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ARTICLE

Prospective Observational Study of Breast Cancer Treatment Outcomes for UK Women Aged 18–40 Years at Diagnosis: The POSH Study

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Background Breast cancer at a young age is associated with poor prognosis. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) was designed to investigate factors affecting prognosis in this patient group.

Methods Between 2000 and 2008, 2956 patients aged 40 years or younger were recruited to a UK multicenter prospective observational cohort study (POSH). Details of tumor pathology, disease stage, treatment received, and outcome were recorded. Overall survival (OS) and distant disease-free interval (DDFI) were assessed using Kaplan-Meier curves. All statistical tests were two-sided.

Results Median age of patients was 36 years. Median tumor diameter was 22 mm, and 50% of patients had positive lymph nodes; 59% of tumors were grade 3, 33.7% were estrogen receptor (ER) negative, and 24% were human epidermal growth factor receptor 2 (HER2) positive. Five-year OS was higher for patients with ER-positive than ER-negative tumors (85.0%, 95% confidence interval [CI] = 83.2% to 86.7% vs 75.7%, 95% CI = 72.8% to 78.4%; $P < .001$), but by eight years, survival was almost equal. The eight-year OS of patients with ER-positive tumors was similar to that of patients with ER-negative tumors in both HER2-positive and HER2-negative subgroups. The flexible parametric survival model for OS shows that the risk of death increases steadily over time for patients with ER-positive tumors in contrast to patients with ER-negative tumors, where risk of death peaked at two years.

Conclusions These results confirm the increased frequency of ER-negative tumors and early relapse in young patients and also demonstrate the equally poor longer-term outlook of young patients who have ER-positive tumors with HER2-negative or -positive disease.

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Breast cancer remains the most common cancer in females in the United Kingdom (1). Approximately 4% of cases occur in women younger than 40 years of age (1). Young age at diagnosis is associated with an increased risk of recurrence and inferior survival compared to older patients (2–12). The exact reasons for this remain unclear.

Numerous publications describe an increased incidence of adverse biological features in tumors from young breast cancer patients. These include high grade (3,5,9,13–15), vascular invasion (5,14,15), lymph node involvement (3,7,9,13,16), absence of hormone receptors (3–5,7,9,14,15), and increased frequency of human epidermal growth factor receptor 2 (HER2) overexpression (15–18). It is controversial whether these adverse features fully explain the poor outcome of young breast cancer patients. The St Gallen 1998 consensus identified diagnosis at age 35 years or younger as a very poor prognostic factor and recommended use of adjuvant chemotherapy regardless of other tumor features, although no evidence was given to support this threshold (19). Evidence that age is an independent marker of poor prognosis remains limited (5,9,20–22).

An underlying genetic predisposition to breast cancer is characterized by young age of disease onset, yet even at a very young age of diagnosis most individuals do not have an identifiable mutation in a known breast cancer predisposition gene (23,24). The primary aim of the Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) is to determine whether the prognosis of patients with breast cancer is altered by inherited genetic factors. In this initial publication, we use Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report presenting characteristics, pathology, treatment, and survival of this large cohort of patients with young-onset breast cancer (25).

Patients and Methods

POSH is a multicenter prospective observational cohort study of young women diagnosed with breast cancer in the United Kingdom between 2000 and 2008 (http://www.southampton.ac.uk/medicine/research/posh.page). The detailed study protocol was published in 2007 (26). This study received approval from the South West Multi-center Research Ethics Committee (MREC 00/6/69).

Patients

Female patients were recruited from 127 UK hospitals. Patients were eligible if diagnosed with invasive breast cancer between January 1, 2000 and January 31, 2008 at an age of 40 years or younger. Potential recruits were identified within 12 months of initial diagnosis. All patients received treatment according to local protocols. Written informed consent was obtained (26).

Women aged 41–50 years were recruited if they had a known *BRCA1/2* gene mutation and were diagnosed with invasive breast cancer, but were excluded from these analyses.

Study Variables and Data Sources

Details of personal characteristics, tumor pathology, disease stage, and treatment received were collected from medical records. Pathology and imaging data were verified with copies of original reports from sites. For patients treated with neoadjuvant chemotherapy, initial tumor diameter was derived from radiological reports. Family history and personal risk factors were collected using a questionnaire completed by participants at recruitment (26).

Detailed clinical follow-up data, including date and site of disease recurrence, were obtained from medical records at 6 and 12 months and at yearly intervals after diagnosis until death or loss to follow-up. Patients were flagged in the National Health Service Medical Research Information Service to facilitate automatic notification of date and cause of death. This article presents analyses conducted on follow-up data received until April 11, 2012.

To rule out any systematic ascertainment bias, cohort characteristics were compared with data from the West Midlands Cancer Intelligence Unit (WMCIU), the lead national registry for breast cancer. Data on all known invasive breast cancers diagnosed within England for the same age range and time period were provided.

Biological Analyses

Estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor status of primary tumors were determined from diagnostic pathology test reports. Tissue microarray (TMA) data from 1336 cases were used to corroborate and supplement missing clinical data on receptor status. Genetic testing results have been recorded for trial participants who underwent formal genetic assessment and diagnostic *BRCA1/2* screening at a regional clinical genetics center. Additional research testing is in progress.

