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Patterns and associated factors of advanced stage at diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population based study

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Abstract

Objective: To describe the patterns and associated factors of advanced stage at diagnosis of cervical cancer in Addis Ababa, Ethiopia

Design: A population based cross sectional study

Setting: The study was conducted in seven prominent cancer diagnosing health facilities in Addis Ababa, Ethiopia.

Participants: All histopathology confirmed incident cervical cancer patients diagnosed from January 2017 to June 2018 among Addis Ababa residents were included.

Outcome measures: A face to face interview was administered to the patients using a structured questionnaire. Additional clinical data were extracted from patients' medical records. Stage at diagnosis was grouped into early (Stage I and II) and advanced (Stage III and IV) according to FIGO staging criteria. Factors associated with advanced stage at diagnosis were examined by multi-variable analysis using Poisson regression with robust variance model.

Results: The mean age of the study participants was 52.9 years (±13.3 years). Nearly two-thirds (60.4%, 95% CI; 53.8%, 66.5%) of patients with cervical cancer were diagnosed at an advanced stage of the disease. Advanced stage at diagnosis was significantly associated with paying medical bill out of pocket (adjusted prevalence ratio (APR) = 1.44, 95% CI; 1.08, 1.91), diagnostic interval >90 days (APR = 1.31, 95% CI; 1.04, 1.71), practicing in religious activities or not taking immediate action following symptom recognition (APR = 1.25, 95% CI; 1.08, 1.91), and visiting more than three different health facilities prior to diagnostic confirmation (APR = 1.24, 95% CI; 1.07, 1.51).

Conclusion: The findings of the study underscore the need to take measures to shorten diagnostic waiting times for cervical cancer, increase the affordability of cancer care and creating awareness on the severity of cervical cancer in addition to screening options.

Key words: Stage at diagnosis, Advanced stage, Delays, Cervical cancer

Article Summary

Strengths and limitations of this study

- It is the first population based study to describe the patterns and associated factors of stage at diagnosis among incident histologically confirmed cervical cancer cases in Addis Ababa, Ethiopia
- The patients were recruited prospectively and primary data collection methods were used.
- Some patients might never have visited the health facilities and were not included in our study.
- Recall bias on the dates of symptom recognition and presentations might have also affected our findings.

Funding statement

This work was supported by American Cancer Society

Conflict of interest

The authors declare that they have no conflict of interests.

Word count of main text: 2011

Introduction

Cervical cancer is the second leading cause of cancer death in females in Ethiopia and other parts of Africa [1, 2]. Although cervical cancer can be prevented by detecting and removal of precancerous lesions and treated successfully if detected early [3], majority of patients in Ethiopia [4, 5] and many other parts of Africa are diagnosed at advanced stage of the disease [6-9], when the choice of treatment is limited and the probability of survival is poor. However, the findings on stage distribution in Ethiopia and in most parts of Africa are based on hospital-based studies rather than population-based studies and they cannot be generalizable.

Several previous studies from Sub-Saharan Africa countries associated advanced-stage cervical cancer diagnosis with low-level community awareness of the disease [10] and with lack of screening services and diagnostic facilities [8, 11]. No previous study in the region, however, examined the associations between advanced-stage diagnosis and source of medical bill coverage, and other health-related patient behaviours and health system factors such as delay in seeking medical consultation after recognition of symptoms and delay in receipt of diagnostic confirmation after healthcare provider consultation. Therefore, this study was conducted (1) to describe the stage distribution of cervical cancer (2) to identify factors associated with advanced stage of the disease in Addis Ababa, capital city of Ethiopia using all patients diagnosed from January 2017 through June 2018 among the residents of the city.

Methods

A multi-center prospective cross-sectional study was conducted among all newly diagnosed patients with cervical cancer among Addis Ababa residents during the 18 months study period from January 1, 2017 to June 30, 2018. There were 234 newly diagnosed patients during the

study period; however, three of them were not included in our study due to their plan to initaite treatment out of Ethiopia. Also 19 patients without stage information were excluded from the study. The study participants were recruited from seven major public and private health facilities in the city (representing 99% of cervical cancer incident cases among Addis Ababa residents). Recruiting and tracing of the patients were guided by the Addis Ababa population-based cancer registry [12].

All the cervical cancer cases were confirmed by histopathology and staged according to FIGO by senior gynecological oncologist or clinical oncologist [13]. Distance metastasis (Stage IVb) was determined by reviewing chest x-ray and abdominal ultrasound findings [14].

The ethical approval of this study was obtained from the institutional review board of Addis Ababa University College of Health Sciences. Written informed consent of the study participants was also obtained. Data from the cervical cancer patients were collected by using structured questionnaire, which was developed by reviewing previously conducted related articles [9, 11]. Initially the questionnaire was prepared by English and later translated to Amharic, the national language. Consistency of the questionnaire translation was checked by back translation by independent translator and its contents were validated by the experts (gynecologists and oncologists). A Face to face interview was administered by trained nurse interviewers at around the time of diagnosis.

For extracting patients' clinical information, medical charts were reviewed and data were extracted by junior oncologists (residents) using a structured checklist. Any inconsistency in the patient information was resolved by consulting senior oncologists during the data extraction. The histological results were extracted from the pathology reports.

Total diagnostic interval was defined as an interval from first date of symptom recognition by the patients to the histological confirmation of the diagnosis. Total diagnostic interval was considered delayed if the interval was >90 days [15-17].

