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Treatment strategies and survival outcomes in older women with breast cancer: A comparative study between the FOCUS cohort and Nottingham cohort

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ABSTRACT

Objective: Clinical trials investigating breast cancer treatment often exclude or misrepresent older adults. This study compares treatment patterns and survival of older women diagnosed with breast cancer between a Dutch and a British observational cohort.
Materials and Methods: Women aged 70 years and older diagnosed with breast cancer after 1990 with a T0-T2 tumor stage and no evidence of metastatic disease were included from a population-based cohort in the Netherlands and a British hospital-based cohort in Nottingham. Main outcomes were proportions of local and systemic treatment, ten-year overall survival and ten-year relative survival for each cohort.
Results: 1439 patients from Nottingham and 2180 patients from the Netherlands were included. Median follow-up was 12.4 years (IQR 11.0–14.0) in the FOCUS cohort and 6.4 years (IQR 6.2–6.8) in the Nottingham cohort. British patients were more likely to receive primary endocrine therapy (50.0% vs 7.5%, $P < 0.001$), and less likely to be managed with mastectomy or breast-conserving surgery (47.8% vs 90.5%, $P < 0.001$). Ten-years overall survival was 39.4% (95% CI 37.4–41.6%) in the FOCUS cohort and 34.3% (95% CI 30.7–38.3) in the Nottingham cohort (adjusted HR 0.97, 95% CI 0.87–1.08, $P = 0.559$). Ten-year relative survival was 82.5% (95% CI 75.6–90.1) in the FOCUS cohort and 77.6% (95% CI 66.4–90.7) in the Nottingham cohort (adjusted relative excess risk 1.67, 95% CI 1.21–2.29, $P = 0.002$).
Conclusion: Patients in the Nottingham cohort were more likely to receive primary endocrine therapy and had worse relative survival compared to the Dutch cohort. These findings encourage further research to equalize survival rates of breast cancer throughout Europe.

1. Introduction

Evidence shows a rapidly growing group of older patients being diagnosed with cancer. For breast cancer the median age at diagnosis is currently 61 years, with 30% of patients above the age of 70 [1]. Clinical trials exploring treatment options offer little data to guide treatment of older patients [2]. This appears to be a result of the exclusion or under-representation of older patients in clinical trials; merely 4% of currently ongoing trials regarding breast cancer treatment specifically aim to include older patients [3]. Moreover, the external validity of trials that do include older patients is limited, since older patients that are included have been shown to have fewer comorbidities, a higher socioeconomic status, better tumor characteristics and better survival outcomes than the general older population [4].

As there is little evidence originating from trials for this group of patients, observational data might provide guidance in the treatment of an ageing population with breast cancer. Registration and the follow-up of observational cohorts of patients diagnosed with breast cancer are widely practiced in European countries [5]. Data from these registries is readily available and has the benefit of overcoming misrepresentation of patients, as there are no exclusion criteria for these cohorts. When using the appropriate methodology, this observational data can provide evidence on the effectiveness of the used treatment strategies for elder patients by evaluating the survival outcomes of the patients included [6].

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The aim of this study was to evaluate and compare the primary and adjuvant treatment strategies and survival outcomes between a Dutch (the FOCUS cohort, a large population-based cohort of older patients with breast cancer) and a British cohort (dedicated Primary Breast Cancer Clinic for Older Women of the Nottingham Breast Unit) including patients aged 70 years and older with early stage breast cancer.

2. Materials and Methods

2.1. Cohorts

Dutch patients were included from the FOCUS cohort (Female breast cancer in the elderly; Optimized Clinical guidelines Using clinic-pathological & molecular data), an observational cohort based on the National Cancer Registry of the Netherlands, a registry of all Dutch incident cancer cases [7]. This cohort contains all patients diagnosed with breast cancer between 1997 and 2004 in the western region of the Netherlands aged 65 years and older. Charts of these patients have been reviewed by trained personnel in order to collect data on patient and tumor characteristics, treatment strategies and survival outcomes. Vital status was recorded through linkage with the municipal population registries.

