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# BMJ Open

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

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3 **1 Patterns and associated factors of advanced stage at diagnosis of cervical**  
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6 **2 cancer in Addis Ababa, Ethiopia: A population based study**  
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## 27 Abstract

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

30 **Design:** A population based cross sectional study

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

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

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

40 **Results:** The mean age of the study participants was 52.9 years ( $\pm 13.3$  years). Nearly two-thirds  
41 (60.4%, 95% CI; 53.8%, 66.5%) of patients with cervical cancer were diagnosed at an advanced  
42 stage of the disease. Advanced stage at diagnosis was significantly associated with paying  
43 medical bill out of pocket (adjusted prevalence ratio (APR) = 1.44, 95% CI; 1.08, 1.91),  
44 diagnostic interval >90 days (APR = 1.31, 95% CI; 1.04, 1.71), practicing in religious activities  
45 or not taking immediate action following symptom recognition (APR = 1.25, 95% CI; 1.08,  
46 1.91), and visiting more than three different health facilities prior to diagnostic confirmation  
47 (APR = 1.24, 95% CI; 1.07, 1.51).

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3 48 **Conclusion:** The findings of the study underscore the need to take measures to shorten  
4  
5 49 diagnostic waiting times for cervical cancer, increase the affordability of cancer care and creating  
6  
7  
8 50 awareness on the severity of cervical cancer in addition to screening options.  
9

10  
11 51 **Key words:** Stage at diagnosis, Advanced stage, Delays, Cervical cancer  
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## 14 52 **Article Summary**

### 15 16 17 53 **Strengths and limitations of this study**

- 18  
19  
20 54 • It is the first population based study to describe the patterns and associated factors of  
21  
22 55 stage at diagnosis among incident histologically confirmed cervical cancer cases in Addis  
23  
24 56 Ababa, Ethiopia
- 25  
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27 57 • The patients were recruited prospectively and primary data collection methods were used.
- 28  
29  
30 58 • Some patients might never have visited the health facilities and were not included in our  
31  
32 59 study.
- 33  
34  
35 60 • Recall bias on the dates of symptom recognition and presentations might have also  
36  
37 61 affected our findings.  
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41  
42 63 This work was supported by American Cancer Society  
43  
44  
45

### 46 64 **Conflict of interest**

47  
48 65 The authors declare that they have no conflict of interests.  
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52 66 **Word count of main text:** 2011  
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## 67 **Introduction**

68 Cervical cancer is the second leading cause of cancer death in females in Ethiopia and other parts  
69 of Africa [1, 2]. Although cervical cancer can be prevented by detecting and removal of  
70 precancerous lesions and treated successfully if detected early [3], majority of patients in  
71 Ethiopia [4, 5] and many other parts of Africa are diagnosed at advanced stage of the disease [6-  
72 9], when the choice of treatment is limited and the probability of survival is poor. However, the  
73 findings on stage distribution in Ethiopia and in most parts of Africa are based on hospital-based  
74 studies rather than population-based studies and they cannot be generalizable.

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

## 85 **Methods**

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

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3 89 study period; however, three of them were not included in our study due to their plan to initiate  
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5 90 treatment out of Ethiopia. Also 19 patients without stage information were excluded from the  
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8 91 study. The study participants were recruited from seven major public and private health facilities  
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10 92 in the city (representing 99% of cervical cancer incident cases among Addis Ababa residents).  
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12 93 Recruiting and tracing of the patients were guided by the Addis Ababa population-based cancer  
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15 94 registry [12].  
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18 95 All the cervical cancer cases were confirmed by histopathology and staged according to FIGO by  
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20 96 senior gynecological oncologist or clinical oncologist [13]. Distance metastasis (Stage IVb) was  
21  
22 97 determined by reviewing chest x-ray and abdominal ultrasound findings [14].  
23