The outcome variable of the study was stage at diagnosis, which was grouped in to two as early (stage I/II) and advanced (stage III/IV). The independent variables considered were: socio-demographic variables (age, educational status, marital status, family income, source of medical expense coverage), tumour related variables (tumour type), patient related factors (comorbidity, diagnostic delays and number of health facility visited prior to diagnostic confirmation).

Descriptive analyses were used to calculate summary statistics of frequencies, proportion, median, mean and standard deviations. Bivariate and multi-variable analysis using a Poisson regression with robust variance method were used to identify factors associated with patient's being at an advanced stage of cervical cancer at diagnosis. The Poisson regression with robust variance method was used to directly estimate the prevalence ratio (the effect measure), since the odds ratio (logistic regression) over-estimates the effect when the prevalence (magnitude) of the outcome variable is not rare (>10%) [18]. Those variables with p value <0.25 in the bivariate analysis were considered for the multi-variable analysis in the Poisson regression model. Level of significance was set at p – value below 0.05 at 95% CI and prevalence ratio (PR) was used to quantify the strength of association for each of the variables. Post estimation fitness of model was checked by chi-square based goodness of fit test and the final model was found to be fit (p value = 0.95). There were no multicollinearity between the variables using the collinearity diagnostics (variance inflation factors (VIF) and tolerance). In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Patient and public involvement

Neither patients nor public were involved in the design of this study.

Results

Socio-demographic and clinical characteristics

The mean age of the study participants (n = 212) was 52.9 years (±13.3 years), where the majority of the patients with cervical cancer were below 60 years old (68.4%), Christians (91.5%), and housewives (63.2%). More than two-thirds (67.5%) of the patients had a family monthly income below 3200 ETB (100 USD) and more than two-thirds (68.4%) were not entitled to free medical service. Only 2.8% of the patients have a family history of cervical cancer. Majority of the patients (98.6%) were non-smokers, however about a quarter (23.6%) of the patients were alcohol users. More than two-thirds (68.4%) of patients pay their medical expenses out of their pockets (Table 1). More than two-thirds (69.8%) of the patients had tumor size of greater than 4cm. Majority of the cervical cancer cases (91.0%) had a squamous cell carcinoma. About one in five (21.7%) cervical cancer patients were HIV positive and all were on antiretroviral therapy (ART).

Table 1: Socio-demographic and clinical characteristics of patients with cervical cancer in Addis Ababa

Variables	Frequency (percent)
Age	
<40 years	42 (19.8%)
40 – 59 years	103 (48.6%)

≥60 years	67 (31.6%)
Formal education	
No	86 (40.6%)
Yes	126 (59.4%)
Family monthly income	
≤3200 ETB	143 (67.5%)
>3200 ETB	69 (32.5%)
Source of medical expenses	
Out of pocket	145 (68.4%)
Free/insured	67 (31.6%)
Immediate action after symptom recognition	
Went to health facility	149 (70.3%)
No action/ Religious activity	63 (29.7%)
Number of different health facilities visited before diagnostic conformation	
≤3 health facilities	142 (67.0%)
>3 health facilities	70 (33.0%)
Diagnostic interval	
≤90 days	68 (32.1%)
>90 days	144 (67.9%)
HIV infection	
Yes	46 (21.7%)
No	166 (78.3%)
Tumor size	
≤4cm	64 (30.2%)
>4cm	148 (69.8%)

Stage at diagnosis of cervical cancer

Nearly two out of three (60.4%, 95% CI; 53.8%, 66.5%) patients with cervical cancer were diagnosed at advanced stage of cancer, majority of them (37.3%) being diagnosed at stage IV (Figure 1). About 5.2% of the patients with cervical cancer had metastasized cancer to lung (2.4%), liver (2.4%) and peritoneum (0.5%) at their diagnosis.

Factors associated with advanced stage at diagnosis of cervical cancer

In a bivariate analysis, advanced stage at diagnosis (stage III-IV) was significantly associated with source of medical expenses, not going to health facilities immediately after symptom recognition, visiting more than 3 different health facilities before diagnostic confirmation and total diagnostic interval >90 days (Table 2).

Table 2: Bivariate association between advanced stage diagnosis of cervical cancer and demographic and clinical characteristics in Addis Ababa, Ethiopia, 2018

Variables	**Advanced stage**		***P* value**
	Yes	**No**	
Source of medical expenses			
Out of pocket	99 (68.3%)	46 (31.7%)	0.001
Free/insured	29 (43.3%)	38 (56.7%)	
Age			
<40 years	16 (38.1%)	26 (61.9%)	
40 – 59 years	42 (40.8%)	61 (59.2%)	0.94
≥60 years	26 (38.8%)	41 (61.2%)	

Formal education			
No	54 (62.8%)	32 (37.2%)	0.51
Yes	74 (58.7%)	52 (41.3%)	
Spouse living together			
Yes	48 (56.5%)	37 (43.5%)	
No	80 (63.0%)	47 (37.0%)	0.42
Family monthly income			
≤3200 ETB	88 (61.5%)	55 (38.5%)	0.73
>3200 ETB	40 (58.0%)	29 (42.0%)	
Immediate action after symptom recognition			
Went to health facility	80 (53.7%)	69 (46.3%)	0.008
No action/ Religious activity	48 (76.2%)	15 (23.8%)	
Number of different health facilities visited before diagnostic conformation			
≤3 health facilities	77 (54.2%)	65 (55.8%)	0.006
>3 health facilities	51 (72.9%)	19 (27.1%)	
Diagnostic interval			
≤90 days	33 (48.5%)	35 (51.5%)	0.02
>90 days	95 (66.0%)	49 (34.0%)	
HIV infection			
Yes	31 (67.4%)	15 (32.6%)	0.35
No	97 (58.4%)	69 (41.6%)	