British patients were included from the dedicated Primary Breast Cancer Clinic for Older Women, established in the Nottingham Breast Unit [8]. Patients were aged 70 years and older, had early operable primary breast cancer and were included between 1973 and 2010. Paper and computerized records from the Histopathology Department were reviewed by trained personnel to obtain clinical information from the date of diagnosis till death or last follow-up.

2.2. Procedures

Patients were included if they were aged 70 years or older, with T-stage T0, T1 or T2 (tumor ≤ 5 cm across), no evidence of metastatic disease and diagnosed after 1990. Patients were excluded if date of birth and/or pathological and clinical T-stage was unknown.

The International Classification of Diseases and Related Health Problems (ICD-10) coding was used to ascertain breast cancer [9]. The tumor-node-metastasis (TNM) Classification of Malignant Tumors for breast cancer 6th edition was used to define stage of disease [10]. If available pathological reports were used to determine T- and N-stage, if missing, clinical T- and N-stage were used to complete TNM staging. If data on metastases was unknown for a patient, this patient was assigned as having no metastases. Morphology was categorised into ductal, lobular, or mixed/other in accordance with the ICD-O-3 classification [11].

2.3. Outcomes

Main outcomes were the proportion of given treatment, ten-year overall survival and ten-year relative survival for each cohort. The following definitions were used: breast surgery as the most extensive breast surgery procedure listed (no surgery, breast-conserving surgery (BCS), mastectomy). In patients that received any type of breast surgery the following subsequent treatments were defined: axillary surgery if any breast surgery (yes or no), radiotherapy (yes or no), adjuvant endocrine therapy (yes or no), adjuvant chemotherapy (yes or no). Primary endocrine therapy was defined as endocrine therapy without receiving surgery (yes or no). Vital status was defined as alive, dead or unknown. Follow-up time for vital status was defined as time in days from diagnosis until death or end of follow-up.

2.4. Statistical Analysis

All analyses were performed in R statistics version 3.3.3 using the prodlim, survival and relsurv packages. Pearson X^2 test was used to compare proportional differences of tumor and treatment characteristics between the cohorts. Kaplan-Meier estimates of overall survival were calculated for each cohort. Univariate and multivariable Cox Proportional Hazards models were used to compare overall survival between the cohorts. The following potential confounders were considered clinically relevant and added in the model: year of diagnosis, tumor stage, tumor grade, morphology and ER status. Ten-year relative survival for each cohort was estimated using the Pohar-Perme method [12]. National life tables from The Human Mortality Database were used to estimate expected survival [13]. To model the effect of covariates on relative survival an additive hazard model was employed. The effect of covariates on the excess hazard was estimated using the expectation-maximisation method [14]. Estimates of the covariates are expressed as relative excess risk of death (RER) and they quantify the relative cancer related excess mortality between the categories of the included covariates in the model [15]. The multivariable model included the confounders as mentioned above.

2.5. Additional Analysis

A sensitivity analysis was performed to assess the impact of variation in time periods between the cohorts on treatment and survival outcomes by only including the years with data available from both cohorts (1997 until 2004). To assess variation over time in local therapy in the UK, local therapy was calculated in two time periods (1990–1999 and 2000–2010).

2.6. Ethics Approval

For the FOCUS cohort anonymised data was provided from the Dutch Cancer Registry. Therefore, informed consent from patients or ethical approval was not required for this study. The Nottingham cohort as a study was part of an ongoing research program approved by local research ethics committee.

3. Results

3.1. Patient Outcomes

In total, 3619 patients were included in the analyses (Fig. 1). Included from the FOCUS cohort were 2180 patients (60.2%), with a median age of 78.1 years (interquartile range (IQR) 73.6–83.6 years) and a median follow-up of 12.4 years (IQR 11.0–14.0). The 1439 patients (39.7%) included from the Nottingham cohort had a median age of 77.9 years (IQR 74.3–82.6 years) and a shorter median follow-up of 6.4 years (IQR 6.2–6.8) compared to the FOCUS cohort patients.

Patient and tumor characteristics for each cohort are presented in Table 1. Patients from the FOCUS cohort were more often diagnosed with a lower T-stage. The Nottingham cohort contains more unknown data on n-stage and morphology due to a lower percentage of Nottingham cohort patients undergoing surgery.

