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Social, demographic and healthcare factors associated with stage at diagnosis of cervical cancer: cross sectional study in a tertiary hospital in Northern Uganda

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Abstract

Objective: To examine patient and primary healthcare factors and stage at diagnosis in women with cervical cancer in Northern Uganda with the intention to identify factors that are associated with advanced stages in order to inform policies to improve survival from cervical cancer in the low- and middle-income countries.

Design: Cross sectional hospital-based study

Setting: Tertiary, not-for-profit private hospital in post-conflict region.

Participants: Consecutive tissue-diagnosed symptomatic cervical cancer patients attending care. Of 166 patients, 149 were enrolled and analysed.

Primary outcome: Cervical cancer stage at diagnosis.

Results: Most women were diagnosed in stages III (45%) or IV (21%). After controlling for age, marital status, educational attainment and number of biological children, there was evidence for association between greater likelihood of advanced stage at diagnosis and pre-referral diagnosis of cancer by primary healthcare professionals (AOR=13.04:95%CI; 3.59-47.3), financial difficulties precluding prompt help-seeking (AOR=5.5:95%CI; 1.58-20.64).

After adjusting for age, marital status, educational attainment and number of biological children, women with 5-9 biological children (Adjusted OR (AOR) = 0.27:95%CI; 0.08-0.96) were less likely to be diagnosed with advanced stage (defined as stages III/IV) cancer. In this pilot study, there was no statistical evidence for associations between stage at diagnosis and factors such as age at diagnosis and marital status.

Conclusions: The study is a first attempt to understand the descriptive epidemiology of cervical cancer in rural Ugandan settings. Understanding individual patient, behavioural characteristics and healthcare factors associated with advanced stage at diagnosis is essential

for targeted effective public health interventions to promote prompt healthcare seeking, diagnosis at early stage and improved survival from cervical cancer.

Key words: Cervical cancer, advanced stage cancer at diagnosis, predictors of late stage, pathways to diagnosis and treatment.

Strengths and limitations of this study

- This is a pioneer study in a low-income country to apply the theoretical framework – the Model of Pathways to Treatment to evaluate factors that may influence symptoms appraisal and help-seeking intervals for symptomatic cervical cancer patients.
- Participants were prospectively recruited thereby minimising methodological concerns associated with retrospective studies.
- Diagnosis of cervical cancer was confirmed by tissue histology and following examinations under anaesthesia and this obviates possibilities of diagnostic misclassifications.
- Potential recall or social desirability biases inherent in patient interview studies. Most patients presented long after onset of symptoms and could have had difficulty in recall of some events.
- This was a hospital-based study involving a selected population of women who had reached the hospital. The characteristics of women who may have cervical cancer but have not reached the study hospital remain unknown.

Background

In Uganda and most LMICs, there is limited evidence about the distribution of stage at diagnosis of cervical cancer, and about factors that contribute to advanced stage at diagnosis. In Nepal, up to 81% of cervical cancer patients are diagnosed with advanced stage cancer. Women who were more likely to be diagnosed with advanced stage cancer included those who did not disclose their symptoms to significant others promptly (adjusted OR=4.27) and those who disclosed symptoms to other relations different from their husbands (adjusted OR=12.70) [3].

A modifiable predictor of treatment outcome is time to diagnosis of symptomatic cervical cancer. Among symptomatically detected women with cervical cancer in Sweden, those with shorter symptom durations had 14% higher chance of cure compared to those with longer symptoms duration [4]. However, in most LMICs, the diagnostic journeys of most women with cervical cancer symptoms are dominated by long patient and primary care intervals. Of 110 symptomatic cervical cancer patients in Nepal, the median total time to diagnosis (diagnostic interval) was 157 days while the median patient and healthcare provider intervals were 68.5 days and 40 days respectively. Fifty seven percent of the patients had experienced longer patient intervals of > 2 months [5]. Diagnosing cervical cancer at an early stage requires that women recognize and appraise the importance of possible cervical cancer symptoms early and seek care promptly [6]. Nonetheless, even when women seek care for cervical cancer symptoms, diagnosis may be delayed because primary healthcare professionals face challenges in promptly recognizing symptoms and referring patients with possible cervical cancer [7 8]. In Uganda data from the Kampala Cancer Registry (which serves a population in close proximity to specialized cancer treatment centres) suggest that women in central Uganda present with advanced stage cervical cancer and have poor prognosis [9 10]. Previous studies however have not been able to examine factors that are likely to influence the

promptness of diagnosis; such factors might vary within and between countries and regions. Understanding of context-specific factors including patient- and primary healthcare-related factors that lead to delay in a particular country can guide development of targeted interventions and policies to increase prompt appraisal of cervical cancer symptoms and enable timely help-seeking.

In spite of cervical cancer being a very common cancer responsible for 2,275 deaths every year (27.2 per 100,000), women with cervical cancer in Uganda are an understudied population [11]. Against this background we set out to examine patient and primary healthcare factors and stage at diagnosis in women with cervical cancer in Northern Uganda with the intention of establishing the feasibility of future larger studies aimed at identifying factors that are associated with advanced stages in broader populations.

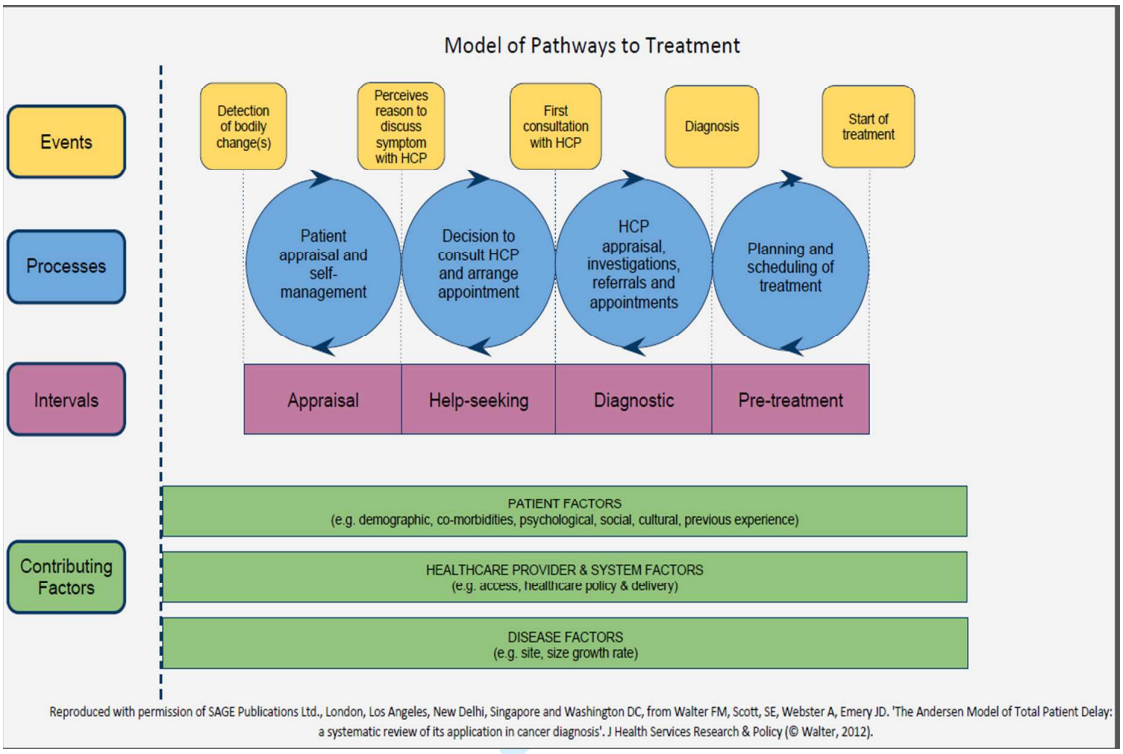
Methods

Theoretical framework

The data collection and analysis in this study were underpinned by the Model of Pathways to Treatment (MPT) [12 13]. In this Model (Figure 1), the cancer journey from symptom recognition through help-seeking, diagnosis and treatment is viewed as an iterative process composed of events and processes with distinguishable intervals. These events and associated intervals are influenced by factors such as patient demographics, healthcare access and disease factors including rate of progressions and histological subtypes. In using the MPT, researchers and policymakers can gain insight into actual points along the journey where delay may occur and hence provide opportunities for design of targeted interventions [13].