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In the multi-variable analysis (Table 3), the proportion of advanced stage at diagnosis of cervical cancer was 1.4 times higher (Adjusted Prevalence Ratio (APR) = 1.44, 95% CI; 1.08, 1.91) among those women who paid their medical expenses out of their pocket as compared to those women who were entitled to free medical service or having health insurance coverage, and it was 1.3 times higher (APR = 1.31, 95% CI; 1.04, 1.71) among women with total diagnostic interval of >90 days than those with ≤ 90 days. Similarly, the proportion of being diagnosed at an advanced stage of cervical cancer was 1.25 times higher (APR = 1.25, 95% CI; 1.05, 1.53) among those women who went to religious practices or do nothing immediately after their symptom recognition as compared to those women who immediately went to the health facilities, and 1.2 times higher (APR = 1.24, 95% CI; 1.08, 1.91) among those women who visited more than three different health facilities prior to diagnostic confirmation compared to those who visited ≤3 health facilities.

Table 3: Multi-variable analysis showing factors associated with advanced stage at diagnosis of cervical cancer in Addis Ababa residents, 2018

Variables	**Advanced stage**		**Crude PR (95% CI)**	**Adjusted PR (95% CI)**	***P* value**
	Yes	No			
Medical expenses					
Out of pocket	99	46	1.54 (1.15, 2.05)	1.44 (1.08, 1.91)	0.003
Free/insured	29	38	1.00	1.00	
Immediate action after symptom					
Went to health facility	80	69	1.00	1.00	

No action/ Religious activity	48	15	1.38 (1.13, 1.69)	1.25 (1.05, 1.53)	0.02
Number of health facilities contacted					
≤3 health facilities	77	65	1.00	1.00	
>3 health facilities	51	19	1.35 (1.10, 1.65)	1.24 (1.07, 1.51)	0.01
Diagnostic interval					
≤90 days	33	35	1.00	1.00	
>90 days	95	49	1.45 (1.10, 1.91)	1.31 (1.04, 1.71)	0.02

Discussion

The present study provides data on cervical cancer stage distribution in Addis Ababa along with its predictors based on a prospective, population-based, representative sample and primary data sources. We found that nearly two-thirds of the patients with cervical cancer in Addis Ababa were diagnosed at an advanced stage of the disease, and that financial hardship to cover medical expenses and delays in diagnosis are major contributors to advanced stage at diagnosis.

Although our finding of high proportion of advanced-stage cervical cancer in Addis Ababa is generally similar to findings from other sub-Saharan African countries [8, 11], it is slightly higher than that reported from Kenya (53.9%) [9] and lower than that reported from Sudan (71.5%) [19]. The higher proportion in Sudan in part reflects the predominantly rural resident study participants, where access to health facilities is limited and health literacy is expected to be lower. In contrast, the lower proportion in Kenyan study may reflect the higher coverage of

recent cervical cancer screening program in the country (14%) [20] as compared to Ethiopia (0.6%) [21]. Additionally, the screening program created awareness on cervical cancer [20].

Our finding also showed that the proportion of advanced stage cervical cancer was considerably higher among women who waited for more than three months to receive diagnostic confirmation after they noticed symptom compared to those waited for ≤3 months. Such long diagnostic waiting time, which may lead to migration to higher-stage disease, in part reflects lack of knowledge about cervical cancer among the general population and healthcare providers, as well as lack of diagnostic infrastructure in the country [10]. These underscore the need for programs to enhance knowledge of cervical cancer in the community in order to shorten delays in the diagnosis of the disease.

More than four out of five patients, who went to practice religious activities immediately after symptom recognition, were found to be diagnosed at advanced stage of cervical cancer. In Ethiopia, it is common to see patients going to religious activities as a solution for their disease [22]. This can affect their prompt health-seeking behavior and may contribute to advanced stage at diagnosis. A qualitative study from Ethiopia reported that patients with cervical cancer have a strong belief that *Tsebel* (holy water)" will cure from the disease [10]. Similarly, seeking traditional and religious practices for cervical cancer care have been associated with advanced-stage disease in other parts of Africa [8].

Financial hardship is barrier to accessing health, leading to cancer progression and poor outcome [23]. Consistent with our findings, previous studies conducted in Sudan [19] and Uganda [11] associated advanced stage with financial difficulties or being uninsured. Other study conducted among gynecologic cancer patients also reported that women with financial hardship are seven

times more likely to avoid or delay their cancer care [24]. Providing free diagnostic and treatment services to all women with cervical cancer needs to be incorporated into the governments´ strategy on cervical cancer care. This will be in line with the WHO's global efforts to ensure universal health coverage [25].

The strengths of this study are the use of population-based cancer registry and rigorous and multiple data collection methods (patients' interview and medical record review) in a prospective approach to document strong association between late-stage diagnosis and patient and health system factors, including diagnosis delay, in African settings. However, the study has limitations because some patients might never have visited the health facilities and were not included in our study. Recall bias on the dates of symptom recognition and presentations might have also affected our findings.

Conclusions

Using a population-based study, we found that more than two-third of cervical cancer patients in Addis Ababa are diagnosed at advanced stage of the disease, which was strongly associated with diagnostic delay, failure to take immediate action following symptom recognition, and paying medical bill out of pocket. These findings underscore the need to take measures to enhance awareness about the severity of the disease and preventive measures among the general population and healthcare providers, expand the availability of screening services, and increase the affordability of cancer care in the city. Of note, implementing free diagnostic service would ensure accessibility to care for increasing number of patients with precancerous lesion or early-stage disease through the ongoing up scaled screening program by the Ethiopian government.

