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BMJ Open Diagnostic pathways for breast cancer in 10 International Cancer Benchmarking Partnership (ICBP) jurisdictions: an international comparative cohort study based on questionnaire and registry data

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ABSTRACT

Objectives A growing body of evidence suggests longer time between symptom onset and start of treatment affects breast cancer prognosis. To explore this association, the International Cancer Benchmarking Partnership Module 4 examined differences in breast cancer diagnostic pathways in 10 jurisdictions across Australia, Canada, Denmark, Norway, Sweden and the UK.

Setting Primary care in 10 jurisdictions.

Participant Data were collated from 3471 women aged >40 diagnosed for the first time with breast cancer and surveyed between 2013 and 2015. Data were supplemented by feedback from their primary care physicians (PCPs), cancer treatment specialists and available registry data.

Primary and secondary outcome measures Patient, primary care, diagnostic and treatment intervals.

Results Overall, 56% of women reported symptoms to primary care, with 66% first noticing lumps or breast changes. PCPs reported 77% presented with symptoms, of whom 81% were urgently referred with suspicion of cancer (ranging from 62% to 92%; Norway and Victoria). Ranges for median patient, primary care and diagnostic intervals (days) for symptomatic patients were 3–29 (Denmark and Sweden), 0–20 (seven jurisdictions and Ontario) and 8–29 (Denmark and Wales). Ranges for median treatment and total intervals (days) for all patients were 15–39 (Norway, Victoria and Manitoba) and 4–78 days (Sweden, Victoria and Ontario). The 10% longest waits ranged between 101 and 209 days (Sweden and Ontario).

Conclusions Large international differences in breast cancer diagnostic pathways exist, suggesting some jurisdictions develop more effective strategies to optimise pathways and reduce time intervals. Targeted awareness interventions could also facilitate more timely diagnosis of breast cancer.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study used an internationally standardised survey methodology to explore and compare key intervals from symptom onset to start of treatment.
- ⇒ Comprehensive data were extracted from state/provincial-level cancer registries and other sources to create as complete a record as possible of patient pathways to diagnosis and treatment.
- ⇒ Minimal recall bias was achieved through triangulation of different data sources and by ensuring that the patients received the questionnaire with a limited time window after the cancer diagnosis.
- ⇒ Some jurisdictions were not able to recruit a sufficient number of patients to meet power requirements.
- ⇒ The cohort is not representative of all patients with breast cancer as there was high self-selection of patients with early-stage breast cancer.

INTRODUCTION

Breast cancer is the most common cancer among women in Western countries. The incidence of female breast cancer is around 80 per 100 000 (standardised world population); by the age of 80, approximately 12% of women will have received a breast cancer diagnosis.¹ Although the prognosis of breast cancer has improved dramatically in recent decades,² there are still important differences in disease-specific mortality and survival, both between and within countries.^{3,4} For example, in 2010–2014, the 5-year net survival varied from 85.6% in the UK to 88.8% in Sweden and 89.5% in Australia.²

Box 1 Routes to diagnosis

- ⇒ Screening.
- ⇒ Symptomatic.
 - ⇒ Visit PCP.
 - ⇒ Visit PCP and then A&E department.
 - ⇒ Direct to A&E.
 - ⇒ Investigation for another problem.
- ⇒ Other/unknown routes to diagnosis.

A&E, accident and emergency; PCP, primary care physician.

Differences in survival may relate to timely cancer diagnosis and access to optimal treatment and can also affect patient experience and healthcare costs.^{5–10} Examining international differences in routes to diagnosis and treatment, together with time intervals from first noticing symptoms until start of treatment, may help explain these differences.

Women differ in their help-seeking behaviours for breast cancer symptoms.¹¹ These behaviours might influence the time interval between first noticing symptoms until they present to a healthcare professional.¹² Further, the organisational features of a healthcare system might affect the way patients seek help, how healthcare professionals respond to these symptoms, and when and how they can refer for further investigations.^{13–16} In some countries, breast cancer diagnosis is standardised or expedited with urgent referrals, where significant breast cancer-specific ‘red flag symptoms’ are present; further, many countries have now implemented breast cancer screening programmes.¹⁷ Therefore, routes to diagnosis and time intervals from first noticing symptoms to breast cancer diagnosis and treatment may vary between countries. This has consequences on patient outcomes and experience, as well as healthcare costs.

To date almost all studies on breast cancer routes to diagnosis have been based within a single country¹⁸; international comparisons can shed light on factors which underpin the observed differences. Accordingly, in this paper we explore pathways to diagnosis and treatment

Box 2 Time intervals

- ⇒ First onset of symptoms: the timepoint when first bodily changes and/or symptoms were first noticed by the patient.
- ⇒ First presentation to healthcare: the timepoint at which the PCP noted a symptom that in retrospect could be due to the underlying cancer.
- ⇒ First referral to secondary care: the timepoint at which the PCP referred the patient (and responsibility) to secondary/specialist care.
- ⇒ Date of diagnosis, following the International Agency for Research on Cancer definition.²¹
- ⇒ Date of treatment start: when the patient started curative/palliative treatment (in Manitoba, only curative treatment was registered).

PCP, primary care physician.

for female breast cancer in 10 jurisdictions across six countries.

METHODS

We undertook an international comparative cohort study based on questionnaire and registry data on female patients aged 40 or over with first-time, newly diagnosed breast cancer.

Study context and management

Within the International Cancer Benchmarking Partnership (ICBP), Module 4 aims to explore differences in routes to diagnosis for four cancers; the methods used are described in detail elsewhere.^{19 20} Briefly, the study was undertaken in 10 jurisdictions across six countries: Australia (Victoria), Canada (Manitoba and Ontario), Denmark, Norway, Sweden and the UK (England, Northern Ireland, Scotland and Wales). We recruited jurisdictions with universal healthcare access (with coverage including breast cancer investigations and screening programmes) and showing variation in breast cancer survival.²⁰

Identification of study population

Eligible patients were women aged 40 years or more with a first diagnosis of invasive breast cancer (International Classification of Diseases 10th Revision (ICD-10) codes C50.0–C50.9), irrespective of symptomatic or screen-based diagnosis. Women with previous diagnoses of other cancers were included, but those with a previous diagnosis of breast cancer or synchronous breast cancer were excluded.

Participants were identified via cancer registries and hospital databases, although processes varied locally. Processes were tested in each jurisdiction to ensure adaptation of data collection, questionnaire logistics and data management to the local settings.²⁰ Each jurisdiction aimed to recruit 200 symptomatic patients with breast cancer, irrespective of the number of screen-based diagnoses. In Ontario and Victoria, the sampling continued beyond 200 patients for use in local studies. In Northern Ireland, the majority of screen-detected women were excluded at the sampling stage by the cancer registry.

