition range from 1 to 6. The breast cancer diagnosis itself was not included in the calculation of the CCI score.

2.3. Socioeconomic status

Disposable income per individual and household, family status (i.e., living in a partnership or in a single household), highest level of education, occupation, and country of birth were obtained from the Swedish Total Population Registry (TPR), the Register on Income and Taxes (IoT), the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), the Swedish Register of Education, and the Swedish Occupational Register, all maintained by Statistics Sweden. Income was adjusted to the Swedish Consumer Price Index (CPI) and calculated for the year prior to delayed DIEP reconstruction or reference date, and then stratified into three levels (i.e. high, intermediate, low) by dividing it into equal percentages. The highest level of education was classified according to the Swedish educational system as primary school, secondary school, post-secondary school $\leq$3 years, or post-secondary school >3 years. Likewise, data on occupation were categorized into the four categories clerk/civil servant, entrepreneur, labourer or unemployed/retired. Data regarding the latter category were delivered such that no distinction between retired women and unemployed individuals was possible.

2.4. Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables as mean (standard deviation) or median (range). The normality of distribution of all continuous variables was tested using the Shapiro–Wilks test, and the Mann-Whitney *U* test was accordingly used for group comparisons. Pearson's $\chi 2$ test and Fisher's exact test were used to analyse the distribution of

categorical variables.

Five-year survival proportions were calculated by Kaplan-Meier (KM) estimates including the Log rank test to compare the cohorts. BCSS was calculated from the date of DIEP reconstruction or the reference date until the date of death from breast cancer (Timescale 1). OS was calculated from the date of DIEP reconstruction or the reference date until death from any cause (Timescale 2). In the absence of events, patients were censored at the date of last medical chart review for OS, and at the date of last clinical follow-up for BCSS.

Uni- and multivariable Cox proportional hazards regression analyses were carried out to assess associations of comorbidity (categorized through the CCI Score), socioeconomic factors (disposable income per household, family status, highest level of education and occupation) and clinical information (year of and age at mastectomy, tumour stage, lymph node status, hormone receptor status (HR), radio- and chemotherapy) with OS and BCSS. Thus, no time-by-covariate interactions were included in the model. Results are presented as hazard ratios (HR) with their 95% confidence intervals (CI). Age at delayed DIEP reconstruction or reference date was not included as a separate factor since it is integrated in the overall CCI score.

For all models, covariate interactions were investigated based on clinical relevance (tumour characteristics) and on SES-by-comorbidity factors. Interaction terms were included to test for effect modification and to estimate the effect of exposure in each stratum of the modifier after investigating the main effects. Statistically significant interaction terms were tested in the multivariable models through the Wald test. The goodness of fit of the model was based on the Akaike information criterion (AIC) and the maximum likelihood, and tested by the log likelihood test.

All reported *P*-values are two-tailed, and a *P*-value of <0.05 was considered significant. Statistical analyses were performed using SPSS® version 25 (IBM, Armonk, New York, USA) and Stata version 16 (StataCorp, Lakeway Drive, Texas, USA). The established database is registered and managed in accordance with the European General Data Protection Regulation (GDPR) (see Table 1).

3. Results

Overall, 250 women with 254 delayed DIEP flap reconstructions constituted the DIEP group and 729 women the matched control group. For clinical background data, see the previously published supplementary Table 1 [3]. As shown in Table 2 the DIEP group represent a population with a higher SES, as demonstrated by a lower proportion of individuals with primary school as the highest level of education or with a low income. In addition, the DIEP group appeared to be healthier than the matched control group with a significantly lower prevalence of congestive heart failure, diabetes and COPD, and lower overall CCI scores.