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Wachemo University (Approval number: WCU/IRB/086/17). All participants of the study were informed about the study and they gave their written consent to be included in the study.

Consent for publication

Not applicable

Availability of data and material

Data can be obtained from the corresponding author upon reasonable request.

Author contributions

ND, AG, AA, AW, MA, AJ were involved in the conception of the study, methodological design of the study, analysis and interpretation of data, and manuscript writing. AA, WT, EK were involved in the methodology of the study, data collection/extraction, visualization of the data and interpretation of the data. All authors have revised the manuscript.

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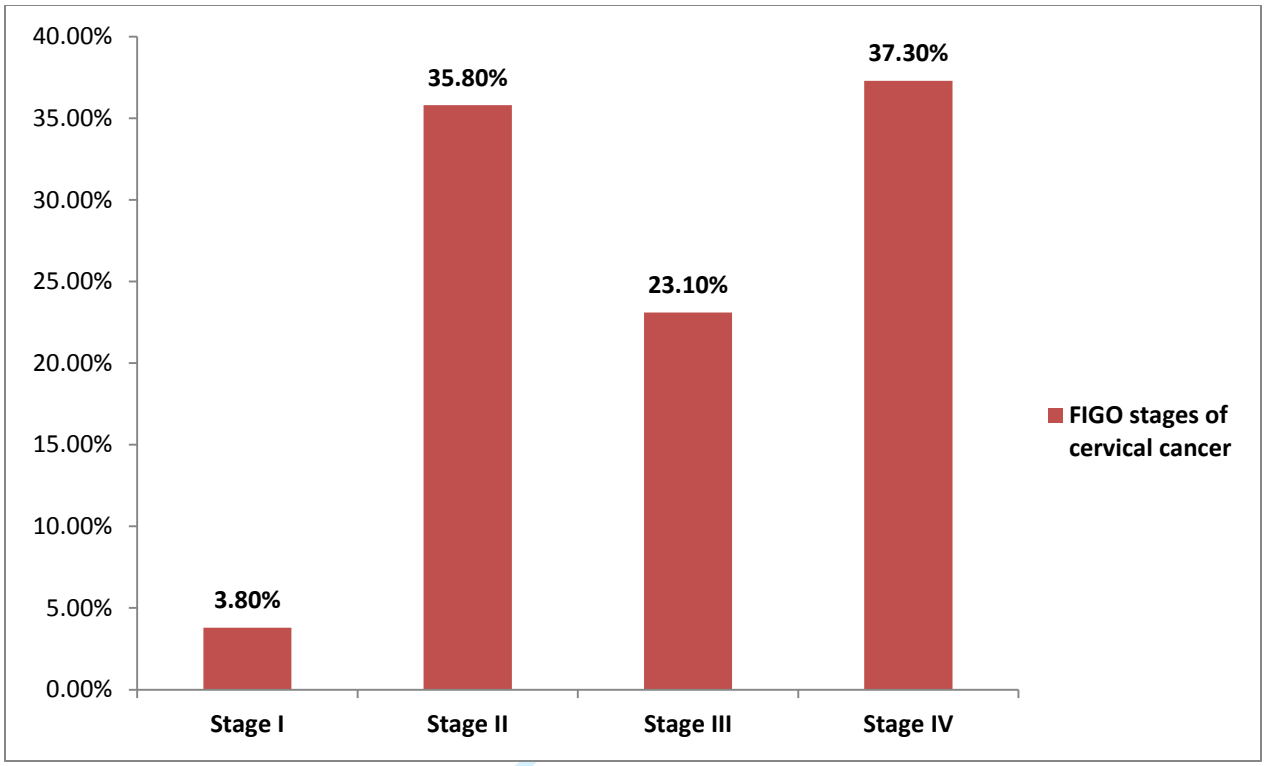
Legend of Figure

Figure 1: FIGO stages of cervical cancer at diagnosis of patients residing in Addis Ababa, 2018



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, Page No.1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, Page No.2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, Page No. 4, Paragraph 1 and 2	
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, Page No. 4, Paragraph 2	
Methods				
Study design	4	Present key elements of study design early in the paper	Methods, Page No. 5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, Page No. 5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods, Page No. 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Data management and analysis, Page No. 6	
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	Methods, Data tools and procedures, Page No. 5	
Bias	9	Describe any efforts to address potential sources of bias	Methods, Data tools and procedures, Page No. 5; Data management and analysis, Page No. 6	
Study size	10	Explain how the study size was arrived at	Methods, Page No. 5, study setting	

			and design	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, Data management and analysis, Page No. 6	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, Data management and analysis, Page 6	
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, Data management and analysis, Page No. 6	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, Page No. 7 and 8	
		(b) Indicate number of participants with missing data for each variable of interest	Results, Page No. 7 and 8	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*N/A*	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*N/A*	
		Cross-sectional study—Report numbers of outcome events or summary measures	Results, Page No. 8	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, Page No. 8	
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	
Discussion				
Key results	18	Summarise key results with reference to study objectives	Discussion, Page No. 9, first paragraph	
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	Discussion, Page No. 11, last paragraph	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusions, Page No. 11	
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, Page No. 11, last paragraph	
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	Source of funding, Page No. 12	

*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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Factors associated with advanced stage at diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population-based study

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Abstract

Objective: To describe the patterns and associated factors of advanced stage at diagnosis of cervical cancer in Addis Ababa residents, Ethiopia

Design: A population based cross sectional study

Setting: Seven major hospitals or diagnostic facilities in Addis Ababa, Ethiopia.