Patient and public involvement

The development of the research question, the questionnaire and the presentation was done in collaboration with patient representatives and cancer charities. Both in the jurisdictions where it was developed, the questionnaire was evaluated and validated among patients and general practitioners and as part of the collaborative work in the ICBP. Patients were involved in the design of how to approach a person with a new cancer diagnosis. The results of this study will be disseminated through the various cancer charities in each jurisdiction.

Data sources

Data were collected primarily from three questionnaires sent to eligible women (online supplemental additional

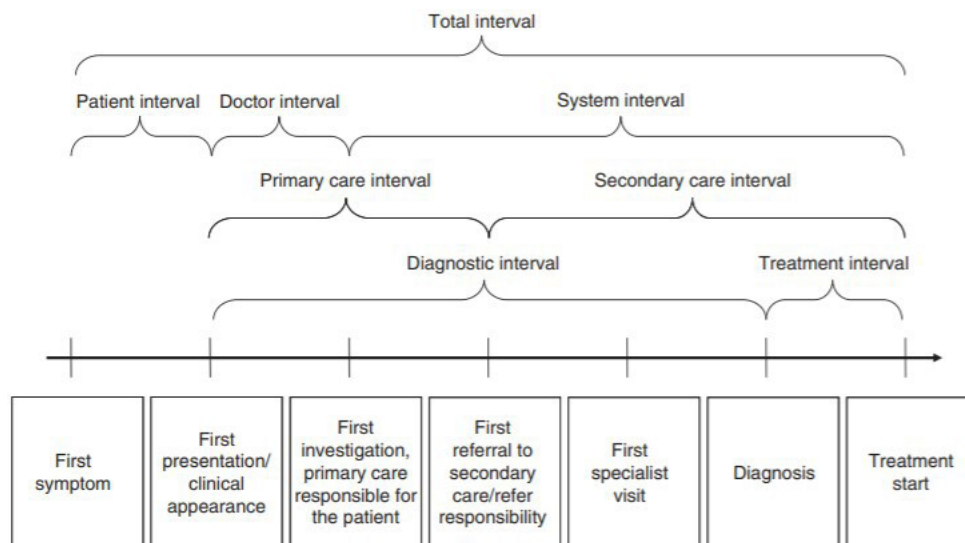


Figure 1 Diagnostic and treatment intervals.²³

file 1), their primary care physician (PCP; Online supplemental additional file 2) and their cancer treatment specialists (CTS; Online supplemental additional file 3). This was supplemented with registry data (including diagnosis date, tumour stage and screening) in all jurisdictions except Ontario and Norway.¹⁹ Data were anonymised prior to transfer to Aarhus University (Denmark) for analysis.

Questionnaire and registry data

The validated questionnaires included items on routes to diagnosis, symptoms, specific milestones from first noticing symptoms to starting treatment, and patient sociodemographics and comorbidity.²⁰ Eligible patients were identified from cancer registries, and patients were either contacted directly or via their PCP.

Women were sent questionnaires 3–9 months after diagnosis; PCPs and CTS were sent questionnaires after patients consented to participate in the study. Completed questionnaires were returned to the local research teams. Where possible, registries and disease databases provided additional checks and information on date of diagnosis, screening status and start of treatment. Date of diagnosis was based on the International Agency for Research on Cancer hierarchy, and tumour stage using the tumour, node, metastasis classification.^{21 22}

Data handling

Curation of questionnaire data was undertaken primarily at a single location (Aarhus University, Denmark) to ensure uniform application across jurisdictions.

A set of algorithms (or ‘rules’) to standardise the validation and combination of data from the different sources was developed (online supplemental additional file 4); they employed a hierarchy principle with regard to the order in which different data sources were used. Any queries were discussed and resolved with the study team.

Routes to diagnosis

Differences in the diagnostic routes were investigated drawing on the checklist from the Aarhus statement.²³ Routes to diagnosis are outlined in [Box 1](#).

Measures of time intervals

Time interval definitions were adapted from the Aarhus statement and included the timepoints outlined in [Box 2](#)²³; the intervals are represented graphically in [figure 1](#).

For screen-detected women, we used the date of the screening test as the start of the diagnostic and total interval measurements. The analyses included intervals for both symptomatic patients with screen-detected breast cancer and all patients with breast cancer. We included a categorical variable where the symptomatic women reported the waiting time for their appointment with the PCP. Cancers were only considered to be screen-detected if the woman or the PCP had indicated a screening route and there were no symptoms nor symptomatic pathway reported. For Wales, England, Scotland, Northern Ireland, Denmark, Manitoba and Sweden, the distinction between a screen-detected and a non-screen-detected breast cancer was based on registry data from public screening programmes ([table 1](#)).

Covariates

General health status was measured using the self-reported general health item from the 12-Item Short Form Health Survey.²⁴ Comorbidity was assessed through the patient questionnaire as presence of any of four chronic diseases (heart or lung diseases, stroke, or diabetes) and categorised into ‘none’, ‘medium’ (one or two) or ‘high’ (three or four). Educational level (from the patient questionnaire) was categorised as ‘low’ (vocational school or lower) and ‘high’ (university or higher). Smoking was categorised into ‘current’, ‘past’ or ‘never’ smoker. Symptoms reported by the PCP were divided into



Table 1 Characteristics of 3471 women (aged 40+) with a first diagnosis of breast cancer (% if nothing else stated)

