Pretreatment health measures and complications after surgical management of elderly women with breast cancer

K. Lavelle[1,3], A. M. Sowerbutts[1,3], N. Bundred[2,3], M. Pilling[1,3] and C. Todd[1,3]

[1]School of Nursing, Midwifery and Social Work, University of Manchester, [2]Nightingale and Genesis Prevention Centre, University Hospital of South Manchester NHS Trust, Wythenshawe Hospital, and [3]Manchester Academic Health Sciences Centre, Core Technology Facility, Manchester, UK
Correspondence to: Dr K. Lavelle, School of Nursing, Midwifery and Social Work, Jean McFarlane Building, University Place, University of Manchester, Oxford Road, Manchester M13 9PL, UK (e-mail: katrina.j.lavelle@manchester.ac.uk)

Background: Elderly patients with breast cancer are less likely to be offered surgery, partly owing to co-morbidities and reduced functional ability. However, there is little consensus on how best to assess surgical risk in this patient group.

Methods: The ability of pretreatment health measures to predict complications was investigated in a prospective cohort study of a consecutive series of women aged at least 70 years undergoing surgery for operable (stage I–IIIa) breast cancer at 22 English breast units between 2010 and 2013. Data on treatment, surgical complications, health measures and tumour characteristics were collected by case-note review and/or patient interview. Outcome measures were all complications and serious complications within 30 days of surgery.

Results: The study included 664 women. One or more complications were experienced by 41·0 per cent of the patients, predominantly seroma or primary/minor infections. Complications were serious in 6·5 per cent. More extensive surgery predicted a higher number of complications, but not serious complications. Older age did not predict complications. Several health measures were associated with complications in univariable analysis, and were included in multivariable analyses, adjusting for type/extent of surgery and tumour characteristics. In the final models, pain predicted a higher count of complications (incidence rate ratio 1·01, 95 per cent c.i. 1·00 to 1·01; $P = 0.004$). Fatigue (odds ratio (OR) 1·02, 95 per cent c.i. 1·01 to 1·03; $P = 0.004$), low platelet count (OR 4·19, 1·03 to 17·12: $P = 0.046$) and pulse rate (OR 0·96, 0·93 to 0·99; $P = 0.010$) predicted serious complications.

Conclusion: The risk of serious complications from breast surgery is low for older patients. Surgical decisions should be based on patient fitness rather than age. Health measures that predict surgical risk were identified in multivariable models, but the effects were weak, with 95 per cent c.i. close to unity.

Introduction

Breast cancer is predominantly a disease of old age, with the incidence doubling from 215 per 100 000 for women aged 45–49 years to 442 per 100 000 for those aged 85 years or more (England 2011)[1]. One-third of all new cases in England are diagnosed in women aged at least 70 years[1]. Within an ageing population, both the number and proportion of older patients requiring treatment at breast units is rising and set to continue to do so for the next 50 years[2].

Primary surgery (mastectomy or wide local excision (WLE) of the tumour) is the recommended initial treatment for early-stage breast cancer[3,4]. However, the percentage of women having surgery for breast cancer in England decreases with age, being around 90 per cent among younger age groups but as low as 40 per cent for patients aged 80 years or more[5,6].

UK treatment guidelines[3,4] state that 'significant co-morbidity' may preclude surgery for patients with early-stage breast cancer. The increase in co-morbidity with older age may account for the lower rates of surgery among elderly patients. However, although co-morbidity does explain some of the decline in surgical rates with increasing age, older women are still less likely to have surgery once adjustment has been made for co-morbidity[5]. Recent research suggests that adjusting for wider measures of health, such as functional decline/frailty, may explain lack of breast surgery for older women up to, but not

beyond, the age of 85 years[7]. This provides evidence that, at least up to the age of 85 years, patient health, rather than chronological age, is the primary consideration when assessing surgical risk.

However, there is little consensus on how best to assess surgical risk in older patients with breast cancer. Because they were precluded from earlier trials, the evidence base on older patients' risks and benefits of treatment is poor[8,9]. A more recent older age-specific trial comparing surgery with endocrine therapy *versus* endocrine therapy alone for patients aged at least 70 years closed owing to slow recruitment[9]. Patients largely opted not to take part in this trial, in which they had a 50 per cent chance of not having surgery, possibly because surgery is now such an accepted mainstay of treatment for early breast cancer. In this context, cohort studies can help bridge the knowledge gap by identifying pretreatment health measures that predict surgical complications.

One such large cohort investigating surgical risk assessment, for all ages and types of surgery, combines measures used within preoperative assessment, such as co-morbidity and body mass index (BMI), into predictive models. The US-based National Surgical Quality Improvement Program (NSQIP)[10] has developed a universal measure of surgical risk based on all surgical procedures at 393 enrolled hospitals. Multivariable models of mortality and morbidity are based on 21 preoperative measures recorded in the data set. Model discrimination is good (area under the curve (AUC) exceeding 0·8), thus presenting a considerable step forward in risk stratification for surgical patients in general. Limitations of this risk tool include restriction to preoperative measures recorded in the data set, and lack of disease- and procedure-specific preoperative measures such as type and extent of surgery[11]. Underestimation of complication rates in the NSQIP data set has also been reported. This may be due to lack of inclusion of procedure-specific complications and inclusion of only academic hospitals enrolled in this quality improvement programme, which have better surgical outcomes than those in the rest of the USA[11,12]. International generalizability is also questionable owing to differences in healthcare systems. Hence NSQIP is likely to increase interest in risk stratification in other countries[12].

Surgical risk assessment specifically for older patients with cancer has been developed to incorporate measures of functional decline and frailty as well. The Comprehensive Geriatric Assessment (CGA) comprises a battery of various health status and functional tests recommended by the International Society for Geriatric Oncology as essential to treatment decision-making with older patients with cancer. However, there is a lack of consensus on which health measures best predict risk and therefore should be included

in a CGA[13]. Functional status and fatigue have been found to predict surgical complications among patients with cancer in general[14]. However, as risk varies considerably for different types of surgery, there is a need to identify health measures that predict surgical risk within specific cancer groups[15].

As part of a wider research programme, a prospective cohort study was undertaken to investigate the extent to which the lack of surgery for patients aged at least 70 years with breast cancer is explained by patient choice or poor health[7]. This paper reports the secondary aim of the study, to investigate the ability of a range of pretreatment health measures to predict 30-day surgical complications among the subset of patients who had surgery.

Methods

This was a prospective, cohort study of a consecutive series of women aged 70 years or more undergoing surgery for operable (stage I–IIIa) breast cancer at 22 breast units, predominantly in north-west England, over 33 months (2010–2013). Data on treatment, surgical complications, a range of preoperative health measures and tumour characteristics were collected by case-note review and/or patient interview[7]. Ethical approval was granted by the National Research Ethics Service (10/H1014/32 and 33).

The primary outcome measure was complications within 30 days of primary surgery (mastectomy or WLE) for operable (stage I–IIIa) breast cancer. All patients were followed up for 90 days after diagnosis. Patients who did not have primary surgery within 90 days of diagnosis were not included in this study. As initial WLE may be followed by mastectomy, patients were classified as receiving mastectomy or WLE based on the most extensive primary surgery. Similarly, axillary node procedure was based on the most extensive dissection. Two measures of complications were used, reflecting both the type and impact of complications: a count of all complications and patients with serious complications. All complications occurring within 30 days of the last primary surgery were recorded. Non-infectious complications were based on a checklist developed from the East Anglian Hip Fracture Audit[16] and the Preoperative Assessment of Cancer in the Elderly project[14], with breast surgery-specific items[17,18]. Infectious complications were based on the national prevalence survey of hospital-acquired infections[19]. Seromas were included only if drainage was recorded clinically, thus reflecting a greater clinical impact. In addition, non-drained seromas are subject to under-reporting, particularly if seen only in the primary-care setting. Complications occurring after the start of adjuvant radiotherapy or chemotherapy were not

included. Patients were classified as having serious complications if they had complications (other than a seroma or primary/minor infection) that warranted readmission as an inpatient, delayed discharge or other procedure. Delayed discharge was defined by being in excess of the median length of stay[20] and the maximum time limits reported as 'usual' in national National Health Service (NHS) patient information sources[21]: more than 1 day for WLE and 5 days or more for mastectomy. Other procedures included as indicating a serious complication were return to the operating theatre, treatment for confirmed hospital-acquired methicillin-resistant *Staphylococcus aureus* infection, stroke or pulmonary embolism, extensive wound repair (excision of necrotic tissue, suturing, wound packing) and blood transfusions.