Statistical Analysis

Details of the target sample size (n = 3000) are reported in the protocol (26). The statistical analysis was conducted according to a prespecified plan (available on request) (25). Analyses were performed with Stata software, version 11.2 on records with complete data (levels of missingness were reported). Summary statistics were used to describe the cohort, and key data were compared with information from the WMCIU. All reported *P* values are two-sided. Overall survival (OS) and distant disease-free interval (DDFI) were assessed using Kaplan-Meier curves. These were defined as time from date of invasive breast cancer diagnosis to death from any cause (OS), and to distant relapse or death from breast cancer (DDFI). Patients who had not experienced an event at the time of analysis were censored at their date of last follow-up. The effect of ER status on survival varies over time (27). Therefore, to assess the effect of ER status, a flexible parametric survival model was fitted to OS and DDFI using the Stata stpm2 command with ER as a time-dependent covariate (28). In each case, we explored varying degrees of freedom for the baseline hazard rate and time-dependent effect using the Akaike information criterion and overlaying the flexible parametric model hazard curves onto the smoothed hazard rates. The best model fit for OS (DDFI) was found by setting the degrees of freedom to three (four) and two (two) for the baseline hazard rate and time-dependent effect, respectively. The model was unadjusted for any other factors. The resulting time-varying hazard ratio and hazard and survival rates were plotted over time by ER status.

Results

The POSH study recruited 3095 patients across England (n = 2695), Scotland, Wales, and Northern Ireland. After excluding 139 trial participants (Figure 1), 2956 patients were included in this analysis. Recruitment peaked in 2005 (Supplementary Figure 1, available online). A total of 11 594 female patients aged 18–40 years were registered with invasive breast cancer in England during 2000–2007 (WMCIU data, Supplementary Table 1, available online). POSH participants recruited from England thus represent 23% of the available population during the recruitment period.

Patient Characteristics

Table 1 demonstrates patient demographics and breast cancer risk factors. Median age at diagnosis of breast cancer was 36 years (range = 18 to 40 years).

Presentation and Diagnostics

Symptomatic presentation accounted for 98% (2900) of the cohort. Thirty women presented with screening-detected malignancies while on surveillance programs due to a previously identified *BRCA1/2* mutation in the patient (n = 3) or family (n = 6) or a strong family history of breast cancer (n = 21). A mammogram was performed in 2687 patients, (90.9%) and ultrasound in 2636 patients (89.2%). Two hundred twenty patients (7.4%) underwent magnetic resonance imaging of the breasts. No imaging modality data were available in 82 patients (2.8%).

Tumor Pathology

Median tumor diameter was 22 mm, and 50% of patients had positive lymph nodes; 59% of tumors were grade 3; 33.7% were ER negative, and 24% were HER2 positive. Despite similar pathological T stage, the difference in nodal status between patients with ER-positive tumors and those with ER-negative tumors was

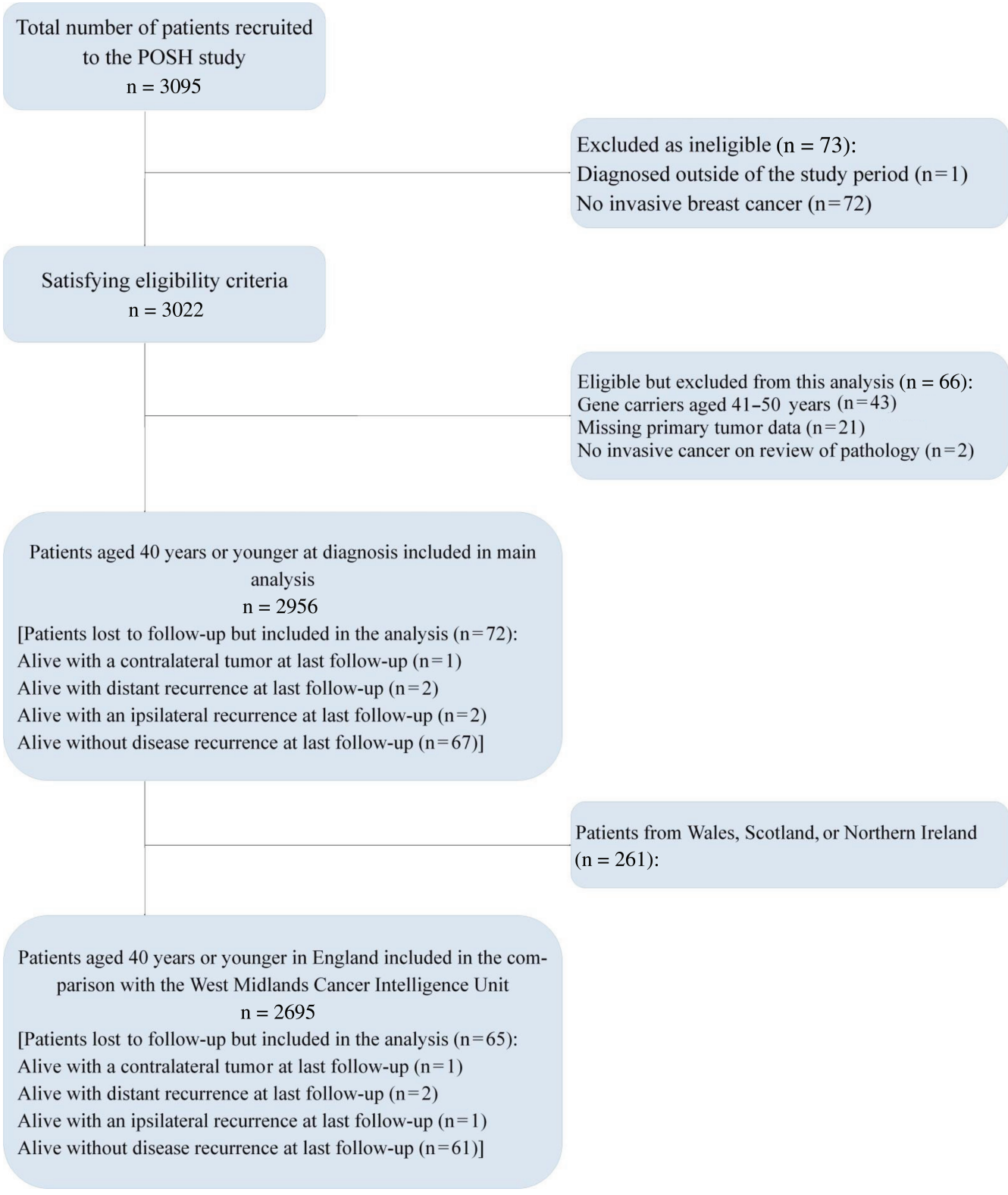

Figure 1. Flow diagram for the Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH).