24  
25 98 The ethical approval of this study was obtained from the institutional review board of Addis  
26  
27 99 Ababa University College of Health Sciences. Written informed consent of the study participants  
28  
29 100 was also obtained. Data from the cervical cancer patients were collected by using structured  
30  
31 101 questionnaire, which was developed by reviewing previously conducted related articles [9, 11].  
32  
33  
34 102 Initially the questionnaire was prepared by English and later translated to Amharic, the national  
35  
36 103 language. Consistency of the questionnaire translation was checked by back translation by  
37  
38 104 independent translator and its contents were validated by the experts (gynecologists and  
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40 105 oncologists). A Face to face interview was administered by trained nurse interviewers at around  
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42  
43 106 the time of diagnosis.  
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46 107 For extracting patients' clinical information, medical charts were reviewed and data were  
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48 108 extracted by junior oncologists (residents) using a structured checklist. Any inconsistency in the  
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51 109 patient information was resolved by consulting senior oncologists during the data extraction. The  
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53 110 histological results were extracted from the pathology reports.  
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3 111 Total diagnostic interval was defined as an interval from first date of symptom recognition by the  
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5 112 patients to the histological confirmation of the diagnosis. Total diagnostic interval was  
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8 113 considered delayed if the interval was >90 days [15-17].  
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10  
11 114 The outcome variable of the study was stage at diagnosis, which was grouped in to two as early  
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13 115 (stage I/II) and advanced (stage III/IV). The independent variables considered were: socio-  
14  
15 116 demographic variables (age, educational status, marital status, family income, source of medical  
16  
17 117 expense coverage), tumour related variables (tumour type), patient related factors (comorbidity,  
18  
19 118 diagnostic delays and number of health facility visited prior to diagnostic confirmation).  
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23 119 Descriptive analyses were used to calculate summary statistics of frequencies, proportion,  
24  
25 120 median, mean and standard deviations. Bivariate and multi-variable analysis using a Poisson  
26  
27 121 regression with robust variance method were used to identify factors associated with patient's  
28  
29 122 being at an advanced stage of cervical cancer at diagnosis. The Poisson regression with robust  
30  
31 123 variance method was used to directly estimate the prevalence ratio (the effect measure), since the  
32  
33 124 odds ratio (logistic regression) over-estimates the effect when the prevalence (magnitude) of the  
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35 125 outcome variable is not rare (>10%) [18]. Those variables with  $p$  value <0.25 in the bivariate  
36  
37 126 analysis were considered for the multi-variable analysis in the Poisson regression model. Level  
38  
39 127 of significance was set at  $p$  – value below 0.05 at 95% CI and prevalence ratio (PR) was used to  
40  
41 128 quantify the strength of association for each of the variables. Post estimation fitness of model  
42  
43 129 was checked by chi-square based goodness of fit test and the final model was found to be fit ( $p$   
44  
45 130 value = 0.95). There were no multicollinearity between the variables using the collinearity  
46  
47 131 diagnostics (variance inflation factors (VIF) and tolerance). In accordance with the journal's  
48  
49 132 guidelines, we will provide our data for the reproducibility of this study in other centers if such is  
50  
51 133 requested.  
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### 134 **Patient and public involvement**

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

## 136 **Results**

### 137 **Socio-demographic and clinical characteristics**

138 The mean age of the study participants (n = 212) was 52.9 years ( $\pm$ 13.3 years), where the  
 139 majority of the patients with cervical cancer were below 60 years old (68.4%), Christians  
 140 (91.5%), and housewives (63.2%). More than two-thirds (67.5%) of the patients had a family  
 141 monthly income below 3200 ETB (100 USD) and more than two-thirds (68.4%) were not  
 142 entitled to free medical service. Only 2.8% of the patients have a family history of cervical  
 143 cancer. Majority of the patients (98.6%) were non-smokers, however about a quarter (23.6%) of  
 144 the patients were alcohol users. More than two-thirds (68.4%) of patients pay their medical  
 145 expenses out of their pockets (Table 1). More than two-thirds (69.8%) of the patients had tumor  
 146 size of greater than 4cm. Majority of the cervical cancer cases (91.0%) had a squamous cell  
 147 carcinoma. About one in five (21.7%) cervical cancer patients were HIV positive and all were on  
 148 antiretroviral therapy (ART).

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

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

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

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### 153 **Stage at diagnosis of cervical cancer**

154 Nearly two out of three (60.4%, 95% CI; 53.8%, 66.5%) patients with cervical cancer were  
 155 diagnosed at advanced stage of cancer, majority of them (37.3%) being diagnosed at stage IV  
 156 (Figure 1). About 5.2% of the patients with cervical cancer had metastasized cancer to lung  
 157 (2.4%), liver (2.4%) and peritoneum (0.5%) at their diagnosis.

### 158 **Factors associated with advanced stage at diagnosis of cervical cancer**

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

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

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

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

165

166 In the multi-variable analysis (Table 3), the proportion of advanced stage at diagnosis of cervical  
 167 cancer was 1.4 times higher (Adjusted Prevalence Ratio (APR) = 1.44, 95% CI; 1.08, 1.91)  
 168 among those women who paid their medical expenses out of their pocket as compared to those  
 169 women who were entitled to free medical service or having health insurance coverage, and it was  
 170 1.3 times higher (APR = 1.31, 95% CI; 1.04, 1.71) among women with total diagnostic interval  
 171 of >90 days than those with  $\leq 90$  days. Similarly, the proportion of being diagnosed at an  
 172 advanced stage of cervical cancer was 1.25 times higher (APR = 1.25, 95% CI; 1.05, 1.53)  
 173 among those women who went to religious practices or do nothing immediately after their  
 174 symptom recognition as compared to those women who immediately went to the health facilities,  
 175 and 1.2 times higher (APR = 1.24, 95% CI; 1.08, 1.91) among those women who visited more  
 176 than three different health facilities prior to diagnostic confirmation compared to those who  
 177 visited  $\leq 3$  health facilities.