Explanatory variables were: age, measures of health, tumour characteristics, demographics and hospital resources. A range of health measures were recorded both from self-report at a patient interview undertaken within 2 weeks of diagnosis and before surgery, or from preoperative assessment as recorded in the case notes (*Table 1*); they represent patients' functional/health status and health-related quality of life, co-morbidity (illnesses in addition to breast cancer[22]) and other clinical measures recorded at the preoperative health assessment. Self-reported measures were selected primarily based on ease of administration, validity, reliability, acceptability to older people[31,32], and prediction of treatment received[33,34] and/or treatment outcomes[13−15]. Clinical measures recorded at preoperative assessment were also considered if data were available for at least 85 per cent of the sample. Classification of blood results was based on the national Pathology Harmony standardization project[35,36].

Pretreatment tumour characteristics (tumour size, stage, grade, nodal and steroid receptor status) were recorded based on clinical, imaging and fine-needle/core biopsy assessments (cTNM classification[29]).

Socioeconomic class was measured using the Office for National Statistics Socio-Economic Classification[30]; it was based on main occupation before retirement if retired, and the highest classification if the participant was married or living with a partner. Ethnicity was recorded based on UK census classification categories[37]. Of the 22 breast units in the study, 19 were in north-west England, two in London and one in the Midlands.

Inclusion criteria and patient accrual

Women aged 70 years or more with early-stage breast cancer (stage I–IIIa), having primary surgery within 90 days of diagnosis of a new episode of operable invasive breast cancer, were offered inclusion. Women aged 70–74 years were

Table 1 Independent variables

Type of surgery (wide local excision *versus* mastectomy)
Extent of axillary node procedures (sentinel node biopsy *versus* axillary node surgery)
Health measures at preoperative assessment
Blood pressure (low, normal, high)
Body mass index (underweight, normal, overweight, obese)*
Smoking status (current, non-smoker)*
Blood tests (9 both continuous and categorical)†
Pulse (beats per min)
Co-morbidity (Charlson index)[22]
ASA physical status classification[23]
Health measures self-reported/assessed at preoperative interview
Functional status
Eastern Cooperative Oncology Group Performance Status[24]
Elderly Population Health Survey – activities of daily living basic/instrumental[25]
Health status (Short Form 12 Physical and Mental Component Summaries)[26]
Health-related quality of life (EORTC QLQ-C30; 15 separate scales)[27]
Six-item Cognitive Impairment Test[28]
Tumour characteristics (preoperative)[29]
Tumour size
Stage
Nodal involvement
Grade
Steroid receptor status (ER- and PR-positive or -negative)
Sociodemographics
Age
Socioeconomic classification[30]
Type of treating hospital (university/teaching *versus* district)

*Taken from self-report at interview if preoperative measures not reported in case notes. †Test included if recorded at preoperative assessment for at least 85 per cent of total sample. ASA, American Society of Anesthesiologist; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ER, oestrogen receptor; PR, progesterone receptor.

included as a reference group, as previous research[6,38−40] indicated that surgical complications may increase and surgical rates decrease from the age of 75 years. Carcinoma *in situ*, stage IIIb, metastatic and recurrent breast cancers were not included as the standards for operable breast cancer do not apply[3,4]. Men were not included as less than 1 per cent of all invasive breast cancers occur in men[1] and surgical management may differ[3,4]. Screening and accrual processes are reported elsewhere[7].

Data collection

Patients who agreed to take part were interviewed within 30 days of diagnosis and before surgery took place. Information on demographic variables and measures of health detailed above was collected at this interview. The case notes of each patient were reviewed up to 3 months after diagnosis, using a pro forma developed to collect data on tumour characteristics at diagnosis, treatments undertaken,

co-morbidity and complications. Inter-rater agreement levels for the pro forma items satisfied the κ more than 0·6 criterion, indicating substantial to perfect agreement[41]. Some 3 per cent of case-note review pro formas and 8 per cent of patient interviews were tested for data input errors. Error rates per data item were below 0·5 per cent, so no further data checking was warranted. The pro formas of patients with complications were assessed initially by two authors independently against the above criteria for serious complications devised with two other authors. Disagreements were resolved by consensus with any final outstanding decisions made by the latter two authors.

Statistical analysis

Explanatory variables were investigated in univariable analysis using Pearson's χ^2 test, Fisher's exact test, χ^2 test for trend and univariable regression analyses (two-tailed with $\alpha = 0.05$). The distribution of continuous variables was assessed for normality using the Shapiro–Wilk W test. Associations between non-normally distributed variables and categorical data were investigated using the non-parametric two-sample Wilcoxon rank sum (Mann–Whitney test) and Kruskal–Wallis equality-of-populations rank test. Associations for normally distributed variables were investigated using the two-sample t test. Owing to the large number of health measures tested for univariable associations with complications, significance was considered after a Bonferroni adjustment for multiple testing had been made.

Independent variables found to be significantly associated with outcomes in univariable analyses were used as independent variables in the subsequent multiple regressions (forward stepwise). Models were built in line with the data analysis plan agreed *a priori* with the project's Independent Data Monitoring Committee, modifying an approach suggested by Hosmer and Lemeshow[42]. Type of surgery (mastectomy *versus* WLE) and extent of axillary node surgery formed the base models based on clinical relevance and previous literature[11,43]. Remaining variables were initially tested against the null model and retained based on: the difference between the model with the additional variable and the previous model using the likelihood ratio test (analysis of deviance); or producing a significant coefficient in the model (both at a 5 per cent significance level). Explanatory variables were considered in three groups and added into the model in order of importance to the secondary aim of the study: health measures, sociodemographics and then tumour characteristics. Within each group the order in which variables were added into the model was determined by minimizing Bayesian information criterion (BIC)

values of each variable added into the model individually. Variables with lower BIC values were added in sequentially, starting with the variable giving the lowest value. At each step an individual variable's contribution to the model was assessed using the above two criteria. To reduce the likelihood of multicollinearity, and to ensure the number of patients in the model could sustain the potentially large number of health measures, they were retained in the model only if they produced both a significant coefficient and likelihood ratio test. Tumour characteristics and sociodemographic variables were retained if they had a significant likelihood ratio test only.

Once each group of variables had been added, variance inflation factors were checked and variables exhibiting factors above 10 investigated to prevent multicollinearity[44]. Logistic regression models were tested for goodness of fit (Hosmer and Lemeshow) and discrimination (area under the receiver operating characteristic (ROC) curve). Variables included in the final models were tested for two-way interactions.

A sensitivity analysis was conducted by additionally performing backwards stepwise regression; this approach led to comparable final models and therefore suggested robust results.

Data were analysed using Stata® version 12.1 (StataCorp LP, College Station, Texas, USA)[45].