statistically significant (Table 2). For larger tumors, downstaging between clinical and pathological T stage was demonstrated, reflecting the more frequent use of neoadjuvant chemotherapy (Supplementary Table 2, available online). Tumors were reported as ER positive in 65.9% and ER negative in 33.7% of cases. HER2 overexpression was recorded in 24.3% (717) of patients overall. However, on randomly selected study-specific TMAs, 243 of 1336 patients (18.2%) had HER2 overexpression. Five hundred eighty-eight (19.9%) patients had ER-, HER2-, and (if available) PR-negative tumors based on clinical report data, and 148

Table 1. Patient characteristics and risk factors*

Characteristic/risk factor	Median (range, IQR) or No. of patients (%)
Age at diagnosis, y	36 (18 to 40, 33 to 38), N = 2956 (100%)
18–25	46 (1.6%)
26–30	270 (9.1%)
31–35	900 (30.5%)
36–40	1740 (58.9%)
Duration of follow-up, mo	60 (1 to 136, 45 to 75), N = 2956 (100%)
Presentation	
Symptomatic	2900 (98.1%)
Screen detected	30 (1.0%)
Other	12 (0.4%)
Missing/unknown	14 (0.5%)
Age at menarche, y	13 (8 to 18, 12 to 14), N = 2956 (100%)
Body mass index, kg/m^2	24.6 (14.7 to 59.5, 22.1 to 28.4), n = 2842 (96.1)
Missing/unknown	114 (3.9%)
Age at first birth, y	27 (13 to 40, 23 to 30), n = 2080 (70.4%)
Missing/unknown	876 (29.6%)
No. with children	2097 (70.9%)
No. of children, median (range, IQR)	2 (1 to 8, 1 to 2)
No. without children	834 (28.2%)
Missing/unknown	25 (0.9%)
Use of contraceptive pill	
Ever	2598 (87.9%)
Never	358 (12.1%)
Smoker	
Ever	1455 (49.2%)
Never	1408 (47.6%)
Missing/unknown	93 (3.2%)
Menopausal status	
Premenopausal	2885 (97.6%)
Perimenopausal	5 (0.2%)
Postmenopausal	7 (0.2%)
Missing/unknown	59 (2.0%)
No. of patients with first- or second-degree relatives with breast cancer	
First degree	418 (14.1%)
Second degree	554 (18.7%)
No. of relatives with breast cancer	
0	1874 (63.4%)
1	702 (23.8%)
2	199 (6.7%)
>2	75 (2.5%)
Missing/unknown	106 (3.6%)

* IQR = interquartile range.

(14.1%) based on study TMA results. Comparing the cohort with available English national data demonstrates that study patients are representative (Supplementary Table 1, available online).

Treatment

Most patients (98.6% [2915]) had surgical treatment, and 27 had only surgery with no other modality of treatment (Table 3). Four hundred sixty (15.6%) patients received neoadjuvant chemotherapy. The majority of these (329) had T1/2 tumors, 57 had T3 tumors, and 68 patients had T4 (including inflammatory cancer). Adjuvant chemotherapy was given to 72.8% (2152) of patients, and 1.8% (54) patients received palliative chemotherapy. Thirty-six different adjuvant regimens were reported; the most common was 5-fluorouracil/epirubicin/cyclophosphamide in 1020 patients. The frequency of the three most common regimens varied over time (Supplementary Figure 1, available online). Use of trastuzumab was reported in 47.6% (363) of HER2-positive/ borderline patients. In patients with ER-positive tumors, tamoxifen use was recorded in 88.6% (1726) and an aromatase inhibitor in 2.8% (55).

BRCA1/BRCA2 Testing

By December 31, 2012, 26% (n = 763) patients have had genetic testing. *BRCA*-tested patients were not representative of the whole cohort, as they were either tested following referral to genetics services or were selected for research testing because of prespecified characteristics (n = 436), such as tumor pathology. Further testing of the cohort is ongoing as part of the study (29). A pathogenic mutation has been found in 218 patients (*BRCA1* in 136, *BRCA2* in 78, *TP53* in four).

Follow-up and Survival

At the time of analysis, length of follow-up ranged from one month to 11 years (median = 5 years). Only 72 patients (2.4%) had been lost to follow-up. There have been 613 deaths (20.7%) and cause of death is breast cancer in 578 patients (94.3% of deaths).

There were two treatment-related deaths, four non-breast cancer deaths, and six noncancer deaths, with missing data in 23 patients. A total of 13 non–breast cancer malignancies have been reported (Supplementary Table 4, available online).

Seven hundred twelve women (24%) developed a distant recurrence, of whom 149 are still alive. Kaplan-Meier survival curves are plotted in Figure 2, A–D. Median survival from date of first distant relapse to death was longer in patients with ER-positive tumors than those with ER-negative tumors (23.4 vs 10.8 months). Isolated local relapse events were few (89 ipsilateral, 63 contralateral) and will be explored in a subsequent article. The estimated five-year OS for the entire POSH cohort was