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

Variables	Advanced stage		Crude PR (95% CI)	Adjusted PR (95% CI)	P value
	Yes	No			
<b>Medical expenses</b>					
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	
<b>Immediate action after symptom</b>					
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
<b>Number of health facilities contacted</b>					
≤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
<b>Diagnostic interval</b>					
≤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

## 180 Discussion

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

186 Although our finding of high proportion of advanced-stage cervical cancer in Addis Ababa is  
 187 generally similar to findings from other sub-Saharan African countries [8, 11], it is slightly  
 188 higher than that reported from Kenya (53.9%) [9] and lower than that reported from Sudan  
 189 (71.5%) [19]. The higher proportion in Sudan in part reflects the predominantly rural resident  
 190 study participants, where access to health facilities is limited and health literacy is expected to be  
 191 lower. In contrast, the lower proportion in Kenyan study may reflect the higher coverage of

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3 192 recent cervical cancer screening program in the country (14%) [20] as compared to Ethiopia  
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5 193 (0.6%) [21]. Additionally, the screening program created awareness on cervical cancer [20].  
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9 194 Our finding also showed that the proportion of advanced stage cervical cancer was considerably  
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11 195 higher among women who waited for more than three months to receive diagnostic confirmation  
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13 196 after they noticed symptom compared to those waited for  $\leq 3$  months. Such long diagnostic  
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15 197 waiting time, which may lead to migration to higher-stage disease, in part reflects lack of  
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17 198 knowledge about cervical cancer among the general population and healthcare providers, as well  
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19 199 as lack of diagnostic infrastructure in the country [10]. These underscore the need for programs  
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21 200 to enhance knowledge of cervical cancer in the community in order to shorten delays in the  
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23 201 diagnosis of the disease.  
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28 202 More than four out of five patients, who went to practice religious activities immediately after  
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30 203 symptom recognition, were found to be diagnosed at advanced stage of cervical cancer. In  
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32 204 Ethiopia, it is common to see patients going to religious activities as a solution for their disease  
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34 205 [22]. This can affect their prompt health-seeking behavior and may contribute to advanced stage  
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36 206 at diagnosis. A qualitative study from Ethiopia reported that patients with cervical cancer have a  
37  
38 207 strong belief that *Tsebel* (holy water) will cure from the disease [10]. Similarly, seeking  
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40 208 traditional and religious practices for cervical cancer care have been associated with advanced-  
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42 209 stage disease in other parts of Africa [8].  
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47 210 Financial hardship is barrier to accessing health, leading to cancer progression and poor outcome  
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49 211 [23]. Consistent with our findings, previous studies conducted in Sudan [19] and Uganda [11]  
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51 212 associated advanced stage with financial difficulties or being uninsured. Other study conducted  
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53 213 among gynecologic cancer patients also reported that women with financial hardship are seven  
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3 214 times more likely to avoid or delay their cancer care [24]. Providing free diagnostic and  
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5 215 treatment services to all women with cervical cancer needs to be incorporated into the  
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7 216 governments' strategy on cervical cancer care. This will be in line with the WHO's global efforts  
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10 217 to ensure universal health coverage [25].  
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13 218 The strengths of this study are the use of population-based cancer registry and rigorous and  
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15 219 multiple data collection methods (patients' interview and medical record review) in a prospective  
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17 220 approach to document strong association between late-stage diagnosis and patient and health  
18  
19 221 system factors, including diagnosis delay, in African settings. However, the study has limitations  
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21 222 because some patients might never have visited the health facilities and were not included in our  
22  
23 223 study. Recall bias on the dates of symptom recognition and presentations might have also  
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25 224 affected our findings.  
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## 30 225 **Conclusions**