IB-IBR was significantly more common in the control than the DIEP group (149 cases (20.4%) versus 21 cases (8.3%), P < 0.001). Women with an IB-IBR in general had higher education levels (postsecondary>3 years, 69 cases (40.6%) versus 153 cases (26.8%), P = 0.001), worked more often as clerks/civil servants (104 cases (62.3%) versus 205 cases (35.3%), P < 0.001), and had more often a high disposable household income (79 cases (46.5%) versus 162 cases (28.1%), P < 0.001) than women with neither IB-IBR nor delayed DIEP. Patients with an IB-IBR were also significantly healthier (CCI group 0–6: 153 cases (90.0%) versus 390 cases (67.2%), P < 0.001). Excluding all IB-IBR cases from the comparison of the DIEP and the control group regarding socioeconomic variables and comorbidity did however not change the above presented group differences.

A higher proportion of smokers (71 cases (17.5%) vs 11 (4.5%), P < 0.001) was seen in the control group. Both groups had a median BMI of 26 (range 20–35 in the DIEP group vs 19–41 in the control group, P = 0.055). Since BMI and smoking were only available in 319 (39.8%) and 651 (66.2%) women, respectively, these covariates were not included in further analyses.

3.1. Survival analyses

The proportional hazards assumption was checked using statistical testing and graphical diagnostics based on the global test of Schoenfeld's residuals without any evidence of time-varying hazard ratios (P = 0.0816). After a median follow-up time of 89 months for the DIEP group and 75 months for the control group (P = 0.053), 37 deaths of any cause had occurred in the DIEP group (14.6%) and 188 (25.8%) in the control group (P < 0.001). Unadjusted 5-year OS was 91.6% for the DIEP group and 84.7% for the control group (Log rank P < 0.001). The higher crude risk of death of any cause (HR 2.08 95% CI 1.40–3.09) in the control group persisted after adjustment for tumour and treatment characteristics, socioeconomic factors and comorbidity (HR 1.88, 95% CI 1.24–2.86). Independent risk factors were younger age at mastectomy, being retired or unemployed, and having a CCI score ≥7 (Table 3). Adjusted survival analyses were also performed excluding all women with IB-IBR but rendered the same results (Table 3).

Thirty-three patients (13.0%) in the DIEP and 132 (18.1%) in the control group had died of breast cancer (P = 0.060). Unadjusted Kaplan-Meier estimates showed a 5-year BCSS of 92.0% and 87.9%, respectively (P = 0.032). The higher crude risk of breast cancer death (HR 1.62, 95% CI 1.07–2.46) in the control group did, however, not persist in adjusted analyses (Table 4). Only when excluding all women with an IB-IBR from multivariable analysis, BCSS was significantly better in the DIEP group (HR 1.79, 95% CI 1.09–2.92). Independent risk factors of breast cancer death were younger age at mastectomy, working as a labourer or having no current employment, and a CCI score ≥7 (Table 4).

4. Discussion

In this matched cohort study, women with a delayed DIEP breast reconstruction had a significantly higher socioeconomic status (SES) and were significantly healthier than women without any delayed breast reconstruction. Furthermore, the control group had a higher crude risk of overall as well as breast cancer-specific death, which persisted after adjustment for treatment, tumour characteristics, socioeconomic factors, and comorbidity.

The majority of studies reporting dissimilarities in SES and comorbidity between women with and without a breast reconstruction focus on the immediate reconstructive setting [17,21–26], and cover both countries with private insurance systems, and thus reimbursement issues as an additional aspect of reconstructive procedures [23,24,26], and countries with public health care [17,27,28]. In Western Australia, England and Denmark, studies using area codes or level of education as proxies for social deprivation found that increased deprivation was significantly associated with lower rates of breast reconstruction [23,29,30]. A Swedish study showed that foreign-born women were more often diagnosed with stage II and III tumours than Swedish-born women [31]. Women with an IB-IBR included in the present study were a similarly privileged population. Such selection mechanisms are undesirable, since the psychosocial benefits of breast reconstruction are not limited to specific subgroups of SES, race or ethnicity [32].

Disparities in SES, however, do not only affect reconstruction rates but also breast cancer stage [33–35] and survival, even in the relatively homogenous Swedish society enjoying a tax-funded

Table 1
Descriptive socioeconomic data comparing the DIEP and control groups.