Sample size

The sample size was determined *a priori* by the study's primary aim, as reported elsewhere[7]. To test the aim reported in this paper, the recommended sample size was determined by the number of explanatory variables included in the multivariable models predicting the two complication outcome measures. However, the sample size of 664 should also be sufficient to support negative binomial (predicting count of complications) as the sample size $\geq 50 + 8p$ and $\geq 104 + p$ (where p is the number of explanatory variables)[46]. Logistic regression (predicting serious complications) should have around ten patients for each explanatory variable for both categories of the dependent variable[47,48], although in other scenarios it has been shown that five patients for each explanatory variable is sufficient[49]. To help meet this guidance, health measures with non-significant coefficients (at the 5 per cent level) were dropped from the model once the total number of variables exceeded this limit during the model-building process. In practice, only one health measure was lost from the model for this reason and the resulting final logistic regression model included five explanatory variables (8 events per variable).

Table 2 Surgery, sociodemographic and tumour characteristics by 30-day surgical complications

		All complications		At least 1 serious complication	
	No. of patients ($n = 664$)	Mean(s.d.) count	$P\ddagger\P$	No. of patients ($n = 43$)	$P\ddagger\#$
Primary surgery			< 0·001		0·139**
Mastectomy	329 (49·5)	0·80(0·95)		26 (7·9)	
Wide local excision	335 (50·5)	0·38(0·68)		17 (5·1)	
Axillary node procedure*			< 0·001		0·087
Sentinel node biopsy	397 (59·8)	0·45(0·74)		19 (4·8)	
Axillary node surgery	262 (39·5)	0·80(0·97)		24 (9·2)	
None	5 (0·8)	0·20(0·45)		0 (0)	
Age (years)			0·512		0·061††
70–74	257 (38·7)	0·55(0·81)		11 (4·3)	
75–79	201 (30·3)	0·57(0·83)		15 (7·5)	
80–84	127 (19·1)	0·65(0·83)		9 (7·1)	
≥ 85	79 (11·9)	0·65(1·04)		8 (10)	
Socioeconomic classification			0·792; 0·922§		0·664; 0·093§
Professional	358 (53·9)	0·60(0·85)		24 (6·7)	
Intermediate	169 (25·5)	0·56(0·84)		8 (4·7)	
Manual	131 (19·7)	0·55(0·79)		9 (6·9)	
Unknown	6 (0·9)	1·00(2·00)		2 (33)	
Ethnicity			0·281; 0·496§		1·000; 0·093§
White	643 (96·8)	0·58(0·84)		41 (6·4)	
Other	14 (2·1)	0·71(0·73)		0 (0)	
Unknown	7 (1·1)	1·14(1·86)		2 (29)	
Hospital type			0·189		0·614**
Teaching/university	287 (43·2)	0·55(0·86)		17 (5·9)	
District	377 (56·8)	0·61(0·85)		26 (6·9)	
Tumour stage			0·001		0·337**
I	293 (44·1)	0·48(0·78)		22 (7·5)	
II and IIIa†	371 (55·9)	0·67(0·90)		21 (5·7)	
Nodal involvement			< 0·001		0·933**
Yes	197 (29·7)	0·72(0·87)		13 (6·6)	
No/not recorded	467 (70·3)	0·53(0·84)		30 (6·4)	
Tumour size (mm)			0·009; 0·021§		0·203; 0·302§
≤ 20	374 (56·3)	0·52(0·81)		27 (7·2)	
> 20, ≤ 50	260 (39·2)	0·66(0·89)		13 (5·0)	
> 50	15 (2·3)	1·07(1·10)		2 (13)	
Unknown	15 (2·3)	0·40(0·51)		1 (7)	
Tumour grade			0·541; 0·656§		0·414††; 0·781§
1	112 (16·9)	0·58(0·89)		8 (7·1)	
2	347 (52·3)	0·57(0·88)		25 (7·2)	
3	146 (22·0)	0·59(0·73)		7 (4·8)	
Unknown	59 (8·9)	0·64(0·92)		3 (5)	
ER- or PR-positive			0·585; 0·824§		
Yes	555 (83·6)	0·59(0·87)		35 (6·3)	
No	68 (10·2)	0·62(0·83)		6 (9)	0·435
Unknown	41 (6·2)	0·51(0·71)		2 (5)	0·684

Values in parentheses are percentages. *Most extensive axillary node procedure. †Includes 14 patients with stage IIIa disease. ER, oestrogen receptor; PR, progesterone receptor. ‡P value reported for complete data, unless indicated otherwise; §P value calculated including missing data. ¶Kruskal–Wallis χ^2 test adjusted for ties. #Fisher's exact test, except **Pearson's χ^2 test and ††χ^2 test for trend.

Results

Eight hundred patients aged at least 70 years were recruited into the main study investigating the extent to which patient health and choice explain lack of surgery; of these, 664 (83·0 per cent) had primary surgery within 90 days and were therefore included in the analyses of prediction of surgical complications reported here. One-half (329, 49·5 per cent) had a mastectomy and one-half (335, 50·5 per cent) WLE; 38·7 per cent were aged 70–74 years, 30·3 per cent 75–79 years, 19·1 per cent 80–84 years and 11·9 per cent were aged 85 years or more (*Table 2*). The sample was predominantly of professional/intermediate social class and white ethnic group. More than half were treated at a district general hospital rather than a university teaching hospital. Some 44·1 per cent had stage I disease recorded
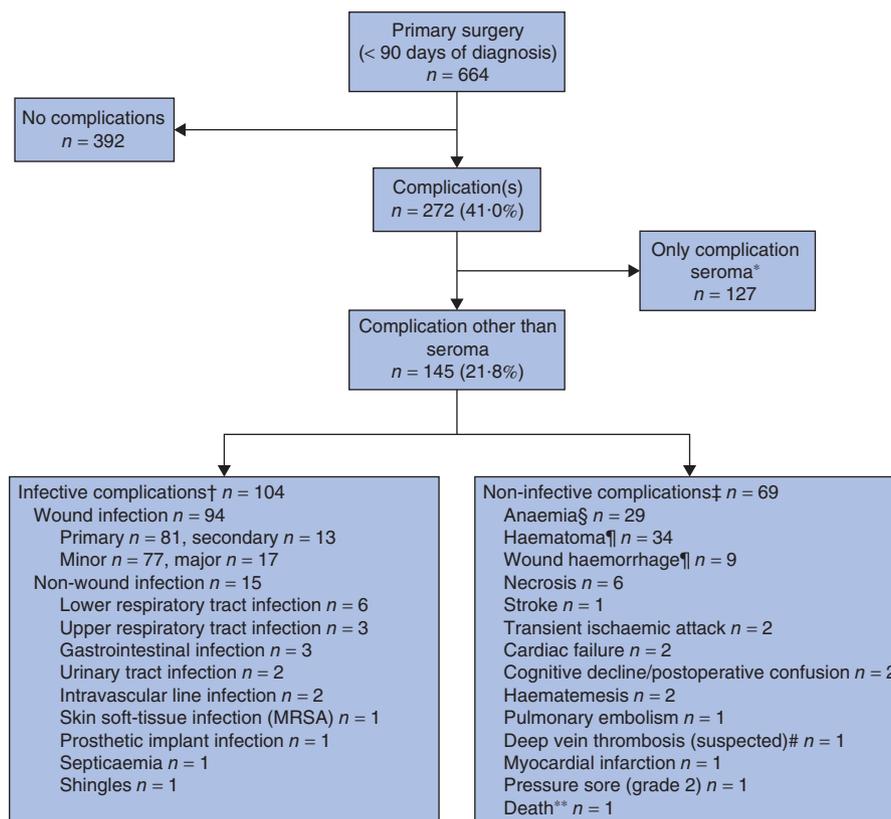
Fig. 1 Summary of complications within 30 days of breast surgery among 664 patients. Complications were classified as serious if they warranted readmission, further procedures or delayed discharge. *Only drained seromas recorded. †Based on the national prevalence survey of hospital-acquired infections[19]; ‡based on a checklist developed from the East Anglian Hip Fracture Audit[16] and Preoperative Assessment of Cancer in the Elderly project[14]. §Patients with a low preoperative haemoglobin level (less than 11·8 g/l) not included unless they received a postoperative blood transfusion. ¶Both haematoma and wound haemorrhage were recorded as occurring simultaneously in six patients (for whom this was counted as 1 complication in the analyses). #Clinically recorded in case notes but no confirmation on ultrasound examination. **Septicaemia was the major cause of death. MRSA, methicillin-resistant *Staphylococcus aureus* infection.

at diagnosis; the remaining 55·9 per cent had stage II or IIIa tumours, and were therefore regarded as having early operable breast cancer[50]. Over two-thirds of the patients (70·3 per cent) had no nodal involvement recorded at diagnosis and 56·3 per cent had small tumours no larger than 20 mm. The vast majority of participants (83·6 per cent) were steroid receptor-positive for either oestrogen or progesterone receptors.