31  
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33 226 Using a population-based study, we found that more than two-third of cervical cancer patients in  
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35 227 Addis Ababa are diagnosed at advanced stage of the disease, which was strongly associated with  
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37 228 diagnostic delay, failure to take immediate action following symptom recognition, and paying  
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39 229 medical bill out of pocket. These findings underscore the need to take measures to enhance  
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41 230 awareness about the severity of the disease and preventive measures among the general  
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43 231 population and healthcare providers, expand the availability of screening services, and increase  
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45 232 the affordability of cancer care in the city. Of note, implementing free diagnostic service would  
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47 233 ensure accessibility to care for increasing number of patients with precancerous lesion or early-  
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49 234 stage disease through the ongoing up scaled screening program by the Ethiopian government.  
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3 235 **Declarations**  
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6 236 **Ethics Approval and Consent to Participate**  
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8  
9 237 This study was approved by the Institutional Review Board (IRB) of Wachemo University  
10  
11 238 (Approval number: WCU/IRB/086/17). All participants of the study were informed about the  
12  
13 239 study and they gave their written consent to be included in the study.  
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17 240 **Consent for publication**  
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19 241 Not applicable  
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23 242 **Availability of data and material**  
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25 243 Data can be obtained from the corresponding author upon reasonable request.  
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28 244 **Author contributions**  
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31 245 ND, AG, AA, AW, MA, AJ were involved in the conception of the study, methodological design  
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33 246 of the study, analysis and interpretation of data, and manuscript writing. AA, WT, EK were  
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35 247 involved in the methodology of the study, data collection/extraction, visualization of the data and  
36  
37 248 interpretation of the data. All authors have revised the manuscript.  
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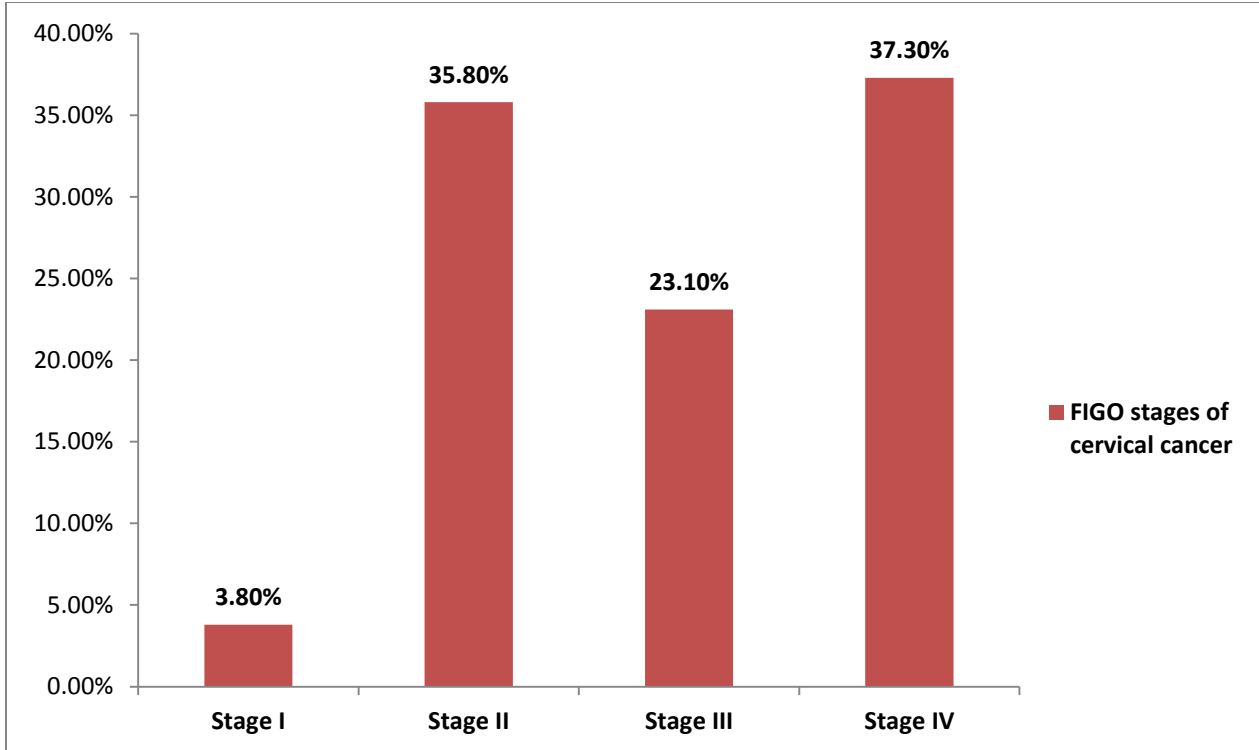
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3 321 **Legend of Figure**  
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5 322 Figure 1: FIGO stages of cervical cancer at diagnosis of patients residing in Addis Ababa, 2018  
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## STROBE 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	
<b>Introduction</b>				
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	
<b>Methods</b>				
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, Page No. 5	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(e) Describe any sensitivity analyses	N/A	
<b>Results</b>				
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	N/A	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A	
		<i>Cross-sectional study</i> —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	
<b>Discussion</b>				
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	
<b>Other information</b>				
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](http://www.strobe-statement.org).