3.2. Treatment Outcomes

Proportions of primary treatment strategies are represented in Fig. 2 and Supplementary Table 1. For patients of the Nottingham cohort primary endocrine therapy (PET) was the predominant primary treatment (50.0%), followed by breast surgery (47.8%), namely mastectomy (31.1%) and BCS (16.7%). Patients from the FOCUS cohort were far less likely to receive PET as a primary treatment (7.5%); predominant primary treatment in the FOCUS cohort consisted of breast surgery (90.5%), with 60.4% of patients undergoing mastectomy and 30.1% of patients undergoing BCS ($P < 0.001$).

Adjuvant treatment strategies for patients that underwent breast surgery (mastectomy or BCS) are shown in Fig. 3. Axillary surgery was more often performed in patients in the FOCUS cohort compared to

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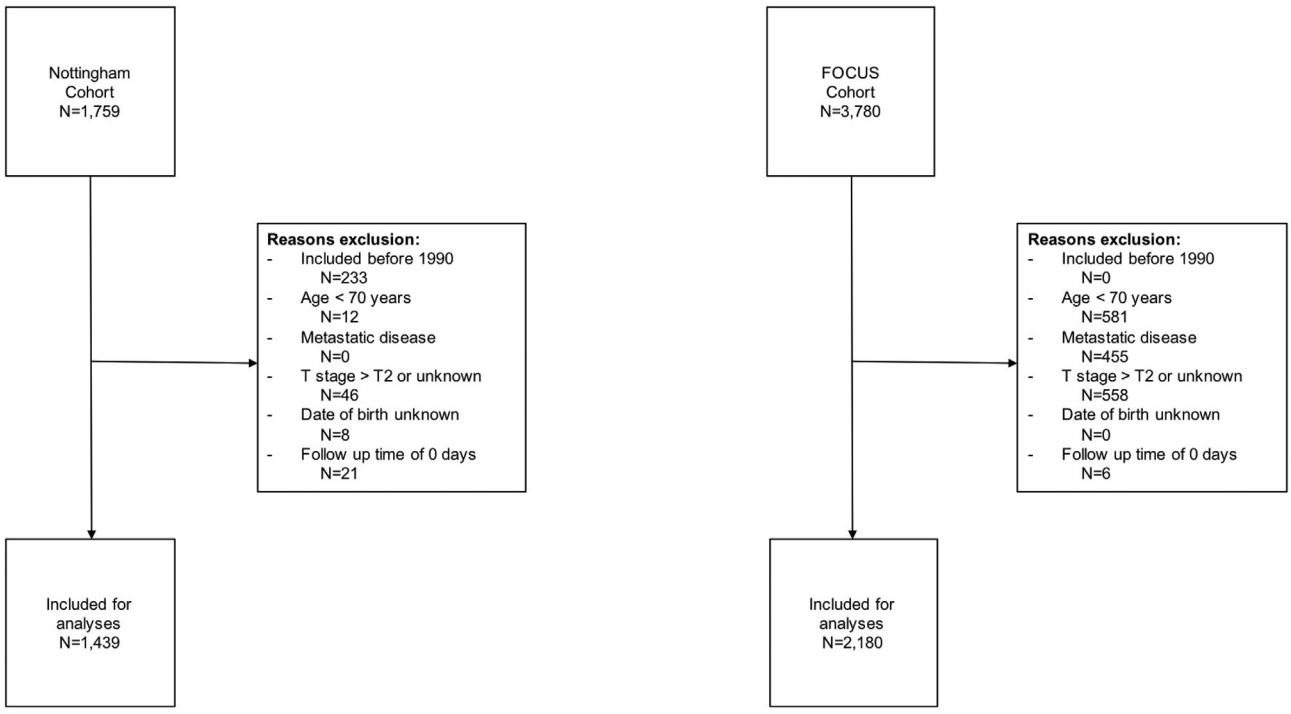

Fig. 1. Flowchart of patient inclusion.

the Nottingham cohort (82.3% vs 71.4%, $P < 0.001$). This was also observed for adjuvant chemotherapy (2.4% vs 0.3%, $P < 0.001$) and adjuvant radiotherapy (38.2% vs 23.4%, $P < 0.001$). There is a larger difference in adjuvant radiotherapy for patients that underwent BCS (80.5% vs 36.9%, $P < 0.001$). However, in the Nottingham cohort 25.7% of data on radiotherapy was unknown. Adjuvant endocrine therapy was provided more often to patients in the Nottingham cohort (40.2% vs 52.4%, $P < 0.001$).