The operational definitions for different measures and markers of promptness of diagnosis used in this study are presented in box 1.These definitions were informed by the MPT model, and an international consensus statement on the measurement of different diagnostic intervals [1] and evidence indicating that the number of pre-referral consultations is a valid marker of the primary care interval [2].

Figure 1: Model of Pathways to Treatment



Design and setting

We carried out a cross-sectional survey of patients with cervical cancer attending St. Mary's hospital Lacor - a tertiary 400-bed not-for-profit hospital in northern Uganda. This was a pragmatic feasibility study to increase knowledge and help pave the way for the conduct of larger multi-site studies.

Study participants and recruitment

We consecutively recruited all women with cervical cancer diagnosed and treated in the gynaecology department. In all women the diagnosis was confirmed with tissue histology and stage was assigned based on the findings of examination under anaesthesia (EUA) carried out by a gynaecologist. Staging was done according to the International Federation of Gynaecology and Obstetrics (FIGO) staging criteria [14]. Sampling was confined to women diagnosed within a maximum period of 6 months from the date of recruitment.

Screening-detected women were a priori excluded. Patients who could not be interviewed because of language problems were also excluded. Altogether, seventeen of 166 women seen in the hospital during the study period were excluded; five were diagnosed more than 6 months before study recruitment, two declined to participate because they wanted to go immediately for radiotherapy in the capital city Kampala, four unexpectedly left hospital soon after EUAs, and five were too sick to be interviewed. An 18-year-old patient with EUA report showing a fungating mucinous cervical mass was excluded because histopathology revealed diagnosis of sarcoma Botryoides. The sample therefore included 149 women.

Data collection

Data were collected from the patients using structured interviews based on a questionnaire administered by the research assistant. We designed the questionnaire based on contributing factors, events and intervals in the Model of Pathways to Treatment, findings from studies on cervical cancer in sub Saharan Africa and our own clinical experiences [13 15]. The questionnaire had three sections: socio-demographic characteristics; knowledge and beliefs about cervical cancer including awareness of risk factors, symptoms and beliefs about treatment and cure; and information about care processes including symptoms appraisal, duration and help-seeking behaviour. The questionnaire also included open-ended questions about symptoms, the distance from home to nearest health unit and to the study hospital, and the number of times health units were visited before coming to study hospital. Responses from the open-ended questions were reviewed and aggregated before further analysis. Symptoms which were reported by fewer than five participants were categorized as "other" and excluded from main analyses.

The study tool was double translated by two independent translators fluent in both English and Luo/Acholi, the main local language spoken in the study area. A third translator reviewed both Luo versions and harmonized them to form the final tool used in data collection.

A female registered nurse with additional and midwifery qualification was trained as research assistant for this study. The research assistant was trained for two days on basic facts on cervical cancer and the study procedures including inclusion criteria, consent procedures and data collection. The research assistant introduced the study to prospective participants after patients were informed of their cancer diagnoses by their attending physicians as part of their standard care. After at least five days from the disclosure of cancer diagnoses, the research assistant administered the questionnaire, mostly in the local language. The research assistant read out the questions and coded responses to the participants and she ticked and/or recorded responses accordingly. However, for the questions concerning risk factors and perceived causes, the research assistant did not prompt recall by reading out the options but ticked all coded responses as the participants mentioned them. She prompted participants to mention as many risk factors/perceived causes as possible by asking "what else? What else do you think may also cause this cancer?" This was done to avoid suggesting risk factors that participants would not have thought about. Administration of questionnaires lasted about 45 – 60 minutes. The research assistant abstracted clinical data such as cancer stage and histology from the patients' case notes and histopathology laboratory record. Recruitment and data collection were conducted from September 2012 to April 2014.

Data analysis

Data entry was performed by two independent clerks using Epidata 3.1 software and analysis done using STATA I/C version 12.0. The outcome measure was cancer stage at diagnosis, dichotomized as early (I/II) or advanced stage (III/IV). Independent variables/covariates included socio-demographic characteristics, time to diagnosis, estimated road distance from study hospital, initial symptoms attributions, pre-referral diagnoses by primary healthcare

professionals, number of pre-referral visits, health seeking intervals and reported reasons for non-prompt health seeking. Bivariate and multivariable logistic regressions were used to determine associations. For multivariable regression analysis, variables were included based on biological plausibility rather that a predetermined p-value in bivariate analyses. Odd ratios and accompanying 95% confidence intervals are reported.

Ethical clearance

Institutional and ethical approval was provided by the Uganda National Council of Science and Technology, Makerere University School of Medicine Ethics Review Committee, and Lacor hospital Institutional Review Committee. Participants were informed of study objectives, consent procedures, and potential benefits and harms, and their right to decline participation and/or withdraw at any time without fear of retribution or compromise to their cancer management plans. All participants provided informed individual consents with a signature or thumb print.

Box 1: Operational definitions.

- Date of first symptom: The date or estimated time in the week, month or year when the patient first felt a bodily change requiring discussion with a healthcare professional and/or with another person with the intention of gaining understanding of the symptoms and/or how to deal with them [1].
- Patient interval: The time period from detection of abnormal bodily sensations to time of visiting first healthcare professional to discuss the symptoms including the period from lower level units to the study hospital for diagnosis of cancer [1].
- Date of first presentation: The time point in the week, month or year including a particular date when the patient first visited a healthcare professional in a private or public health facility to discuss the symptoms which she had and which have since been attributed to cervical cancer at the study hospital [1].
- Date of diagnosis: Date when examinations under anesthesia for clinical diagnosis and staging was done [1].
- Pre-referral consultations: Any visits to a healthcare professional in an established healthcare setting including lower level healthcare facilities and private clinics before presentation and diagnosis in the study hospital [2].
- Pre-referral suspicion/diagnosis of cancer: Any reports by participants referring to being told of a cancer diagnosis by primary healthcare professionals before referral to study hospital.

Results

Characteristics of participants

One hundred forty nine women with cervical cancer were included in the analysis. The mean age (±SD) was 48±13 years. 57% of participants were married; 45% reported no formal education and 89% were not formally employed. 72% of participants had five children or more while 39% of participants lived more than 100 kilometres from the study hospital (median distance=80km, range; 2-375km). Most participants had stage III (45%) or IV (21%) disease at diagnosis. Squamous cell carcinoma (75%) was the predominant histological subtype of cancer identified (Table 1).

Total time to diagnosis at study hospital (appraisal and help-seeking intervals)

More than half (55%) of the participants presented at the study hospital after 3 months or more from reported date of onset of symptoms. Of these, 71.8% (51/71) had advanced stage cervical cancer. Although not statistically significant, participants who took longer time to presentation tended to be diagnosed in advanced stage (Table 3).

Patients- and healthcare-related factors and cancer stage at diagnosis

Patients-related factors

Participants' socio-demographics

Older women (≥ 30 years) and women who were not married (divorced and widowed) tended to have higher risk of being diagnosed with advanced stage cervical cancer but this association was not statistically significant. In bivariate analyses, participants with secondary and tertiary education were less likely to be diagnosed with advanced stage cancer compared with those who have not attained formal education (crude odds ratio = 0.16 (95%CI; 0.03-0.87). After adjusting for age, marital status and educational attainment, the odds of advanced

stage cancer among patients with 5-9 children was 0.27 (95%CI: 0.08-0.96) times the odds of advanced cancer among women with less than four children (Table 2).

Initial symptoms attribution

Most participants (90.3%) didn't attribute their initial symptoms to cervical cancer (Table 2). After controlling for age, marital status, educational attainment and number of biological children, the odds ratio of advanced stage cervical cancer among patients who perceived their symptoms as due to a serious illness or cancer were 0.43 (0.20 – 0.96) as compared to those who perceived their symptoms as not due to a serious illness/cancer (Table 3).