Complication rates

Of the 664 women, 272 (41·0 (95 per cent c.i. 37·2 to 44·7) per cent) had some form of complication within 30 days of surgery (*Fig. 1*). However, only 145 (21·8 (18·7 to 25·0) per cent) had complications other than seroma, predominantly related to wound infection at the surgical site. The number of complications experienced by women varied from 0 to 5

Table 3 Distribution of 30-day surgical complications

Count of complications	No. of patients ($n = 664$)
0	392 (59·0)
1	188 (28·3)
2	62 (9·3)
3	14 (2·1)
4	6 (0·9)
5	2 (0·3)

Values in parentheses are percentages. Mean(s.d.) number of complications 0·58(0·85); variance 0·73. Count of complications does not follow a Poisson distribution as mean does not equal variance.

(mean(s.d.) 0·58(0·85)) (*Table 3*). In 43 women (6·5 (4·6 to 8·4) per cent) complications warranted delayed discharge, readmission to hospital or further procedure, and were classified as serious complications.

Univariable analyses

Participants who underwent mastectomy had a higher mean number of complications ($P < 0.001$), but were no more likely to have serious complications ($P = 0.139$) than those having WLE (*Table 2*). Similarly, those undergoing more extensive axillary node procedures had a greater number of complications ($P < 0.001$) but were not significantly more likely to experience serious complications ($P = 0.087$). No association was found between number of complications and age ($P = 0.512$), and the number of complications did not increase significantly with each year of age (incidence rate ratio (IRR) 1.02, 95 per cent c.i. 1.00 to 1.04; $P = 0.109$). Although the proportion experiencing serious complications increased from 4.3 per cent for patients aged 70–74 years to 10 per cent for those aged at least 85 years, this effect failed to reach statistical significance at the 5 per cent level, regardless of whether age was measured in groups (P for trend = 0.061) or continuously ($P = 0.060$, two-sample t test with equal variances). Participants presenting with larger ($P = 0.009$), later-stage ($P = 0.001$) tumours and nodal involvement ($P < 0.001$) had a larger number of complications. However, no tumour characteristics were associated with serious complications.

Health measures

Of the 46 separate health measures tested (*Table 1*), 14 were found to be univariably associated with number of complications and 19 with serious complications at the 5 per cent level (*Tables 4* and *5*). Bonferroni's adjustment[51] (applied at $\alpha/n = 0.05/46 = 0.001$) was also considered.

Among the categorical measures of health (*Table 4*), smoking status, blood pressure and cognitive impairment (Six-Item Cognitive Impairment Test) had no association with postoperative complications. At the 5 per cent significance level, a BMI indicative of obesity or underweight was associated with a higher count of all complications, but not serious complications. A dependent Eastern Cooperative Oncology Group (ECOG) Performance Status and abnormal haemoglobin level were associated with both total and serious complications. Co-morbidity (Charlson index), a high American Society of Anesthesiologists (ASA) risk score and low platelet count were associated with serious complications only. However, none of these measures retained significance once Bonferroni's adjustment had been applied at 0.1 per cent.

Of the continuous measures of health (*Table 5*), lack of functional ability to undertake both basic activities of daily living (ADL) (for example self-care/hygiene) and

more advanced 'instrumental' activities (such as shopping/cooking) predicted increased count of all, and odds of serious, complications at the 5 per cent level. However, only instrumental ADL's prediction of complication count retained significance at the 0.1 per cent level. Similarly, better physical health status, as measured by the Short Form 12 (SF-12®; QualityMetric, Lincoln, Rhode Island, USA) Physical Component Summary, predicted a lower complication count at the 0.1 per cent (Bonferroni adjusted) level, but predicted lower odds of serious complications only at the 5 per cent level. Of the 15 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLC) C30 health-related quality-of-life domains, ten were associated with complications at the 5 per cent level. However, for most of the domains, the 95 per cent c.i. were close to unity (indicating a weak effect) and only four domains were significant at the 0.1 per cent level; better physical and role function predicted a lower count of all and serious complications, and increased pain and fatigue predicted a higher count of complications and serious complications respectively.

However strongly preoperative health measures are associated with complications univariably, multivariable analyses are needed to establish the extent to which the health measures continue to predict complications once the effects of potential confounding variables have been adjusted for. Therefore, all health measures that significantly predicted complications at the 5 per cent level were considered for inclusion in multivariable analyses adjusting for a range of variables (including extent of surgery, sociodemographics and tumour characteristics).

In the multivariable analyses, a higher count of complications was predicted for women undergoing a mastectomy compared with WLE (IRR 1.64, 95 per cent c.i. 1.27 to 2.12; $P < 0.001$) and more extensive axillary node surgery as opposed to sentinel node biopsy (IRR 1.43, 1.13 to 1.82: $P = 0.003$) (*Table 6*). Of the health measures, only increased pain predicted outcome, with the total number of complications increasing by 1.01 (95 per cent c.i. 1.00 to 1.01; $P = 0.004$) for each point increase (indicating worsening pain) on the EORTC QLQ-C30 pain scale.

Neither type of primary surgery nor extent of axillary node procedure predicted odds of serious complications in the multivariable logistic regression analysis (*Table 7*). Three health measures retained in the model predicted serious complications significantly. Patients with an abnormally low platelet count had over four times the odds of serious complications compared with patients who had a

Table 4 Preoperative health measures (categorical) by 30-day surgical complications

