Predictors of Unemployment After Breast Cancer Surgery: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Purpose

Breast cancer surgery is associated with unemployment. Identifying high-risk patients could help inform strategies to promote return to work. We systematically reviewed observational studies to explore factors associated with unemployment after breast cancer surgery.

Methods

We searched MEDLINE, EMBASE, CINAHL, and PsycINFO to identify studies that explored risk factors for unemployment after breast cancer surgery. When possible, we pooled estimates of association for all independent variables reported by more than one study.

Results

Twenty-six studies (46,927 patients) reported the association of 127 variables with unemployment after breast cancer surgery. Access to universal health care was associated with higher rates of unemployment (26.6% v 15.4%; test of interaction $P = .05$). High-quality evidence showed that unemployment after breast cancer surgery was associated with high psychological job demands (odds ratio [OR], 4.26; 95% CI, 2.27 to 7.97), childlessness (OR, 1.30; 95% CI, 1.11 to 1.53), lower education level (OR, 1.15; 95% CI, 1.05 to 1.25), lower income level (OR, 1.46; 95% CI, 1.24 to 1.73), cancer stage II, III or IV (OR, 1.43; 95% CI, 1.13 to 1.82), and mastectomy versus breast-conserving surgery (OR, 1.18; 95% CI, 1.07 to 1.30). Moderate-quality evidence suggested an association with high physical job demands (OR, 2.11; 95% CI, 1.52 to 2.93), African-American ethnicity (OR, 1.89; 95% CI, 1.21 to 2.96), and receipt of chemotherapy (OR, 1.95; 95% CI, 1.36 to 2.79). High-quality evidence demonstrated no significant association with part-time hours, blue-collar work, tumor size, positive lymph nodes, or receipt of radiotherapy or endocrine therapy; moderate-quality evidence suggested no association with age, marital status, or axillary lymph node dissection.

Conclusion

Addressing high physical and psychological job demands may be important in reducing unemployment after breast cancer surgery.

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INTRODUCTION

Breast cancer is the most common cancer among women and is diagnosed most often in working-age adults. Ten-year survival rates have improved markedly, particularly in developed countries (eg, 86% in the United States in 2017,¹ 78% in the United Kingdom in 2010 to 2011²); however, cancer survivorship is associated with unemployment.³ Rates of return to work within 1 year of diagnosis range from 43% to 93%,⁴ and a meta-analysis found that breast cancer survivors were more

likely to be unemployed compared with healthy control participants (35.6% v 31.7%; pooled relative risk [RR], 1.28; 95% CI, 1.11 to 1.49).³ Indirect costs, including sick leave and disability benefits, constitute 70% of the total costs associated with breast cancer.⁵

Unemployment among breast cancer survivors is associated with reduced quality of life⁶⁻⁸ and increased mortality,⁸⁻¹⁰ whereas resuming employment is associated with better social functioning, greater financial security, improved health, and higher self-esteem.^{4,11-18} Knowledge of risk factors for unemployment could help inform optimal

ASSOCIATED CONTENT

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treatment to facilitate return to work; however, previous systematic reviews of factors associated with unemployment after breast cancer surgery have several limitations, including outdated searches, inadequate risk of bias assessment, lack of statistical pooling of measures of association, and failure to evaluate the quality of evidence.^{4,11,19-21} To address these limitations, we conducted a systematic review and meta-analysis of observational studies to identify risk factors for employment status after breast cancer surgery.

METHODS

We completed our systematic review in accordance with the reporting of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement²² and registered our protocol with PROSPERO (CRD42014013338). Before performing our analysis, we included an additional subgroup analysis to explore whether lack of availability of universal health care was associated with lower rates of unemployment after breast cancer surgery. Specifically, the United States does not provide universal health care, and most working-age Americans receive health insurance coverage through their employer.²³ Maintaining health insurance may provide a powerful incentive to return to work. We also conducted a post hoc subgroup analysis to explore whether a higher proportion of patients employed at baseline was associated with lower unemployment after breast cancer surgery.