	Wales (n=232)	England (n=363)	Scotland (n=371)	Northern Ireland (n=331)				Denmark (n=369)	Ontario (n=403)	Norway (n=372)	Manitoba (n=368)	Victoria (n=370)	Sweden (n=292)	Total (N=3471)
Age (years), median (IQR)	63 (53–70)	63 (53–70)	63 (54–70)	60 (51–70)	64 (55–71)	63 (55–69)	61 (52–69)	63 (55–72)	58 (50–67)	63 (54–71)	62 (53–70)	62 (53–70)	62 (53–70)	
Age (years) (symptomatic women), median (IQR)	(n=115) 62 (49–76)	(n=207) 62 (50–75)	(n=208) 62 (52–75)	(n=242) 60 (49–72)	(n=231) 68 (54–77)	(n=201) 61 (53–69)	(n=235) 61 (50–73)	(n=205) 62 (50–75)	(n=198) 56 (48–68)	(n=120) 68 (54–77)	(n=1962) 62 (50–74)	(n=1962) 62 (50–74)	(n=1962) 62 (50–74)	
Age (years) (screen-detected women), median (IQR)	(n=116) 63 (58–68)	(n=155) 64 (58–68)	(n=162) 63 (58–67)	(n=86) 60 (54–67)	(n=134) 62 (56–66)	(n=198) 65 (59–69)	(n=132) 62 (57–67)	(n=162) 65 (59–70)	(n=172) 61 (53–67)	(n=171) 61 (54–69)	(n=1488) 63 (57–68)	(n=1488) 63 (57–68)	(n=1488) 63 (57–68)	
Health state														
Good	81.0	81.0	79.3	77.7	78.1	90.3	74.7	85.6	88.4	80.8	81.8	81.8	81.8	
Fair	14.7	13.0	13.7	14.2	14.6	8.2	17.5	9.2	9.5	12.3	12.6	12.6	12.6	
Poor	3.5	4.7	5.1	5.4	3.5	1	6.2	2.7	1.6	3.8	3.7	3.7	3.7	
Missing	0.9	1.3	1.9	2.7	3.8	0.5	1.6	2.5	0.5	3.1	1.9	3.1	1.9	
Comorbidity*														
No	74.1	75.1	69.0	78.6	62.9	61.3	73.9	70.4	76.5	80.5	71.8	80.5	71.8	
Medium	24.6	23.1	29.4	19.9	34.1	25.1	23.7	27.7	23.2	16.1	25.0	16.1	25.0	
High	0.9	0.8	1.1	0.9	0.8	0.0	1.1	0.5	0.0	0.3	0.6	0.3	0.6	
Missing	0.4	0.8	0.5	0.6	2.2	13.6	1.3	1.4	0.3	3.1	2.6	3.1	2.6	
Education														
Low	71.6	78.2	69.0	77.0	71.8	64.3	63.7	74.7	70.0	68.8	70.8	68.8	70.8	
High	22.4	14.9	19.7	16.3	14.6	33.5	31.5	19.8	28.9	28.8	23.1	28.8	23.1	
Missing	6.0	6.9	11.3	6.7	13.6	2.2	4.8	5.4	1.1	2.4	6.1	2.4	6.1	
Ethnicity														
White	97.9	97.8	98.9	99.1	94.3	89.9	98.7	85.6	97.3	96.2	95.4	96.2	95.4	
Asian	0.4	1.1	0.0	0.0	1.1	5.7	0.8	7.6	1.9	1.0	2.1	1.0	2.1	
Black	0.4	0.8	0.3	0.0	0.0	2.0	0.0	0.5	0.0	0.0	0.4	0.0	0.4	
Other	0.0	0.0	0.0	0.0	0.0	1.2	0.0	6.0	0.0	0.0	0.8	0.0	0.8	
Missing	1.3	0.3	0.8	0.9	4.6	1.2	0.5	0.3	0.8	2.8	1.3	2.8	1.3	
Smoking														
Currently	7.3	7.2	8.4	11.8	15.2	4.0	15.1	7.9	5.7	19.6	9.2	19.6	9.2	
In the past	35.3	38.0	41.2	33.2	41.7	43.9	40.9	44.6	36.7	41.1	39.9	41.1	39.9	
Never	56.5	54.5	49.3	53.5	40.9	51.6	43.5	46.2	57.3	46.9	49.8	46.9	49.8	
Missing	0.9	0.3	1.1	1.5	2.2	0.5	0.5	1.3	0.3	2.4	1.1	2.4	1.1	
Tumour stage (TNM) (all women)														
0	1.7	0.6	0.0	0.0	0.3	0.3	0.0	0.0	0.3	0.0	0.3	0.0	0.3	

Continued

Table 1 Continued

	Wales (n=232)	England (n=363)	Scotland (n=371)	Northern Ireland (n=331)	Denmark (n=369)	Ontario (n=403)	Norway (n=372)	Manitoba (n=368)	Victoria (n=370)	Sweden (n=292)	Total (N=3471)
I	50.4	44.9	47.4	45.3	45.0	51.6	11.3	50.8	52.7	62.0	45.7
II	37.9	36.4	35.6	35.1	33.1	38.0	4.6	34.5	34.6	31.5	31.9
III	5.6	8.3	7.8	13.6	9.5	8.2	1.9	10.3	10.8	4.1	8.1
IV	0.9	3.0	4.6	2.7	2.4	1.0	0.8	1.6	1.1	0.7	1.9
Missing	3.5	6.9	4.5	3.3	9.8	1.0	81.5	2.7	0.5	1.7	12.1
Tumour stage (TNM) (symptomatic women)	(n=115)	(n=207)	(n=208)	(n=242)	(n=231)	(n=201)	(n=235)	(n=205)	(n=198)	(n=120)	(n=1966)
0	1.7	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.3
I	33.0	34.8	32.7	37.2	36.4	32.8	8.1	32.7	37.9	40.8	32.1
II	49.6	41.6	45.7	39.3	35.1	50.0	5.5	48.3	44.4	50.8	39.5
III	8.7	10.6	9.6	17.4	11.7	14.0	2.6	13.2	15.2	3.3	11.0
IV	1.7	4.4	6.7	2.9	3.9	2.0	0.9	2.4	1.0	1.7	2.9
Missing	5.2	7.7	5.3	3.3	13.0	0.5	83.0	3.4	1.0	3.3	14.3
Tumour stage (TNM) (screen-detected women)	(n=116)	(n=155)	(n=162)	(n=86)	(n=134)	(n=198)	(n=132)	(n=162)	(n=172)	(n=171)	(n=1484)
0	1.7	0.0	0.0	0.0	0.8	0.5	0.0	0.0	0.0	0.0	0.3
I	68.1	58.1	66.1	67.4	59.7	69.2	16.7	74.1	69.8	77.2	63.5
II	25.9	29.7	22.8	23.3	29.1	26.3	2.3	17.3	23.3	18.1	21.9
III	2.6	5.2	5.6	3.5	6.0	2.5	0.8	6.8	5.8	4.1	4.4
IV	0.0	1.3	1.9	2.3	0.0	0.0	0.0	0.6	1.2	0.0	0.7
Missing	1.7	5.8	3.7	3.5	4.5	1.5	80.3	1.2	0.0	0.6	9.3

Norwegian data on tumour stage were incomplete, resulting in a high number of missing data on stage.

*Comorbidity coded as none: none reported; medium: 1–2 reported; and high: 3+ reported. IQI, interquartile interval; TNM, tumour, node, metastasis.

Table 2 Proportion of screen-detected or symptomatic patients (%) and place of initial symptomatic presentation across jurisdictions

	Wales (n=232)	England (n=363)	Scotland (n=371)	Northern Ireland* (n=331)	Denmark (n=369)	Ontario (n=403)	Norway (n=373)	Manitoba (n=368)	Victoria (n=370)	Sweden (n=292)	Total (N=3471)
Symptomatic	49.6	57.0	56.1	73.1	62.6	49.9	63.2	55.7	53.5	41.1	56.5
Visit PCP, visit PCP and then A&E†	91.3	93.7	92.3	88.0	84.4	69.2	81.3	88.3	90.9	75.0	85.6
A&E directly‡	1.7	1.0	0.5	0.4	1.3	2.5	0.9	1.0	0.5	0.8	1.0
Investigation for another problem†	0.9	1.0	4.8	1.2	6.1	7.5	4.7	2.4	1.5	10.0	3.9
Other†	6.1	4.3	2.4	10.3	8.2	20.9	13.2	8.3	7.1	14.2	9.5
Screening	50.0	42.7	43.7	26.0	36.3	49.1	35.5	44.0	46.5	58.6	42.9
Other	0.4	0.3	0.3	0.9	1.1	1.0	1.2	0.3	0.0	0.3	0.6

*In Northern Ireland, the proportion of screen-detected breast cancers was lower as many of these women were excluded from the eligible group at the start of inclusion.