	DIEP group (n = 254)	Control group (n = 729)	*P*-value
Family status Partner/married	145 (57.1)	406 (55.7)	**0.024***
Single	107 (42.1)	311 (42.7)	
Missing	*2 (0.8)*	*12 (1.6)*	
Own birth country			0.243
Sweden	187 (73.6)	574 (78.7)	
Europe, not Sweden	38 (15.0)	89 (12.2)	
Outside of Europe	29 (11.4)	66 (9.1)	
Missing	*0 (0)*	*0 (0)*	
Highest level of education			**0.026**
Primary school	29 (11.4)	118 (16.2)	
Secondary school	110 (43.3)	273 (37.5)	
Postsecondary school, < 3 years	52 (20.5)	111 (15.2)	
Postsecondary school, ≥ 3 years	63 (24.8)	218 (29.9)	
Missing	*0 (0)*	*9 (1.2)*	
Occupation			0.086
Clerk/civil servant	136 (53.5)	334 (45.8)	
Entrepreneur	6 (2.4)	27 (3.7)	
Labourer	47 (18.5)	119 (16.3)	
Unemployed/retired	55 (21.7)	204 (28.0)	
Missing	*10 (3.9)*	*45 (6.2)*	
Income per person			**<0.001**
Low	61 (24.0)	266 (36.5)	
Middle	112 (44.1)	215 (29.5)	
High	81 (31.9)	245 (33.6)	
Missing	*0 (0)*	*3 (0.4)*	
Income per household			0.287
Low	75 (29.5)	252 (34.6)	
Middle	87 (34.3)	240 (32.9)	
High	92 (36.2)	234 (32.1)	
Missing	*0 (0)*	*3 (0.4)*	

Values in parentheses are percentages. For comparison of the two groups, the Chi-Square or Fisher's exact test was employed.
*Fisher's exact test.

Table 2
Descriptive data on comorbidity in the DIEP and control groups.

	DIEP group (n = 254)	*Control group (n = 729)*	*P*-value
Acute myocardial infarction			0.502*
Yes	6 (2.4)	22 (3.0)	
No	247 (97.2)	663 (91.0)	
Missing	*1 (0.4)*	*44 (6.0)*	
Congestive heart failure			**0.030**
Yes	5 (2.0)	36 (4.9)	
No	248 (97.6)	649 (89.0)	
Missing	*1 (0.4)*	*44 (6.0)*	
Peripheral vascular disease			0.432
Yes	3 (1.2)	16 (2.2)	
No	250 (98.4)	669 (91.8)	
Missing	*1 (0.4)*	*44 (6.0)*	
Cerebrovascular accident			0.448
Yes	7 (2.8)	26 (3.6)	
No	246 (96.8)	659 (90.4)	
Missing	*1 (0.4)*	*44 (6.0)*	
Dementia			0.332
Yes	0 (0)	5 (0.7)	
No	253 (99.6)	680 (93.3)	
Missing	*1 (0.4)*	*44 (6.0)*	
Pulmonary disease			**0.003**
Yes	5 (2.0)	46 (6.3)	
No	248 (97.6)	639 (87.7)	
Missing	*1 (0.4)*	*44 (6.0)*	
Connective tissue disorde			1.000*
Yes	2 (0.8)	6 (0.8)	
No	251 (98.8)	679 (93.2)	
Missing	*1 (0.4)*	*44 (6.0)*	
Peptic ulcer			1.000*
Yes	1 (0.4)	5 (0.7)	
No	252 (99.2)	680 (93.3)	
Missing	*1 (0.4)*	*44 (6.0)*	
Liver disease			1.000*
Yes	0 (0)	1 (0.2)	

Table 2 (*continued*)