Participants: All histopathology confirmed incident cervical cancer patients diagnosed from January 01, 2017 to June 30, 2018 among Addis Ababa residents.

Outcome measures: The proportion of cervical cancer patients diagnosed at early-stage (Stage I and II) and advanced-stage (Stage III and IV) diseases according to FIGO staging criteria, and adjusted prevalence ratio (APR) for factors associated with advanced-stage diagnosis using Poisson regression with robust variance model.

Results: The mean age of the study participants was 52.9 years (±13.3 years). Nearly two-thirds (60.4%, 95%CI; 53.8%, 66.5%) of patients with cervical cancer were diagnosed at an advanced stage of the disease. Advanced stage at diagnosis was significantly associated with paying medical bill out of pocket (APR = 1.44, 95%CI; 1.08, 1.91), diagnostic interval >90 days (APR = 1.31, 95%CI; 1.04, 1.71), practicing religion as a remedy or not taking immediate action following symptom recognition (APR = 1.25, 95%CI; 1.08, 1.91), and visiting >3 different health facilities prior to diagnostic confirmation (APR = 1.24, 95%CI; 1.07, 1.51).

Conclusion: Our findings of the high proportion advanced-stage diagnosis of cervical cancer in Addis Ababa and its strong associations with out of pocket medical bill, seeking care out of conventional medicine settings, and multiple visits to healthcare facilities before diagnostic

confirmations underscore the need for public policies to improve the affordability of cancer care, and enhance community awareness about the severity of the disease and referral system, in addition to expanding cervical cancer screening.

Key words: Stage at diagnosis, Advanced stage, Delays, Cervical cancer

Article Summary

Strengths and limitations of this study

- It is the first population-based study to describe factors associated with advanced stage cervical cancer diagnosis in African setting.
- All cervical incident cases in Addis Ababa may not have been included in the study because some patients might never have visited healthcare facilities or visited local healthcare facilities that do not report incident cancers to the central cancer registry.
- Recall bias about dates of symptom recognition and of presentations might have also affected our findings.

Funding statement

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Conflict of interest

The authors declare that they have no conflict of interests.

Word count of main text: 2050

Introduction

Cervical cancer is the second leading cause of cancer death in females in Ethiopia and other parts of Africa (1, 2). Although cervical cancer can be prevented by detection and removal of precancerous lesions and treated successfully if detected early (3), the majority of patients in Ethiopia (4, 5) and many other parts of Africa are diagnosed at advanced stage of the disease (6-9), when the choice of treatment is limited and the probability of survival is poor. Previous findings on stage distribution in Ethiopia and in most parts of Africa, however, may not be generalizable as they were hospital-based studies rather than population-based studies.

Several previous studies from Sub-Saharan Africa countries associated advanced-stage cervical cancer diagnosis with low-level community awareness of the disease (10) and with lack of screening services and diagnostic facilities (8, 11). No previous study in the region, however, examined the associations between advanced-stage diagnosis and source of medical bill coverage, and other health-related patient behaviours and health system factors such as delay in seeking medical consultation after recognition of symptoms and delay in receipt of diagnostic confirmation after healthcare provider consultation. Therefore, this study was conducted to describe the stage distribution of cervical cancer in Addis Ababa residents and to identify factors associated with advanced stage of the disease based on all incident cancer cases diagnosed from January 01, 2017 through June 30, 2018 among the residents of the city.

Methods

A multi-center cross-sectional study was conducted among all newly diagnosed patients with cervical cancer among Addis Ababa residents during the 18 months study period from January 1, 2017 to June 30, 2018. Patients were considered to be residents of the city if they lived at least 6 months before date of diagnosis. Study participants were recruited from seven major hospitals or diagnostic facilities aided by the Addis Ababa Population-based Cancer Registry, which actively registers all incident cancer cases among the residents of the city (12). During the study period, 234 histopathologically comfirmed newly diagnosed patients were recorded in the registry. Of these patients, 22 patient were excluded from the study because of they sought treatment abroad (3 patients) or because of lack of stage information in their medical records (19 patients). .

All the cervical cancer cases were confirmed by histopathology and staged according to the 2014 International Federation of Gynaecology and Obstetrics (FIGO) criteria by senior gynaecological oncologist or clinical oncologist (13). In addition to physical examination, distant metastasis (Stage IVb) was determined by reviewing chest x-ray and abdominal ultrasound findings (14).

The ethical approval of this study was obtained from the Institutional Review Board of Addis Ababa University College of Health Sciences. Written informed consent of the study participants was also obtained. A face to face interview was administered by trained nurse interviewers at around the time of diagnosis to collect data on socio-demographic and health behaviors using a structured questionnaire, adapted from previous surveys (9, 11). Initially the questionnaire was prepared by English and later translated to Amharic, the national language. Consistency of the questionnaire translation was checked by back translation by an independent translator and its contents were validated by the experts (gynaecologists and oncologists).

Patient's clinical characteristics were extracted from medical charts by junior oncologists (residents) using a structured checklist and any inconsistencies was resolved by consulting senior oncologists. Information on histology type and date of diagnostic confirmation was obtained from pathology reports.

Total diagnostic time interval was defined as the interval from t date of first symptom(s) recognition by the patient to date of the histological confirmation of the diagnosis. Total diagnostic interval was considered delayed if the interval was >90 days (15-17).