Socio-economic factors

After adjusting for the patients' socio-demographics, patients who reported lack of money as reason for non-prompt health seeking were more likely to be diagnosed in advanced stage cervical cancer while those who perceived their symptoms as serious or due to cancer were less likely to be diagnosed in advanced stage cancer. The odds of advanced stage cancer among patients who self-reported financial difficulty is 5.7 times (95%CI: 1.58 – 20.64) that of the odds of advanced cancer among the patients who did not report financial difficulty as a reason for non-prompt health seeking (Table 3).

Health system factors

About 1 in 3 cervical cancer patients resided > 100 kilometres from the study hospital (Table 1). About a quarter of the participants attended care for about 3 – 5 times before referral (Table 3). After controlling for patients' demographics, the odds of advanced stage cervical cancer among patients who were assigned pre-referral diagnoses of cancer is 13.04 times (95%CI: 3.59 – 47.30) the odds among those assigned non-cancer related diagnoses (Table 3).

Discussion

The study provides early insights about the range of psychosocial and healthcare factors that are likely to be associated with prolonged intervals and advanced stage at diagnosis of cervical cancer in Uganda, and should motivate the conduct of multi sites studies to establish more independent predictors of advanced stage cervical cancer at diagnoses in the LMICs. The findings suggest that several patient's characteristics (including age, educational attainment, marital status and number of biological children) and primary healthcare factors may influence diagnostic intervals, and the stage of cervical cancer at diagnosis. More than half of cervical cancer patients attending care at Lacor hospital during the study period were diagnosed in advanced stage.

The odds of advanced stage cancer were high among older women. Similarly, in Sudan, older age was found to be an independent predictor of advanced stage cervical cancer [16]. In other LMICs, older women were also found to have long help-seeking intervals for their symptoms and were more likely to be diagnosed with advanced stage cervical cancer [5 16-18]. Older women are likely to be post-menopausal and may be less keen to seek care promptly for gynaecologic symptoms. We also found that women with secondary and tertiary education were less likely to be diagnosed with advanced stage cancer. Similarly, higher level of education was found to be associated with earlier stage at diagnosis in Nepal [3]. There is evidence that the association between low education level (or other markers of low socio-economic status) and advanced stage cervical cancer seem to be mediated by early onset of sexual activity among women with low education [19].

The odds of advanced stage cervical cancer among widowed and divorced women were 1.8 – 2.3 times the odds among the married women. Similar findings were reported in studies conducted in North Africa and India [18 20]. In the North Africa study, unmarried women were

found to be five times as likely to be diagnosed in advanced stage compared to the married women [20]. Unmarried women in the United States were also more likely to be diagnosed with advanced stage cervical cancer [21]. Perhaps married women enjoy emotional and financial support from their spouses and therefore tend to seek help promptly. Evidence indicating a supportive role of husbands is alluded to by findings from Nepal where women who discussed their symptoms with friends were more likely to be diagnosed in advanced stage compared to those who discussed symptoms with their husbands [3]. Married women are perhaps less likely to ignore vaginal bleeding and pain because of associated discomfort during sexual intercourse. If married women have a higher frequency of intercourse, this may also lead to a higher symptom burden if the disease is present (e.g. painful intercourse, post-coital bleeding), therefore prompting earlier presentation.

Patients' attribution of their symptoms and perceptions of their likely causes may influence time to help-seeking and diagnosis of cancer. We found that patients who initially attributed their symptoms to sexually transmitted diseases and or who never perceived their symptoms as due to a serious illness or cancer were more likely to be diagnosed with advanced stage cervical cancer compared to those who didn't attribute their symptoms to STDs and those who perceived their symptoms as due to a serious illness or cancer. For instance, when adjusted for effect of age, marital status, educational attainment and number of biological children, women who perceived their symptoms to be due to a serious disease or cancer were statistically significantly less likely to be diagnosed in advanced stage (0.43: 95%CI; 0.20 – 0.96) compared to those who didn't perceive their symptoms as due to a serious illness or cancer. In a recent systematic review it was shown that non-recognition of symptoms seriousness was related with advanced stage cancer [22]. Similarly, patients with oral cancers did not initially take their symptoms seriously and attributed such symptoms to common oral conditions for which they responded by self-medication [23].

Apart from the socio-demographic characteristics of women, advanced stage at diagnosis may relate to other factors that prolong the help-seeking intervals, for example long distances from diagnostic facilities, lack of money for transport and medical bills and/or non-recognition of cancer symptoms by the primary healthcare professionals. Non-prompt help-seeking because of self-reported lack of money was associated with advanced stage at diagnosis. On adjusting for age, marital status, educational attainment and number of biological children, women who reported lack of money as reason for non-prompt help-seeking were 5.7 times more likely to be diagnosed with advanced stage cancer compared to those who did not report lack of money as reasons for non-prompt help-seeking. Similarly, financial constraints was reported as a main reason for not promptly seeking help in India even among patients who suspected cancer [24].

Delayed recognition and/or referral by primary healthcare clinicians can nonetheless lead to advanced cancer stage at diagnosis in the referral facilities. In this study, while about half of the cancer patients received pre-referral diagnoses of cancers at the primary healthcare facilities, the primary healthcare professionals did not recognize symptoms and or suspected cancer in the patients with early stage cancers and referred symptomatic patients with other diagnoses not related to cancer. On adjusting for age, marital status, educational attainment and number of biological children, the odds of advanced cervical cancer among patients assigned pre-referral diagnoses of cancer were 13 times the odds of advanced cancer among women who were assigned other pre-referral diagnoses not related to cancer. In Nepal, healthcare professionals in lower level units made other diagnoses in 90% of the initial pre-referral consultations by patients with cervical cancer symptoms and delayed referral to cancer diagnostic centre [3]. In a qualitative study in South Africa, primary healthcare professionals were also blamed for prolonged diagnostic intervals in symptomatic women [8]. Lack of specificity of cervical cancer symptoms and inadequate facilities to aid diagnosis of

cervical cancer by healthcare professionals may account for the misinterpretations of cervical cancer symptoms and subsequent diagnosis of non-cervical cancer conditions [25].

Strengths and limitations

Strengths to this study include the use of a theoretical model (Figure 1) to evaluate factors that may influence symptoms appraisal and help-seeking intervals. Furthermore, participants were prospectively recruited minimising methodological concerns associated with retrospective studies. Finally, diagnosis of cervical cancer was confirmed by tissue histology and examination following EUAs and this obviates possibilities of diagnostic misclassifications.

The findings are subject to potential recall or social desirability biases inherent in patient interview studies. Most patients presented at the study hospital long after onset of symptoms and could have had difficulty in recall of some events. We had no independent way to ascertain dates of first help-seeking in primary care units since records of the lower level health units were not accessible to us for independent verification. However, even when primary care records of patients subsequently diagnosed with cancer are used, there is still a potential for inaccurate measurement of patient interval in particular, and ideally both primary care and patient-reported data needed to be studied (which was impossible in our setting) [26].We facilitated recall accuracy by use of calendar landmark techniques and allowed time between disclosure of cancer diagnosis and questionnaire administration [27]. In addition, other diseases that present with similar symptoms to what have eventually been diagnosed as cervical cancer could also affect determining the exact time when the actual symptoms of cervical cancer could have started. Measurement of time of onset of symptoms and time intervals during help-seeking is known to be challenging [25]. Second, this was a hospital-based study involving a selected population of women who had reached the hospital. The

characteristics of women who may have cervical cancer but have not reached the study hospital remain unknown. Generalization of these findings needs to take these issues into consideration.