	DIEP group (n = 254)	*Control group (n = 729)*	*P*-value
No	253 (99.6)	684 (93.8)	
Missing	*1 (0.4)*	*44 (6.0)*	
Severe liver disease			1.000*
Yes	1 (0.4)	3 (0.4)	
No	252 (99.2)	682 (93.6)	
Missing	*1 (0.4)*	*44 (6.0)*	
Diabetes			**0.029**
Yes	6 (2.4)	40 (5.5)	
No	247 (97.2)	645 (88.5)	
Missing	*1 (0.4)*	*44 (6.0)*	
Diabetes complications			0.770*
Yes	3 (1.2)	11 (1.5)	
No	250 (98.8)	674 (92.5)	
Missing	*1 (0.4)*	*44 (6.0)*	
Paraplegia			1.000*
Yes	2 (0.8)	5 (0.7)	
No	251 (98.8)	680 (93.3)	
Missing	*1 (0.4)*	*44 (6.0)*	
Kidney disease			1.000
Yes	4 (1.6)	10 (1.4)	
No	249 (98.0)	675 (92.6)	
Missing			0.541
Solid tumour[a]	*1 (0.4)*	*44 (6.0)*	
Yes	19 (7.5)	60 (8.2)	
No	234 (92.1)	625 (85.8)	
Missing Metastatic cancer [b]	*1 (0.4)*	*44 (6.0)*	0.147
Yes	68 (26.8)	221 (31.7)	
No	186 (73.2)	477 (68.3)	
Missing	*0 (0)*	*44 (6.0)*	
Lymphoma			0.123*
Yes	1 (0.4)	8 (1.1)	
No	252 (99.2)	677 (92.9)	
Missing	*1 (0.4)*	*44 (6.0)*	
Leukemia			0.690*
Yes	1 (0.4)	7 (1.0)	
No	252 (99.2)	678 (93.0)	
Missing	*1 (0.4)*	*44 (6.0)*	
HIV			–
Yes	0 (0)	0 (0)	
No	253 (99.6)	685 (94.0)	
Missing **CCI Score**[3]	*1 (0.4)*	*44 (6.0)*	0.070
CCI 0-6	203 (79.9)	526 (72.2)	
CCI 7–8	40 (15.7)	102 (14.0)	
CCI≥9	10 (3.9)	57 (7.8)	
Missing	1 (0.4)	44 (6.0)	
Median CCI Score	1 (range 0–13)	2 (range 0–16)	**0.021**

*Fisher's exact test.
Percentages may not sum to 100.0 due to rounding.
[a] Breast cancer not included as solid tumour as all cases share the same diagnosis.
[b] Metastatic cancer was observed in 289 cases, and was unrelated to breast cancer in 65 cases.

health care system and free access to education [4,35,36]. A recent meta-analysis confirmed this on an international level, showing an association between higher SES, income and education and better breast cancer-specific survival [37]. In addition, comorbidity is more prevalent in socioeconomically weaker populations [10].

Comorbidity, i.e., the presence of additional conditions concurrent with the breast cancer diagnosis, is an important factor affecting both the selection for breast reconstruction [23,25,26,28,38–41] and survival [14]. Women with an IB-IBR have even fewer comorbid conditions relative to those who receive delayed reconstruction or none at all [42], which is in line with the presented findings. Hernandez et al. on the other hand, found higher comorbidity scores in women opting for implant reconstruction than those undergoing autologous reconstruction, probably because implant reconstruction poses less surgical stress on the patient than autologous options [24].

Comorbidity not only affects survival but also chemotherapy use and completion rates, likely due to an impaired ability to tolerate systemic treatment [11]. In a previous report from the present cohort [3], a significantly lower proportion of women in the control group received adjuvant chemotherapy which is probably associated with the higher CCI scores in this group. Therefore, adjuvant chemotherapy was adjusted for in the present survival analyses. Some clinical factors associated with chemotherapy indications, such as HER2 status, tumour histological grade, and proliferation, could not be included in adjusted analyses due to high proportions of missing data, and thus, chemotherapy may have served as a surrogate marker for more aggressive disease.