Table 2. Tumor characteristics

Characteristic	ER negative (n = 997) (33.7%) No. of patients	ER positive* (n = 1947) (65.9%) No. of patients	Total† (N = 2956) (100%) No. of patients	*P*‡
Histological grade				
1	6 (0.6%)	155 (8.0%)	163 (5.5%)	<.001
2	100 (10.0%)	871 (44.7%)	972 (32.9%)	
3	864 (86.7%)	871 (44.7%)	1742 (58.9%)	
Missing/unknown	27 (2.7%)	50 (2.6%)	79 (2.7%)	
Histological type				
Ductal	909 (91.2%)	1637 (84.1%)	2556 (86.5)	<.001
Lobular	7 (0.7%)	127 (6.5%)	134 (4.5%)	
Ductal and lobular	8 (0.8%)	70 (3.6%)	78 (2.6%)	
Medullary	28 (2.8%)	3 (0.2%)	31 (1.1%)	
Metaplastic	10 (1.0%)	1 (0.1%)	11 (0.4%)	
Mixed	6 (0.6%)	19 (1.0%)	26 (0.9%)	
Other	7 (0.7%)	56 (2.9%)	64 (2.2%)	
Unclassified adenocarcinoma	9 (0.9%)	8 (0.4%)	17 (0.6%)	
Not graded§	0 (0%)	2 (0.1%)	2 (0.1%)	
Missing/unknown	13 (1.3%)	24 (1.2%)	37 (1.3%)	
Distribution of cancer				
Multifocal	176 (17.7%)	620 (31.8%)	797 (27.0%)	<.001
Localized	709 (71.1%)	1156 (59.4%)	1873 (63.4%)	
Missing/unknown	112 (11.2%)	171 (8.8%)	286 (9.7%)	
PR status‖				
Negative	813 (81.5%)	219 (11.3%)	1033 (35.0%)	<.001
Positive	80 (8.0%)	1261(64.8%)	1342 (45.4%)	
Missing/unknown	104 (10.4%)	467 (24.0%)	581 (19.7%)	
HER2 status‖				
Negative	631 (63.3%)	1205 (61.9%)	1839 (62.2%)	.431
Positive	256 (25.7%)	461 (23.7%)	717 (24.3%)	
Borderline	12 (1.2%)	33 (1.7%)	45 (1.5%)	
Missing/unknown	98 (9.8%)	248 (12.7%)	355 (12.0%)	
M stage				
M0	969 (97.2%)	1880 (96.6%)	2860 (96.8%)	.350
M1	21 (2.1%)	52 (2.7%)	74 (2.5%)	
Missing/unknown	7 (0.7%)	15 (0.8%)	22 (0.7%)	
Pathological T stage (all patients)				
T0	39 (3.9%)	33 (1.7%)	73 (2.5%)	.005
T1	448 (44.9%)	959 (49.3%)	1411 (47.7%)	
T2	397 (39.8%)	765 (39.3%)	1167 (39.5%)	
T3	65 (6.5%)	123 (6.3%)	189 (6.4%)	
T4	3 (0.3%)	3 (0.2%)	6 (0.2%)	
Tis	10 (1.0%)	11 (0.6%)	21 (0.7%)	
Tx	27 (2.7%)	49 (2.5%)	77 (2.6%)	
Missing/unknown	8 (0.8%)	4 (0.2%)	12 (0.4%)	
Pathological T stage (excluding neoadjuvant patients¶)				
T0	2 (0.3%)	4 (0.2%)	6 (0.2%)	.703
T1	398 (48.8%)	869 (51.9%)	1270 (50.9%)	
T2	352 (43.2%)	689 (41.2%)	1044 (41.8%)	
T3	47 (5.8%)	89 (5.3%)	137 (5.5%)	
T4	0 (0%)	2 (0.1%)	2 (0.1%)	
Tis	0 (0%)	2 (0.1%)	2 (0.1%)	
Tx	10 (1.2%)	18 (1.1%)	29 (1.2%)	
Missing/unknown	6 (0.7%)	0 (0%)	6 (0.2%)	

(Table continues)

Table 2 (Continued).

Characteristic	ER negative (n = 997) (33.7%) No. of patients	ER positive* (n = 1947) (65.9%) No. of patients	Total† (N = 2956) (100%) No. of patients	P‡
N stage (excluding neoadjuvant patients¶)				
N0	456 (56.0%)	753(45.0%)	1213 (48.6%)	<.001
N1	348 (42.7%)	903 (54.0%)	1252 (50.2%)	
1–3	220 (63.2%)	597 (66.1%)	817 (65.3%)	
4–9	78 (22.4%)	200 (22.2%)	279 (22.3%)	
≥10	49 (14.1%)	106 (11.7%)	155 (12.4%)	
Missing/unknown	1 (0.3%)	0 (0)	1 (0.1%)	
Missing/unknown	11 (1.4%)	17 (1.0%)	31 (1.2%)	
	Median (range, IQR) or No. of patients	**Median (range, IQR) or No. of patients**	**Median (range, IQR) or No. of patients**	**P#**
Maximum diameter invasive tumor, mm	22 (1 to 199,15 to 31)	22 (0 to 170,15 to 35)	22 (0 to 199,15 to 33)	.156
(all patients)	912 (91.5%)	1840 (94.5%)	2763 (93.5%)	
Missing/unknown	85 (8.5%)	107 (5.5%)	193 (6.5%)	
Maximum diameter invasive¶ tumor, mm	22 (1.5 to 199, 15 to 30)	22 (1 to 150, 16 to 33)	22 (1 to 199, 15 to 32)	.206
(exc neoadjuvant)	796 (79.8%)	1643 (84.4%)	2446 (82.8%)	
Missing/unknown	19 (2.3%)	30 (1.8%)	50 (2.0%)	
Maximum tumor diameter**, mm	26 (0.6 to 199, 18 to 37)	27 (0 to 190, 19 to 42)	27 (0 to 199,18 to 40)	.005
(all patients)	928 (93.1%)	1856 (95.3%)	2795 (94.6%)	
Missing/unknown	69 (6.9%)	91 (4.7%)	161 (5.5%)	
Maximum tumor diameter**¶, mm	26 (3 to 199, 18 to 35),	27 (1 to 190, 19 to 41)	26 (1 to 199, 19 to 40)	.006
(exc neoadjuvant patients)	801 (80.3%)	1653 (84.9%)	2461 (83.3%)	
Missing/unknown	14 (1.7%)	20 (1.2%)	35 (1.4%)	
No. of axillary lymph nodes recovered	13 (0 to 46, 8 to 18)	12 (0 to 53, 7 to 17)	12 (0 to 53, 8 to 17)	.022
(all patients)	981 (98.4%)	1920 (98.6%)	2910 (98.4%)	
Missing/unknown	16 (1.6%)	27 (1.4%)	46 (1.6%)	
No. of axillary lymph nodes recovered	13 (0 to 46, 8 to 18)	12 (0 to 53, 7 to 17)	12 (0 to 53, 7 to 17)	.088
(exc neoadjuvant patients)¶	807 (99.0%)	1660 (99.2%)	2472 (99.0%)	
Missing/unknown	8 (1.0%)	13 (0.8%)	24 (1.0%)	
No. of positive axillary lymph nodes	3 (1 to 42, 1 to 6)	2 (1 to 50, 1 to 5)	2 (1 to 50, 1 to 5)	.212
(all patients)	426 (42.7%)	1067 (54.8%)	1495 (50.6%)	
Missing/unknown	22 (2.2%)	34 (1.8%)	59 (2.0%)	
No. of positive axillary lymph nodes (exc	2 (1 to 42, 1 to 5)	2 (1 to 50, 1 to 5)	2 (1 to 50, 1 to 5)	.708
neoadjuvant patients)¶	349 (35.0%)	910 (46.7%)	1260 (42.6%)	
Missing/unknown	13 (1.3%)	18 (0.9%)	34 (1.2%)	