# BMJ Open

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

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3 **1 Factors associated with advanced stage at diagnosis of cervical cancer in**  
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6 **2 Addis Ababa, Ethiopia: A population-based study**  
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9 3 Nebiyu Dereje<sup>1\*</sup>, Alem Gebremariam<sup>2</sup>, Adamu Addissie<sup>3</sup>, Alemayehu Worku<sup>4</sup>, Mathewos  
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## 27 **Abstract**

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

30 **Design:** A population based cross sectional study

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

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

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

38 **Results:** The mean age of the study participants was 52.9 years ( $\pm 13.3$  years). Nearly two-thirds  
39 (60.4%, 95%CI; 53.8%, 66.5%) of patients with cervical cancer were diagnosed at an advanced  
40 stage of the disease. Advanced stage at diagnosis was significantly associated with paying  
41 medical bill out of pocket (APR = 1.44, 95%CI; 1.08, 1.91), diagnostic interval >90 days (APR =  
42 1.31, 95%CI; 1.04, 1.71), practicing religion as a remedy or not taking immediate action  
43 following symptom recognition (APR = 1.25, 95%CI; 1.08, 1.91), and visiting >3 different  
44 health facilities prior to diagnostic confirmation (APR = 1.24, 95%CI; 1.07, 1.51).

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

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3 48 confirmations underscore the need for public policies to improve the affordability of cancer care,  
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5 49 and enhance community awareness about the severity of the disease and referral system, in  
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8 50 addition to expanding cervical cancer screening.  
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11 51 **Key words:** Stage at diagnosis, Advanced stage, Delays, Cervical cancer  
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## 14 52 **Article Summary**

### 15 16 17 53 **Strengths and limitations of this study**

- 18  
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20 54 • It is the first population-based study to describe factors associated with advanced stage  
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22 55 cervical cancer diagnosis in African setting.
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25 56 • All cervical incident cases in Addis Ababa may not have been included in the study  
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27 57 because some patients might never have visited healthcare facilities or visited local  
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29 58 healthcare facilities that do not report incident cancers to the central cancer registry.
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32 59 • Recall bias about dates of symptom recognition and of presentations might have also  
33  
34 60 affected our findings.  
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### 37 38 61 **Funding statement**

39  
40 62 This work was supported by the American Cancer Society. Award/Grant number is not  
41  
42 63 applicable.  
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### 45 46 64 **Conflict of interest**

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48 65 The authors declare that they have no conflict of interests.  
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51 66 **Word count of main text:** 2050  
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## 67 **Introduction**

68 Cervical cancer is the second leading cause of cancer death in females in Ethiopia and other parts  
69 of Africa ([1](#), [2](#)). Although cervical cancer can be prevented by detection and removal of  
70 precancerous lesions and treated successfully if detected early ([3](#)), the majority of patients in  
71 Ethiopia ([4](#), [5](#)) and many other parts of Africa are diagnosed at advanced stage of the disease ([6](#)-  
72 [9](#)), when the choice of treatment is limited and the probability of survival is poor. Previous  
73 findings on stage distribution in Ethiopia and in most parts of Africa, however, may not be  
74 generalizable as they were hospital-based studies rather than population-based studies.

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

85



## 86 **Methods**

87 A multi-center cross-sectional study was conducted among all newly diagnosed patients with  
88 cervical cancer among Addis Ababa residents during the 18 months study period from January 1,  
89 2017 to June 30, 2018. Patients were considered to be residents of the city if they lived at least 6  
90 months before date of diagnosis. Study participants were recruited from seven major hospitals or  
91 diagnostic facilities aided by the Addis Ababa Population-based Cancer Registry, which actively  
92 registers all incident cancer cases among the residents of the city ([12](#)). During the study period,  
93 234 histopathologically confirmed newly diagnosed patients were recorded in the registry. Of  
94 these patients, 22 patient were excluded from the study because of they sought treatment abroad  
95 (3 patients) or because of lack of stage information in their medical records (19 patients).

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

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

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3 108 Patient's clinical characteristics were extracted from medical charts by junior oncologists  
4  
5 109 (residents) using a structured checklist and any inconsistencies was resolved by consulting senior  
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7  
8 110 oncologists. Information on histology type and date of diagnostic confirmation was obtained  
9  
10 111 from pathology reports.

11  
12 112 Total diagnostic time interval was defined as the interval from t date of first symptom(s)  
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14 113 recognition by the patient to date of the histological confirmation of the diagnosis. Total  
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16 114 diagnostic interval was considered delayed if the interval was >90 days ([15-17](#)).