†Percentage of the symptomatic route.

‡A&E, accident and emergency; PCP, primary care physician.

‘breast cancer specific symptoms’ or ‘other symptoms’. This was based on symptom coding, drawing on local clinical guidelines.^{17 24 25}

Statistical analysis

Patients with missing data on age, date of diagnosis and/or date of consent were excluded. Quantile regression²⁶ was used to estimate the differences in intervals at the 50th, 75th and 90th percentiles between all jurisdictions, with Wales as the reference. Intervals were derived by counting days, using the ‘qcount’ procedure.^{27 28} The differences in intervals were calculated as marginal effects after quantile regression by setting the continuous covariates to their mean values and the categorical covariates to their modes.

Due to zero inflation, quantile regression could not be used for the primary care interval. Here a generalised linear model with Poisson family, log link and robust error variance was used to calculate the association based on prevalence ratio, between longer primary care intervals and jurisdiction. Longer intervals were defined as those over 5 or 14 days to test both intervals. The analyses were adjusted for age (as a continuous variable) and comorbidity (as a categorical variable). The significance level was set to 0.05 or less, and 95% CIs were calculated when appropriate. Statistical analyses were carried out using STATA V.14 software.

Sensitivity and validity analyses

Analyses were repeated using the per-protocol definition of a maximum of 6 months between diagnosis and patient consent, to assess the impact of including patients who consented at 9 months postdiagnosis. To estimate the effect of using patient-reported intervals only, a sensitivity analysis based solely on patient questionnaire data was performed.

Kappa coefficients were used to assess the agreement on routes to diagnosis (screening and symptomatic presentation) between the different data sources. Lin’s concordance correlation coefficient (CCC) was used to assess the agreement on dates between the different data sources.²⁹

RESULTS

Patient characteristics and participation

Across all jurisdictions, 15 421 eligible women were identified between May 2013 and August 2015. A total of 4593 (39.9%) of those contacted returned completed questionnaires, of which 3471 (75.6%) were included in the analyses. The patient flow, with identification, exclusion and responses for each jurisdiction, is detailed in online supplemental additional file 4. The response rates ranged from 24.1% in Norway to 77.9% in Denmark (online supplemental table 1). Participating women were younger and had a less advanced tumour stage distribution than the total sample of women eligible for inclusion (online

Table 3 The first symptoms reported by women* and the first presenting symptoms reported by PCPs (%)

	Northern Ireland*										Total (N=1962)
	Wales (n=115)	England (n=207)	Scotland (n=208)	Ireland* (n=242)	Denmark (n=231)	Ontario (n=201)	Norway (n=235)	Manitoba (n=205)	Victoria (n=198)	Sweden† (n=120)	
First symptom (reported by women)	76	70	75	62	63	63	55	60	71	73	66
Lump/swelling/thickening of breast	9	15	11	14	11	10	13	6	6	14	11
Change in the nipple	16	10	9	12	5	17	11	12	14	9	11
Fatigue	12	13	10	10	5	16	8	10	15	11	11
Change in the size and contour	6	5	4	14	3	5	7	9	15	6	8
Pain/tenderness in the breast	5	5	0.5	4	4	0	2	2	0	0.8	2
Flattening/indentation in the breast	21	23	20	17	10	13	18	19	16	12	17
Other	8	2	4	8	11	10	9	17	5	10	8
No symptoms	0	0.4	4	6	10	2	13	4	1	0	5
Missing	(n=97)	(n=169)	(n=160)	(n=0)	(n=153)	(n=74)	(n=109)	(n=123)	(n=128)	(n=0)	(n=1013)
Presenting symptom (reported by PCP)	73	64	64	n/a	67	34	55	46	64	n/a	60
Lump/swelling/thickening of breast	2	8	5	n/a	5	7	5	0.8	6	n/a	5
Change in the nipple	0	0	0	n/a	0	0	0.9	0.8	0	n/a	0.2
Fatigue	4	4	0	n/a	6	0	0.9	3	5	n/a	3
Change in the size and contour	10	6	4	n/a	7	7	4	10	13	n/a	7
Pain/tenderness in the breast	2	2	1	n/a	0	3	2	3	0	n/a	2
Flattening/indentation in the breast	13	12	9	n/a	7	24	13	13	2	n/a	11
Other	1	0.6	0.6	n/a	0.7	11	0	12	2	n/a	3
No symptoms	8	11	17	n/a	18	18	21	24	20	n/a	17
Missing											
Cancer specificity of presenting symptom‡											
Cancer-specific symptom	88	85	79	n/a	78	69	70	59	78	n/a	77
Non-specific symptom	3	3	4	n/a	3	3	9	4	0	n/a	4
No symptoms/missing	9	12	18	n/a	18	28	21	37	22	n/a	20

*These figures represent only women who had a symptom-based cancer diagnosis. More than one symptom could be stated (sum over 100%).

†Sweden and Northern Ireland did not include PCP questionnaire data.

‡Based on the PCP reported symptom/sign and categorised by two researchers. n/a, not applicable; PCP, primary care physician.



Table 4 Time intervals (days) for each jurisdiction depicted as median, 75th and 90th percentiles