The main outcome variable of the study was stage at diagnosis, which was grouped in to two: early (stage I/II) and advanced (stage III/IV). The independent variables include socio-demographic characteristics (age, educational status, marital status, family income, source of medical expense coverage), clinical characteristics (histologic type, comorbidity), and other patient or provider related factors (diagnostic delays and number of health facility visited prior to diagnostic confirmation).

Descriptive analyses were used to calculate summary statistics of frequencies, proportion, median, mean and standard deviations. Bivariate and multi-variable analysis using a Poisson regression with robust variance method were used to identify factors associated with patient's being at an advanced stage of cervical cancer at diagnosis. The Poisson regression with robust variance method was used to directly estimate the prevalence ratio (the effect measure), since the odds ratio (logistic regression) over-estimates the effect when the prevalence (magnitude) of the outcome variable is not rare (>10%) (18). Those variables with p value <0.25 in the bivariate analysis were considered for the multi-variable analysis in the Poisson regression model. Level of significance was set at p – value below 0.05 at 95% CI and prevalence ratio (PR) was used to quantify the strength of association for each of the variables. Post estimation fitness of this model

was checked by chi-square based goodness of fit test and the final model was found to be fit (*p* value = 0.95). There was no multicollinearity between the variables using the collinearity diagnostics (variance inflation factors (VIF) and tolerance). In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Patient and public involvement

Neither patients nor the public were involved in the design of this study.

Results

Socio-demographic and clinical characteristics

The mean age of the study participants (n = 212) was 52.9 years (±13.3 years), with the majority of them (68.4) below 60 years old (68.4%), Christians (91.5%), and housewives (63.2%). More than two-thirds (67.5%) of the patients had a family monthly income below 3200 ETB (100 USD). Only 2.8% of the patients had a family history of cervical cancer. Majority of the patients (98.6%) were non-smokers; however, about a quarter (23.6%) of the patients were alcohol users. More than two-thirds (68.4%) of patients have paid their medical expenses out of pocket (**Table 1**). The extents of delays to diagnosis of cervical cancer (patient and diagnostic) were described in previous publication (19).

More than two-thirds (69.8%) of the patients had tumor size of greater than 4cm. Majority of the cervical cancer cases (91.0%) were a squamous cell carcinoma. About one in five (21.7%) cervical cancer patients were HIV positive and all were on antiretroviral therapy (ART).

Table 1: Socio-demographic and clinical characteristics of patients with cervical cancer in Addis Ababa

Variables	Frequency (percent)
Age	
<40 years	42 (19.8%)
40 – 59 years	103 (48.6%)
≥60 years	67 (31.6%)
Formal education	
No	86 (40.6%)
Yes	126 (59.4%)
Family monthly income	
≤3200 ETB	143 (67.5%)
>3200 ETB	69 (32.5%)
Source of medical expenses	
Out of pocket	145 (68.4%)
Free/insured	67 (31.6%)
Immediate action after symptom recognition	
Went to health facility	149 (70.3%)
No action/ Religious activity	63 (29.7%)
Number of different health facilities visited before diagnostic confirmation	
≤3 health facilities	142 (67.0%)
>3 health facilities	70 (33.0%)
Diagnostic interval	
≤90 days	68 (32.1%)
>90 days	144 (67.9%)
HIV infection	
Yes	46 (21.7%)

No	166 (78.3%)
Tumor size	
≤4cm	64 (30.2%)
>4cm	148 (69.8%)

Stage at diagnosis of cervical cancer

Nearly two out of three (60.4%, 95%CI; 53.8%, 66.5%) patients with cervical cancer were diagnosed at advanced stage of cancer, with 37.3% of them diagnosed at stage IV (**Figure 1**). Further, for about 5.2% of the patients, the disease had metastasized to lung (2.4%), liver (2.4%) or peritoneum (0.5%) at diagnosis.

Factors associated with advanced stage at diagnosis of cervical cancer

In a bivariate analysis (Supplementary material), advanced stage at diagnosis (stage III-IV) was significantly associated with source of medical expenses, not going to healthcare facilities immediately after symptom recognition, and visiting >3 different healthcare facilities before diagnostic confirmation and total diagnostic interval >90 days.

In the multi-variable analysis (**Table 2**), the proportion of advanced stage at diagnosis of cervical cancer was 1.4 times higher (Adjusted Prevalence Ratio (APR) = 1.44, 95%CI; 1.08, 1.91) among those women who paid their medical expenses out of pocket as compared to those women who were entitled to free medical service or having health insurance coverage. The proportion was 1.3 times higher (APR = 1.31, 95%CI; 1.04, 1.71) among women with total diagnostic interval of >90 days than those with ≤ 90 days. Similarly, the proportion of being diagnosed at an advanced stage of cervical cancer was 1.25 times higher (APR = 1.25, 95%CI; 1.05, 1.53) among

those women who went to religious practices or did nothing immediately after their symptom recognition as compared to those women who immediately went to the healthcare facilities, and 1.2 times higher (APR = 1.24, 95%CI; 1.08, 1.91) among those women who visited >3 different healthcare facilities prior to diagnostic confirmation compared to those who visited ≤3 healthcare facilities.