The complexity of the analysis lies in that both lower socioeconomic status and significant co-morbidities are confounding factors for tumour stage at breast cancer diagnosis as well as for treatment, thus acting as competing causes of death. These factors will affect overall survival but also breast cancer-specific survival by modulating adjuvant treatments such as chemotherapy and radiotherapy. The persistence of a survival difference between the DIEP flap and control group after adjustments suggests either the presence of hitherto unmeasured confounders or a cumulative effect of multiple covariates that may interact in complex and

Table 3
Uni- and multivariable Cox regression analyses with death of any cause as the endpoint, including only cases with non-missing information in all covariates in both models.

Total	*Including IBR cases*						*Excluding IBR cases*			
	Number of cases	Number of deaths	Univariable analysis	Multivariable analysis			Number of cases	Number of deaths	Multivariable analysis	
	827	*173*	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value	683	160	Hazard ratio (95%CI)	*P*-value
Cohort										
DIEP group	219	30	1.00 (reference)		1.00 (reference)		201	26	1.00 (reference)	
Control group	608	143	2.08 (1.40–3.09)	<0.001	1.88 (1.24–2.86)	**0.003**	482	134	2.27 (1.44–3.55)	**<0.001**
Age at mastectomy										
<40	200	38	0.94 (0.63–1.39)	0.757	1.77 (1.13–2.77)	**0.013**	142	33	1.74 (1.08–2.79)	**0.022**
41–50	328	61	0.84 (0.60–1.19)	0.327	1.26 (0.86–1.86)	0.241	260	54	1.22 (0.81–1.83)	0.337
>50	299	74	1.00 (reference)		1.00 (reference)		281	73	1.00 (reference)	
Year of mastectomy										
1980–1999	176	75	1.00 (reference)		1.00 (reference)		169	74	1.00 (reference)	
2000–2005	299	68	0.72 (0.51–1.02)	0.060	0.92 (0.63–1.35)	0.662	253	59	0.88 (0.59–1.31)	0.532
2006–2012	352	30	0.65 (0.41–1.03)	0.063	1.07 (0.65–1.76)	0.778	261	27	1.17 (0.70–1.96)	0.547
Invasive tumour size										
T1	199	36	1.00 (reference)		1.00 (reference)		162	35	1.00 (reference)	
T2	443	89	1.20 (0.81–1.76)	0.365	1.02 (0.67–1.57)	0.914	358	81	0.96 (0.62–1.49)	0.851
T3	185	48	1.78 (1.16–2.75)	0.009	1.36 (0.83–2.21)	0.224	163	44	1.19 (0.71–1.99)	0.501
Hormone receptor status										
Negative	162	31	1.00 (reference)		1.00 (reference)		141	29	1.00 (reference)	
Positive	665	142	1.26 (0.85–1.86)	0.245	1.16 (0.76–1.78)	0.480	542	131	1.18 (0.76–1.82)	0.471
Lymph node status										
Negative	344	50	1.00 (reference)		1.00 (reference)		259	46	1.00 (reference)	
Positive	483	123	1.65 (1.19–2.29)	0.003	1.29 (0.87–1.91)	0.208	424	114	1.26 (0.84–1.89)	0.270
Radiotherapy										
Yes	583	123	1.00 (reference)		1.00 (reference)		499	117	1.00 (reference)	
No	244	50	0.81 (0.58–1.21)	0.200	0.80 (0.54–1.20)	0.286	184	43	0.73 (0.48–1.12)	0.150
Chemotherapy										
Yes	667	136	1.00 (reference)		1.00 (reference)		550	123	1.00 (reference)	
No	160	37	0.84 (0.58–1.23)	0.372	0.78 (0.50–1.21)	0.260	133	37	0.89 (0.57–1.40)	0.625
Highest level of education										
Primary school	119	30	1.58 (0.97–2.58)	0.065	0.90 (0.53–1.54)	0.705	108	30	0.88 (0.52–1.51)	0.648
Secondary school	318	72	1.51 (1.06–2.26)	0.047	1.02 (0.65–1.59)	0.947	269	66	0.92 (0.57–1.47)	0.718
Postsecondary school,<3 years	143	36	1.80 (1.13–2.87)	0.013	1.45 (0.89–2.37)	0.134	120	31	1.29 (0.77–2.16)	0.341
Postsecondary school, >3 years	247	35	1.00 (reference)		1.00 (reference)		186	33	1.00 (reference)	
Occupation										
Clerk	420	71	1.00 (reference)		1.00 (reference)		328	62	1.00 (reference)	
Entrepreneur	30	4	0.83 (0.30–2.28)	0.718	0.70 (0.25–1.96)	0.499	26	4	0.80 (0.29–2.25)	0.674
Labourer	149	29	1.23 (0.80–1.90)	0.346	1.54 (0.95–2.49)	0.078	116	28	1.92 (1.17–3.17)	**0.010**
retired/unemployed	228	69	2.28 (1.63–3.20)	<0.001	2.05 (1.38–3.04)	**<0.001**	213	66	2.11 (1.40–3.18)	**<0.001**
Family status										
Partnership	469	88	1.00 (reference)		1.00 (reference)		377	80	1.00 (reference)	
Single	358	85	1.40 (1.04–1.89)	0.029	1.13 (0.72–1.78)	0.585	306	80	1.10 (0.69–1.76)	0.686
Income per household										
Low	256	69	1.00 (reference)		1.00 (reference)		228	66	1.00 (reference)	
Middl	276	65	0.86 (0.61–1.21)	0.380	0.85 (0.54–1.35)	0.488	231	59	0.80 (0.50–1.28)	0.355
High	295	39	0.57 (0.38–0.84)	0.005	1.04 (0.57–1.92)	0.894	224	35	1.07 (0.57–2.02)	0.827
CCI score										
CCI 0-6	657	66	1.00 (reference)		1.00 (reference)		514	58	1.00 (reference)	
CCI 7-8	131	66	4.85 (3.44–6.83)	<0.001	4.96 (3.39–7.27)	**<0.001**	119	63	4.74 (3.20–7.10)	**<0.001**
CCI ≥ 9	53	41	7.95 (5.38–11.74)	<0.001	8.67 (5.59–13.47)	**<0.001**	50	39	7.86 (5.02–12.31)	**<0.001**