Data Sources and Searches

We searched MEDLINE, EMBASE, CINAHL, and PsycINFO from inception to March 1, 2017, without language restrictions. An experienced academic librarian developed search strategies for each electronic database (Data Supplement). We screened the reference lists of all eligible studies and 11 previous reviews^{3,4,7,10,11,19-21,24-26} for additional studies.

We included cohort or case-control studies that used an adjusted analysis to explore risk factors for unemployment after breast cancer surgery. We included both direct (eg, not returning to work, not working, unemployment) and indirect (eg, sick leave, unemployment benefits, disability pension, loss of work productivity) measures of unemployment. We excluded conference abstracts. Studies were ineligible if they included, in all available models, significant associations with variables collected after baseline; in such instances, the status of the predictor may be a result rather than a cause of employment status. When study populations overlapped by > 50% among articles, we included only the study with the largest sample size and longest follow-up. Studies excluded for population overlap or significant factors collected after baseline are listed in the Data Supplement.

Study Selection

Paired reviewers independently screened the titles and abstracts of identified citations and full texts of potentially eligible studies. Reviewers resolved any disagreements by discussion or with the help of an adjudicator. We used online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada) to facilitate literature screening.

Quality Assessment and Data Extraction

Using standardized, pilot-tested data extraction forms and a detailed instruction manual, pairs of reviewers extracted data from all eligible studies, independently and in duplicate. We used the following four criteria from the Users' Guides to the Medical Literature²⁷ to assess the risk of bias: (1) representativeness of the study population; (2) validity of outcome assessment; (3) loss to follow-up ($\geq 20\%$ was considered a high risk of bias); and (4) whether predictive models were adjusted for age, severity of breast cancer, adjuvant therapy, and work-related factors. We also explored

whether factors included in the final models were data driven (only those significant in bivariable analysis, and thus more vulnerable to chance) or theory driven. We used predefined criteria to select one model for data extraction if a study reported multiple regression models (Data Supplement). Two reviewers, blinded to results, independently categorized dependent variables as direct or indirect measures of unemployment and as high or low thresholds for resuming employment.

Data Synthesis and Analysis

We used the kappa statistic (κ) to measure inter-rater agreement of full-text screening.²⁸ We pooled the prevalence of unemployment among eligible studies using random-effects models after performing a Freeman-Tukey double arcsine transformation to stabilize the variance.²⁹ When possible, we pooled all factors associated with employment status that were reported by more than one study and presented odds ratios (ORs) and associated 95% CIs. When studies provided the measure of association as a relative risk (RR) or hazard ratio, we converted them to an OR if the baseline risk (ie, the proportion of patients in the reference or unexposed group who were unemployed at follow-up) was available.^{30,31} We considered ethnicity to be a social construct and did not collapse categories such as African American, Black African, and Black Caribbean into a single group.³²

We calculated a single OR for converting categorical variables to continuous variables (eg, age) using methods described in the Data Supplement. For studies that reported separate RR estimates for subgroups (eg, income quartiles), we pooled related associations using the inverse variance method to generate an overall measure of association.³³ We used random-effects models for all meta-analyses. We explored the consistency of association between our pooled results and studies reporting the same predictors that were not possible to pool. We used the following three criteria to identify predictors that were not amenable to pooling and showed promise for future research: (1) a statistically significant association with unemployment of $P \leq .01$, (2) a large magnitude of association ($OR \geq 2.0$); and (3) a sample size ≥ 500 .³⁴

To avoid overestimating the strength of association, we used an OR of 1 for predictors that were tested in bivariable analyses but were excluded from adjusted analyses because of nonsignificance or were included in multivariable analyses with the only information provided that they were not significant. We imputed an associated variance for all such predictors using the hot deck approach.³⁵ To facilitate interpretation, we calculated the absolute risk increase (ARI) for each predictor amenable to meta-analysis. We estimated the baseline risk for unemployment (10% in the low-risk group, who reported the highest quartile income) using data from the study eligible for review with the largest sample size among studies at low risk of bias.³⁶ We used Stata statistical software version 15 (StataCorp, College Station, TX) for all statistical analyses. All comparisons were two tailed, with a threshold P of .05.