Implications of findings

This study provides an initial experience with the conduct of such studies, proving both their feasibility and the need for larger and multi-site data collection. Acknowledging power limitations, the findings suggest that advanced stage at diagnosis and long help-seeking intervals could be attributable to patients' misattributions of their symptoms, primary healthcare providers treating cervical cancer symptoms for different common conditions, and a lack of prompt healthcare seeking mainly because of lack of money for transport and medical bills. These findings may have far-reaching implications for clinical care, public health and policy. First, interventions to increase symptoms' recognition need to target both women and clinicians and may take the form of public awareness campaigns and continuous professional development (CPD) for healthcare professionals, respectively. Women who are older, with no or low levels of formal education and widowed/divorced may constitute a special group for interventions to promote prompt help-seeking and diagnosis of cervical cancer. Second, to reduce the proportion of advanced stage cervical cancer at diagnoses, policymakers in the LMICs ought to prioritize cervical cancer control programs that include establishment of population-based cervical screening and prompt treatment of pre-invasive and early invasive cervical lesions. However, in the meantime, policies on cervical cancer early detection of pre-invasive and early invasive lesions through scheduled CPDs to healthcare professionals and public awareness campaigns on cervical cancer to the public can be adopted as they have been shown to be feasible and affordable and can lead to increased survival from cervical cancer [28].

Future studies in Uganda and other LMICs seeking to detect and explain independent predictors of advanced stage cervical cancer may need to include interviews of the primary healthcare providers in the lower level health facilities in order to provide corroborating evidence and establish reasons for long patient intervals in patients with symptoms of cancer.

Competing interest

The authors declare that they have no competing interest.

Author contributions

ADM spearheaded the study design, data collection, analysis and drafting of manuscript. COG, HW, GL and MR participated in study design and critical review of manuscript. EMW prepared database, supervised data entry and prepared data for analysis. All authors read and approved the final manuscript and agreed on its submission.

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Table 1: Demographic characteristics of patients and disease characteristics

Characteristics	Number (N = 149)	Percentage
Age group (Years)		
18 – 29	7	4.7
30 – 44	52	34.6
45 – 59	63	42.7
≥ 60	25	16.7
Missing	2	1.3
Mean age (±SD) years	48.4±12.6	
Median age	49.0 (23 – 80)	
Marital status		
Married	84	56.4
Divorced	21	14.1
Widowed	44	29.5
Mean age at marriage (years)	17.7±2.3	
Median age 18 (13 – 27)		
Education attainment		
No formal education	67	45.0
Primary education	72	48.3
Secondary education	7	4.7
Tertiary education	2	1.3
Missing	1	0.7
Occupation		
Housewife/peasant	132	88.6
Petty trader	10	6.7
Formally employed	4	2.7
Missing	3	2.0
Number of biological children		
No child	2	1.3
1 – 4	28	18.7
5 - 10	108	72.0
11 - 15	10	6.7
Missing	1	0.7
Stage of cancer at diagnosis (FIGO)		
Stage I	17	11.4
Stage II	29	19.5
Stage III	67	45.0
Stage IV	31	20.8
Missing	5	3.3
Histological subtypes		
Squamous cell carcinoma	111	74.5
Adenocarcinoma	12	8.1
Anaplastic type	1	0.7
Missing	25	16.7
Estimated distance from home to study hospital (Kilometres)		
Less than 40	41	27.5
40 - 80	35	23.5
81 - 100	13	8.7
101 - 375	58	38.9
Missing	2	1.3
Median (Range)	80 (2 – 375)	

Table 2: Adjusted odds ratio for patients' socio-demographic characteristics and stage at diagnosis

Patient demographic characteristics	Population responding	Cancer stage at diagnosis		Crude OR (COR) (95% CI)	Adjusted OR (AOR) (95%CI)*
		Early stage Number (%)	Advance stage Number (%)		
Age group (years)					
< 30	6 (4.2)	3 (6.5)	3 (3.1)	1.00	1.00
30 – 59	111 (78.2)	40 (87.0)	71 (74.0)	1.78 (0.34 – 9.21)	2.62 (0.33 – 21.1)
≥ 60	25 (17.6)	3 (6.5)	22 (22.9)	7.33 (0.99 – 54.4)	9.82 (0.81 – 118.9)
Marital status					
Married	81 (56.3)	31 (67.4)	50 (51.0)	1.00	1.00
Divorced	19 (13.2)	4 (8.7)	15 (15.3)	2.32 (0.71 – 7.65)	1.81 (0.49 – 6.72)
Widowed	44 (30.5)	11 (23.9)	33 (33.7)	1.86 (0.82 – 4.21)	1.26 (0.51 – 3.12)
Education attainment					
No formal education	67 (48.2)	22 (47.8)	45 (46.4)	1.00	1.00
Primary education	68 (47.6)	18 (39.1)	50 (51.6)	1.36 (0.65 – 2.85)	1.44 (0.62 – 3.34)
Secondary and/or tertiary education	8 (5.6)	6 (13.0)	2 (2.0)	**0.16 (0.03 – 0.87)**	0.18 (0.03 – 1.22)
Number of biological children					
0 – 4	28 (19.6)	5 (11.1)	23 (23.5)	1.00	1.00
5 – 9	89 (62.2)	34 (75.6)	55 (56.1)	0.35 (0.12 – 1.01)	**0.27 (0.08 – 0.96)**
10 – 15	26 (18.2)	6 (13.3)	20 (20.4)	0.72 (0.19 – 2.74)	0.45 (0.1 – 2.09)

***Adjusted for age, marital status, education attainment and number of biological children.**

Table 3: Primary care factors and stage at diagnosis

Primary care factors	Population responding	Cancer stage at diagnosis		Crude OR (COR) (95% CI)	Adjusted OR* (95%CI)
		Early stage Number (%)	Advanced stage Number (%)		
Symptoms were initially attributed by the patient to:					
Sexually transmitted diseases					
No	121 (84.0)	41 (89.1)	80 (81.6)	1.00	1.00
Yes	23 (16.0)	5 (10.9)	18 (18.4)	1.85 (0.64 – 5.32)	3.24 (0.93 – 11.32)
Cancer					
No	130 (90.3)	39 (84.8)	91 (92.9)	1.00	1.00
Yes	14 (9.7)	7 (15.2)	7 (7.1)	0.43 (0.14 – 1.30)	0.30 (0.08 – 1.16)
Pre-referral diagnoses by primary healthcare professional					
Non-cancer related	21 (15.4)	16 (37.2)	5 (5.4)	1.00	1.00
Cancer diagnosis	75 (55.2)	16 (37.2)	59 (63.4)	**11.8 (3.75 – 37.12)**	**13.04 (3.59 – 47.30)**
Not told diagnosis	40 (29.4)	11 (25.6)	29 (31.2)	**8.44 (2.10 –28.6)**	**8.35 (2.13 – 32.79)**
Number of pre-referral visits at primary healthcare facilities					
Once	54 (48.2)	17 (43.6)	37 (50.7)	1.00	1.00
Twice	29 (25.9)	13 (33.3)	16 (21.9)	0.57 (0.22 – 1.43)	0.68 (0.24 – 1.94)
Three to five or more	29 (25.9)	9 (23.1)	20 (27.4)	1.02 (0.39 – 2.70)	0.87 (0.28 – 2.65)
Health seeking interval (months)					
< 3	59 (45.4)	23 (53.5)	36 (41.4)	1.00	1.00
3 – 6	51 (39.2)	15 (34.9)	36 (41.4)	1.53 (0.69 – 3.41)	1.55 (0.62 – 3.86)
7 – 24	20 (15.4)	5 (11.6)	15 (17.2)	1.92 (0.61 – 5.99)	1.93 (0.52 – 7.23)
Reasons for lack of promptness in seeking care					
Lack of money					
No	108 (75.0)	43 (93.5)	65 (66.3)	1.00	1.00
Yes	36 (25.0)	3 (6.5)	33 (33.7)	**7.28 (2.10 – 25.22)**	**5.70 (1.58 – 20.64)**
Still using other treatments					
No	84 (58.3)	23 (50.0)	61 (62.2)	1.00	1.00
Yes	60 (41.7)	23 (50.0)	37 (37.8)	0.61 (0.30 – 1.23)	0.66 (0.30 – 1.43)
Perceived illness as not serious or cancer					
No	86 (59.7)	20 (43.5)	66 (67.4)	1.00	1.00
Yes	58 (40.3)	26 (56.5)	32 (32.6)	**0.37 (0.18 – 0.77)**	**0.43 (0.20 – 0.96)**

***:** Odds ratio adjusted for patients' socio-demographic characteristics in table 2.

STROBE 2007 (v4) Statement—Checklist of items in included: Cervical cancer stage at diagnosis and associated factors

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7 & 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 & 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Not applicable
Bias	9	Describe any efforts to address potential sources of bias	*8, 9 & 17*
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 & 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9 & 10
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable

		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 & 8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	26 & 27
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17 & 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Social, demographic and healthcare factors associated with stage at diagnosis of cervical cancer: cross sectional study in a tertiary hospital in Northern Uganda

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Social, demographic and healthcare factors associated with stage at diagnosis of cervical cancer: cross sectional study in a tertiary hospital in Northern Uganda

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Abstract

Objective: To examine patient and primary healthcare factors and stage at diagnosis in women with cervical cancer in Northern Uganda with the intention to identify factors that are associated with advanced stages in order to inform policies to improve survival from cervical cancer in the low- and middle-income countries.