3.3. Survival Outcomes

As shown in Table 2, 1534 of 2180 patients died during follow-up in the FOCUS cohort and 668 of 1439 patients died in the Nottingham cohort. Ten-years overall survival was 39.4% (95% confidence interval (CI) 37.4–41.6%) in the FOCUS cohort and 34.3% (95% CI 30.7–38.3) in the Nottingham cohort (Fig. 4). In univariate survival analysis, overall survival was slightly worse for patients of the Nottingham cohort when

Table 1
patient and tumor characteristics per cohort.

	FOCUS (NL) $N = 2180$		Nottingham (UK) $N = 1439$		*P*-value
Age in years. Median (IQR)	78 (74–84)		78 (74–83)		0.69
	FOCUS (NL) $N = 2180$		Nottingham (UK) $N = 1439$		*P*-value
	N	%	*N*	%	
T-stage					<0.001
0	160	7.3	20	1.4	
T_1	1008	46.2	496	34.5	
T_2	1012	46.4	923	64.1	
N-stage					<0.001
N_0	1415	64.9	311	21.6	
N_1	598	27.4	150	10.4	
N_2/N_3	48	2.2	58	4.0	
Unknown	119	5.5	920	63.9	
Tumor grade					0.02
1	293	13.4	160	11.1	
2	655	30.0	473	32.9	
3	451	20.7	331	23.0	
Unknown	781	35.8	475	33.0	
Oestrogen receptor status					<0.001
Positive	1361	62.4	1061	66.9	
Negative	336	15.4	239	16.6	
Unknown	483	22.2	139	9.7	
Morphology					<0.001
Ductal	1594	73.1	1047	72.8	
Lobular	190	8.7	65	5.2	
Other/unknown	396	18.2	317	22.0	

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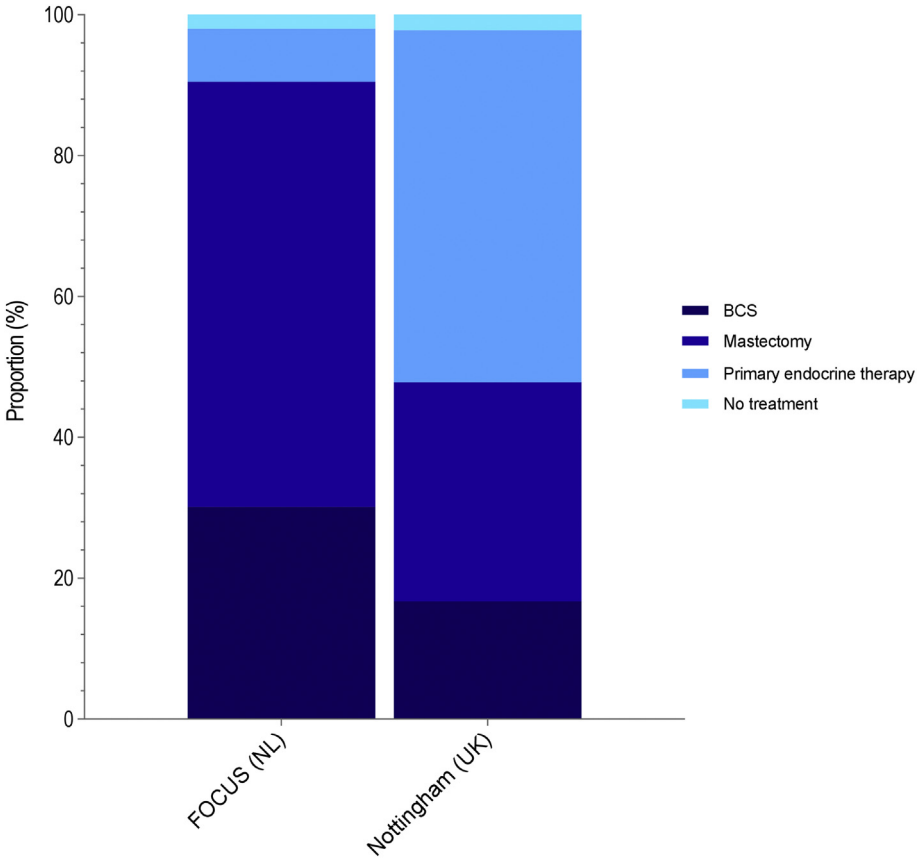

Fig. 2. Treatment strategies per cohort.