Publication Bias

We explored for publication bias by visual assessment of asymmetry of the funnel plot for each pooled predictor and calculation of Begg's rank correlation test,³⁷ when there were at least 10 studies in a meta-analysis.^{33,38}

Subgroup Analyses, Metaregression, and Sensitivity Analyses

We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots,³⁸ because statistical tests of heterogeneity can be misleading when sample sizes are large and associated measures of precision are therefore narrow.³⁹

We generated four a priori hypotheses to explain variability among studies, assuming a larger association with unemployment and (1) a shorter duration of follow-up, (2) a direct measure of unemployment, (3) a lower threshold for employment, and (4) a greater risk of bias on a criteria-by-criteria basis. We conducted subgroup analyses only if each subgroup contained two or more studies. We performed sensitivity

analyses to examine the effect of imputing data for nonsignificant postulated predictors, of converting categorical data for age to continuous data, and of different cutoffs for a higher versus a lower level of education.

Quality of Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the quality of evidence for all meta-analyses as high, moderate, low, or very low.³⁸ Given a 10% baseline risk of unemployment after breast cancer surgery,³⁶ we estimated that a 5% increase in absolute risk would likely be sufficient to address modifiable risk factors, which can be directly targeted in an effort to reduce unemployment. We further estimated that an absolute increase in risk of 10% for a nonmodifiable factor would be sufficient to identify high-risk candidates for intervention. Therefore, we rated down for imprecision if the 95% CI associated with the ARI included 5% for modifiable risk factors or 10% for nonmodifiable risk factors.

RESULTS

We identified 20,770 unique records, of which we retrieved 179 articles in full text; 26 cohort studies proved eligible (Fig 1). There was near perfect agreement ($\kappa = 0.83$) among reviewers at the full-text review stage. We successfully contacted three of nine authors to confirm eligibility⁴⁰ or to verify data.^{41,42}

Among our 26 eligible studies, nine were conducted in the United States,⁴³⁻⁵¹ 14 in Europe (including Sweden,^{41,52-56} the Netherlands,^{57,58} Denmark,^{36,59} France,¹² Germany,⁴² Norway,⁶⁰ and the United Kingdom⁶¹), two in South Korea,^{62,63} and one in Canada.⁶⁴ The median sample size was 337 (interquartile range, 149-1,220), and the median duration of follow-up was 30 months (interquartile range, 12-46 months). Most studies (58% [15 of 26]) reported that all patients were employed at baseline,^{12,36,41,43-47,49,50,53,54,57,61,64} four

studies reported that $> 75\%$ but $< 100\%$ were employed at baseline,^{48,52,56,60} and five studies^{42,58,59,62,63} reported employment rates ranging from 40.3% to 69.2% at baseline; two studies^{51,55} did not report the rate of employment at baseline. Eleven studies (42%) used indirect measures of unemployment,^{36,47,49,51,52,54-56,58-60} and five studies (19%) used a high threshold for resuming employment (eg, working to the same extent as before the breast cancer, working full time^{46,53,55,57,64}; Data Supplement).

Risk of Bias

Reporting of methodologic safeguards against risk of bias was limited among eligible studies, with 77% (20 of 26) not meeting at least one of our risk of bias items^{12,41,42,45-49,52,54-64} (Data Supplement). Fourteen studies (54%) either failed to report loss to follow-up^{46,58,63} or reported $\geq 20\%$ loss to follow-up.^{42,47,48,50,54-57,61,62,64} Only nine studies (35%) reported adequately adjusted regression models.^{36,43,44,48-51,53,64} Seven studies (27%) only included variables significant in bivariable analysis in their final regression model,^{45,48,49,53,56,62,64} and 16 studies (62%) failed to present data for nonsignificant predictors in their adjusted analysis.^{12,41,43,45,47,49,51,53,54,56,57,59-62,64} (Data Supplement). We detected no evidence of publication bias (Table 1; Data Supplement).

Prevalence of Unemployment

Twenty-five studies^{12,36,41-63} reported prevalence of unemployment after breast surgery, which ranged from 5.6% to 56.3%. Only access to universal health care explained between-study heterogeneity, suggesting that patients in the United States were less likely to be unemployed (15.4%; 95% CI, 10.0% to

Fig 1. Flow diagram of study selection.