		All complications		At least 1 serious complication	
	No. of patients (n = 664)	Mean(s.d.) count	P‡¶	No. of patients (n = 43)	P‡#
Charlson co-morbidity index			0·195		0·028**
0	371 (55·9)	0·53(0·79)		20 (5·4)	
1	179 (27·0)	0·59(0·86)		9 (5·0)	
≥ 2	114 (17·2)	0·75(1·02)		14 (12·3)	
Body mass index (kg/m²)			0·019		0·253
< 18·5	9 (1·4)	0·89(0·93)		2 (22)	
18·5–24·9	201 (30·3)	0·48(0·78)		11 (5·5)	
25·0–29·9	238 (35·8)	0·55(0·86)		15 (6·3)	
≥ 30·0	216 (32·5)	0·70(0·89)		15 (6·9)	
Smoker			0·761		0·766
No	612 (92·2)	0·58(0·84)		39 (6·4)	
Yes	52 (7·8)	0·65(0·95)		4 (8)	
Blood pressure (mmHg)*			0·978; 0·994§		0·305; 0·395§
Normal	186 (28·0)	0·56(0·78)		11 (5·9)	
High (> 140/90)	411 (61·9)	0·59(0·84)		25 (6·1)	
Low (< 90/60)	41 (6·2)	0·63(1·07)		5 (12)	
Unknown	26 (3·9)	0·65(1·13)		2 (8)	
Pulse (beats/min)			0·226; 0·395§		0·062; 0·120§
Normal	538 (81·0)	0·58(0·85)		35 (6·5)	
High (≥ 100)	32 (4·8)	0·41(0·56)		0 (0)	
Low (< 60)	45 (6·8)	0·76(0·93)		6 (13)	
Unknown	49 (7·4)	0·59(0·91)		2 (4)	
ECOG PS			0·001; 0·004§		0·002††; 0·002§
0–1	476 (71·7)	0·52(0·80)		21 (4·4)	
2–4	170 (25·6)	0·78(0·97)		19 (11·2)	
Unknown	18 (2·7)	0·50(0·62)		3 (17)	
ASA physical status grade			0·097; 0·054§		0·014††; 0·007§
I–II	411 (61·9)	0·57(0·82)		23 (5·6)	
III–IV	155 (23·3)	0·70(0·95)		18 (11·6)	
Unknown	98 (14·8)	0·47(0·80)		2 (2)	
6CIT (cognitive impairment)			0·812; 0·971§		0·071; 0·061§
≤ 7 (none)	518 (78·0)	0·58(0·85)		35 (6·8)	
> 7 (mild/moderate)	76 (11·4)	0·61(0·87)		1 (1)	
Unknown	70 (10·5)	0·59(0·88)		7 (10)	
Blood results†					
Haemoglobin level			0·016; 0·014§		0·008; 0·003§
Low	75 (11·3)	0·75(0·97)		9 (12)	
Normal	482 (72·6)	0·52(0·80)		21 (4·4)	
High	43 (6·5)	0·72(0·77)		5 (12)	
Unknown	64 (9·6)	0·78(1·05)		8 (13)	
Platelet count			0·094; 0·055§		0·042; 0·032§
Low	13 (2·0)	0·85(1·07)		3 (23)	
Normal	555 (83·6)	0·56(0·82)		32 (5·8)	
High	21 (3·2)	0·24(0·54)		0 (0)	
Unknown	75 (11·3)	0·80(1·07)		8 (11)	

Values in parentheses are percentages. *Blood pressure classed as high or low based on limits for hypertension[52] and hypotension[53]. †Nine blood results investigated. Reported only if significantly associated with complications ($P < 0.050$); level of neutrophils, lymphocytes, white blood cells, sodium, potassium, urea, creatinine therefore not reported. Blood results classification was based on the National Pathology Harmony standardization project[35,36]. ECOG PS, Eastern Cooperative Oncology Group – Performance Status (categories 0–5 indicate decreasing functional status); ASA, American Society of Anesthesiologists; 6CIT, Six-Item Cognitive Impairment Test (scale 0–28, increase indicates worse cognitive impairment; 0–7 indicates normal). ‡P value reported for complete data, unless indicated otherwise; §P value calculated including missing data. No variables retained significance once Bonferroni's correction was applied at α/number of tests $= 0.05/46 = 0.001$. ¶Kruskal–Wallis χ^2 test adjusted for ties. #Fisher's exact test, except **χ^2 test for trend and ††Pearson's χ^2 test.

Table 5 Preoperative health measures (continuous) by 30-day surgical complications

	No. of patients	All complications – count		At least 1 serious complication	
		Incidence rate ratio*	P	Odds ratio†	P
ELPHS ADL functional status					
Basic ADL	661	1·37 (1·12, 1·68)	0·002	2·08 (1·25, 3·47)	0·005
Instrumental ADL	648	1·26 ((1·11, 1·43)	< 0·001‡	1·65 (1·15, 2·36)	0·006
SF-12® PCS	648	0·98 (0·98, 0·99)	< 0·001‡	0·97 (0·94, 0·99)	0·006
EORTC QLQ-C30 function scales					
Global quality of life	638	0·99 (0·99, 1·00)	0·002	0·98 (0·97, 0·99)	0·001
Physical	656	0·99 (0·99, 1·00)	< 0·001‡	0·98 (0·97, 0·99)	< 0·001‡
Role	652	0·99 (0·99, 1·00)	< 0·001‡	0·98 (0·97, 0·99)	< 0·001‡
Cognitive	652	0·99 (0·99, 1·00)	0·028	–	–
Social	643	0·99 (0·99, 1·00)	0·001	–	–
EORTC QLQ-C30 symptom scales					
Fatigue	652	1·01 (1·00, 1·01)	0·001	1·02 (1·01, 1·04)	< 0·001‡
Pain	655	1·01 (1·00, 1·01)	< 0·001‡	1·01 (1·00, 1·02)	0·025
Dyspnoea	655	1·01 (1·00, 1·01)	0·003	1·01 (1·00, 1·02)	0·027
Constipation	652	–	–	1·01 (1·00, 1·02)	0·026
Appetite loss	654	–	–	1·01 (1·00, 1·02)	0·044
Pulse (beats/min)	615	–	–	0·96 (0·93, 0·98)	0·002
Blood results					
Sodium (mmol/l)	613	–	–	0·89 (0·82, 0·98)	0·012
Potassium(mmol/l)	608	–	–	2·53 (1·20, 5·34)	0·015

Values in parentheses are 95 per cent c.i. ELPHS ADL, Elderly Population Health Survey activities of daily living (scale 1–4; increase indicates worse functional status); basic ADL include basic self-care and mobility, whereas instrumental ADL include more advanced activities such as housework and shopping. SF-12® PCS, Short Form 12 Physical Component Summary (scale 1–100; increase indicates better health). EORTC QLQ-C30, European Organization for Research on Treatment of Cancer Quality of Life Questionnaire, version 3 (scales 1–100; increase indicates better function and worse symptoms). *Generated by univariable negative binomial regression; †generated by univariable logistic regression. ‡Significance retained once Bonferroni's adjustment applied at α/number of tests = 0·05/46 = 0·001. Health measures are reported only if significantly associated with complications ($P < 0.050$); the following measures are therefore not reported: EORTC QLQ-C30 emotional functioning, insomnia, financial problems, nausea/vomiting and diarrhoea; SF-12® Mental Component Summary; blood results: levels of urea, creatinine, haemoglobin, platelets, white blood cells, neutrophils and lymphocytes.

Table 6 Multivariable negative binomial regression model predicting count of all 30-day surgical complications (622 patients)

	Adjusted incidence rate ratio†	Standard error	P
Primary surgery			
Wide local excision	1·00 (reference)		
Mastectomy	1·64 (1·27, 2·12)	0·21	< 0·001
Axillary node procedure*			
Sentinel node biopsy only	1·00 (reference)		
Axillary node surgery	1·43 (1·13, 1·82)	0·17	0·003
None	0·46 (0·06, 3·50)	0·48	0·454
EORTC QLQ-C30 global quality of life	1·00 (0·99, 1·00)	0·00	0·207
EORTC QLQ-C30 pain	1·01 (1·00, 1·01)	0·00	0·004
Tumour size (mm)	1·00 (1·00, 1·01)	0·00	0·340
Constant	0·37 (0·22, 0·60)	0·09	< 0·001
α	0·19 (0·06, 0·60)	0·11	

Values in parentheses are 95 per cent c.i. *Most extensive axillary node procedure. EORTC QLQ-C30, European Organization for Research on Treatment of Cancer Quality of Life Questionnaire (global quality-of-life scale: 1–100, increase indicates better health; pain scale: 1–100, increase indicates worse pain). †Adjusted for all other variables in the table. The following health measures had no significant effect in the initial multivariable model and were not included: body mass index, Eastern Cooperative Oncology Group – Performance Status, haemoglobin, Elderly Population Health Survey activities of daily living functional status, Short Form 12 Physical Component Summary, EORTC QLQ-C30 scales physical, role, cognitive and social functions, fatigue and dyspnoea. Tumour stage and nodal status were removed as they did not significantly improve the fit of the model.