Table 2: Multi-variable analysis showing factors associated with advanced stage at diagnosis of cervical cancer in Addis Ababa residents, 2018

Variables	**Advanced stage**		**Crude PR (95%CI)**	**Adjusted PR (95%CI)**	***P* value**
	Yes	No			
Medical expenses					
Out of pocket	99	46	1.54 (1.15, 2.05)	1.44 (1.08, 1.91)	0.003
Free/insured	29	38	1.00	1.00	
Immediate action after symptom					
Went to health facility	80	69	1.00	1.00	
No action/ Religious activity	48	15	1.38 (1.13, 1.69)	1.25 (1.05, 1.53)	0.02
Number of healthcare facilities contacted					
≤3 healthcare facilities	77	65	1.00	1.00	
>3 healthcare facilities	51	19	1.35 (1.10, 1.65)	1.24 (1.07, 1.51)	0.01
Diagnostic interval					

≤90 days	33	35	1.00	1.00	
>90 days	95	49	1.45 (1.10, 1.91)	1.31 (1.04, 1.71)	0.02

Discussion

The present study provides data on cervical cancer stage distribution in Addis Ababa along with its predictors based on a population-based study. We found that nearly two-thirds of patients with cervical cancer in Addis Ababa were diagnosed at an advanced stage of the disease, and that advanced stage at diagnosis was strongly associated with out of pocket medical bill coverage and with delays in diagnosis confirmation.

Although our finding of high proportion of advanced-stage cervical cancer in Addis Ababa is generally similar to findings from other sub-Saharan African countries (8, 11), it is slightly higher than that reported from Kenya (53.9%) (9) and lower than that reported from Sudan (71.5%) (20). The higher proportion in Sudan in part reflects the predominantly rural resident study participants, where access to healthcare facilities is limited and health literacy is expected to be lower. In contrast, the lower proportion in the Kenyan study may reflect the higher coverage of a recent cervical cancer screening program in the country (14%) (21) as compared to Ethiopia (0.6%) (22). Additionally, the screening program created awareness on cervical cancer (21).

Our findings also showed that the proportion of advanced stage cervical cancer was considerably higher among women who waited for more than three months to receive diagnostic confirmation after they noticed symptom compared to those waited for ≤3 months. This may in part reflect differences in knowledge about cervical cancer early detection and treatments between the two groups of women, as well as differences in access to care (10). Thus, there is a need for

concerted efforts to enhance community awareness about cervical cancer prevention and early detection in order to minimize delays in the diagnosis of the disease.

More than four out of five patients, who went to practice religious activities immediately after symptom recognition, were found to be diagnosed at advanced stage of cervical cancer. In Ethiopia, it is not uncommon for patients to seek prayer or use holly water (Tsebel) as a remedy for their illnesses before turning to conventional medicine. (23). A qualitative study from Ethiopia reported that patients with cervical cancer have a strong belief that *Tsebel* (holy water)" will cure one from the disease (10). Similarly, seeking traditional and religious practices for cervical cancer care has been associated with advanced-stage disease in other parts of Africa (8).

Financial hardship is a barrier to accessing healthcare, leading to cancer progression and poor outcome (24). Consistent with our findings, previous studies conducted in Sudan (20) and Uganda (11) associated advanced stage with financial difficulties or being uninsured. Another study conducted among gynaecologic cancer patients also reported that women with financial hardship are seven times more likely to avoid or delay their cancer care (25). Providing free diagnostic and treatment services to all women with cervical cancer needs to be incorporated into the governments´ strategy on cervical cancer care. This will be in line with the WHO's global efforts to ensure universal health coverage (26).

The strengths of this study is the use of population-based cancer registry to document strong association between late-stage diagnosis and patient and health system factors, including diagnosis delay, in African settings. The registry, however, may not capture all incident cases diagnosed in the city because some patients might have never visited healthcare facilities or visited local healthcare facilities that do not report cases to the cancer registry. Also,

interpretation of our findings may be affected by recall bias about dates of symptom recognition and presentations though we do not expect the biases differ between patients diagnosed with early and advanced stage diseases.

Conclusions

Using a population-based study, we found that more than two-thirds of cervical cancer patients in Addis Ababa are diagnosed at advanced stage of the disease, which was strongly associated with diagnostic delay, failure to take immediate action following symptom recognition, and paying medical bill out of pocket. These findings underscore the need for public health campaigns and programs to raise awareness about the severity of the disease and preventive measures and to expand the availability of screening services, and for policies to improve the affordability of cancer care in the city. Of note, implementing free diagnostic service would ensure accessibility to care for increasing number of patients with precancerous lesion or early-stage disease through the ongoing scaled-up screening program by the Ethiopian government.

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Addis Ababa University, College of Health Sciences (Approval number: 005/19/SPH). All participants of the study were informed about the study and they gave their written consent to be included in the study.

Consent for publication

Not applicable

Availability of data and material

Data can be obtained from the corresponding author upon reasonable request.

Author contributions

ND, AG, AA, AW, MA, AJ were involved in the conception of the study, methodological design of the study, analysis and data interpretation. ND and AJ wrote the first draft of the manuscript. AA, WT, EK were involved in the methodology of the study, data collection/extraction, visualization of the data and data interpretation. All authors have revised the manuscript.