Table 1. GRADE Evidence Profile: Predictors of Unemployment After Breast Cancer Surgery

Table 1. GRADE Evidence Profile: Predictors of Unemployment After Breast Cancer Surgery									
No. of Participants; No. of Studies; Follow-Up (months)	Quality Assessment					Summary of Findings			
	Risk of Bias*	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Relative Effect, OR (95% CI)	Anticipated Absolute Effects	
								Baseline Risk† (%)	Risk Difference (95% CI)
Predictor 1. Physical job demands: high v low									
16,472; 5; 1-120	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision‡	Uncertain: only five studies	Moderate due to imprecision	2.11 (1.52 to 2.93)	10	9.0 more (4.4 to 14.6 more) patients with high physical demands experiencing unemployment
Predictor 2. Psychological job demands: high v low									
1,943; 5; 4-49	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only five studies	High	4.26 (2.27 to 7.97)	10	22.1 more (10.1 to 37.0 more) patients with high psychological job demands experiencing unemployment
Predictor 3. Ethnicity: African Americans v European Americans									
951; 3; 3-9	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision‡	Uncertain: only four studies	Moderate due to imprecision	1.89 (1.21 to 2.96)	10	7.4 more (1.9 to 14.7 more) African-American patients experiencing unemployment
Predictor 4. Having a child or children: no v yes									
2,984; 7; 9-60	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only seven studies	High	1.30 (1.11 to 1.53)	10	2.6 more (1.0 to 4.5 more) patients having no child experiencing unemployment
Predictor 5. Education level: lower v higher									
12,629; 8 (with optimally adjusted models); 4-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	1.15 (1.05 to 1.25)	10	1.3 more (0.4 to 2.2 more) patients with lower education experiencing unemployment
Predictor 6. Income level: lower v higher									
20,703; 8; 4-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: Only eight studies	High	1.46 (1.24 to 1.73)	10	4.0 more (2.1 to 6.1 more) patients with lower income level experiencing unemployment
Predictor 7. Cancer stage: stage II, III, or IV v 0 or I									
5,819; 8; 4-72	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only eight studies	High	1.43 (1.13 to 1.82)	10	3.7 more (1.2 to 6.8 more) patients with stage II, III, or IV cancer experiencing unemployment
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Table 1. GRADE Evidence Profile: Predictors of Unemployment After Breast Cancer Surgery (continued)

Table 1. GRADE Evidence Profile: Predictors of Unemployment After Breast Cancer Surgery (continued)								
No. of Participants; No. of Studies; Follow-Up (months)	Quality Assessment					Summary of Findings		
	Risk of Bias*	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Relative Effect, OR (95% CI)	Anticipated Absolute Effects
								Baseline Risk† (%)
Predictor 8. Breast surgery: mastectomy v breast-conserving surgery								
31,494; 12; 1.5-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test P = 1.0	High	1.18 (1.07 to 1.30)	10 1.6 more (0.6 to 2.6 more) patients with mastectomy experiencing unemployment
Predictor 9. Chemotherapy: yes v no								
5,409; 9 (with direct measure of unemployment); 4-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate due to imprecision	1.95 (1.36 to 2.79)	10 7.8 more (3.1 to 13.7 more) patients with chemotherapy experiencing unemployment
Predictor 10. Age: every 10-year increment								
26,489; 18; 3-120	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Detected; Asymmetric funnel plot; Begg's test P = 0.50	Moderate due to inconsistency	1.10 (0.99 to 1.23)	10 for age 18 years¶ 0.9 more (0.1 less to 2.0 more) patients with per 10-year increment of age experiencing unemployment
Predictor 11. Marital status: married v not married								
22,143; 15; 1.5-120	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test P = 0.49	Moderate due to inconsistency	0.97 (0.66 to 1.44)	10 0.3 less (3.2 less to 3.8 more) married patients experiencing unemployment
Predictor 12. Work hours: part-time v full-time								
2,048; 6; 9-72	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only six studies	High	1.19 (0.78 to 1.80)	10 1.7 more (2 less to 6.7 more) patients having part-time job experiencing unemployment
Predictor 13. Job category: white- or pink-collar v blue-collar								
2,313; 7; 4-60	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only seven studies	High	1.44 (0.99 to 2.08)	10 3.8 more (0.1 less to 8.8 more) patients having blue-collar job experiencing unemployment
Predictor 14. Tumor size: > 10mm v 0-10mm								
18,845; 2; 60-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only two studies	High	1.04 (0.98 to 1.10)	10 0.4 more (0.2 less to 0.9 more) patients with tumor size > 10 mm experiencing unemployment
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Table 1. GRADE Evidence Profile: Predictors of Unemployment After Breast Cancer Surgery (continued)