Table 7 Multivariable logistic regression model predicting at least one serious complication by 30 days after surgery (537 patients*)

	Adjusted odds ratio§	Standard error	P
Primary surgery			
Wide local excision	1·00 (reference)		
Mastectomy	1·04 (0·47, 2·32)	0·43	0·922
Axillary node procedure†			
Sentinel lymph node biopsy only	1·00 (reference)		
Axillary node surgery	1·75 (0·80, 3·82)	0·70	0·162
Platelet count			
Normal/high‡	1·00 (reference)		
Low	4·19 (1·03, 17·12)	3·01	0·046
Pulse (beats/min)	0·96 (0·93, 0·99)	0·02	0·010
EORTC QLQ-C30 fatigue	1·02 (1·01, 1·03)	0·01	0·004
Constant	0·64 (0·05, 7·75)	0·81	0·722

Values in parentheses are 95 per cent c.i. *Reduced numbers owing to missing data. †Most extensive axillary node procedure; none of the five patients who had no axillary node procedure are retained in the final model. ‡Retained 19 patients with high platelet count amalgamated with 555 patients with normal platelet count (high category omitted owing to lack of events). EORTC QLQ-C30, European Organization for Research on Treatment of Cancer Quality of Life Questionnaire (fatigue scale: 1–100, increase indicates worse fatigue). §Adjusted for all other variables in the table. The following health measures had no significant effect in the initial multivariable model and were not included: Charlson co-morbidity index, Eastern Cooperative Oncology Group – Performance Status, haemoglobin, Elderly Population Health Survey activities of daily living functional status, American Society of Anesthesiologists grade, potassium level, Short Form 12 Physical Component Summary, and EORTC QLQ-C30 scales global quality of life, physical function, role function, pain, dyspnoea, constipation and appetite loss. Sodium level was removed from the model as it produced variance inflation factors exceeding 100. Goodness-of-fit test: χ^2 Hosmer–Lemeshow = 7·34, 8 d.f., $P = 0.500$; area under receiver operating characteristic (ROC) curve 0·745; sensitivity and specificity 71·9 per cent, false-positive and -negative rate 28·1 per cent (probability cut-off point set to 0·063).

normal or high platelet count (odds ratio (OR) 4·19, 95 per cent c.i. 1·03 to 17·12; $P = 0.046$). The odds of serious complications decreased with higher pulse rate (OR 0·96, 0·93 to 0·99; $P = 0.010$) and increased by 1·02 (1·01 to 1·03) times ($P = 0.004$) for each point increase on the EORTC QLQ-C30 fatigue domain (indicating worsening fatigue). There was no significant difference between the observed and final model predicted values (goodness-of-fit test χ^2 (Hosmer–Lemeshow) = 7·34, 8 d.f., $P = 0.500$), and model discrimination (AUC 0·745) was considered 'acceptable'[42]. However, even when the model's probability cut-off point (0·5 by default) was set to 0·063, maximizing sensitivity and specificity, these were still low (71·9 per cent) and the false-positive and -negative rates high (28·1 per cent). In addition, the 95 per cent c.i. for all four health measures predicting complications in both final models were close to unity, indicating weak effects.

Discussion

Although a large proportion (41·0 per cent) of the older women in this study experienced one or more complications, these were predominantly seroma or minor infections. A relatively low percentage (6·5 per cent) experienced serious complications that necessitated delayed discharge, readmission or further procedures. Only one person died (major cause septicaemia) and the frequency of life-threatening complications such as stroke and cardiac failure was low (*Fig. 1*). More extensive primary and axillary node surgery was associated with a greater number of all complications, but not serious complications. Older age did not predict an increase in risk of complications. Several health measures were associated with complications in univariable analysis. In the multivariable analyses self-reported pain predicted a higher count of all complications, whereas fatigue, along with low platelet count and pulse rate, predicted serious complications.

Previous studies[11,54] have reported a wide range of overall rates of breast surgery complications, from 2 to 50 per cent. At the higher end of this range, the present estimates are similar to those in previous studies of older patients with breast cancer[17,55,56]; for example, Chatzidaki and colleagues[55] reported overall and major complication rates of 37·1 and 5·7 per cent respectively. Although other studies of older patients with breast cancer have documented somewhat lower overall complication rates (between 18 and 26 per cent[38,39,57]), considerable variation across studies is to be expected depending on co-morbid conditions, time period of data collection and follow-up, completeness of data sources, as well as the definition and assessment of complications. Rocco and co-workers[39] highlighted that their estimated complication rate of 18·2 per cent among patients aged 65 years and over with breast cancer may have been low owing to the use of retrospective records from 1997 to 2012. However, attempts to benchmark breast surgery complication rates have been reported elsewhere[43,55]. The aim of the study reported here was to investigate predictors of surgical risk among older women with breast cancer. In doing so, two outcome measures were used: a count of complications overall as well as the impact of more serious complications, reflecting the importance of capturing both aspects of surgical risk within an older population in which surgical recovery may be of particular concern[58].

Consistent with previous studies[11,38,43,55], more extensive surgery, in terms of both type of primary surgery (mastectomy *versus* WLE) and axillary node dissection, strongly predicted a higher count of all complications. Conversely, the extent of surgery did not predict serious complications. This appears to contradict the findings of Chatzidaki

et al.[55] that greater extent of surgery predicted major complications. However, the small number of patients experiencing major complications (8 of 140 participants) limits the generalizability of Chatzidaki and colleagues' findings. In addition, the effect of extent of surgery on all complications may be driven largely by wound complications, which have been found to be strongly associated with extent of surgery[11,43]. Wound complications make up a large proportion of complications overall[54] but were under-represented in the present measure of serious complications, which included only secondary/major wound infections.

Older age predicted neither number nor seriousness of complications. Although older age was found to predict breast surgery complications in earlier[59,60] and smaller[39] studies, many other investigations reported no association[11,17,43,56,57]. Notably, in the US-based NSQIP cohort[43], older age did not predict wound complications after breast surgery in either the 3107 patients with breast cancer treated from 2001 to 2004, or the follow-up study[11] of 26 988 patients treated from 2005 to 2007. The authors argued that employing multivariable analyses and controlling for a variety of potentially confounding preoperative factors enabled them to demonstrate this in a large and diverse cohort of patients[11]. However, de Glas and colleagues[38], in a cohort of 3179 patients diagnosed with breast cancer from 1997 to 2004, found that women aged at least 85 years had 1·58 (95 per cent c.i. 1·14 to 2·16) the odds of one or more complications following breast surgery compared with those aged 65–69 years, after adjusting for co-morbidities, type of surgery and tumour stage. Hence an increased surgical risk for older patients with breast cancer cannot be ruled out, albeit one of small magnitude limited to the oldest patients.

Several preoperative health measures predicted complications in the univariable analyses. As in previous studies, co-morbidity[38,39,55], BMI[11,43,55], ASA risk score[14,55] and functional status[14] (as measured by ADL and ECOG Performance Status) demonstrated some association with surgical risk at the 5 per cent level. These findings are far from consistent, with other studies finding no association between surgical risk and co-morbidity[14,57], BMI[38,39], ASA grade[11] and functional status[43]. Smoking status showed no association with surgical complications in the present study. Although the weight of literature indicates that smoking predicts surgical complications from breast surgery[11,38,39,61], this finding is not universal[17,43]. For example, El-Tamer and colleagues[43] investigated the influence of a range of patient variables among 3107 patients with breast cancer and found that smoking had no significant association with postoperative wound complications.

