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Research article

Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis

Minjoung Monica Koo[a,*], Christian von Wagner[a], Gary A. Abel[b], Sean McPhail[a,c], Greg P. Rubin[d], Georgios Lyratzopoulos[a,c,e]

[a] University College London, 1-19 Torrington Place, London WC1E 6BT, UK
[b] University of Exeter, St Luke's Campus, Heavitree Road, Exeter EX1 2LU, UK
[c] National Cancer Registration and Analysis Service, Public Health England Zone A, 2nd Floor, Skipton House, 80 London Road, London SE1 6LH, UK
[d] School of Medicine, Pharmacy and Health, Durham University, Stockton on Tees TS17 6BH, UK
[e] Cambridge Centre for Health Services Research, University of Cambridge, Cambridge CB2 0SR, UK

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ABSTRACT

Introduction: Most symptomatic women with breast cancer have relatively short diagnostic intervals but a substantial minority experience prolonged journeys to diagnosis. Atypical presentations (with symptoms other than breast lump) may be responsible.
Methods: We examined the presenting symptoms of breast cancer in women using data from a national audit initiative (n = 2316). Symptoms were categorised topographically. We investigated variation in the length of the patient interval (time from symptom onset to presentation) and the primary care interval (time from presentation to specialist referral) across symptom groups using descriptive analyses and quantile regression.
Results: A total of 56 presenting symptoms were described: breast lump was the most frequent (83%) followed by non-lump breast symptoms, (e.g. nipple abnormalities (7%) and breast pain (6%)); and non-breast symptoms (e.g. back pain (1%) and weight loss (0.3%)).
Greater proportions of women with 'non-lump only' and 'both lump and non-lump' symptoms waited 90 days or longer before seeking help compared to those with 'breast lump only' (15% and 20% vs. 7% respectively). Quantile regression indicated that the differences in the patient interval persisted after adjusting for age and ethnicity, but there was little variation in primary care interval for the majority of women.
Conclusions: About 1 in 6 women with breast cancer present with a large spectrum of symptoms other than breast lump. Women who present with non-lump breast symptoms tend to delay seeking help. Further emphasis of breast symptoms other than breast lump in symptom awareness campaigns is warranted.

1. Introduction

Breast lump is the most common presenting symptom among women with breast cancer and has relatively high predictive value for malignancy [1,2]. Consequently, it has long been the focus of public health education campaigns about cancer symptom awareness [3,4]. Although women with breast cancer typically experience short diagnostic intervals compared to other cancer patients, some women continue to experience long diagnostic intervals [2,5–8]. This is concerning as longer intervals to diagnosis have been shown to be associated with lower five-year survival of breast cancer patients, and additionally, a prolonged diagnostic experience may lead to poorer experience of subsequent cancer care [9–11]. Further, inequalities in stage at diagnosis and survival of breast cancer patients have been linked to variation in the length of the patient interval [12–14].

Prior literature exploring reasons for delayed help-seeking suggests that women subsequently diagnosed with breast cancer

* Corresponding author at: Epidemiology of Cancer Healthcare and Outcomes (ECHO) Group, Research Dept. of Behavioural Science and Health, University College London, 1-19 Torrington Place, London WC1E 7HB, UK.
E-mail address: monica.koo14@ucl.ac.uk (M.M. Koo).

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may attribute non-lump breast symptoms to other non-malignant causes such as hormonal changes, trauma, or breastfeeding [15–17]. While this provides an explanation of why some women may experience long intervals to presentation, there has been limited examination of diagnostic timeliness using population-based studies and large representative samples of women with breast cancer. Moreover, existing studies often dichotomise presenting symptoms based on the presence or absence of breast lump, limiting the appreciation of the large spectrum of presenting symptoms within the 'non-lump' breast symptoms category [18–21].

Motivated by the above considerations, we aimed to describe the diverse range of presenting symptoms in a large representative sample of women with breast cancer in England, and to examine associations between different symptomatic presentations and the length of diagnostic intervals. Our broader aim was to provide underpinning evidence to inform the content and targeting of public health campaigns and decision-support interventions in primary care.