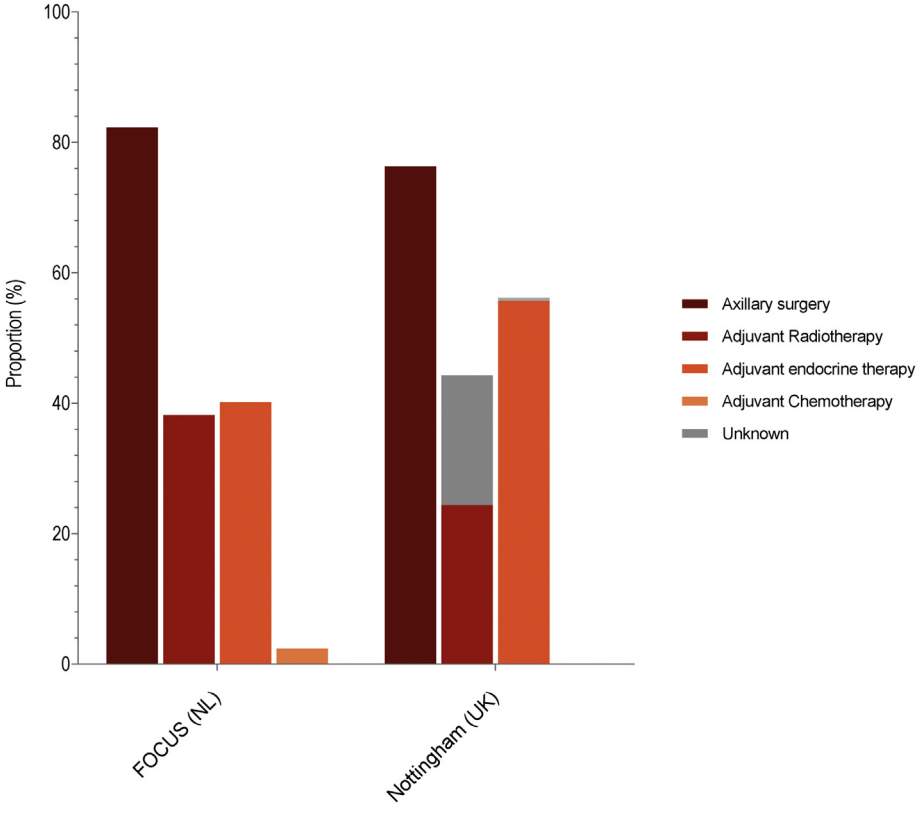

Fig. 3. Adjuvant therapy for patients undergone surgery.

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Table 2
Univariate and multivariable analysis of overall survival.

	Number of events/number at risk	Univariate			Multivariable[a]		
		Hazard ratio	95% CI	*P*-value	Hazard ratio[a]	95% CI	*P*-value
FOCUS (NL)	1534/2176	1.00			1.00		
Nottingham (UK)	668/1439	1.09	0.99–1.94	0.078	0.97	0.87–1.08	0.559

[a] Adjusted for the following confounders: age, year of diagnosis, tumor stage, tumor grade, morphology and ER status.

compared to the FOCUS cohort (hazard ratio (HR) 1.09, 95% CI 0.99–1.19, $P = 0.078$). When taking into account the possible confounders no difference was observed (HR 0.97, 95% CI 0.87–1.08, $P = 0.559$).