Quality Assessment							Summary of Findings		
No. of Participants; No. of Studies; Follow-Up (months)	Risk of Bias*	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Relative Effect, OR (95% CI)	Anticipated Absolute Effects	
								Baseline Risk† (%)	Risk Difference (95% CI)
Predictor 15. Positive lymph nodes: yes v no 18,845; 2; 60-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Uncertain: only two studies	High	0.96 (0.81 to 1.14)	10	0.4 less (1.7 less to 1.2 more) patients with one or more positive lymph nodes experiencing unemployment
Predictor 16. Axillary lymph nodes dissection (ALND): yes v no 20,738; 8; 1.5-120	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision†	Uncertain: only eight studies	Moderate due to imprecision	1.37 (0.94 to 2.00)	10	3.2 more (0.5 less to 8.2 more) patients with ALND experiencing unemployment
Predictor 17. Radiotherapy: yes v no 26,482; 15; 4-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test <i>P</i> = 0.20	High	1.10 (0.91 to 1.34)	10	0.9 more (0.8 less to 3.0 more) patients with radiotherapy experiencing unemployment
Predictor 18. Endocrine therapy: yes v no 27,400; 12; 10-120	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test <i>P</i> = 0.30	High	0.96 (0.89 to 1.04)	10	0.4 less (1 less to 0.4 more) patients with endocrine therapy experiencing unemployment

Abbreviations: ALND, axillary lymph nodes dissection; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

*We did not rate down for risk of bias, because our subgroup analyses and metaanalysis did not identify any significant difference between each risk of bias component and the estimates of association.

†Baseline risk from the subpopulation of highest quartile income with lowest absolute risk of unemployment in the study with the largest sample size among the studies at low risk of bias.³⁵

#We rated down because of imprecision, because the 95% CI associated with the risk difference included our threshold of 5% for modifiable factors and 10% for nonmodifiable factors, which means clinical actions on the basis of the estimates in the lower or upper boundary may be different.

§Significant subgroup effects were found for education (regression models v not optimally adjusted, interaction $P = .01$) and chemotherapy (direct v indirect outcome measures, interaction $P = .03$).||We did not rate down because of imprecision, although the 95% CI for the pooled effect overlaps a risk difference of 0 (no effect), because clinical actions on the basis of the estimates in the lower or upper boundary will not change, on the basis of our threshold of $\geq 10\%$ for nonmodifiable factors.¶We obtained the reference group for age at 18 years old from the largest study among the studies with a low risk of bias that explored this predictor.³⁶

21.6%) compared with patients from countries with universal health care (26.6%; 95% CI, 20.0% to 33.9%; $P = .05$ for the interaction; Data Supplement) No significant subgroup effects were detected for direct versus indirect measures of unemployment, high versus low threshold for return to work, and risk of bias (interaction P values ranged from 0.35 to 0.89), or metaregression for unemployment and duration of follow-up ($P = .62$) or proportion of patients employed at baseline ($P = .31$).

Predictors of Unemployment

Twenty-six studies involving 46,927 patients reported the association of 127 independent variables with unemployment after

breast cancer surgery, 18 of which were suitable for meta-analysis on the basis of our criteria.