	Wales	England	Scotland	Northern Ireland	Denmark	Ontario	Norway	Manitoba	Victoria	Sweden*
Patient interval (symptomatic)	n	111	201	198	219	213	206	172	189	101
	Median	11	7	7	8	3	12	14	7	29
	75th percentile	34	30	30	31	22	48	47	31	56
	90th percentile	73	92	88	114	63	157	86	117	90
Primary care interval (symptomatic)	n	97	167	160	172	141	99	109	142	n/a
	Median	0	0	0	0	0	0	17	7	
	75th percentile	0	0	1	0	0	0	30	15	
	90th percentile	3	7	6	3	10	14	82	38	
Diagnostic interval (symptomatic)	n	111	200	197	216	207	203	184	191	101
	Median	29	12	19	14	8	20	28	13	13
	75th percentile	54	18	35	21	26	37	42	21	24
	90th percentile	92	36	49	49	49	71	79	46	48
Diagnostic interval (screen-detected)	n	113	153	159	86	131	126	125	152	158
	Median	25	15	20	19	24	27	23	21	15
	75th percentile	45	21	29	26	36	44	43	32	25
	90th percentile	58	34	42	41	48	66	113	40	41
Diagnostic interval (all)	n	224	353	356	302	338	329	309	343	259
	Median	29	13	20	15	14	22	26	16	14
	75th percentile	49	21	33	21	31	39	42	28	25
	90th percentile	70	36	48	43	49	68	94	45	41
Treatment interval (symptomatic)	n	115	203	202	241	230	216	198	196	113
	Median	24	29	24	21	20	19	38	14	22
	75th percentile	33	41	37	29	29	27	55	24	29
	90th percentile	45	55	54	40	44	34	72	33	42
Treatment interval (screen-detected)	n	115	155	158	86	134	120	155	170	165
	Median	27	31	34	24	19	13	39	19	21
	75th percentile	36	40	44	35	29	21	51	28	29
	90th percentile	49	62	69	44	36	28	66	38	40
Treatment interval (all)	n	231	359	361	330	368	341	353	366	278
	Median	25	30	29	22	20	15	39	15	22
	75th percentile	35	41	41	31	29	24	54	27	29
	90th percentile	46	57	61	41	41	33	71	36	41

Continued

Table 4 Continued

	Wales	England	Scotland	Northern Ireland	Denmark	Ontario	Norway	Manitoba	Victoria	Sweden*
Total interval (symptomatic)										
n	104	190	186	205	189	173	184	155	177	98
Median	70	57	58	50	42	92	54	92	42	71
75th percentile	96	82	99	78	73	158	121	128	89	101
90th percentile	218	138	149	147	170	273	231	188	170	169
Total interval (all)										
n	217	343	341	291	320	354	298	277	327	253
Median	60	52	55	46	44	78	48	76	42	42
75th percentile	81	70	84	69	68	116	79	116	63	68
90th percentile	123	114	129	127	118	209	168	182	120	101

*In Sweden, data on the primary care interval were not collected. n/a, not applicable.

supplemental additional file 5). The characteristics of the included women are detailed in [table 1](#).

First presentation and symptoms

[Table 2](#) shows the routes to diagnosis; 42.9% had a screen-detected breast cancer, with the highest proportion in Sweden (58.6%) (Note that the proportion of screen-detected cancers in Northern Ireland is lower due to the initial exclusion of screen-detected cancers.). For symptomatic patients, primary care was the place of first presentation for 85.6% of women, ranging from 69.2% in Ontario to 93.7% in England. According to the PCP, 81.1% of symptomatic women were urgently referred with a suspicion of cancer, ranging from 62.4% in Norway to 92.2% in Victoria (data not shown).

[Table 3](#) shows the first symptom or sign reported by women, together with those reported by the PCP (for Sweden, only patient data were collected). Two-thirds of symptomatic women noticed a lump or change in the breast. This was also the most commonly reported sign by PCPs, followed by pain/tenderness and change in the nipple. According to the PCP, 77% of women presented with a symptom or sign indicative of breast cancer. While 1 in 10 women indicated fatigue as a symptom, this was rarely noted by the PCPs.

Time intervals

The median patient interval for symptomatic women varied from 3 days in Denmark to 29 days in Sweden (see [table 4](#)). Based on the quantile regression, patient interval was 7 days shorter in Denmark and 17 days longer in Sweden compared with Wales ([figure 2](#) and online supplemental additional file 6). When comparing the 90th percentile, Norway (157 days) and Ontario (142 days) had the longest patient intervals ([table 4](#)). Quantile regression showed that Norway had a significantly longer patient interval for the 90th percentile compared with Wales (74 days) ([figure 2](#)).

The median primary care interval for symptomatic women (in days) was 0, except in the two Canadian provinces and in Victoria ([table 4](#)). Women in these three jurisdictions had longer primary care intervals (both for >5 and >14 days) than women in Wales; this was statistically significant ([table 5](#)).

The median diagnostic interval for symptomatic women ranged from 8 days in Denmark to 29 days in Wales ([table 4](#)). At the 90th percentile, the diagnostic interval ranged from 36 days in England to 202 days in Ontario ([table 4](#)). Compared with Wales, all jurisdictions except Ontario had shorter diagnostic intervals ([figure 2](#)). For women with a screen-detected breast cancer, the time intervals and pattern were similar, although screen-detected patients had significantly shorter 90th percentiles compared with symptomatic patients.

The median treatment intervals for all women ranged from 15 days in Norway and Victoria to 39 days in Manitoba. Women in England, Scotland, Ontario and Manitoba waited more than 28 days (4 weeks) for treatment after