* ER positive defined as hormone receptor level equivalent to Allred score of ≥3. ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

† Total column includes data from the whole cohort, ie, ER positive, ER negative, and ER status unknown (12 patients).

‡ *P* values obtained from the Pearson χ^2 test between ER status and each categorical variable (excluding missing/unknown data). All statistical tests were two-sided.

§ Not graded as pathology from axillary node, no primary detected.

‖ Includes data from tissue microarray as well as primary POSH data.

¶ Total number of patients excluding neoadjuvant (n = 2496).

P values obtained from the Mann-Whitney test between ER status and each continuous variable (excluding missing/unknown data). All statistical tests were two-sided.

** Maximum tumor diameter includes ductal carcinoma in situ.

81.9%, and DDFI was 76.6%. Patients with ER-positive tumors had an estimated five-year OS of 85.0% compared with 75.7% for those with ER-negative tumors ($P < .001$ at five years). DDFI at five years was 78.5% for patients with ER-positive tumors and 72.7% for patients with ER-negative tumors ($P < .001$ at five years). At eight years, OS for the whole cohort was 67.6% and there was no difference in survival (67.5% vs 67.7%, $P = .931$ at eight years) or DDFI (68.3% vs 68.1%, $P = .965$ at eight years) between patients with ER-positive and ER-negative tumors. The flexible parametric survival model for OS (Figure 2, E and F; Supplementary Table 3 and Supplementary Figure 3, available online) shows the hazard ratio and hazard and survival rates over time by ER status. It graphically illustrates that the risk of death prior to five years is greater for patients with ER-negative tumors and after five years is greater for patients with ER-positive tumors. The result is that by eight years the survival curves converge. The OS model survival and hazard rate estimates closely match the Kaplan-Meier estimates and smoothed hazard rate, estimates respectively, indicating a good model fit (Figure 2D compared to Figure 2F; Supplementary Table 3, available online). The change

Table 3. Treatment details

Characteristic	ER negative (n = 997) (33.7%)	ER positive (n = 1947) (65.9%)	Total* (N = 2956) (100%)
Definitive breast surgery, no.			
Breast conserving surgery	521 (52.2%)	879 (45.1%)	1497 (50.6%)
Mastectomy	458 (45.9%)	1037 (53.3%)	1409 (47.7%)
Nodal surgery only	3 (0.3%)	6 (0.3%)	9 (0.3%)
No surgery	13 (1.3%)	25 (1.3%)	39 (1.3%)
Missing/unknown	2 (0.2%)	0 (0%)	2 (0.1%)
Chemotherapy timing, no.			
Adjuvant†	772 (77.4%)	1378 (70.8%)	2152 (72.8%)
Neoadjuvant	182 (18.2%)	274 (14.1%)	460 (15.6%)
Palliative	17 (1.4%)	36 (1.8%)	54 (1.8)
Not applicable	26 (2.6%)	259 (13.3%)	290 (9.8%)
Missing/unknown	0 (0%)	0 (0%)	0 (0%)
Chemotherapy regimen, no.			
Anthracycline based	690 (69.2%)	1245 (63.9%)	1938 (65.6%)
Anthracycline and taxane	264 (26.5%)	416 (21.4%)	684 (23.1%)
Taxane based	13 (1.3%)	7 (0.4%)	20 (0.7%)
Other‡	4 (0.4%)	20 (1.0%)	24 (0.8%)
None	26 (2.6%)	259 (13.3)	290 (9.8%)
Missing/unknown	0 (0%)	0 (0%)	0 (0%)
Adjuvant trastuzumab, no.			
Yes	129 (12.9%)	234 (12.0%)	363 (12.3%)
Other treatment period/no/ missing/unknown§	868 (87.1%)	1713 (88.0%)	2593 (87.7%)
Adjuvant radiotherapy, no.			
Yes	816 (81.9%)	1536 (78.9%)	2358 (79.8%)
BCS + adjuvant RT	490 (60.1%)	844 (55.0%)	1339 (56.8%)
Mastectomy + adjuvant RT	321 (39.3%)	685 (44.6%)	1007 (42.7%)
Nodal surgery only	2 (0.3%)	3 (0.2%)	6 (0.3%)
No surgery	3 (0.4%)	4 (0.3%)	6 (0.3%)
No/missing/unknown	167 (16.8%)	367 (18.8%)	598 (20.2%)
Adjuvant hormone treatment, no.			
Yes	98 (9.8%)	1790 (91.9%)	1823 (61.7%)
No/missing/unknown	899 (90.2%)	157 (8.1%)	1133 (38.3%)
Ovarian suppression (in any treatment period), no.			
Medical (LHRH agonist)	122 (12.2%)	659 (33.8%)	784 (26.5%)
Irradiation	0 (0%)	11 (0.6%)	11 (0.4%)
Oophorectomy	73 (7.3%)	325 (16.7%)	398 (13.5%)