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19  
20 115 The main outcome variable of the study was stage at diagnosis, which was grouped in to two:  
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22 116 early (stage I/II) and advanced (stage III/IV). The independent variables include socio-  
23  
24 117 demographic characteristics (age, educational status, marital status, family income, source of  
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26 118 medical expense coverage), clinical characteristics (histologic type, comorbidity), and other  
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28 119 patient or provider related factors (diagnostic delays and number of health facility visited prior to  
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30 120 diagnostic confirmation).

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34  
35 121 Descriptive analyses were used to calculate summary statistics of frequencies, proportion,  
36  
37 122 median, mean and standard deviations. Bivariate and multi-variable analysis using a Poisson  
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39 123 regression with robust variance method were used to identify factors associated with patient's  
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41 124 being at an advanced stage of cervical cancer at diagnosis. The Poisson regression with robust  
42  
43 125 variance method was used to directly estimate the prevalence ratio (the effect measure), since the  
44  
45 126 odds ratio (logistic regression) over-estimates the effect when the prevalence (magnitude) of the  
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47 127 outcome variable is not rare (>10%) ([18](#)). Those variables with  $p$  value <0.25 in the bivariate  
48  
49 128 analysis were considered for the multi-variable analysis in the Poisson regression model. Level  
50  
51 129 of significance was set at  $p$  – value below 0.05 at 95% CI and prevalence ratio (PR) was used to  
52  
53 130 quantify the strength of association for each of the variables. Post estimation fitness of this model

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3 131 was checked by chi-square based goodness of fit test and the final model was found to be fit ( $p$   
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5 132 value = 0.95). There was no multicollinearity between the variables using the collinearity  
6  
7 133 diagnostics (variance inflation factors (VIF) and tolerance). In accordance with the journal's  
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9 134 guidelines, we will provide our data for the reproducibility of this study in other centers if such is  
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11 135 requested.  
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## 15 136 **Patient and public involvement**

16  
17  
18 137 Neither patients nor the public were involved in the design of this study.  
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20

## 21 138 **Results**

### 22 139 **Socio-demographic and clinical characteristics**

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28 140 The mean age of the study participants ( $n = 212$ ) was 52.9 years ( $\pm 13.3$  years), with the majority  
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30 141 of them (68.4) below 60 years old (68.4%), Christians (91.5%), and housewives (63.2%). More  
31  
32 142 than two-thirds (67.5%) of the patients had a family monthly income below 3200 ETB (100  
33  
34 143 USD). Only 2.8% of the patients had a family history of cervical cancer. Majority of the patients  
35  
36 144 (98.6%) were non-smokers; however, about a quarter (23.6%) of the patients were alcohol users.  
37  
38 145 More than two-thirds (68.4%) of patients have paid their medical expenses out of pocket (**Table**  
39  
40 146 **1**). The extents of delays to diagnosis of cervical cancer (patient and diagnostic) were described  
41  
42 147 in previous publication ([19](#)).  
43  
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47 148 More than two-thirds (69.8%) of the patients had tumor size of greater than 4cm. Majority of the  
48  
49 149 cervical cancer cases (91.0%) were a squamous cell carcinoma. About one in five (21.7%)  
50  
51 150 cervical cancer patients were HIV positive and all were on antiretroviral therapy (ART).  
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55 151

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

153 Ababa

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

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

154

### 155 **Stage at diagnosis of cervical cancer**

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

### 160 **Factors associated with advanced stage at diagnosis of cervical cancer**

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

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

172 those women who went to religious practices or did nothing immediately after their symptom  
 173 recognition as compared to those women who immediately went to the healthcare facilities, and  
 174 1.2 times higher (APR = 1.24, 95%CI; 1.08, 1.91) among those women who visited >3 different  
 175 healthcare facilities prior to diagnostic confirmation compared to those who visited ≤3 healthcare  
 176 facilities.

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

Variables	Advanced stage		Crude PR (95%CI)	Adjusted PR (95%CI)	P value
	Yes	No			
<b>Medical expenses</b>					
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	
<b>Immediate action after symptom</b>					
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
<b>Number of healthcare facilities contacted</b>					
≤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
<b>Diagnostic interval</b>					

≤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

## 179 Discussion

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

185 Although our finding of high proportion of advanced-stage cervical cancer in Addis Ababa is  
 186 generally similar to findings from other sub-Saharan African countries (8, 11), it is slightly  
 187 higher than that reported from Kenya (53.9%) (9) and lower than that reported from Sudan  
 188 (71.5%) (20). The higher proportion in Sudan in part reflects the predominantly rural resident  
 189 study participants, where access to healthcare facilities is limited and health literacy is expected  
 190 to be lower. In contrast, the lower proportion in the Kenyan study may reflect the higher  
 191 coverage of a recent cervical cancer screening program in the country (14%) (21) as compared to  
 192 Ethiopia (0.6%) (22). Additionally, the screening program created awareness on cervical cancer  
 193 (21).