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Legend of Figure

Figure 1: FIGO stages of cervical cancer at diagnosis of patients residing in Addis Ababa, 2018

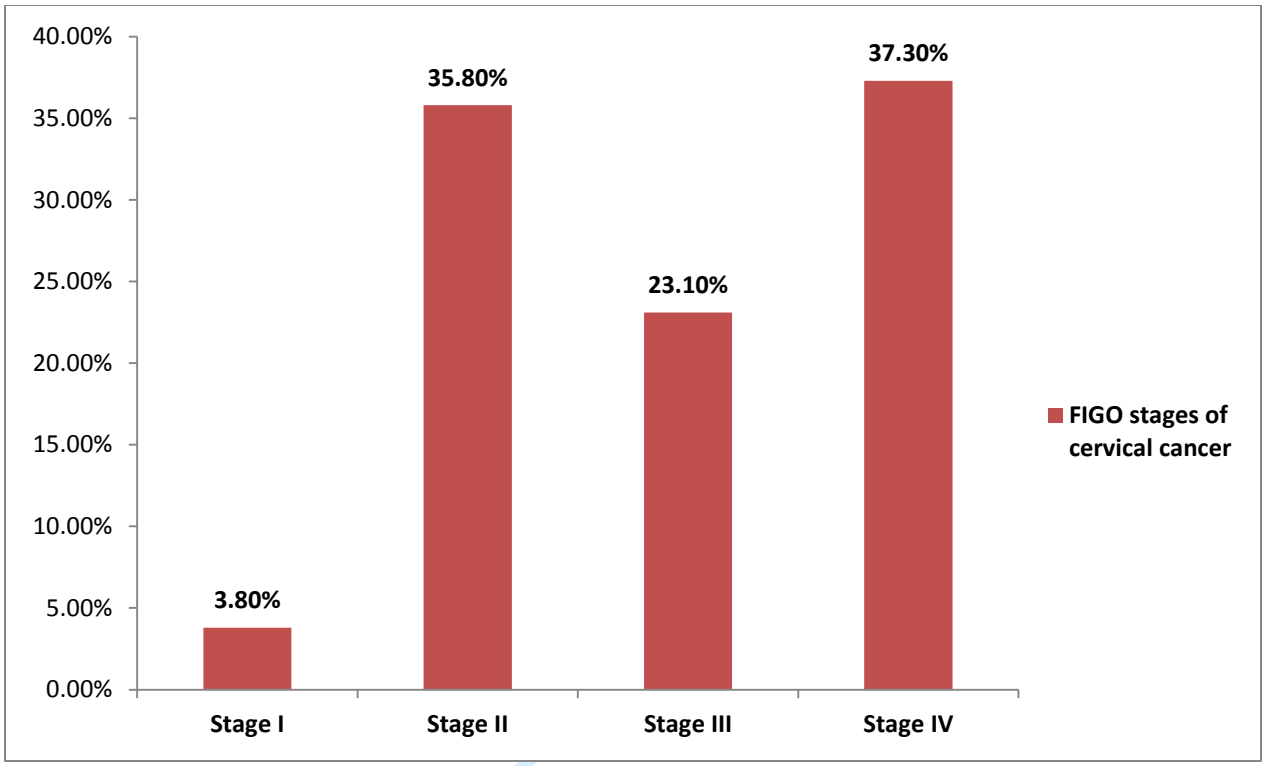

Table: Bivariate association between advanced stage diagnosis of cervical cancer and demographic and clinical characteristics in Addis Ababa, Ethiopia, 2018

Variables	Advanced stage		*P* value
	Yes	No	
Source of medical expenses			
Out of pocket	99 (68.3%)	46 (31.7%)	0.001
Free/insured	29 (43.3%)	38 (56.7%)	
Age			
<40 years	16 (38.1%)	26 (61.9%)	
40 – 59 years	42 (40.8%)	61 (59.2%)	0.94
≥60 years	26 (38.8%)	41 (61.2%)	
Formal education			
No	54 (62.8%)	32 (37.2%)	0.51
Yes	74 (58.7%)	52 (41.3%)	
Spouse living together			
Yes	48 (56.5%)	37 (43.5%)	
No	80 (63.0%)	47 (37.0%)	0.42
Family monthly income			
≤3200 ETB	88 (61.5%)	55 (38.5%)	0.73
>3200 ETB	40 (58.0%)	29 (42.0%)	
Immediate action after symptom recognition			
Went to health facility	80 (53.7%)	69 (46.3%)	0.008

No action/ Religious activity	48 (76.2%)	15 (23.8%)	
Number of different health facilities visited before diagnostic conformation			
≤3 health facilities	77 (54.2%)	65 (55.8%)	0.006
>3 health facilities	51 (72.9%)	19 (27.1%)	
Diagnostic interval			
≤90 days	33 (48.5%)	35 (51.5%)	0.02
>90 days	95 (66.0%)	49 (34.0%)	
HIV infection			
Yes	31 (67.4%)	15 (32.6%)	0.35
No	97 (58.4%)	69 (41.6%)	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, Page No.1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, Page No.2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, Page No. 4, Paragraph 1 and 2	
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, Page No. 4, Paragraph 2	
Methods				
Study design	4	Present key elements of study design early in the paper	Methods, Page No. 5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, Page No. 5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods, Page No. 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Data management and analysis, Page No. 6	
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	Methods, Data tools and procedures, Page No. 5	
Bias	9	Describe any efforts to address potential sources of bias	Methods, Data tools and procedures, Page No. 5; Data management and analysis, Page No. 6	
Study size	10	Explain how the study size was arrived at	Methods, Page No. 5, study setting	

			and design	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, Data management and analysis, Page No. 6	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, Data management and analysis, Page 6	
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, Data management and analysis, Page No. 6	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, Page No. 7 and 8	
		(b) Indicate number of participants with missing data for each variable of interest	Results, Page No. 7 and 8	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*N/A*	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*N/A*	
		Cross-sectional study—Report numbers of outcome events or summary measures	Results, Page No. 8	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, Page No. 8	
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	
Discussion				
Key results	18	Summarise key results with reference to study objectives	Discussion, Page No. 9, first paragraph	
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	Discussion, Page No. 11, last paragraph	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusions, Page No. 11	
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, Page No. 11, last paragraph	
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	Source of funding, Page No. 12	

*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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.