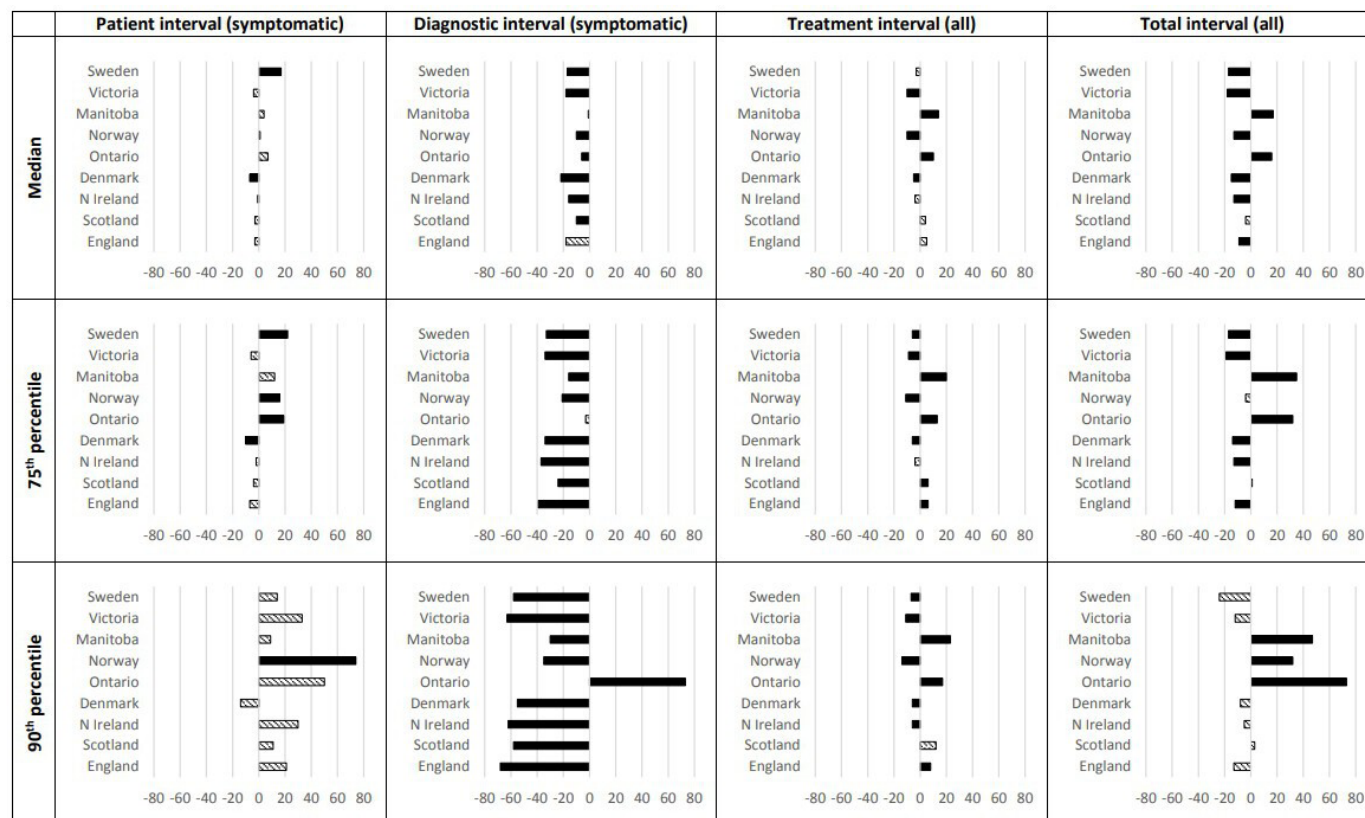


Figure 2 Time intervals for each jurisdiction compared with Wales (reference). Adjusted for differences in comorbidity and age. Differences in interval lengths (in days) are shown for the median, 75th and 90th percentiles compared with the reference used for the regression analyses, Wales. Wales is represented by the axis, with jurisdictions with shorter intervals shown to the left of the axis and jurisdictions with longer intervals shown to the right of the axis for each graph. Solid-fill bars indicate statistically significant differences compared with Wales. Primary care interval is not shown (see table 6).

diagnosis (table 4). Quantile regression showed smaller statistically significant differences in treatment intervals, with Manitoba and Ontario consistently having longer treatment intervals for the three percentiles (figure 2). The treatment intervals were similar for screen-detected cancers.

The median total interval for all women from first symptom or date of screening test to start of treatment ranged from 42 days in Sweden and Victoria to 78 days in Ontario (table 6). In Manitoba and Ontario, 25% of women had a total interval that was 30 days longer compared with Wales (81 days), whereas 25% of women in England, Northern Ireland, Denmark, Victoria and Sweden had a total interval that was between 12 and 19 days shorter compared with Wales (figure 2 and online supplemental additional file 6). In Ontario, 10% of women waited 73 days or more from first presentation until treatment started compared with women in Wales. Including screen-detected breast cancers made the total interval shorter, with less variation between the jurisdictions.

There were differences in the time taken from women deciding to seek help getting an appointment with a PCP. Getting an appointment 'within oneweek' was less often reported by women in Sweden (43%), Manitoba (50%), Ontario (58%) and Northern Ireland (64%) compared with women in other jurisdictions (above 70% in the other six

jurisdictions, with 84% in England and Victoria) (data not shown).

Validity tests

Comparing patient and PCP-reported screening with available screening registry data showed an almost perfect agreement ($\kappa > 0.80$) (online supplemental additional file 7). Comparing the dates between the different data sources showed a high agreement between all data sources (patient, PCP, CTS and register where applicable) for all types of dates (CCC=0.94 for date of first presentation to primary care, CCC ≥ 0.94 for date of diagnosis and CCC=0.93 for date of treatment).

DISCUSSION

Main findings

This international survey of patients with breast cancer diagnosed between 2013 and 2015 revealed that 4 out of 10 were screen-detected and more than half of women presented with symptoms, with the majority of these diagnosed after a visit to primary care. Three-quarters of symptomatic patients had a symptom or sign indicative of breast cancer, and roughly 8 in 10 were urgently referred. Thus, despite the existence of screening programmes,

Table 5 Prevalence ratio (PR)* of experiencing differing primary care intervals for symptomatic patients with breast cancer

	Wales (n=97)	England (n=167)	Scotland (n=160)	Northern Ireland (n=172)	Denmark (n=141)	Ontario (n=70)	Norway (n=99)	Manitoba (n=109)	Victoria (n=142)	Sweden† (n=0)
Interval ≥5 days										
PR (95% CI)	Ref	1.7 (0.7 to 4.2)	2.0 (0.8 to 4.9)	1.3 (0.5 to 3.3)	2.0 (0.8 to 4.8)	12.9 (5.9 to 28.2)	2.2 (0.9 to 5.6)	12.9 (5.9 to 28.1)	11.1 (5.1 to 24.4)	n/a
Interval ≥14 days										
PR (95% CI)	Ref	1.6 (0.5 to 4.9)	1.5 (0.5 to 4.7)	1.4 (0.5 to 4.3)	2.1 (0.7 to 6.3)	15.1 (5.7 to 40.1)	2.4 (0.8 to 7.4)	14.3 (5.4 to 37.8)	6.7 (2.5 to 18.1)	n/a

Bold indicates significance level at $p \leq 0.05$.
 *Adjusted for differences in age and comorbidity among patients, with Wales as reference.
 †In Sweden, no information on primary care interval was collected.
 n/a, not applicable; ref, reference.

the majority still had their breast cancer diagnosed based on ‘red flag’ symptoms.

The median time from women first noticing symptoms to start of treatment varied from 42 to 92 days across jurisdictions; this is attributable mainly to differences after first presentation. Less variation is seen in patient interval across jurisdictions.

We found that in some jurisdictions there is a ‘tail’ of women with excessively long waiting times from first noticing symptoms to presentation to the healthcare system.

Strengths and weaknesses

A major strength is our novel use of a standardised questionnaire survey in several countries to systematically examine routes to diagnosis and treatment. To ensure validity across jurisdictions, we drew on existing instruments and went through an extensive process of cognitive testing, piloting, translation and adaptation.²⁰ Data were enriched with information from national or state/provincial-level cancer registries via our ICBP Module 4 Working Group (online supplemental additional file 8) for screening status, date of diagnosis and tumour stage. We developed algorithms to identify screen-detected cases, place of first presentation and time intervals, which showed good agreement for those jurisdictions where validation was possible. Using registries and undertaking clinical validation of patients with breast cancer ensured minimal selection and information biases. It also made it possible to exclude women who previously had breast cancer, thus providing a reasonably homogeneous group of patients.

We included all patients with a first diagnosis of breast cancer, irrespective of route to diagnosis, and recruited at least 200 symptomatic cases per jurisdiction. We developed and implemented validated rules for identifying the screening route, which showed high agreement with screening registries.