Predictors of surgical risk identified from studies testing large numbers of preoperative measures may reach statistical significance only because of the increased chance of finding an association the greater the number of variables tested. Raising the significance level in line with the total number of variables tested can adjust for this effect (for example Bonferroni's adjustment)[51]. Although there are examples of previous studies[38,43,55] investigating risk prediction of large numbers of preoperative measures for breast surgery, none of the papers cited made either Bonferroni or similar adjustments. In the present study, once Bonferroni's adjustment had been applied, only six of the 22 preoperative measures that significantly predicted surgical complications at the original 5 per cent level remained significant at the adjusted 0·1 per cent level. Consistent with a previous study investigating surgical risk of solid tumours[14], increasing dependence in instrumental ADL (such as shopping and housework) predicted complications along with the SF-12® measure of physical health status and four domains of the EORTC QLC-C30 (pain, fatigue, physical and role function). These measures were originally selected into the main study on ability to predict treatment[7,34], and/or their high validity/reliability, particularly in older populations[31], yet they displayed stronger associations with surgical complications than many of the traditional preoperative health measures. Moreover, pain and fatigue predicted complications in the final multivariable models, although many health measures failed to do so.

Few previous studies have undertaken similar multivariable analyses specifically predicting risk of breast surgery[11,38,43]. However, similar to the present findings, Audisio and co-workers[14] reported that moderate–severe self-reported fatigue increased the risk of complications from surgery for solid tumours among patients aged at least 70 years, after adjustment for type/stage of tumour, operative severity, and patient age and sex. Fatigue may also increase the impact of complications (such as delayed discharge), as suggested by the present measure of serious complications. Generalized neuropathic preoperative pain has been found to be predictive of postoperative pain after surgery for breast cancer[62] but has not previously been investigated regarding other complications. Conceivably, self-reported pain may be acting as a proxy indicator of poorly managed/symptomatic co-morbidities. In contrast to the present results, El-Tamer *et al.*[43] found no association between platelet counts and wound complications after breast surgery, in analyses adjusting for a range of tumour characteristics, sociodemographics and other preoperative health measures. This inconsistency may be due to the difference in outcome measures as primary/minor wound infections were not included in

the measure of serious complications here. Lower pre-operative pulse rate, as a continuous measure, predicted serious complications, suggesting that underlying conditions indicated by bradycardia (such as ischaemic heart disease) may be increasing surgical risk. However, when preoperative pulse rate was instead categorized as bradycardia, normal or tachycardia, this became borderline non-significant ($P = 0.062$), possibly because of the small numbers of patients with abnormal pulse rates. Low preoperative pulse rate may also be indicative of poorly controlled medication (such as antihypertensives), which may have increased the complication rate. The complication rate may also have been exacerbated by use of other medications; for example haematoma may be precipitated by the high frequency of aspirin use among older age groups.

Although the preoperative measures retained in the final model accounted for the variation in complications more strongly than the health measures eliminated in the modelling process, it should be noted that their effects in the final model are still weak, with 95 per cent c.i. around estimates close to unity. Moreover, although discrimination of the final model predicting serious complications (AUC 0·745) is classified as statistically 'acceptable'[42], sensitivity and specificity only just exceed 70 per cent and false-positives/negatives are far from clinically acceptable, with this model failing to predict complications, and incorrectly predicting complications, in almost 30 per cent of patients. Further research is clearly needed to identify and confirm strong predictors of surgical risk for older patients that demonstrate clinically acceptable levels of discrimination.

A large number of initially significant health measures were narrowed down to relatively few predictors in the final model. Although somewhat disappointing, it can be argued that this is the result of a thorough statistical process that should be employed particularly when developing tools for clinical use. As potential users of such risk prediction tools, clinicians should be wary and ensure that the claimed prediction of such assessments are not due to multiple testing, without correction for the increased chance of finding a significant effect, that multivariable analyses (adjusting for potential confounders) were undertaken, and that sensitivity/specificity as well as overall discrimination are reported. No located previous literature investigating prediction of complications from breast surgery met all these criteria. As part of the US-based NSQIP, the work of El-Tamer and colleagues[43] comes closest, reporting a similar reduction in variables in the final model and model discrimination just slightly lower than that of the present model (AUC 0·709 *versus* 0·745).

The strengths of this study include the large sample size (adequate to predict risk with the necessary degree of precision), the range of potential predictors (including health measures collected before surgery), robust statistical analyses and the collection of data across 22 English breast units, including a diverse population of 664 patients who received surgery from a cohort of 800 women[7]. However, collection of data on this scale presents inevitable limitations. Data on complications were collected primarily from case-note review and thereby restricted to the completeness of this data source. However, the outcomes of this study measure more than just the proportion having complications[14,38,39], and encompass the impact of more serious complications on surgical recovery, which may be of particular concern for older patients with breast cancer[58].

This study was restricted to analyses of the secondary outcome of an existing cohort[7] and as such was limited to the sample size, geographical area and preoperative health measures included in the main study. Therefore, measures such as polypharmacy, social support/networks, not initially included, could not be investigated but may have influenced complications and delayed discharge. Only patients who had surgery were included in this study, which therefore represents an analysis of complications in patients already selected for surgery. However, as the outcome is complications from surgery, this is inevitable and common to previously published studies on surgical risk[11,14,38,39,55]; it is not clear that it makes sense to include patients who have not had surgery in an analysis of surgical complications. Only patients aged at least 70 years were included. However, previous research[6,38−40] indicates that surgical complication rates increase and rates of surgery decrease from the age of 75 years. The present cohort should therefore include the age group in which assessment of surgical risk is most crucial. Other limitations of the main study are discussed elsewhere[7]. Of most relevance to the analysis reported here is the under-representation of women aged 85 years and over, limiting the generalizability of these findings to the oldest age group. However, under-representation of the oldest patients in any study requiring patient consent is likely as capacity for informed consent decreases with older age[63]. Future studies need either to focus on the oldest age group with ethical approval for vulnerable adults/consent by proxy, or to examine a few preoperative health measures that most strongly predict risk within routine/large clinical data sets collected for all patients.

This paper reports the results of a large prospective cohort study investigating surgical complications for older patients with breast cancer treated the UK,

testing prediction of an unprecedented range of pre-operative health measures and adjusting for extent of surgery, tumour characteristics and sociodemographics in multivariable analyses. Although subject to potential bias, no significant increase in surgical risk with older age was found. In line with national guidance, older patients with breast cancer should be given the same consideration for surgery as younger women, basing the treatment decision on fitness for surgery rather than chronological age[4].

Acknowledgements

References

1 Office for National Statistics. *Cancer Statistics Registrations: Registrations of Cancer Diagnosed in 2011, England. Series MB1 No. 42*. http://www.statistics.gov.uk [accessed 18 August 2014].

2 Moody H. *Aging: Concepts and Controversies*. Pine Forge Press: Thousand Oaks, 2009.

3 Association of Breast Surgeons at Baso 2009. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009; **35**(Suppl 1): 1–22.

4 National Institute for Health and Clinical Excellence (NICE). *Early and Locally Advanced Breast Cancer: Diagnosis and Treatment*. NICE: London, 2009.

5 Lavelle K, Downing A, Thomas JD, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? *Br J Cancer* 2012; **107**: 1175–1180.

6 Lawrence G, Kearins O, Lagord C, Cheung S, Sidhu J, Sagar C. *The Second All Breast Cancer Report*. National Cancer Intelligence Network: London, 2011.

7 Lavelle K, Sowerbutts A, Bundred N, Pilling M, Degner L, Stockton C *et al.* Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *Br J Cancer* 2014; **110**: 573–583.

8 Balducci L, Extermann M, Carreca I. Management of breast cancer in the older woman. *Cancer Control* 2001; **8**: 431–441.

9 Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H *et al.* The treatment of early breast cancer in women over the age of 70. *Br J Cancer* 2011; **105**: 189–193.

10 Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY *et al.* Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg* 2013; **217**: 833–842.

11 de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias A, Sharma R *et al.* High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26 988 patients from the National Surgical Quality Improvement Program database. *Ann Surg* 2012; **225**: 551–555.

12 Shah N, Hamilton M. Clinical review: Can we predict which patients are at risk of complications following surgery? *Crit Care* 2013; **17**: 226.

13 Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I *et al.* Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; **13**: e148–e160.