Ten-year relative survival analysis for each cohort is presented in Table 3. Ten-year relative survival was 82.5% (95% CI 75.6–90.1) in the FOCUS cohort and 77.6% (95% CI 66.4–90.7) in the Nottingham cohort. The relative excess risk (RER) of death for patients in the Nottingham cohort compared to patients in the FOCUS cohort was 1.87 (95% CI 1.33–2.62, $P < 0.001$). A multivariable analysis confirmed a higher risk of dying due to breast cancer for patients of the Nottingham cohort (RER 1.67, 95% CI 1.21–2.29, $P = 0.002$).

3.4. Additional Analyses

The sensitivity analysis performed for the period 1997–2004 showed little differences for the treatment strategies for the Nottingham cohort for this period compared to treatment strategies over the whole inclusion period of this cohort (Supplementary Table 2). PET has consistently been an often used standard primary treatment over time in the Nottingham cohort; PET was the primary treatment strategy for 60.1% of patients in the period 1990–1999 and 41.7% of patients in 2000–2010 (Supplementary Fig. 1).

In contrast to the main analysis, overall survival was comparable between both cohorts for the period 1997–2004 in univariate regression analysis (HR 1.06, 95% CI 0.95–1.20, $P = 0.25$, Supplementary Table 3). Consistent with the main analysis no significant difference was found in overall survival between the two cohorts for the period 1997–2004 in multivariable regression analysis (HR 1.05, 95% CI 0.94–1.18, $P = 0.39$, Supplementary Table 3). Relative survival analysis of this period showed a relative ten-year survival of 72.6% (95% CI 57.9–91.1) for the Nottingham cohort, which is slightly lower compared to the ten-year survival found over the whole inclusion period. Consequently, excess risk of death (RER) was higher compared to the findings from the main analysis between the cohorts (univariate RER 2.28, 95% CI 1.68–3.10, $P < 0.001$; multivariable RER 2.04, 95% CI 1.52–2.75, $P < 0.001$, Supplementary Table 4).

4. Discussion

In this study, we observed significant differences between the FOCUS cohort and the Nottingham cohort in treatment and relative