Design: Cross sectional hospital-based study

Setting: Tertiary, not-for-profit private hospital in post-conflict region.

Participants: Consecutive tissue-diagnosed symptomatic cervical cancer patients attending care. Of 166 patients, 149 were enrolled and analysed.

Primary outcome: Cervical cancer stage at diagnosis.

Results: Most women were diagnosed in stages III (45%) or IV (21%). After controlling for age, marital status, educational attainment and number of biological children, there was evidence for association between greater likelihood of advanced stage at diagnosis and pre-referral diagnosis of cancer by primary healthcare professionals (Adjusted OR (AOR)=13.04:95%CI; 3.59-47.3), financial difficulties precluding prompt help-seeking (AOR=5.5:95%CI; 1.58-20.64).

After adjusting for age, marital status, and educational attainment, women with 5-9 biological children (AOR = 0.27:95%CI; 0.08-0.96) were less likely to be diagnosed with advanced stage (defined as stages III/IV) cancer. In this pilot study, there was no statistical evidence for associations between stage at diagnosis and factors such as age at diagnosis and marital status.

Conclusions: This study is a first attempt to understand the descriptive epidemiology of cervical cancer in rural Ugandan settings. Understanding individual patient factors, patients'

behavioural characteristics and healthcare factors associated with advanced stage at diagnosis is essential for targeted effective public health interventions to promote prompt health seeking, diagnosis at early stage and improved survival from cervical cancer.

Key words: Cervical cancer, advanced stage cancer at diagnosis, predictors of late stage, pathways to diagnosis and treatment.

Strengths and limitations of this study

- This is a pioneer study in a low-income country to apply the theoretical framework – the Model of Pathways to Treatment to evaluate factors that may influence symptoms appraisal and help-seeking intervals for symptomatic cervical cancer patients.
- Participants were prospectively recruited thereby minimising methodological concerns associated with retrospective studies.
- Diagnosis of cervical cancer was confirmed by tissue histology and following examinations under anaesthesia and this obviates possibilities of diagnostic misclassifications.
- Potential recall or social desirability biases inherent in patient interview studies. Most patients presented long after onset of symptoms and could have had difficulty in recall of some events.
- This was a hospital-based study involving a selected population of women who had reached the hospital. The characteristics of women who may have cervical cancer but have not reached the study hospital remain unknown.

Background

In Uganda and most low- and middle-income countries (LMICs), there is limited evidence about the distribution of stage at diagnosis of cervical cancer, and about factors that contribute to advanced stage at diagnosis. In Nepal, up to 81% of cervical cancer patients are diagnosed with advanced stage cancer. Women who were more likely to be diagnosed with advanced stage cancer included those who did not disclose their symptoms to significant others promptly (adjusted odds ratio (AOR)=4.27) and those who disclosed symptoms to other relations different from their husbands (AOR=12.70) [1].

A modifiable predictor of treatment outcome is time to diagnosis of symptomatic cervical cancer. Among symptomatically detected women with cervical cancer in Sweden, those with shorter symptom durations had 14% higher chance of cure compared to those with longer symptom duration [2]. However, in most LMICs, the diagnostic journeys of most women with cervical cancer symptoms are dominated by long patient and primary care intervals. Of 110 symptomatic cervical cancer patients in Nepal, the median total time to diagnosis (diagnostic interval) was 157 days while the median patient and healthcare provider intervals were 68.5 days and 40 days respectively. Fifty seven percent of the patients had experienced longer patient intervals of > 2 months [3]. Diagnosing cervical cancer at an early stage requires that women recognize and appraise the importance of possible cervical cancer symptoms early and seek care promptly [4]. Nonetheless, even when women seek care for cervical cancer symptoms, diagnosis may be delayed because primary healthcare professionals face challenges in promptly recognizing symptoms and referring patients with possible cervical cancer [5, 6]. In Uganda, data from the Kampala Cancer Registry (which serves a population in close proximity to specialized cancer treatment centres) suggest that women in central Uganda present with advanced stage cervical cancer and have poor prognosis [7, 8]. Previous studies however have not been able to examine factors that are

likely to influence the promptness of diagnosis; such factors might vary within and between countries and regions. Understanding of context-specific factors including patient- and primary healthcare-related factors that lead to delay in a particular country can guide development of targeted interventions and policies to increase prompt appraisal of cervical cancer symptoms and enable timely help-seeking.

In spite of cervical cancer being a very common cancer responsible for 2,275 deaths every year (27.2 per 100,000), women with cervical cancer in Uganda are an understudied population [9]. Against this background we set out to examine patient and primary healthcare factors and stage at diagnosis in women with cervical cancer in Northern Uganda with the intention of establishing the feasibility of future larger studies aimed at identifying factors that are associated with advanced stages in broader populations.

Methods

Theoretical framework

The data collection and analysis in this study were underpinned by the Model of Pathways to Treatment (MPT) [10, 11]. In this Model (Figure 1), the cancer journey from symptom recognition through help-seeking, diagnosis and treatment is viewed as an iterative process composed of events and processes with distinguishable intervals. These events and associated intervals are influenced by factors such as patient demographics, healthcare access and disease factors including rate of progressions and histological subtypes. In using the MPT, researchers and policymakers can gain insight into actual points along the journey where delay may occur and hence provide opportunities for design of targeted interventions [11].

The operational definitions for different measures and markers of promptness of diagnosis used in this study are presented in Table 1.These definitions were informed by the MPT model, and an international consensus statement on the measurement of different diagnostic intervals [12] and evidence indicating that the number of pre-referral consultations is a valid marker of the primary care interval [13].

Design and setting

We carried out a cross-sectional survey of patients with cervical cancer attending St. Mary's hospital Lacor - a tertiary 400-bed not-for-profit hospital in northern Uganda. This was a pragmatic feasibility study to increase knowledge and help pave the way for the conduct of larger multi-site studies.

Participants and recruitment

We consecutively recruited all women with cervical cancer diagnosed and treated in the gynaecology department over the study period of one and half years. In all women the diagnosis was confirmed with tissue histology and stage was assigned based on the findings of examination under anaesthesia (EUA) carried out by a gynaecologist. Staging was done

according to the International Federation of Gynaecology and Obstetrics (FIGO) staging criteria [14]. Sampling was confined to women diagnosed within a maximum period of 6 months from the date of recruitment.

Screening-detected women were a priori excluded. Patients who could not be interviewed because of language problems were also excluded. Altogether, seventeen of 166 women seen in the hospital during the study period were excluded; five were diagnosed more than 6 months before study recruitment, two declined to participate because they wanted to go immediately for radiotherapy in the capital city Kampala, four unexpectedly left hospital soon after EUAs, and five were too sick to be interviewed. An 18-year-old patient with EUA report showing a fungating mucinous cervical mass was excluded because histopathology revealed diagnosis of sarcoma Botryoides. The sample therefore included 149 women.

Data collection

Data were collected from the patients using structured interviews based on a questionnaire administered by the research assistant. We designed the questionnaire based on contributing factors, events and intervals in the Model of Pathways to Treatment, findings from studies on cervical cancer in sub Saharan Africa and our own clinical experiences [11, 15]. The questionnaire had three sections: socio-demographic characteristics; knowledge and beliefs about cervical cancer including awareness of risk factors, symptoms and beliefs about treatment and cure; and information about care processes including symptoms appraisal, duration and help-seeking behaviour. The questionnaire also included open-ended questions about symptoms, the distance from home to nearest health unit and to the study hospital, and the number of times health units were visited before coming to study hospital. Responses from the open-ended questions were reviewed and aggregated before further analysis. Symptoms which were reported by fewer than five participants were categorized as “other” and excluded from main analyses.