Work-related factors. We found a significant association between two modifiable factors and unemployment after breast cancer surgery: high psychological job demands (OR, 4.26 [95% CI, 2.27 to 7.97]; high-quality evidence; Fig 2A; ARI, 22.1% [95% CI, 10.1% to 37.0%]) and high physical job demands (OR, 2.11 [95% CI, 1.52 to 2.93]; moderate-quality evidence; Fig 2B; ARI, 9.0% [95% CI, 4.4% to 14.6%]; Table 1). Psychological job factors included job strain (low job decision control and high psychological job demands)⁵³; perceived psychological or organizational constraints at work¹²; and employment support or accommodation in flexible work schedule, paid leave, and/or modifications of job

Fig 2. Meta-analysis of the association of significant predictors for unemployment. (A) Psychological job demands (high v low). (B) Physical job demands (high v low). (C) Chemotherapy (yes v no; interaction $P = .03$). OR, odds ratio. Note that weights are from random-effects analysis.

Fig 2. (Continued).

tasks.^{48,49,61} Definitions of high physical job demands included manual work,^{36,53} strenuous work postures,⁵⁴ and physically demanding jobs.^{12,44}

We considered job type (blue collar *v* pink or white collar) and work hours (part time *v* full time) as nonmodifiable factors, because they are rarely modified in practice. High-quality evidence suggested no significant association between unemployment and blue-collar versus white- or pink-collar work (OR, 1.44; 95% CI, 0.99 to 2.08; Data Supplement) or part-time employment (OR, 1.19; 95% CI, 0.78 to 1.80; Data Supplement; Table 1).

Sociodemographic factors. We found high-quality evidence for a significant association between unemployment and childlessness (OR, 1.30 [95% CI, 1.11 to 1.53]; Data Supplement; ARI 2.6% [95% CI, 1.0% to 4.5%]), lower education level (OR, 1.15 [95% CI, 1.05 to 1.25]; Data Supplement; ARI, 1.3% [95% CI, 0.4% to 2.2%]), and lower income level (OR, 1.46 [95% CI, 1.24 to 1.73]; Data Supplement; ARI, 4.0% [95% CI, 2.1% to 6.1%]); and moderate-quality evidence for a significant association with African-American ethnicity (OR, 1.89 [95% CI, 1.21 to 2.96]; Data Supplement; ARI, 7.4% [95% CI, 1.9% to 14.7%; Table 1). Moderate-quality evidence showed no significant association between unemployment and age (OR for every 10-year increment, 1.10; 95% CI, 0.99 to 1.23; Data Supplement) or marital status (OR for married *v* not married, 0.97; 95% CI, 0.66 to 1.44; Data Supplement; Table 1).

Medical factors. We found high-quality evidence for a significant association between unemployment and cancer stage II, III, or IV versus 0 or I (OR, 1.43 [95% CI, 1.13 to 1.82]; Data Supplement; ARI, 3.7% [95% CI, 1.2% to 6.8%]) and mastectomy versus breast-conserving surgery (OR, 1.18 [95% CI, 1.07 to 1.30]; Data Supplement; ARI, 1.6% [95% CI, 0.6% to 2.6%]); and moderate-quality evidence for an association with receipt of chemotherapy (OR, 1.95 [95% CI, 1.36 to 2.79]; Fig 2C; ARI, 7.8% [95% CI, 3.1% to 13.7%]; Table 1).

High-quality evidence showed no significant association between unemployment and tumor size (OR for > 10 mm *v* 0 to 10 mm, 1.04; 95% CI, 0.98 to 1.10; Data Supplement), positive lymph nodes (OR, 0.96; 95% CI, 0.81 to 1.14; Data Supplement), receipt of radiotherapy (OR, 1.10; 95% CI, 0.91 to 1.34; Data Supplement), or endocrine therapy (OR, 0.96; 95% CI, 0.89 to 1.04; Data Supplement; Table 1). Moderate-quality evidence suggested no association between unemployment and axillary lymph node dissection (OR, 1.37; 95% CI, 0.94 to 2.00; Data Supplement).

Factors not amenable to pooling. The Data Supplement presents the associations with unemployment for the 109 factors that were not amenable to meta-analysis. Seven of these predictors were consistently associated with unemployment: (1) sickness absence 1 year before breast cancer diagnosis, (2) paid disability

leave, (3) physician-advised work absence, (4) no regular endurance exercise before diagnosis, (5) preferred provider organization or point of service with capitation versus basic or comprehensive health plan, (6) receipt of multimodal cancer therapy, and (7) baseline perception of lower control over effects of cancer at work (Data Supplement). Two of these factors (sickness absence 1 year before breast cancer diagnosis and physician-advised work absence) met our criteria as promising for future study. Ninety-five factors were consistently not associated with unemployment (Data Supplement), and seven factors (country of birth, place of residence, unemployment status before and at diagnosis, lymphedema, shoulder function impairment, fatigue, and quality of life—physical functioning after surgery) showed conflicting associations across studies (Data Supplement).