IBR: immediate breast reconstruction.

Table 4
Uni- and multivariable Cox regression analyses with breast cancer death as the endpoint, including only cases with non-missing information in all covariates in both models.

	Including IBR cases						Excluding IBR cases			
	Number of cases	Number of breast cancer deaths	Univariable analysis	Multivariable analysis			Number of cases	Number of breast cancer deaths	Multivariable analysis	
	827	*136*	Hazard ratio (95% CI)	*P*-value	Hazard ratio	*P*-value	*683*	*124*	Hazard ratio (95% CI)	*P*-value
Cohort										
DIEP group	219	28	1.00 (reference)		1.00 (reference)		201	24	1.00 (reference)	
Control group	608	108	1.62 (1.07–2.46)	**0.023**	1.51 (0.96–2.38)	0.076	482	100	1.79 (1.09–2.92)	**0.020**
Age at mastectomy										
<40	200	35	1.39 (0.90–2.16)	0.142	3.11 (1.85–5.21)	**<0.001**	142	30	2.83 (1.64–4.88)	**<0.001**
41–50	328	54	1.22 (0.83–1.81)	0.315	1.95 (1.23–3.08)	**0.005**	260	47	1.78 (1.09–2.89)	**0.020**
>50	299	47	1.00 (reference)		1.00 (reference)		281	47	1.00 (reference)	
Year of mastectomy										
1980–1999	176	59	1.00 (reference)		1.00 (reference)		169	58	1.00 (reference)	
2000–2005	299	53	0.67 (0.45–0.98)	**0.040**	1.10 (0.71–1.10)	0.678	253	45	0.98 (0.62–1.56)	0.932
2006–2012	352	24	0.59 (0.36–0.99)	0.044	1.20 (0.69–2.08)	0.521	261	21	1.30 (0.73–2.32)	0.381
Invasive tumour size										
T1	199	27	1.00 (reference)		1.00 (reference)		162	26	1.00 (reference)	
T2	443	68	1.24 (0.79–1.93)	0.350	0.92 (0.56–1.53)	0.758	358	61	0.84 (0.49–1.42)	0.506
T3	185	41	2.05 (1.26–3.34)	0.004	1.37 (0.78–2.41)	0.271	163	37	1.19 (0.66–2.17)	0.565
Hormone receptor status										
Negative	162	23	1.00 (reference)		1.00 (reference)		141	22	1.00 (reference)	
Positive	665	113	1.33 (0.85–2.08)	0.214	1.17 (0.72–1.91)	0.522	542	102	1.08 (0.65–1.78)	0.768
Lymph node status										
Negative	344	35	1.00 (reference)		1.00 (reference)		259	31	1.00 (reference)	
Positive	483	101	1.94 (1.32–2.85)	**0.001**	1.22 (0.77–1.91)	0.396	424	93	1.24 (0.77–2.00)	0.375
Radiotherapy										
Yes	244	34	1.00 (reference)		1.00 (reference)		499	96	1.00 (reference)	
No	583	102	0.66 (0.44–0.97)	0.035	0.79 (0.50–1.25)	0.308	184	28	0.68 (0.41–1.12)	0.129
Chemotherapy										