The study tool was double translated by two independent translators fluent in both English and Luo/Acholi, the main local language spoken in the study area. A third translator reviewed both Luo versions and harmonized them to form the final tool used in data collection.

A female registered nurse with additional and midwifery qualification was trained as research assistant for this study. The research assistant was trained for two days on basic facts on cervical cancer and the study procedures including inclusion criteria, consent procedures and data collection. The research assistant introduced the study to prospective participants after patients were informed of their cancer diagnoses by their attending physicians as part of their standard care. After at least five days from the disclosure of cancer diagnoses, the research assistant administered the questionnaire, mostly in the local language. The research assistant read out the questions and coded responses to the participants and she ticked and/or recorded responses accordingly. However, for the questions concerning risk factors and perceived causes, the research assistant did not prompt recall by reading out the options but ticked all coded responses as the participants mentioned them. She prompted participants to mention as many risk factors/perceived causes as possible by asking "what else do you think may also cause this cancer?" This was done to avoid suggesting risk factors that participants would not have thought about. Administration of questionnaires lasted about 45 – 60 minutes. The research assistant abstracted clinical data such as cancer stage and histology from the patients' case notes and histopathology laboratory record. Recruitment and data collection were conducted from September 2012 to April 2014.

Data analysis

Data entry was performed by two independent clerks using Epidata 3.1 software and analysis done using STATA I/C version 12.0. The outcome measure was cancer stage at diagnosis, dichotomized as early (I/II) or advanced stage (III/IV). Independent variables/covariates

included socio-demographic characteristics, time to diagnosis, estimated road distance from study hospital, initial symptoms attributions, pre-referral diagnoses by primary healthcare professionals, number of pre-referral visits, health seeking intervals and reported reasons for non-prompt health seeking. Bivariate and multivariable logistic regressions were used to determine associations. For multivariable regression analysis, variables were included based on biological plausibility rather that a predetermined p-value in bivariate analyses. Odd ratios and accompanying 95% confidence intervals are reported.

Ethical clearance

Institutional and ethical approval was provided by the Uganda National Council of Science and Technology, Makerere University School of Medicine Research & Ethics Committee (SOMREC), and Lacor hospital Institutional Review Committee. Participants were informed of study objectives, consent procedures, and potential benefits and harms, and their right to decline participation and/or withdraw at any time without fear of retribution or compromise to their cancer management plans. All participants provided informed individual consents with a signature or thumb print.

Results

Characteristics of participants

One hundred forty nine women with cervical cancer were included in the analysis. The mean age (±SD) was 48±13 years. 57% of participants were married; 45% reported no formal education and 89% were not formally employed. 72% of participants had five children or more while 39% of participants lived more than 100 kilometres from the study hospital (median distance=80km, range; 2-375km). Most participants had stage III (45%) or IV (21%) disease at diagnosis. Squamous cell carcinoma (75%) was the predominant histological subtype of cancer identified (Table 2).

Patients-related factors and cancer stage at diagnosis

Participants' socio-demographics

In bivariate analyses, participants with secondary and tertiary education were less likely to be diagnosed with advanced stage cancer compared with those who have not attained formal education (crude odds ratio = 0.16 (95%CI; 0.03-0.87). After adjusting for age, marital status and educational attainment, the odds of advanced stage cancer among patients with 5-9 children was 0.27 (95%CI: 0.08-0.96) times the odds of advanced cancer among women with less than four children (Table 3).

Initial symptoms attribution

Most participants (90.3%) didn't attribute their initial symptoms to cervical cancer (Table 4). After controlling for age, marital status, educational attainment and number of biological children, the odds ratio of advanced stage cervical cancer among patients who perceived their symptoms as due to a serious illness or cancer were 0.43 (0.20 – 0.96) as compared to those who perceived their symptoms as not due to a serious illness/cancer (Table 4).

Socio-economic factors

After adjusting for the patients' socio-demographics, patients who reported lack of money as reason for non-prompt health seeking were more likely to be diagnosed in advanced stage cervical cancer while those who perceived their symptoms as serious or due to cancer were less likely to be diagnosed in advanced stage cancer. The odds of advanced stage cancer among patients who self-reported financial difficulty is 5.7 times (95%CI: 1.58 – 20.64) that of the odds of advanced cancer among the patients who did not report financial difficulty as a reason for non-prompt health seeking (Table 4).

Health system factors and cancer stage at diagnosis

About 1 in 3 cervical cancer patients resided > 100 kilometres from study hospital (Table 2). About a quarter of the participants attended care for about 3 – 5 times before referral (Table 4). After controlling for patients' demographics, the odds of advanced stage cervical cancer among patients who were assigned pre-referral diagnoses of cancer is 13.04 times (95%CI: 3.59 – 47.30) the odds among those assigned non-cancer related diagnoses (Table 4).

Total time to diagnosis at study hospital (appraisal and help-seeking intervals)

More than half (55%) of the participants presented at the study hospital after 3 months or more from reported date of onset of symptoms. Of these, 71.8% (51/71) had advanced stage cervical cancer. Although not statistically significant, participants who took longer time to presentation tended to be diagnosed in advanced stage (Table 4).

Discussion

The study provides early insights about the range of psychosocial and healthcare factors that are likely to be associated with prolonged intervals and advanced stage at diagnosis of cervical cancer in Uganda, and should motivate the conduct of multi-site studies to establish more independent predictors of advanced stage cervical cancer at diagnoses in the LMICs. The findings suggest that several patient's characteristics (including age, educational attainment, marital status and number of biological children) and primary healthcare factors may influence diagnostic intervals, and the stage of cervical cancer at diagnosis. More than half of cervical cancer patients attending care at Lacor hospital during the study period were diagnosed in advanced stage.

The odds of advanced stage cancer were high among older women. Similarly, in Sudan, older age was found to be an independent predictor of advanced stage cervical cancer [16]. In other LMICs, older women were also found to have long help-seeking intervals for their symptoms and were more likely to be diagnosed with advanced stage cervical cancer [3, 16-18]. Older women are likely to be post-menopausal and may be less keen to seek care promptly for gynaecologic symptoms. We also found that women with secondary and tertiary education were less likely to be diagnosed with advanced stage cancer. Similarly, higher level of education was found to be associated with earlier stage at diagnosis in Nepal [1]. There is evidence that the association between low education level (or other markers of low socio-economic status) and advanced stage cervical cancer seem to be mediated by early onset of sexual activity among women with low education [19].

The odds of advanced stage cervical cancer among widowed and divorced women were 1.8 – 2.3 times the odds among the married women. Similar findings were reported in studies conducted in North Africa and India [18, 20]. In the North Africa study, unmarried women

were found to be five times as likely to be diagnosed in advanced stage compared to the married women [20]. Unmarried women in the United States were also more likely to be diagnosed with advanced stage cervical cancer [21]. Perhaps married women enjoy emotional and financial support from their spouses and therefore tend to seek help promptly. Evidence indicating a supportive role of husbands is alluded to by findings from Nepal where women who discussed their symptoms with friends were more likely to be diagnosed in advanced stage compared to those who discussed symptoms with their husbands [1]. Married women are perhaps less likely to ignore vaginal bleeding and pain because of associated discomfort during sexual intercourse. If married women have a higher frequency of intercourse, this may also lead to a higher symptom burden if the disease is present (e.g. painful intercourse, post-coital bleeding), therefore prompting earlier presentation.