Subgroup Analyses, Metaregression, and Sensitivity Analyses

We found significant subgroup effects for the associations of receipt of chemotherapy (interaction $P = .03$ for direct ν indirect outcome measures; Table 1; Fig 2C) and low education level (interaction $P = .01$ for optimally adjusted models ν not optimally adjusted models; Table 1; Data Supplement) with unemployment, and presented results for direct outcome measures and optimally adjusted models, respectively (Table 1). No additional subgroup analysis or metaregression was significant (Data Supplement). Our sensitivity analyses found no important differences in results whether we incorporated missing data for nonsignificant predictors, used different cutoffs for high versus low education level, or included data for age that we converted from categorical to continuous data (Data Supplement).

DISCUSSION

Rates of unemployment after breast cancer surgery are variable and are significantly lower in the United States (15.4%) than in countries with universal health care (26.6%). We found high-quality evidence that high psychological job demands; African-American ethnicity; childlessness; lower education; lower income level; cancer stage II, III, or IV; and mastectomy are associated with unemployment after breast cancer surgery; and moderate-quality evidence for an association with high physical job demands and receipt of chemotherapy. The strongest of these associations were for high psychological job demands and high physical job demands, with an absolute increase in risk of unemployment of 22% and 9%, respectively (Table 1). High-quality evidence demonstrated no significant association between part-time or full-time work, job category (blue ν white- or pink-collar job), tumor size, positive lymph nodes, receipt of radiotherapy, or endocrine therapy with unemployment; and moderate-quality evidence found no significant association for age, marital status or axillary lymph nodes dissection (Table 1). Investigators have tested 109 additional predictors that could not be statistically pooled (Data Supplement). Of these, sickness absence 1 year before diagnosis⁵² and physician-advised work absence⁶⁴ warrant additional study.

The strengths of our review include explicit eligibility criteria and a comprehensive search with no language restrictions that

identified 16 cohort studies^{36,42-44,48-52,54-56,58,59,61,62} that were not included in previous systematic reviews.^{4,11,19-21} We used the GRADE approach to appraise the quality of evidence, imputed data for missing nonsignificant predictors to avoid overestimating associations, and conducted subgroup and sensitivity analysis that confirmed robust effects. We presented both relative risk increases and ARIs, which more clearly convey the importance of associations.

Limitations include the inability to pool data for predictors from studies that used different continuous outcome measures to assess unemployment in linear regression models,^{47,51} because the estimates of association are outcome specific. The results of these studies were generally consistent with the results of studies amenable to pooling (Data Supplement). We pooled measures of association reported at the longest follow-up time, which ranged from 1 to 120 months; however, metaregression found no systematic differences attributable to length of follow-up. The studies included in our meta-analyses used different outcome measures for unemployment (Data Supplement); however, we conducted subgroup analyses for direct versus indirect measures of unemployment and high versus low thresholds of return to work and restricted our findings to direct or high-threshold outcomes when significant interactions were identified. Use of employment measures endorsed by national statistical agencies, such as the United States Bureau of Labor Statistics⁶⁵ and Statistics Canada,⁶⁶ may prove helpful for both clinical practice and research purposes.