14 Audisio RA, Pope D, Ramesh HS, Gennari R, van Leeuwen BL, West C *et al.*; PACE participants. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. *Crit Rev Oncol Hematol* 2008; **65**: 156–163.

15 Audisio RA, Zbar AP, Jaklitsch MT. Surgical management of oncogeriatric patients. *J Clin Oncol* 2007; **25**: 1924–1929.

16 Todd CJ, Freeman CJ, Camilleri-Ferrante C, Palmer CR, Hyder A, Laxton CE *et al.* Differences in mortality after fracture of hip: the East Anglian audit. *BMJ* 1995; **310**: 904–908.

17 Forouhi P, Dixon JM, Leonard RC, Chetty U. Prospective randomized study of surgical morbidity following primary systemic therapy for breast cancer. *Br J Surg* 1995; **82**: 79–82.

18 O'Brien W, Hasselgren PO, Hummel RP, Coith R, Hyams D, Kurtzman L *et al.* Comparison of postoperative wound complications and early cancer recurrence between patients undergoing mastectomy with or without immediate breast reconstruction. *Am J Surg* 1993; **166**: 1–5.

19 National prevalence survey of hospital acquired infections: definitions. A preliminary report of the Steering Group of the Second National Prevalence Survey. *J Hosp Infect* 1993; **24**: 69–76.

20 Marla S, McMillan DC, Stallard S. Factors influencing postoperative length of hospital stay after breast cancer surgery. *Breast* 2013; **22**: 289–294.

21 NHS Choices. *Mastectomy – Recovery*; 2012. http://www.nhs.uk/Conditions/Mastectomy/Pages/Recovery.aspx [accessed 18 August 2014].

22 Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.

23 American Society of Anesthesiologists. *ASA Physical Status Classification System*; 2014. http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx [accessed 18 August 2014].

24 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–655.

25 Sharples LD, Todd CJ, Caine N, Tait S. Measurement properties of the Nottingham Health Profile and Short Form 36 health status measures in a population sample of elderly people living at home: results from ELPHS. *Br J Health Psychol* 2000; **5**: 217–233.

26 Ware J, Konsinski M, Turner-Bowker D, Gandek B. *How to Score Version 2 of the SF-12® Health Survey (with a Supplement Documenting Version 1)*. QualityMetric: Lincoln, 2002.

27 Osoba D, Aaronson N, Zee B, Sprangers M, te Velde A. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. *Qual Life Res* 1997; **6**: 103–108.

28 Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. *Int J Geriatr Psychiatry* 1999; **14**: 936–940.

29 Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours* (7th edn). Wiley-Blackwell: Oxford, 2009.

30 Office for National Statistics. *SOC2010 Volume 3: the National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010)*; 2013. http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html [accessed 18 August 2014].

31 Haywood K, Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. *Health Status and Quality of Life in Older People: a Structured Review of Patient-assessed Health Instruments. Reported from the Patient-assessed Health Instruments Group to the Department of Health*. Department of Health: London, 2004.

32 Sturgis P, Thomas R, Purdon S, Bridgewood A, Dodd T. *Comparative Review and Assessment of Key Health State Measures of the General Population*. Department of Health: London, 2001.

33 Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *Br J Surg* 2007; **94**: 1209–1215.

34 Mandelblatt JS, Hadley J, Kerner JF, Schulman KA, Gold K, Dunmore-Griffith J *et al.* Patterns of breast carcinoma treatment in older women: patient preference and clinical and physician influences. *Cancer* 2000; **89**: 561–573.

35 Berg J. The approach to pathology harmony in the UK. *Clin Biochem Rev* 2012; **33**: 89–93.

36 Clinical Laboratory Medicine, Royal Liverpool and Broadgreen University Hospitals NHS Trust. *Blood Sciences*; 2014. http://pathlabs.rlbuht.nhs.uk/home.htm [accessed 18 August 2014].

37 Office for National Statistics. *Ethnic Group (2001 Census)*; 2010. http://data.gov.uk/dataset/ethnic_group_2001_census [accessed 18 August 2014].

38 de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ *et al.* Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast Cancer Res Treat* 2013; **138**: 561–569.

39 Rocco N, Rispoli C, Pagano G, Rengo G, Compagna R, Danzi M *et al.* Breast cancer surgery in elderly patients: postoperative complications and survival. *BMC Surg* 2013; **13**(Suppl 2): S25.

40 Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women > or = 65 years. *Br J Cancer* 2007; **96**: 1197–1203.

41 Landis J, Koch G. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159–174.

42 Hosmer DW, Lemeshow S. *Applied Logistic Regression* (2nd edn). John Wiley: New York, 2000.

43 El-Tamer MB, Ward BM, Schifftner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. *Ann Surg* 2007; **245**: 665–671.

44 Kutner M, Nachtsheim C, Neter J. *Applied Linear Regression Models* (4th edn). McGraw-Hill Irwin: New York, 2004.

45 StataCorp. *Stata Statistical Software: Release 12*. StataCorp LP: College Station, 2011.

46 Tabachnick B, Fidell L. *Using Multivariate Statistics* (4th edn). Alleyn & Bacon: Needham Heights, 2001.

47 Bland M. *An Introduction to Medical Statistics* (3rd edn). Oxford University Press: Oxford, 2005.

48 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**: 1373–1379.

49 Vittinghoff E, McCulloch C. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**: 710–718.

50 Scottish Intercollegiate Guidelines Network (SIGN). *Breast Cancer in Women: a National Clinical Guideline Recommended for Use in Scotland*. Royal College of Physicians: Edinburgh, 1998.

51 Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995; **310**: 170.

52 National Institute for Health and Clinical Excellence (NICE). *Hypertension: Clinical Managment of Primary Hypertension in Adults*. NICE: London, 2011.

53 NHS Choices. *Low Blood Pressure (Hypotension); 2013.* http://www.nhs.uk/conditions/blood-pressure-(low)/Pages/Introduction.aspx [accessed 18 August 2014].

54 Vitug AF, Newman LA. Complications in breast surgery. *Surg Clin North Am* 2007; **87**: 431–451.

55 Chatzidaki P, Mellos C, Briese V, Mylonas I. Perioperative complications of breast cancer surgery in elderly women (>80 years). *Ann Surg Oncol* 2011; **18**: 923–931.

56 Wyld L, Garg D, Kumar I, Brown H, Reed M. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. *Br J Cancer* 2004; **90**: 1486–1491.

57 Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ *et al.* Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *Br J Cancer* 2004; **90**: 2332–2337.

58 Lally RM. In the moment: women speak about surgical treatment decision making days after a breast cancer diagnosis. *Oncol Nurs Forum* 2009; **36**: E257–E265.

59 Nieto A, Lozano M, Moro MT, Keller J, Carralafuente C. Determinants of wound infections after surgery for breast cancer. *Zentralbl Gynakol* 2002; **124**: 429–433.

60 Vinton AL, Traverso LW, Jolly PC. Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection. *Am J Surg* 1991; **161**: 584–588.

61 Sørensen LT, Hørby J, Friis E, Pilsgaard B, Jørgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery. *Eur J Surg Oncol* 2002; **28**: 815–820 [Erratum appears in *Eur J Surg Oncol* 2003; **29**: 482].

62 Bruce J, Thornton AJ, Scott NW, Marfizo S, Powell R, Johnston M *et al.* Chronic preoperative pain and psychological robustness predict acute postoperative pain outcomes after surgery for breast cancer. *Br J Cancer* 2012; **107**: 937–946.

63 Sugarman J, McCrory DC, Hubal RC. Getting meaningful informed consent from older adults: a structured literature review of empirical research. *J Am Geriatr Soc* 1998; **46**: 517–524.

Hip replacement surgery 2 © 2014 Helen Purdie. All rights reserved. http://www.helenpurdie.co.uk/w/doku.php