* Total column includes data the whole cohort, ie, ER positive, ER negative, and ER status unknown (12 patients). BCS = breast conserving surgery; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; LHRH = Luteinising Hormone Releasing Hormone; PR = progesterone receptor; RT = radiotherapy.

† Excluding any treatment for M1 disease.

‡ For example, cyclophosphamide, methotrexate, and 5-fluorouracil or any regimen not containing an anthracycline or taxane.

§ Due to the data collection methods and emerging knowledge of HER2 and guidance through the study, this is likely to be inaccurate.

in hazard ratios over time by ER status is still apparent even after adjustment for tumor size, grade, and nodal status in a multivariable flexible parametric model (Supplementary Figure 3, available online).

Although HER2-positive compared to HER2-negative tumors showed lower OS and DDFI at all time points in patients with ER-positive tumors, the difference was only statistically significant for DDFI at five years (five-year DDFI: 71.4% vs 78.3%, $P = .00823$; eight-year DDFI: 60.3% vs 66.3%, $P = .227$; five-year OS: 81.4% vs 84.1%, $P = .206$; eight-year OS: 57.6% vs 65.4%, $P = .159$) (Figure 3).

For patients with ER-negative tumors, again, HER2-positive compared to HER2-negative tumors were associated with worse DDFI and OS at all time points. The difference in DDFI was statistically significant at five and eight years (five-year DDFI: 62.2% vs 73.9%, $P = .00141$; eight-year DDFI: 53.4% vs 70.7%, $P = .00438$) and OS was statistically significantly lower at 8 years (five-year OS: 70.2% vs 75.2%, $P = .154$; eight-year OS: 58.4% vs 68.3%, $P = .0476$) (Figure 3).

Discussion

We present the first outcome analysis of a large prospective cohort study of young-onset breast cancer patients receiving modern breast cancer treatment. As anticipated, the major cause of death in this young trial cohort was breast cancer. The estimated five-year OS of our cohort (82%) is almost identical to 2005–2009 relative survival national statistics in 15- to 39-year-olds with breast cancer (83.5%). This confirms that the POSH cohort is representative of the wider population and that the survival of patients younger