There were different classification systems for ethnicity and education across jurisdictions. We excluded these variables from the regression model to avoid introducing information bias in the model, which would have compromised its validity. Although this likely induced some residual confounding, it is unlikely that educational or ethnic differences could have produced the observed variation in time intervals.

We used a set of rules to ensure validity and consistency and to preserve statistical precision.²⁰ The validity and sensitivity analyses suggested this approach was effective. To minimise misclassification, data interpretation during data entry by the local teams was reduced to an absolute minimum and all apparent data errors were checked against source data by local teams.

The effect of recall bias was minimised by triangulation of data sources (eg, patient, PCP, CTS and registry data) and by ensuring that the women received the questionnaire within a limited time window after diagnosis.

Table 6 Differences in interval lengths (days) between Wales, the reference, and the other nine jurisdictions

	Wales	England	Scotland	Northern Ireland	Denmark	Ontario	Norway	Manitoba	Victoria	Sweden
Patient interval (symptomatic)										
n	111	201	198	219	213	170	206	172	189	101
Median	11 (ref)	-3 (-9, 3)	-3 (-8, 3)	-1 (-8, 6)	-7 (-12, -2)	7 (-1, 16)	1 (-7, 9)	4 (-2, 11)	-4 (-9, 2)	17 (11, 22)
75th percentile	34 (ref)	-7 (-21, 7)	-4 (-12, 3)	-2 (-8, 5)	-10 (-16, -4)	19 (5, 33)	16 (7, 25)	12 (-1, 25)	-6 (-16, 4)	22 (8, 36)
90th percentile	73 (ref)	21 (-19, 61)	11 (-45, 66)	30 (-13, 73)	-14 (-64, 35)	50 (-9, 110)	74 (31, 117)	9 (-35, 54)	33 (-13, 80)	14 (-31, 60)
Diagnostic interval (symptomatic)										
n	111	200	197	216	207	166	203	184	191	101
Median	29 (ref)	-18 (-22, -15)	-10 (-14, -6)	-16 (-19, -13)	-22 (-25, -18)	-6 (-9, -2)	-10 (-15, -5)	-1 (-5, 4)	-18 (-22, -14)	-17 (-23, -12)
75th percentile	54 (ref)	-39 (-45, -33)	-24 (-29, -19)	-37 (-42, -33)	-34 (-40, -28)	-3 (-13, 6)	-21 (-36, -6)	-16 (-23, -8)	-34 (-52, -15)	-33 (-39, -27)
90th percentile	92 (ref)	-68 (-88, -48)	-58 (-91, -25)	-62 (-80, -45)	-55 (-75, -35)	73 (35, 112)	-35 (-62, -8)	-30 (-46, -15)	-63 (-78, -47)	-58 (-81, -35)
Diagnostic interval (screen-detected)										
n	113	153	159	86	131	184	126	125	152	158
Median	25 (ref)	-11 (-22, 1)	-7 (-18, 5)	-7 (-19, 4)	-1 (-17, 15)	0 (-12, 12)	1 (-11, 13)	-2 (-15, 10)	-5 (-17, 6)	-12 (-24, 0)
75th percentile	45 (ref)	-24 (-36, -13)	-17 (-28, -6)	-20 (-31, -8)	-9 (-21, 2)	-3 (-15, 8)	-1 (-15, 13)	-4 (-15, 7)	-14 (-25, -3)	-21 (-34, -7)
90th percentile	58 (ref)	-23 (-30, -16)	-16 (-22, -11)	-19 (-26, -12)	-10 (-14, -6)	9 (-6, 24)	8 (-3, 20)	55 (38, 71)	-17 (-26, -8)	-17 (-20, -13)
Diagnostic interval (all)										
n	224	353	356	302	338	350	329	309	343	259
Median	29 (ref)	-14 (-16, -12)	-8 (-11, -6)	-13 (-15, -11)	-14 (-16, -11)	-2 (-5, 1)	-6 (-9, -2)	-1 (-5, 2)	-12 (-15, -10)	-14 (-17, -11)
75th percentile	49 (ref)	-30 (-34, -25)	-18 (-23, -14)	-29 (-33, -25)	-20 (-25, -16)	-5 (-15, 4)	-11 (-20, -2)	-8 (-12, -3)	-22 (-26, -19)	-25 (-32, -17)
90th percentile	70 (ref)	-35 (-39, -31)	-23 (-30, -16)	-26 (-34, -19)	-21 (-40, -2)	20 (9, 31)	-1 (-16, 14)	22 (7, 38)	-27 (-40, -13)	-29 (-36, -21)
Treatment interval (symptomatic)										
n	115	203	202	241	230	201	216	198	196	113
Median	24 (ref)	6 (1, 11)	1 (-3, 5)	-3 (-7, 1)	-3 (-7, 1)	12 (8, 16)	-5 (-11, 1)	15 (11, 19)	-10 (-14, -6)	-2 (-6, 2)
75th percentile	33 (ref)	8 (4, 12)	4 (-1, 9)	-3 (-8, 1)	-4 (-9, 0)	16 (11, 21)	-6 (-9, -2)	22 (18, 26)	-9 (-16, -2)	-4 (-13, 5)
90th percentile	45 (ref)	10 (-1, 20)	11 (-4, 26)	-4 (-19, 11)	-1 (-14, 12)	20 (10, 31)	-11 (-23, 2)	28 (10, 46)	-11 (-26, 4)	-3 (-15, 10)
Treatment interval (screen-detected)										
n	115	155	158	86	134	195	120	155	170	165
Median	27 (ref)	5 (1, 8)	8 (4, 11)	0 (-5, 5)	-6 (-10, -1)	9 (7, 12)	-12 (-15, -10)	12 (9, 16)	-5 (-12, 1)	-3 (-6, -1)
75th percentile	36 (ref)	4 (-2, 10)	10 (-3, 22)	0 (-6, 7)	-7 (-16, 3)	11 (3, 20)	-15 (-27, -4)	15 (7, 23)	-7 (-16, 2)	-6 (-17, 5)
90th percentile	49 (ref)	5 (-8, 18)	15 (4, 25)	-9 (-20, 3)	-14 (-26, -2)	9 (-4, 22)	-24 (-35, -13)	12 (-1, 24)	-14 (-27, -1)	-11 (-21, 0)
Treatment interval (all)										
n	231	359	361	330	368	400	341	353	366	278
Median	25 (ref)	5 (0, 11)	4 (0, 8)	-4 (-8, 1)	-5 (-9, -1)	10 (6, 14)	-10 (-14, -6)	14 (9, 18)	-10 (-14, -6)	-3 (-7, 0)
75th percentile	35 (ref)	6 (2, 10)	6 (1, 10)	-4 (-8, 0)	-6 (-10, -2)	13 (10, 17)	-11 (-16, -6)	20 (16, 23)	-9 (-13, -5)	-6 (-10, -2)
90th percentile	46 (ref)	8 (2, 14)	12 (-1, 26)	-6 (-10, -2)	-6 (-9, -2)	17 (11, 23)	-14 (-17, -12)	23 (16, 29)	-11 (-14, -9)	-7 (-10, -4)
Total interval (symptomatic)										
n	104	190	186	205	189	173	184	155	177	98
Median	70 (ref)	-14 (-24, -3)	-12 (-23, -2)	-20 (-31, -8)	-25 (-38, -11)	28 (15, 42)	-15 (-34, 5)	22 (12, 31)	-28 (39, -17)	-1 (-11, 10)
75th percentile	96 (ref)	-16 (-27, -5)	-5 (-18, 9)	-18 (-33, -3)	-25 (-39, -12)	69 (31, 107)	27 (8, 46)	30 (8, 53)	-13 (-27, 0)	3 (-30, 35)
90th percentile	218 (ref)	-71 (-102, -41)	-60 (-85, -34)	-57 (-66, -48)	-41 (-66, -16)	79 (66, 93)	8 (-15, 30)	-17 (-34, -1)	-21 (-67, 26)	-39 (-67, -10)