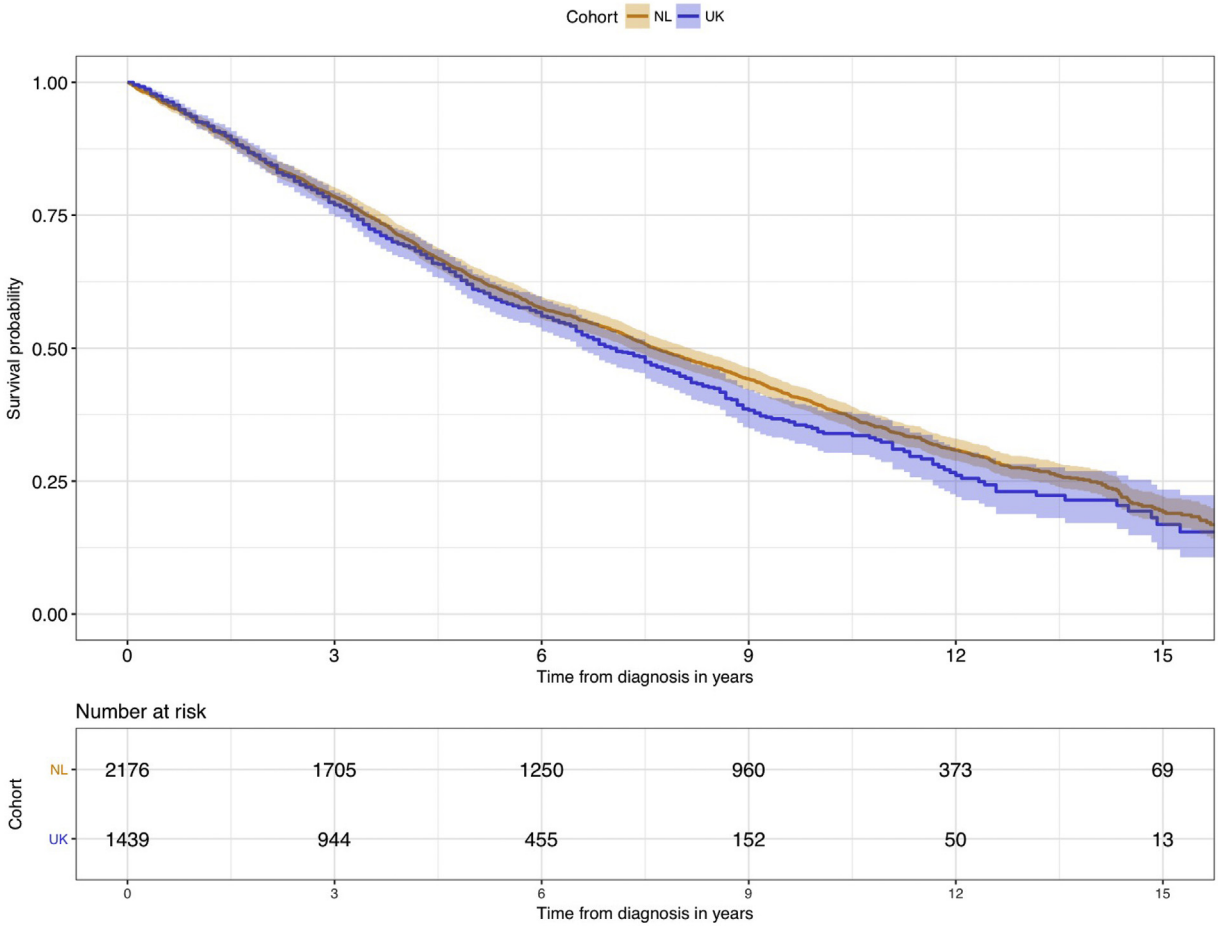

Fig. 4. Overall survival per cohort.

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Table 3
Univariate and multivariable analysis of relative survival.

	Relative survival ten year after diagnosis (95% CI)	Univariate			Multivariable[a]		
		RER	95% CI	*P*-value	RER[a]	95% CI	*P*-value
FOCUS (NL)	82.5 (75.6–90.1)	1.00			1.00		
Nottingham (UK)	77.6 (66.4–90.7)	1.87	1.33–2.62	<0.001	1.66	1.21–2.29	0.002

[a] Adjusted for the following confounders: age, year of diagnosis, tumor stage, tumor grade, morphology and ER status.

survival of women aged 70 years and older diagnosed with early stage breast cancer. The study shows that patients included in the FOCUS cohort were more likely to be diagnosed with a T0 or T1 stage than their Nottingham counterparts. We observed substantial variation in primary treatment strategies between the two regions: PET was far more likely to be received by patients included in the Nottingham cohort, while breast surgery was preferred primary treatment option for patients of the FOCUS cohort. Ten-year overall survival was similar between cohorts after adjustment for potential confounders. Ten-year relative survival was significantly lower in Nottingham patients compared to FOCUS patients, even after adjustment for the confounders.

Variation in tumor size at time of diagnosis could possibly be explained by variation in population-based screening practices between the Netherlands and the UK, specifically England. The upper age limit for participation in the NHS Breast Screening Programme was 64 until the screening policy changed in 2001, with the age limit extending to include women aged 65–70. In the Netherlands screening was provided till the age of 69 until 1998, when the upper age limit was extended to 75 years [16]. Variation in tumor size could also be caused by patient delay due to variation in breast cancer awareness between the two countries.

PET was the predominant primary treatment option in the Nottingham cohort and was used for a far smaller proportion of patients in the FOCUS cohort. This finding corresponds to the results found in previous studies including smaller cohort studies, cancer registry findings and a UK breast surgeon survey on treatment of older patients [17–20]. Growing evidence suggest poor locoregional control with PET: systemic literature review of randomised controlled trials and non-randomised studies has shown benefits for surgery over PET in treatment of older patients in improving disease control and a probable survival benefit in patients with a life expectancy of five years or more [21,22]. It is therefore that the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) only recommend PET for patients with a life expectancy of <2 years, or those patients considered unfit for surgery or refuse surgery [2]. It is questionable whether this was the case for all patients receiving PET in these cohorts. The wide use of PET in the Nottingham cohort was mostly historical given the availability of evidence at the time – in fact Nottingham was the centre of two historical randomised controlled trials comparing PET with surgery, out of a total of seven such trials conducted at the time, as reported in a Cochrane review [23–25]. From 2000, with the introduction of a combined surgical/oncology clinic for assessment taking into account of biology, frailty and patient choice, 41.7% of the patients received PET as opposed to 60.1% in the 1990–1999 period (Supplementary Fig. 1).