2. Materials and methods

2.1. Data

We analysed data from the English National Audit of Cancer Diagnosis in Primary Care (2009–10) which collected information on the diagnostic pathway of cancer patients in 14% of all English general practices [22]. Patients were selected on a continuous basis, minimising the potential for selection bias. The patient population was representative of the age, sex, and cancer case-mix of incident cancer patients in England, and participating practices were also comparable to non-participating practices in respective (former) Cancer Networks [22,23]. Our analysis sample comprised 2316 women with breast cancer with complete and valid information on age, ethnicity, and presenting symptoms. Among these women, 1883 (81%), 2201 (95%), and 2002 (86%) had complete information on the patient interval, the primary care interval, and the number of pre-referral consultations respectively (Supplementary Fig. A.1). Women with missing interval or pre-referral consultation data were less likely to have presented in general practice, or were older (70 years or over) without evidence for variation by ethnicity, symptom group, or number of symptoms (data not shown).

2.2. Presenting symptoms

As part of the audit, general practitioners within participating practices provided free-text information on the main presenting symptom(s) of patients, based on information in their records. Informed by the principles of natural language processing (NLP), free-text descriptions were coded into symptoms without using any prior construct definitions or restrictions [24]. Symptom were initially assigned by MMK, and subsequently verified by GL and GPR. Where there was diverging opinion, consensus was reached by discussion.

2.3. Diagnostic intervals

As previously reported, the length of the patient and primary care intervals were derived based on information in the patients' primary care records [25,26]. Concordant with international consensus statements, the patient interval was defined as the number of days between symptom onset and the first presentation, and the primary care interval as the number of days between first presentation and the first specialist referral [27]. The number of pre-referral consultations was also examined, as a strongly correlated marker of the length of the primary care interval [6]. Pre-referral consultations were parameterised as a binary outcome (1 pre-referral consultation vs 2 or more pre-referral consultations) as the great majority of women (90%) had a single consultation.

2.4. Analytic methods

Firstly, we described the frequency of recorded presenting symptoms and associated exact confidence intervals, and the distribution of the patient and primary care intervals for each symptom among women with complete interval values. Beyond summarising mean, median and key centile interval values, we have also reported the proportion of women with each symptom that experienced 2 or more pre-referral consultations [6]. Additionally, we calculated the proportion of women with interval values exceeding 90 days, given prior evidence of poorer survival among women experiencing diagnostic intervals of 3 months or longer [11].

We developed a taxonomy of presenting symptoms by classifying individual symptoms into three main symptom categories: (a) *breast lump*, (b) *non-lump breast symptoms* (including breast pain, breast skin or shape abnormalities and nipple abnormalities), and (c) *non-breast symptoms* (including fatigue, breathlessness, axillary symptoms, neck lump, and back pain) (see Fig. 2 and Fig. A.2 in Supplementary materials). Some women had multiple symptoms across different symptom categories. From the resulting seven combinations of the three symptom categories, we focused on the four largest groups ('lump', 'lump and non-lump', 'non-lump', and 'non-breast').

We used Kruskal-Wallis and Chi-squared tests to compare observed diagnostic intervals and the number of pre-referral consultations by symptom groups, and other covariates. Subsequently, regression was used to examine the variation in patient and primary care intervals by symptom group adjusted for age and ethnicity. Specifically, as the outcome data (length of patient interval and primary care interval) were highly right-skewed, a continuity correction and log-transformation was applied to both variables before using quantile regression across different centiles of interest, and significance testing was based on bootstrapping. Detailed methods and findings of quantile regression modelling are available in the Supplementary materials. All analyses were conducted in STATA SE v.13 (StataCorp, College Station, TX, USA).

3. Results

3.1. Symptom signature of breast cancer – individual symptoms

A total of 2316/2783 (83%) of symptomatic women with breast cancer were included in the analysis (see Supplementary Fig. A.1 for sample derivation). Among them, 2543 symptoms were recorded, averaging 1.1 symptoms per woman. A total of 56 distinct presenting symptoms were reported in the study population (Table 1), in 95 unique phenotypes. Breast lump was the most common symptom, recorded in about four-fifths of all women (83%). The next most commonly reported presenting symptoms were nipple abnormalities (7%), breast pain (6%), and breast skin abnormalities (2%).

Overall, 164 women (9% of those with patient interval values) waited longer than 90 days before seeking help. Among the larger non-lump breast symptoms, more than one in five women with breast ulceration (50%), nipple abnormalities (23%) and breast infection or inflammation (21%) had patient intervals of more than 90 days (Table 1). In contrast to the substantial proportion of women with patient intervals longer than 3 months (9%, as above), only 2% of women had recorded primary care interval values of