Patients' attribution of their symptoms and perceptions of their likely causes may influence time to help-seeking and diagnosis of cancer. We found that patients who initially attributed their symptoms to sexually transmitted diseases and or who never perceived their symptoms as due to a serious illness or cancer were more likely to be diagnosed with advanced stage cervical cancer compared to those who didn't attribute their symptoms to STDs and those who perceived their symptoms as due to a serious illness or cancer. For instance, when adjusted for effect of age, marital status, educational attainment and number of biological children, women who perceived their symptoms to be due to a serious disease or cancer were statistically significantly less likely to be diagnosed in advanced stage (0.43: 95%CI; 0.20 – 0.96) compared to those who didn't perceive their symptoms as due to a serious illness or cancer. In a recent systematic review it was shown that non-recognition of symptoms seriousness was related with advanced stage cancer [22]. Similarly, patients with oral cancers did not initially take their symptoms seriously and attributed such symptoms to common oral conditions for which they responded by self-medication [23].

Apart from the socio-demographic characteristics of women, advanced stage at diagnosis may relate to other factors that prolong the help-seeking intervals, for example long distances from diagnostic facilities, lack of money for transport and medical bills and/or non-recognition of cancer symptoms by the primary healthcare professionals. Non-prompt help-seeking because of self-reported lack of money was associated with advanced stage at diagnosis. On adjusting for age, marital status, educational attainment and number of biological children, women who reported lack of money as reason for non-prompt help-seeking were 5.7 times more likely to be diagnosed with advanced stage cancer compared to those who did not report lack of money as reasons for non-prompt help-seeking. Similarly, financial constraints was reported as a main reason for not promptly seeking help in India even among patients who suspected cancer [24].

Delayed recognition and/or referral by primary healthcare clinicians can nonetheless lead to advanced cancer stage at diagnosis in the referral facilities. In this study, while about half of the cancer patients received pre-referral diagnoses of cancers at the primary healthcare facilities, the primary healthcare professionals did not recognize symptoms and or suspected cancer in the patients with early stage cancers and referred symptomatic patients with other diagnoses not related to cancer. On adjusting for age, marital status, educational attainment and number of biological children, the odds of advanced cervical cancer among patients assigned pre-referral diagnoses of cancer were 13 times the odds of advanced cancer among women who were assigned other pre-referral diagnoses not related to cancer. In Nepal, healthcare professionals in lower level units made other diagnoses in 90% of the initial pre-referral consultations by patients with cervical cancer symptoms and delayed referral to cancer diagnostic centre [1]. In a qualitative study in South Africa, primary healthcare professionals were also blamed for prolonged diagnostic intervals in symptomatic women [6]. Lack of specificity of cervical cancer symptoms and inadequate facilities to aid diagnosis of

cervical cancer by healthcare professionals may account for the misinterpretations of cervical cancer symptoms and subsequent diagnosis of non-cervical cancer conditions [25].

Strengths and limitations

Strengths to this study include the use of a theoretical model (Figure 1) to evaluate factors that may influence symptoms appraisal and help-seeking intervals. Furthermore, participants were prospectively recruited minimising methodological concerns associated with retrospective studies. Finally, diagnosis of cervical cancer was confirmed by tissue histology and examination following EUAs and this obviates possibilities of diagnostic misclassifications.

The findings are subject to potential recall or social desirability biases inherent in patient interview studies. Most patients presented at the study hospital long after onset of symptoms and could have had difficulty in recall of some events. We had no independent way to ascertain dates of first help-seeking in primary care units since records of the lower level health units were not accessible to us for independent verification. However, even when primary care records of patients subsequently diagnosed with cancer are used, there is still a potential for inaccurate measurement of patient interval in particular, and ideally both primary care and patient-reported data needed to be studied (which was impossible in our setting) [26].We facilitated recall accuracy by use of calendar landmark techniques and allowed time between disclosure of cancer diagnosis and questionnaire administration [27]. In addition, other diseases that present with similar symptoms to what have eventually been diagnosed as cervical cancer could also affect determining the exact time when the actual symptoms of cervical cancer could have started. Measurement of time of onset of symptoms and time intervals during help-seeking is known to be challenging [25]. Second, this was a hospital-based study involving a selected population of women who had reached the hospital.

The characteristics of women who may have cervical cancer but have not reached the study hospital remain unknown. Generalization of these findings needs to take these issues into consideration.

Implications of findings

This study provides an initial experience with the conduct of such studies, proving both their feasibility and the need for larger and multi-site data collection. Acknowledging power limitations, the findings suggest that advanced stage at diagnosis and long help-seeking intervals could be attributable to patients' misattributions of their symptoms, primary healthcare providers treating cervical cancer symptoms for different common conditions, and a lack of prompt healthcare seeking mainly because of lack of money for transport and medical bills. These findings may have far-reaching implications for clinical care, public health and policy. First, interventions to increase symptoms' recognition need to target both women and clinicians and may take the form of public awareness campaigns and continuous professional development (CPD) for healthcare professionals, respectively. Women who are older, with no or low levels of formal education and widowed/divorced may constitute a special group for interventions to promote prompt help-seeking and diagnosis of cervical cancer. Second, to reduce the proportion of advanced stage cervical cancer at diagnoses, policymakers in the LMICs ought to prioritize cervical cancer control programs that include establishment of population-based cervical screening and prompt treatment of pre-invasive and early invasive cervical lesions. However, in the meantime, policies on cervical cancer early detection of pre-invasive and early invasive lesions through scheduled CPDs to healthcare professionals and public awareness campaigns on cervical cancer to the public can be adopted as they have been shown to be feasible and affordable and can lead to increased survival from cervical cancer [28].

Future studies in Uganda and other LMICs seeking to detect and explain independent predictors of advanced stage cervical cancer may need to include interviews of the primary healthcare providers in the lower level health facilities in order to provide corroborating evidence and establish reasons for long patient intervals in patients with symptoms of cancer.

Competing interest

The authors declare that they have no competing interest.

Author contributions

ADM spearheaded the study design, data collection, analysis and drafting of manuscript. COG, HW, GL and MR participated in study design and critical review of manuscript. EMW prepared database, supervised data entry and prepared data for analysis. All authors read and approved the final manuscript and agreed on its submission.

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Data sharing

No additional data available.

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Table 1: Operational definitions

Term/concept	Definition	Author
Date of first symptom	The date or estimated time in the week, month or year when the patient first felt a bodily change requiring discussion with a healthcare professional and/or with another person with the intention of gaining understanding of the symptoms and/or how to deal with them.	Weller, D., et al [12]
Patient interval	The time period from detection of abnormal bodily sensations to time of visiting first healthcare professional to discuss the symptoms including the period from lower level units to the study hospital for diagnosis of cancer	Weller, D., et al [12]
Date of first presentation	The time point in the week, month or year including a particular date when the patient first visited a healthcare professional in a private or public health facility to discuss the symptoms which she had and which have since been attributed to cervical cancer at the study hospital.	Weller, D., et al [12]
Date of diagnosis	Date when examinations under anaesthesia for clinical diagnosis and staging was done.	Weller, D., et al [12]
Pre-referral consultations	Any visits to a healthcare professional in an established healthcare setting including lower level healthcare facilities and private clinics before presentation and diagnosis in the study hospital.	Lyratzopoulos, G., et al[13]
Pre-referral suspicion or diagnosis of cancer	Any reports by participants referring to being told of a cancer diagnosis by primary healthcare professionals before referral to study hospital.	