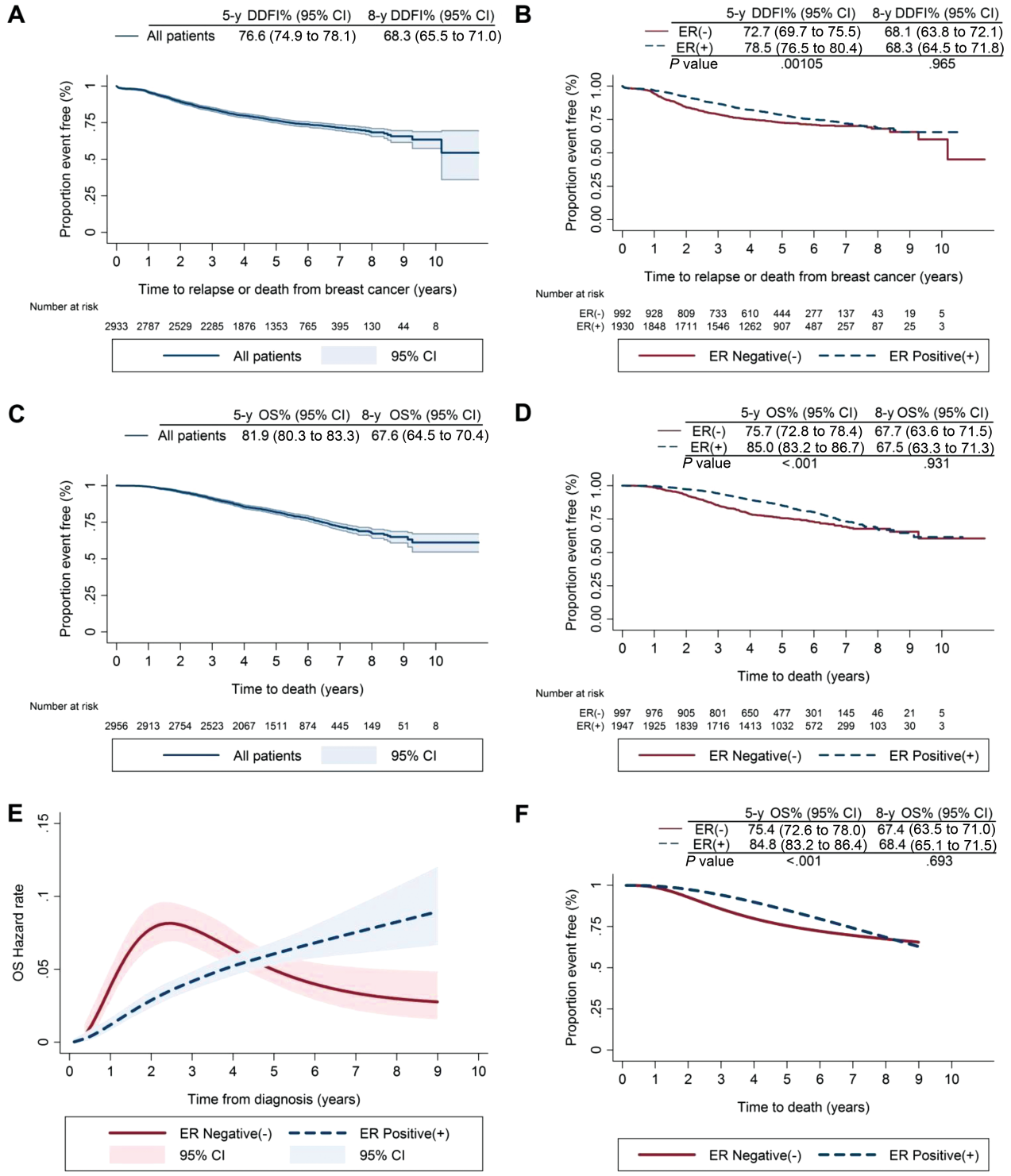

Figure 2. Kaplan-Meier distant relapse-free survival estimates for all patients **(A)** and for patients with estrogen receptor (ER)–negative and -positive tumors **(B)**. Kaplan-Meier overall survival (OS) estimates for all patients **(C)** and patients with ER-negative and -positive tumors **(D)**. Time-varying hazard OS estimates for patients with ER-negative and -positive tumors, showing the time-varying hazard rates by ER status **(E)** and survival rates by ER status **(F)**. All statistical tests were two-sided. CI = confidence interval; DDFI = distant disease-free interval.

than 40 years of age at diagnosis is worse than that of patients aged 40–69 years (five-year relative survival = 89.1% to 90.4%) (1).

Our prospective data clearly demonstrate the influence of ER status over time on recurrence risk and OS in young patients. The estimated five-year OS of patients with ER-positive tumors was 9% higher than patients with ER-negative tumors; however, by eight years the survival of young breast cancer patients with ER-positive tumors was no better than that of patients with ER-negative tumors. Whereas our data indicated falling ER-negative hazard rates and rising ER-positive hazard ratios after

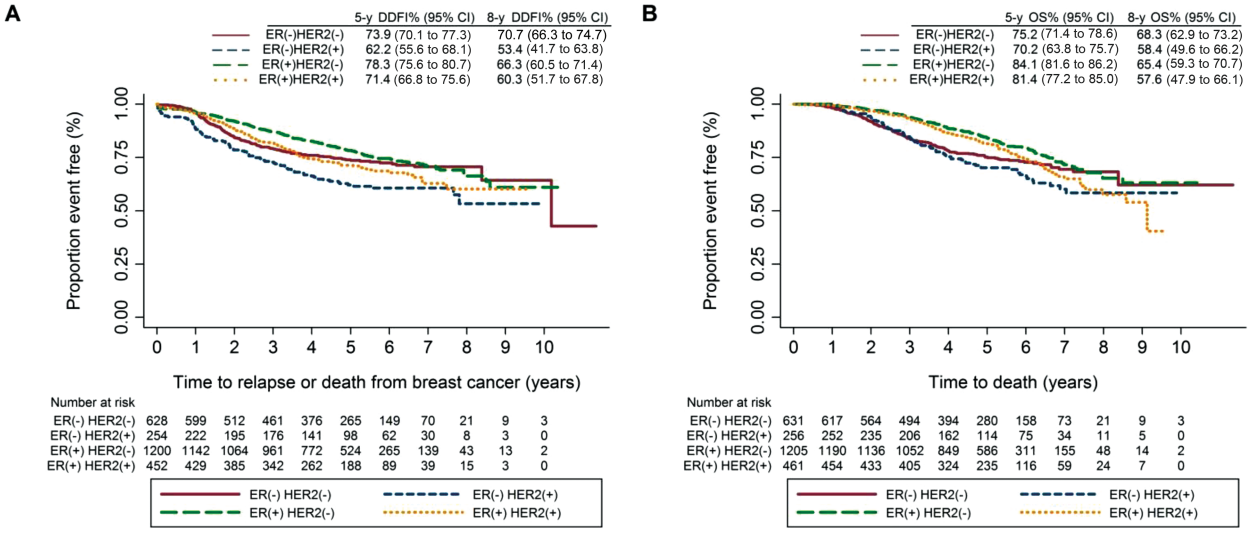

Figure 3. Kaplan-Meier distant relapse-free survival **(A)** and overall survival (OS) **(B)** estimates, by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status. All statistical tests were two-sided. CI = confidence interval; DDFI = distant disease-free interval.

five years, a previous analysis of Surveillance Epidemiology and End Results (SEER) data showed falling ER-negative hazard rates and constant ER-positive rates crossing at seven years; however, this latter analysis was in non-age-selected patients (30). A more recent report using SEER data observed that patients younger than 40 years of age with ER-positive tumors had an increased hazard of breast cancer–specific mortality compared with that for patients with ER-negative tumors at 5–10 years after diagnosis (31). The increase in breast cancer–specific mortality hazard was notably less marked in older patients with ER-positive tumors. It should, however, be noted that our 10-year follow-up data are currently limited.

Notably, 10.2% of POSH patients with ER-positive tumors relapse between five and eight years (Figure 2B). Adjuvant hormone therapy is generally prescribed for a five-year period. Our results raise the question of duration of hormonal therapy in some premenopausal women. Although the National Surgical Adjuvant Breast and Bowel Project B-14 extension indicated that continuation of adjuvant tamoxifen beyond five years did not confer additional benefits, this trial was limited to node-negative patients and only 31% of patients were younger than 49 years of age (32). Data from the MA.17 clinical trial suggests that extended hormone therapy with letrozole may be beneficial in patients who are premenopausal at diagnosis but became amenorrheic during adjuvant treatment (33). This is more likely to occur in women aged 41–50 years than in those aged 40 years and younger, so further investigation is clearly required to confirm the optimum length of hormone treatment in the youngest age groups. The recently published Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) randomized trial, which included 1270 women aged 45 years or younger at diagnosis with ER-positive tumors, indicates that continuation of tamoxifen for 10 years rather than stopping at five years reduces breast cancer recurrence and mortality in both pre- and postmenopausal women (34).