Yes	160	22			1.00 (reference)		550	102	1.00 (reference)	
No	667	114	0.60 (0.37–0.95)	**0.030**	0.56 (0.33–0.96)	**0.035**	133	22	0.63 (0.36–1.09)	0.097
Highest level of education										
Primary school	119	19	1.12 (0.63–1.99)	0.694	0.66 (0.35–1.24)	0.196	108	19	0.62 (0.33–1.17)	0.143
Secondary school	318	59	1.43 (0.92–2.22)	0.11	0.83 (0.51–1.38)	0.477	269	53	0.72 (0.42–1.22)	0.223
Postsecondary school,< 3 Years	143	28	1.58 (0.94–2.64)	0.084	1.32 (0.77–2.28)	0.315	120	24	1.16 (0.65–2.07)	0.614
Postsecondary school, > 3 Years	247	30	1.00 (reference)		1.00 (reference)		186	28	1.00 (reference)	
Occupation										
Clerk	420	56	1.00 (reference)		1.00 (reference)		328	47	1.00 (reference)	
Entrepreneur	30	4	1.06 (0.38–2.92)	0.915	0.92 (0.32–2.61)	0.871	26	4	1.13 (0.40–3.25)	0.817
Labourer	149	26	1.41 (0.89–2.25)	0.147	1.76 (1.04–2.98)	**0.036**	116	25	2.33 (1.33–4.08)	**0.003**
Retired/ unemployed	228	50	1.96 (1.33–2.88)	**0.001**	2.13 (1.35–3.35)	**0.001**	213	48	2.26 (1.40–3.65)	**0.001**
Family status										
Partnership	469	75					377	67		

(*continued on next page*)

Table 4 (*continued*)

	Including IBR cases						Excluding IBR cases			
	Number of cases	Number of breast cancer deaths	Univariable analysis	Multivariable analysis			Number of cases	Number of breast cancer deaths	Multivariable analysis	
	827	*136*	Hazard ratio (95% CI)	*P*-value	Hazard ratio	*P*-value	*683*	*124*	Hazard ratio (95% CI)	*P*-value
			1.00 (reference)		1.00 (reference)				1.00 (reference)	
Single	358	61	1.13 (0.81 −1.59)	0.480	0.95 (0.57 −1.58)	0.846	306	57	0.92 (0.54 −1.55)	0.745
Income per household										
Low	256	47	1.00 (reference)		1.00 (reference)		228	45	1.00 (reference)	
Middle	276	55	1.10 (0.75 −1.62)	0.633	0.93 (0.55 −1.57)	0.772	231	49	0.84 (0.49 −1.44)	0.521
High	295	34	0.74 (0.47 −1.15)	0.180	1.10 (0.55 −2.18)	0.786	224	30	1.07 (0.52 −2.19)	0.850
CCI score										
CCI 0-6	644	41	1.00 (reference)		1.00 (reference)		514	34	1.00 (reference)	
CCI 7-8	130	61	7.39 (4.97 −10.99)	**<0.001**	9.41 (5.99 −14.79)	**<0.001**	119	58	9.05 (5.63-	**<0.001**
CCI ≥ 9	53	34	10.07 (6.39 −15.87)	**<0.001**	15.29 (9.11 −25.67)	**<0.001**	50	32	14.04 (8.19-	**<0.001**

IBR: immediate breast reconstruction.

synergistic ways.