Table 2: Demographic characteristics of patients and disease characteristics

Characteristics	Number (N = 149)	Percentage
Age group (Years)		
18 – 29	7	4.7
30 – 44	52	34.6
45 – 59	63	42.7
≥ 60	25	16.7
Missing	2	1.3
Mean age (±SD) years	48.4±12.6	
Median age	49.0 (23 – 80)	
Marital status		
Married	84	56.4
Divorced	21	14.1
Widowed	44	29.5
Mean age at marriage (years)	17.7±2.3	
Median age 18 (13 – 27)		
Education attainment		
No formal education	67	45.0
Primary education	72	48.3
Secondary education	7	4.7
Tertiary education	2	1.3
Missing	1	0.7
Occupation		
Housewife/peasant	132	88.6
Petty trader	10	6.7
Formally employed	4	2.7
Missing	3	2.0
Number of biological children		
No child	2	1.3
1 – 4	28	18.7
5 - 10	108	72.0
11 - 15	10	6.7
Missing	1	0.7
Stage of cancer at diagnosis (FIGO)		
Stage I	17	11.4
Stage II	29	19.5
Stage III	67	45.0
Stage IV	31	20.8
Missing	5	3.3
Histological subtypes		
Squamous cell carcinoma	111	74.5
Adenocarcinoma	12	8.1
Anaplastic type	1	0.7
Missing	25	16.7
Estimated distance from home to study hospital (Kilometres)		
Less than 40	41	27.5
40 - 80	35	23.5
81 - 100	13	8.7
101 - 375	58	38.9
Missing	2	1.3
Median (Range)	80 (2 – 375)	

Table 3: Adjusted odds ratio for patients' socio-demographic characteristics and stage at diagnosis

Patient demographic characteristics	Population responding	Cancer stage at diagnosis		Crude OR (COR) (95% CI)	Adjusted OR (AOR) (95% CI)*
		Early stage Number (%)	Advance stage Number (%)		
Age group (years)					
< 30	6 (4.2)	3 (6.5)	3 (3.1)	1.00	1.00
30 – 59	111 (78.2)	40 (87.0)	71 (74.0)	1.78 (0.34 – 9.21)	2.62 (0.33 – 21.1)
≥ 60	25 (17.6)	3 (6.5)	22 (22.9)	7.33 (0.99 – 54.4)	9.82 (0.81 – 118.9)
Marital status					
Married	81 (56.3)	31 (67.4)	50 (51.0)	1.00	1.00
Divorced	19 (13.2)	4 (8.7)	15 (15.3)	2.32 (0.71 – 7.65)	1.81 (0.49 – 6.72)
Widowed	44 (30.5)	11 (23.9)	33 (33.7)	1.86 (0.82 – 4.21)	1.26 (0.51 – 3.12)
Education attainment					
No formal education	67 (48.2)	22 (47.8)	45 (46.4)	1.00	1.00
Primary education	68 (47.6)	18 (39.1)	50 (51.6)	1.36 (0.65 – 2.85)	1.44 (0.62 – 3.34)
Secondary and/or tertiary education	8 (5.6)	6 (13.0)	2 (2.0)	**0.16 (0.03 – 0.87)**	0.18 (0.03 – 1.22)
Number of biological children					
0 – 4	28 (19.6)	5 (11.1)	23 (23.5)	1.00	1.00
5 – 9	89 (62.2)	34 (75.6)	55 (56.1)	0.35 (0.12 – 1.01)	**0.27 (0.08 – 0.96)**
10 – 15	26 (18.2)	6 (13.3)	20 (20.4)	0.72 (0.19 – 2.74)	0.45 (0.1 – 2.09)

***Adjusted for age, marital status, education attainment and number of biological children.**

Table 4: Primary care factors and stage at diagnosis

Primary care factors	Population responding	Cancer stage at diagnosis		Crude OR (COR) (95% CI)	Adjusted OR* (95% CI)
		Early stage Number (%)	Advanced stage Number (%)		
Symptoms were initially attributed by the patient to:					
Sexually transmitted diseases					
No	121 (84.0)	41 (89.1)	80 (81.6)	1.00	1.00
Yes	23 (16.0)	5 (10.9)	18 (18.4)	1.85 (0.64 – 5.32)	3.24 (0.93 – 11.32)
Cancer					
No	130 (90.3)	39 (84.8)	91 (92.9)	1.00	1.00
Yes	14 (9.7)	7 (15.2)	7 (7.1)	0.43 (0.14 – 1.30)	0.30 (0.08 – 1.16)
Pre-referral diagnoses by primary healthcare professional					
Non-cancer related	21 (15.4)	16 (37.2)	5 (5.4)	1.00	1.00
Cancer diagnosis	75 (55.2)	16 (37.2)	59 (63.4)	**11.8 (3.75 – 37.12)**	**13.04 (3.59 – 47.30)**
Not told diagnosis	40 (29.4)	11 (25.6)	29 (31.2)	**8.44 (2.10 –28.6)**	**8.35 (2.13 – 32.79)**
Number of pre-referral visits at primary healthcare facilities					
Once	54 (48.2)	17 (43.6)	37 (50.7)	1.00	1.00
Twice	29 (25.9)	13 (33.3)	16 (21.9)	0.57 (0.22 – 1.43)	0.68 (0.24 – 1.94)
Three to five or more	29 (25.9)	9 (23.1)	20 (27.4)	1.02 (0.39 – 2.70)	0.87 (0.28 – 2.65)
Health seeking interval (months)					
< 3	59 (45.4)	23 (53.5)	36 (41.4)	1.00	1.00
3 – 6	51 (39.2)	15 (34.9)	36 (41.4)	1.53 (0.69 – 3.41)	1.55 (0.62 – 3.86)
7 – 24	20 (15.4)	5 (11.6)	15 (17.2)	1.92 (0.61 – 5.99)	1.93 (0.52 – 7.23)
Reasons for lack of promptness in seeking care					
Lack of money					
No	108 (75.0)	43 (93.5)	65 (66.3)	1.00	1.00
Yes	36 (25.0)	3 (6.5)	33 (33.7)	**7.28 (2.10 – 25.22)**	**5.70 (1.58 – 20.64)**
Still using other treatments					
No	84 (58.3)	23 (50.0)	61 (62.2)	1.00	1.00
Yes	60 (41.7)	23 (50.0)	37 (37.8)	0.61 (0.30 – 1.23)	0.66 (0.30 – 1.43)
Perceived illness as not serious or cancer					
No	86 (59.7)	20 (43.5)	66 (67.4)	1.00	1.00
Yes	58 (40.3)	26 (56.5)	32 (32.6)	**0.37 (0.18 – 0.77)**	**0.43 (0.20 – 0.96)**

***:** Odds ratio adjusted for patients' socio-demographic characteristics in table 3.

Figure 1: Model of Pathways to Treatment

Figure 1 – Model of Pathways to Treatment [18]

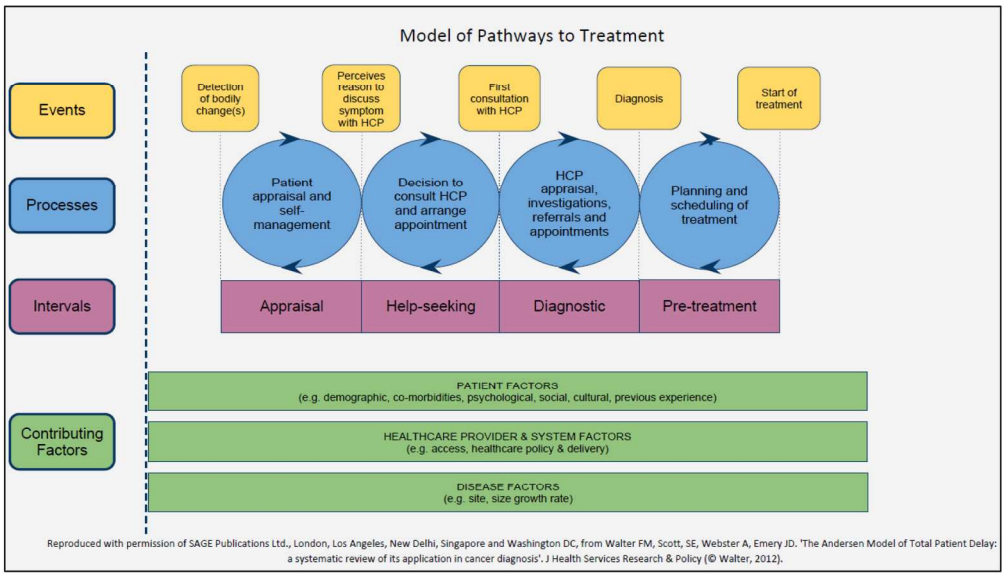

Figure 1: Model of Pathway to Treatment
170x119mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items in included: Cervical cancer stage at diagnosis and associated factors

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 & 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7 & 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 & 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Not applicable
Bias	9	Describe any efforts to address potential sources of bias	*8, & 15*
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 & 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9 & 10
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable

		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 & 8
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	10 & 24
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10 & 11; 25 & 26
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16 & 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15 & 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.