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

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3 199 concerted efforts to enhance community awareness about cervical cancer prevention and early  
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5 200 detection in order to minimize delays in the diagnosis of the disease.  
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9 201 More than four out of five patients, who went to practice religious activities immediately after  
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11 202 symptom recognition, were found to be diagnosed at advanced stage of cervical cancer. In  
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13 203 Ethiopia, it is not uncommon for patients to seek prayer or use holy water (*Tsebel*) as a remedy  
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15 204 for their illnesses before turning to conventional medicine. (23). A qualitative study from  
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17 205 Ethiopia reported that patients with cervical cancer have a strong belief that *Tsebel* (holy water)”  
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19 206 will cure one from the disease (10). Similarly, seeking traditional and religious practices for  
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21 207 cervical cancer care has been associated with advanced-stage disease in other parts of Africa (8).  
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25 208 Financial hardship is a barrier to accessing healthcare, leading to cancer progression and poor  
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27 209 outcome (24). Consistent with our findings, previous studies conducted in Sudan (20) and  
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29 210 Uganda (11) associated advanced stage with financial difficulties or being uninsured. Another  
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31 211 study conducted among gynaecologic cancer patients also reported that women with financial  
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33 212 hardship are seven times more likely to avoid or delay their cancer care (25). Providing free  
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35 213 diagnostic and treatment services to all women with cervical cancer needs to be incorporated into  
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37 214 the governments’ strategy on cervical cancer care. This will be in line with the WHO’s global  
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39 215 efforts to ensure universal health coverage (26).  
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45 216 The strengths of this study is the use of population-based cancer registry to document strong  
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47 217 association between late-stage diagnosis and patient and health system factors, including  
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49 218 diagnosis delay, in African settings. The registry, however, may not capture all incident cases  
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51 219 diagnosed in the city because some patients might have never visited healthcare facilities or  
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53 220 visited local healthcare facilities that do not report cases to the cancer registry. Also,  
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3 221 interpretation of our findings may be affected by recall bias about dates of symptom recognition  
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5 222 and presentations though we do not expect the biases differ between patients diagnosed with  
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8 223 early and advanced stage diseases.  
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## 10 11 224 **Conclusions**

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14 225 Using a population-based study, we found that more than two-thirds of cervical cancer patients  
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16 226 in Addis Ababa are diagnosed at advanced stage of the disease, which was strongly associated  
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18 227 with diagnostic delay, failure to take immediate action following symptom recognition, and  
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20 228 paying medical bill out of pocket. These findings underscore the need for public health  
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22 229 campaigns and programs to raise awareness about the severity of the disease and preventive  
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24 230 measures and to expand the availability of screening services, and for policies to improve the  
25  
26 231 affordability of cancer care in the city. Of note, implementing free diagnostic service would  
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28 232 ensure accessibility to care for increasing number of patients with precancerous lesion or early-  
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30 233 stage disease through the ongoing scaled-up screening program by the Ethiopian government.  
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## 36 234 **Declarations**

### 37 38 39 235 **Ethics Approval and Consent to Participate**

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42 236 This study was approved by the Institutional Review Board (IRB) of Addis Ababa University,  
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44 237 College of Health Sciences (Approval number: 005/19/SPH). All participants of the study were  
45  
46 238 informed about the study and they gave their written consent to be included in the study.  
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### 50 239 **Consent for publication**

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52 240 Not applicable  
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3 241 **Availability of data and material**  
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6 242 Data can be obtained from the corresponding author upon reasonable request.  
7

8  
9 243 **Author contributions**  
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11  
12 244 ND, AG, AA, AW, MA, AJ were involved in the conception of the study, methodological design  
13

14 245 of the study, analysis and data interpretation. ND and AJ wrote the first draft of the manuscript.  
15

16 246 AA, WT, EK were involved in the methodology of the study, data collection/extraction,  
17

18  
19 247 visualization of the data and data interpretation. All authors have revised the manuscript.  
20  
21

22 248 **Acknowledgement**  
23  
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26