Further differences were observed in adjuvant treatment strategies, but that could also explain poorer relative survival in the Nottingham cohort. Axillary surgery and adjuvant radiotherapy were more often observed in the FOCUS cohort; however these differences were smaller when only taking into account the same periods of inclusion (Supplementary Table 2). Adjuvant endocrine therapy was used more often in the Nottingham cohort. The amount of patients receiving adjuvant chemotherapy was small in both cohorts. The proportion of no administration of primary treatment whatsoever was similar. For patients who had undergone surgery, the ratio of BCS and mastectomy surgery was fairly similar between cohorts.

Relative survival was significantly worse for patients in the Nottingham cohort compared to those in the FOCUS cohort. This is in line with findings of the EUROCARE-5 and EURECCA studies, which reported large variation in survival outcomes between European countries. They reported a worse relative survival rates in the UK compared to most other Western European countries, including the Netherlands [20,26]. One of the explanations named by the EUROCARE-5 study as an explanation for lower survival rates in the UK is more advanced stage of disease at diagnosis, as a result of late detection. Indeed, we observed larger tumor-stages in the Nottingham cohort compared to the FOCUS cohorts, but relative survival was still significantly worse for the Nottingham cohort after adjustment for confounders including tumor stage. We hypothesize that the differences in relative survival that were found in our observational cohorts could be related to the differences we observed in primary treatment. The frequent use of PET in the Nottingham cohort might have led to worse disease control in these patients and a higher likelihood of death due to breast cancer. Overall survival did not differ significantly between cohorts over the complete follow-up, although the survival curves appear to diverge after six years, with slightly worse overall survival for the Nottingham cohort (Fig. 4).

Aside from treatment strategy, other explanations for the difference in relative survival should be considered. Suboptimal access to healthcare was named in the EUROCARE-5 study as a possible cause of lower relative survival. General health of a country's populations has also been described as an influence on cancer survival [27]. If patients are unfit to undergo surgery, radiotherapy or chemotherapy because of comorbidities unrelated to cancer, cancer survival might be affected. Additionally, socio-economic status has been shown to have a correlation with cancer survival [28]. Unfortunately, comorbidities and information on socio-economic status were not available for patients of these cohorts and could not be compared. Differences in these characteristics might partly explain the choices for different primary treatment strategies between cohorts.

Further limitations of our data include the differences between the populations of our cohorts: the time period for inclusion was broader in the Nottingham cohort. However, sensitivity analyses did not alter the main findings. Furthermore, the data was not complete. Both cohorts had several incomplete tumor and treatment characteristics, specifically the Nottingham cohort had more unknown data on radiotherapy and tumor characteristics due to less histology being performed as a results of a smaller share of patients undergoing surgery. Additionally, the Nottingham cohort is a hospital based registry and this gives way to possible selection bias. It has not been established to what extend the patients who reach this hospital are representative of the general population. Selection bias did not occur in the FOCUS cohort, because it included all consecutive cases of breast cancer in a well-defined region.

In conclusion, this study showed significant differences in treatment strategies, with a higher proportion of patients receiving primary endocrine therapy in a dedicated breast cancer clinic in Nottingham (United Kingdom) compared to western region of the Netherlands. Among many other factors that might influence survival, this might be explained by the higher use of primary endocrine therapy in Nottingham. This study should be seen as an addition to existing literature suggesting primary endocrine therapy is a viable treatment option for a small group of patients with poor life expectancy and it encourages further

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research to continue equalizing survival rates of breast cancer throughout Europe.

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Author Contributions

MD, GJL, KLC, and EB conceived the idea and HS and MD wrote the manuscript. HS, MD and EB performed the analyses. GJL, JP, CvdV, BS, AG and IO contributed to the design of the study and the acquisition of the data. GJL is the principal investigator of the FOCUS cohort. All authors contributed to interpretation of the data and drafting or critically revising the manuscript and gave final approval of the final version to be published.

Disclosures and Conflict of Interest Statements

The authors have declared no conflicts of interest.

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