Previous systematic reviews^{4,11,19-21} have qualitatively summarized risk factors for unemployment after breast cancer surgery. We have confirmed and quantified these associations, which include African-American ethnicity, lower educational or income level, more advanced cancer, mastectomy, receipt of chemotherapy, and heavy physical work demands. We have also identified two additional predictors: childlessness and high psychological job demands. In addition, we found moderate- to high-quality evidence that age, marriage status, part-time work, job type, tumor size, positive lymph nodes, axillary lymph nodes dissection, receipt of radiotherapy, and endocrine therapy are not associated with unemployment, despite having been proposed as risk factors by three prior reviews.^{4,20,21}

We found that breast cancer survivors residing in the United States are more likely to return to work, and this may be influenced by the American health care system. Specifically, the United States is the only developed country without universal health care,⁶⁷ and most workers have access to health care insurance through their employers.²³ Even with insurance, the mean family health insurance premium (combining both employer and employee contributions) represented 33.9% of median US household income in 2015.⁶⁸ More than 60% of all personal bankruptcies in the United States are the result of medical expenses,⁶⁹ and fear of losing health insurance has been shown to influence return to work after cancer treatment.⁴⁶ What is not known is whether higher rates of employment in the United States after breast cancer surgery are sustained.

Our review identified two work-related factors (physical and psychological job demands) that showed associations with unemployment sufficiently large to suggest targeted interventions. A 2017 systematic review found that high-intensity exercise improved the ability to work after cancer treatment.⁷⁰ A 2015

Cochrane review found moderate-quality evidence that multidisciplinary interventions, involving physical, psychoeducational, and vocational components, improve the rate of return to work among patients with cancer.⁷¹ Furthermore, a 2017 scoping review found evidence to recommend the development of multicomponent interventions that include both the clinic and the workplace to meet the particular needs of patients with breast cancer.⁷² Our findings suggest that physicians should consider inquiring about high psychological and physical job demands among patients undergoing breast cancer surgery; however, the optimal means by which to capture this information is unclear.⁷³ Future research should also explore whether screening for job demands leads to better patient outcomes.

Mastectomy, compared with breast-conserving surgery, was associated with a statistically significant, but modest, increase in unemployment after surgery. Mastectomy has also been associated with poor body image; reduced quality of life; and lower social functioning, role functioning, and physical functioning among patients with breast cancer.⁷⁴⁻⁷⁶ There was a significant decline in mastectomy rates from 2005 to 2010 ($P < .01$) in Europe with a progressive reduction of 4.24% per year.⁷⁷ In the United States, mastectomy rates increased from 34.3% in 1998% to 37.8% in 2011 among patients eligible for breast-conserving surgery (adjusted OR, 1.34; 95% CI, 1.31 to 1.38).⁷⁸ Moreover, breast-conserving surgery has shown similar long-term survival and equivalent recurrence rates compared with mastectomy in patients with early breast cancer⁷⁹⁻⁸⁶; however, mastectomy rates among patients with early breast cancer are considerably lower in Europe (25.1%) than in the United States (35.5%).^{78,87} Our findings provide additional information helpful for shared decision making between surgeons and patients undergoing breast cancer surgery who are eligible for breast-conserving surgery.

We did not find any individual nonmodifiable risk factor, on the basis of our criteria, that would warrant targeting for intervention. However, a combination of risk factors, for instance, low income level and receipt of chemotherapy, might constitute a population warranting special attention. There is preliminary evidence that behavioral interventions and high-intensity exercise may decrease the length of absence from work among patients with cancer.^{20,70,88}

Our review adds to a growing body of evidence suggesting that nonmedical factors may be more important than injury or disease

burden in predicting return to function.⁸⁹⁻⁹² Although high-quality evidence supports a strong association between axillary lymph node dissection and the development of persistent pain after breast cancer surgery (ARI, 21%; 95% CI, 13% to 29%),³⁴ we found moderate-quality evidence for no significant association with axillary lymph node dissection and return to work. Our results suggest that rehabilitation programs that focus only on addressing medical issues and symptoms associated with breast cancer will be unlikely to improve return-to-work rates.

Unemployment after breast cancer surgery was associated with high psychological or physical job demands; African-American ethnicity; childlessness; lower education; lower income level; cancer stage II, III, or IV; mastectomy; and receipt of chemotherapy. Observational studies are required to determine if lower rates of unemployment are sustained among patients with breast cancer in the United States. Future research should also establish the association between sickness absence before cancer diagnosis or physician-advised work absence and unemployment and determine whether interventions targeting high workplace demands can improve return-to-work rates after breast cancer surgery.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Predictors of Unemployment After Breast Cancer Surgery: A Systematic Review and Meta-analysis of Observational Studies**

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