27 250 Addis Ababa University College of Health Sciences for the administrative support. The authors  
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29  
30 251 are also grateful to the study participants for their cooperation.  
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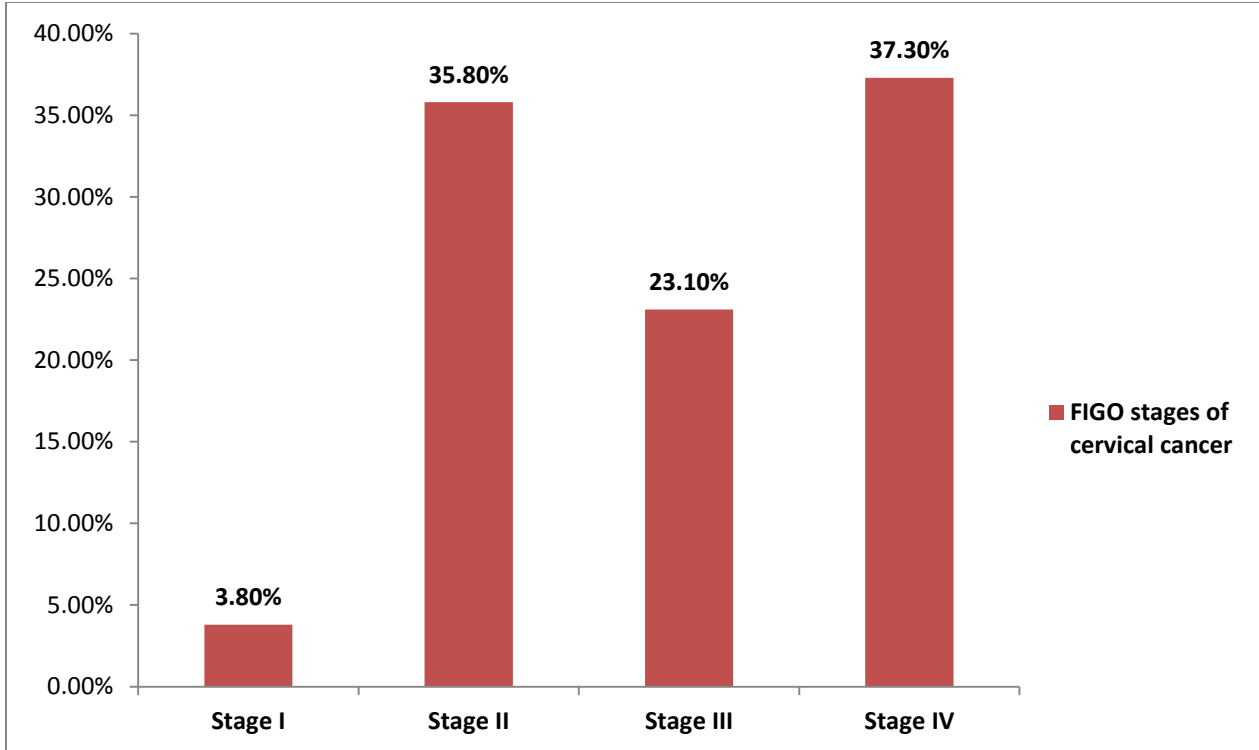
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3 322 **Legend of Figure**  
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5 323 Figure 1: FIGO stages of cervical cancer at diagnosis of patients residing in Addis Ababa, 2018  
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Table: Bivariate 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	
<b>Source of medical expenses</b>			
Out of pocket	99 (68.3%)	46 (31.7%)	0.001
Free/insured	29 (43.3%)	38 (56.7%)	
<b>Age</b>			
<40 years	16 (38.1%)	26 (61.9%)	0.94
40 – 59 years	42 (40.8%)	61 (59.2%)	
≥60 years	26 (38.8%)	41 (61.2%)	
<b>Formal education</b>			
No	54 (62.8%)	32 (37.2%)	0.51
Yes	74 (58.7%)	52 (41.3%)	
<b>Spouse living together</b>			
Yes	48 (56.5%)	37 (43.5%)	0.42
No	80 (63.0%)	47 (37.0%)	
<b>Family monthly income</b>			
≤3200 ETB	88 (61.5%)	55 (38.5%)	0.73
>3200 ETB	40 (58.0%)	29 (42.0%)	
<b>Immediate action after symptom recognition</b>			
Went to health facility	80 (53.7%)	69 (46.3%)	0.008

No action/ Religious activity	48 (76.2%)	15 (23.8%)	
<b>Number of different health facilities visited before diagnostic conformation</b>			
≤3 health facilities	77 (54.2%)	65 (55.8%)	0.006
>3 health facilities	51 (72.9%)	19 (27.1%)	
<b>Diagnostic interval</b>			
≤90 days	33 (48.5%)	35 (51.5%)	0.02
>90 days	95 (66.0%)	49 (34.0%)	
<b>HIV infection</b>			
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	
<b>Introduction</b>				
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	
<b>Methods</b>				
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, Page No. 5	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(e) Describe any sensitivity analyses	N/A	
<b>Results</b>				
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	N/A	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A	
		<i>Cross-sectional study</i> —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	
<b>Discussion</b>				
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	
<b>Other information</b>				
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](http://www.strobe-statement.org).