A major strength of this study is the high coverage and validity of nationwide population-based registers [43] along with detailed individual clinical data obtained from medical charts leading to low missingness. All breast cancer patients in Sweden are treated within a tax-funded health care system, minimizing economical and reimbursement implications as a confounder to SES. All women included in this study were operated in Stockholm, thereby reducing any regional variations in treatment, selection criteria, or preoperative patient information. As a limitation, two important selection criteria that are associated with both SES and comorbidity, i.e. smoking and body mass index (BMI), could not be entered into analyses since data were too incomplete. In Sweden, active smoking is a contraindication for DIEP flap reconstruction since it is significantly associated with impaired wound healing, infection and postoperative complications such as flap loss, hematoma or fat necrosis [44–46]. Also a high BMI is a contraindication for DIEP flap reconstruction, since patients with a BMI >30 kg/m^2 are more likely to experience surgical as well as medical postoperative complications [47–49]. Swedish recommendations state that patients undergoing DIEP should have a BMI <30 kg/m^2, quit smoking at least four weeks before surgery and be free of cancer relapse [2]. It is thus likely that women in the DIEP group would have lower rates of smoking and a lower BMI than those in the control group, affecting the presented results. Of note, both BMI and smoking are also associated with lower SES and significantly affect survival, and would therefore have been highly relevant factors to adjust for in survival analyses. Other unmeasured conditions not included in the CCI score that influence survival estimates and represent selection criteria for a DIEP flap reconstruction are psychiatric disorders, alcohol and drug abuse, immunosuppressive therapy, bleeding disorders and previous major abdominal surgery, thereby leading to limited accuracy of the measurement in regards to comorbidity. Data on SES were obtained from national registries and could be considered as reliable since for instance, data on income derive from electronic tax reports. Data on education are reported by schools and universities through achieved and registered examinations and certifications.

A further selection bias may lie in the fact that access to microvascular breast reconstruction in Sweden was limited in the years 1999–2013, and mainly women who had been treated with radiotherapy were then offered DIEP flap reconstruction. While this selection bias could have resulted in higher tumour stages and a higher proportion of node positivity among women in the DIEP group, this was not the case after the initial matching procedure.

5. Conclusions

Patients undergoing delayed DIEP flap reconstruction represent a subset of women with a higher SES and generally better health than those undergoing mastectomy with no delayed reconstruction. The previously reported higher survival proportions for women in the DIEP group persisted after adjustments for relevant clinical factors, SES and comorbidity, suggesting that further, unmeasured factors or the cumulative effect of multiple covariates that may interact in a complex and synergistic ways that may influence survival in this setting.

Declaration of competing interest

None.

Acknowledgements

The authors gratefully appreciate the use of data from then Swedish National Breast Cancer Register, from Statistics Sweden and the National Board of Health and Welfare. J.d.B is supported by grants from the Swedish Cancer Society and Stockholm County Council together with the Karolinska Institute (ALF grant). This study was also supported by the Percy Falk Foundation. Supplementary table 1 was *previously published in BJS 2018;105(11): 1435–1445: Risk of recurrence and death in patients with breast cancer after delayed deep inferior epigastric perforator flap reconstruction DOI: 10.1002/bjs.10866).*

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.07.001.

Role of the funding source

This study was supported by the Percy Falk Foundation. J.d.B is supported by grants from the Swedish Cancer Society and Stockholm County Council together with the Karolinska Institutet (ALF grant). Funding sources had no impact on study design, collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

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