Continued

Table 6 Continued

	Wales	England	Scotland	Northern Ireland	Denmark	Ontario	Norway	Manitoba	Victoria	Sweden
Total interval (all)	n	343	337	291	320	354	298	277	327	253
Median	60 (ref)	-9 (-14, -3)	-4 (-11, 2)	-13 (-18, -8)	-15 (-26, -4)	16 (6, 26)	-13 (-21, -6)	17 (9, 24)	-18 (-24, -12)	-17 (-25, -10)
75th percentile	81 (ref)	-12 (-20, -4)	1 (-9, 10)	-13 (-20, -6)	-14 (-20, -9)	32 (24, 41)	-4 (-12, 4)	35 (21, 48)	-19 (-25, -12)	-17 (-26, -7)
90th percentile	123 (ref)	-13 (-34, 9)	3 (-12, 18)	-5 (-22, 11)	-8 (-38, 22)	73 (33, 114)	32 (2, 62)	47 (13, 82)	-12 (-37, 13)	-24 (-51, 4)

The differences for the median, 75th and 90th percentiles are calculated as marginal effects after quantile regression by setting the continuous covariate age to its mean value and comorbidity to the mode. Significant results are shown in bold. Note that analyses of primary care intervals are presented in the table. The actual number of days included for Wales is shown in table 5. ref, reference.

The overall response rate of 40% was comparable with similar studies among patients and PCPs,³⁰ but varied markedly between jurisdictions, with a response rate of 78% in Denmark and 24% in Norway. This may have resulted in differential selection bias across jurisdictions. However, comparing the participants on a number of variables (eg, tumour stage, presenting symptom, comorbidity, self-assessed health, smoking status) did not show any meaningful differences. Nevertheless, as recruitment strategies differed, with some women contacted directly by the registries and others via PCPs (and via nurses in Northern Ireland) assessing eligibility, some selection bias might have been introduced through differing impact of self-selection. This is underlined by the higher-than-expected proportion of stage I tumours among our respondents, when compared with an earlier registry-based breast cancer study.³ Women with early-stage breast cancer are more able to participate in studies of this kind, compared with women with late-stage disease.

The statistical precision of the study was sufficient as we were able to show clinically significant differences of 1 week in time intervals, appropriate for clinically relevant differences.

Comparison with other studies

Median patient intervals for breast cancer have varied in previous studies; in Denmark, the interval was 14 days in a 2004 study³⁰ and only 3 days in 2015 (using similar methods),³¹ possibly reflecting cancer pathway improvements over this period. Other studies have identified the interval as 13 days (UK),³² 14 days (New Zealand),³³ 16 days (Germany)³⁴ and 7 days (Sweden).³⁵ Reasons for discrepancies may reflect a difference in the time-points and data sources used to define patient interval or changes over time in access to primary care.

Diagnostic intervals vary; a UK study on patients diagnosed in 1999–2000 found a median diagnostic interval of 30 days,³⁶ while other UK studies found a diagnostic interval of 14–27 days.^{37–39} Lower intervals in more recent studies possibly reflect the introduction of urgent referrals in 2010. A Danish study demonstrated an 18-day interval in 2010,³⁹ compared with 8 days in our study.³⁹ Similarly, a study in Manitoba in 2009–2010 demonstrated an interval of 35 days compared with 28 days in our study.⁴⁰ The primary care interval has had less attention in the literature, although a Manitoban study reported an interval of 15 days, comparable with our finding of 17 days.⁴⁰ It also reported a total interval of 78 days, which is comparable with the 76 days found in our study. A recent Swedish study focusing on the time from referral to treatment, which roughly corresponds to a combined diagnostic and treatment interval, reported a median interval of 20 days, compared with 35 days in our study.³⁵

Clinical referral for a suspected breast cancer (eg, lump) is often expedited.^{37 38} Thus, the high proportion of women with ‘red flag’ symptoms or signs may mean that time intervals for breast cancer diagnosis vary less than other common cancers, as differential diagnosis

is easier and investigations and referral pathways more straightforward. Nevertheless, we found important variations in intervals for symptomatic women, possibly reflecting methodological differences, but also temporal and international differences in diagnostic pathways. We would expect these differences to primarily impact on the median primary care interval, 0 days for all jurisdictions except Manitoba, Ontario and Victoria. Note, however, that in these jurisdictions primary care is more often responsible for confirming the breast cancer diagnosis, thus extending the interval. Indeed, a study from Manitoba confirms that PCPs experience significant waiting time when they order a mammogram.⁴⁰

CONCLUSION AND IMPLICATIONS FOR CLINICAL PRACTICE AND HEALTHCARE ORGANISATION

Despite the existence of well-established screening programmes, the diagnostic route for breast cancer remains critically important, as over half of patients are diagnosed this way. Awareness and recognition of warning signs impact patient intervals⁴¹; we found, in some jurisdictions, significant numbers of women waiting more than 90 days before presenting with symptoms. Targeted awareness interventions could facilitate more timely diagnosis of breast cancer. The variation in waiting times for an appointment in primary care, which might affect perceived access, could also be addressed.

The possible impact of variations in routes to diagnosis, diagnostic/treatment intervals and key outcomes (eg, disease-free survival and mortality) cannot be assessed from our study. There is, nevertheless, growing evidence of an association between time intervals, the use of urgent referrals and mortality.^{10 41–44} More research are warranted to explore this relationship.

This study illustrates the need to optimise diagnostic routes for breast cancer internationally. Awareness of international differences in key time intervals is an important step in optimising pathways. Ideally, routine and standardised collection of time interval and route to diagnostic information will become the norm internationally; this will greatly assist in optimisation of breast cancer diagnostic pathways.

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