Ovarian suppression (medical, irradiation, and/or oophorectomy) was documented in 703 of the POSH patients with ER-positive tumors. Although chemotherapy-induced amenorrhea has been associated with improved prognosis, the use of ovarian suppression in addition to chemotherapy and tamoxifen remains controversial (35). Our data reflect the timing of this trial prior to guidance from the National Institute for Clinical Excellence in the UK, recommending use of ovarian suppression plus chemotherapy and tamoxifen in a clinical trial setting only (36).

The vast majority of POSH patients (88%) with early breast cancer received chemotherapy in addition to local treatments, suggesting general compliance with the 1998 St Gallen recommendations (19). Most patients received anthracycline-based chemotherapy. Inevitably, standard systemic treatment regimens changed during the recruitment period of this study, including the incorporation of taxanes into adjuvant regimens. Kroman et al. reported that a diagnosis of breast cancer at a young age (particularly younger than 35 years) was a poor prognostic factor, but that the age effect was only clinically significant in patients who did not receive systemic cytotoxic therapy (37). However, in Kroman's series a much smaller proportion of stage 1–3 patients (65%) received chemotherapy than in POSH. Similarly, Fredholm et al. found that the excess risk in young women was most evident in women with early tumors but also reported low frequency of chemotherapy in these patients (9). A recent meta-analysis confirms that absolute benefits from systemic therapy are higher in patients younger than 45 years of age but that the proportional reduction in risk of relapse is largely independent of age (38). A more detailed exploration of the age effect is beyond the scope of this descriptive publication but will be addressed in future analyses.

Numerous previous publications have reported larger tumors in younger patients with increased nodal involvement. Our findings are consistent with these reports; there was a lower frequency of T1 tumors in our cohort than reported recently for unselected UK patients (47.7% vs 58.2%) and a larger frequency of positive lymph nodes (50.2% vs 38.4%) (39). This may explain why the POSH cohort mastectomy rate (51%) is higher than that reported for non-age-selected symptomatic and screening-detected UK patients (43% in 2007) (39). The upper age criterion for this trial is

below the minimum age for the UK breast screening program and this trial excluded previous history of malignancy; therefore, our data do not include any examples of routine screening-detected or radiation-induced breast cancer. However, 30 patients were undergoing early screening because of a family history of breast cancer or known *BRCA1/2* mutation.

Biological characteristics of tumors were consistent with other published series of women aged younger than 35 or 40 years with a high proportion of grade 3 (59%) and ER-negative (34%) tumors (3,5,9,14–16). Patients with an ER-negative tumor were twice as likely to have a grade 3 tumor than those with ER-positive tumors; but ER-positive tumors had a higher frequency of nodal involvement (54.0% vs 42.7% of ER-negative tumors). Although the reported frequency of HER2 overexpression was 24%, HER2 status was not routinely tested in the United Kingdom prior to 2006. Retrospective testing of primary tumors at subsequent presentation of metastatic disease would be likely to inflate the proportion of positive results among those tested. For the 1336 tumors tested on TMAs, the proportion of HER2-positive tumors was 18.2%. This is within the range reported elsewhere for all breast tumors. Overall, 19.9% of our patients were negative for HER2 overexpression, ER, and (where available) PR. Other series have described triple-negative tumors in 23%–25% of patients aged 40 years and younger (16,40).

As anticipated, a positive HER2 status is associated with a lower five-year and eight-year OS in both patients with ER-positive and those with ER-negative tumors; however, this difference is only statistically significant for patients with ER-negative tumors at eight years. Our data indicate that the eight-year OS of ER-positive/HER2-positive patients is no better than that of ER-negative/HER2-positive patients and is inferior that of to ER-positive and ER-negative patients with HER2-negative tumors. However, use of adjuvant trastuzumab was recorded for less than 50% of our cohort, which may be explained by the fact that 53.3% of the POSH cohort was diagnosed before 2005 when adjuvant trastuzumab came into routine use in the United Kingdom. It is therefore likely that these figures are not entirely representative of the modern oncological management of HER2-positive breast cancer. Most of these patients who did not receive adjuvant trastuzumab received it for metastatic disease.

POSH is a cohort study and we have therefore not directly compared our data with older women. However, we have reported according to the STROBE guidelines to ensure complete transparency in relation to our findings and future analyses. Although national registry data are incomplete, the data presented in this study appear to be comparable with national data over the same time period so are likely to be representative. One limitation of the data presented here is that ER, PR, and HER2 results were obtained from local pathology reports with variations in scoring systems. PR testing was not routinely performed at many sites during recruitment. A slightly lower proportion of our patients (2.5%) had distant metastases at presentation than in retrospective series of women younger than 35 years (3.2%) (9) or 40 years of age (2.9%–7·0%) (9–16). This may represent bias against recruitment of this group to an observational study.

As one of the few prospective studies on medium-term outcome in this age group, POSH already provides a unique data set. Further analysis from the POSH study data will provide important insights into long-term outcomes for early-onset breast cancer and the influences of genetic variation on tumor pathology and response to treatment.

We have described the presenting characteristics, pathology, and treatment of 2956 women diagnosed with breast cancer aged 40 years or younger in the United Kingdom. Despite modern oncological treatments, this group of women has a poor prognosis. Our data confirm the high frequency of ER-negative tumors in young breast cancer patients and the association of this phenotype with high tumor grade and risk of early disease recurrence. However the equally poor medium-term outcome of ER-positive tumors in this patient group, in both HER2-positive and HER2-negative subgroups, highlights the need for new treatment approaches in all younger women, including extended adjuvant hormonal therapy and possibly age-selected trials.

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