Cervical cancer still presents symptomatically 20 years after the introduction of a structured national screening programme

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Objective: To investigate the pattern of presentation of cervical cancer and to identify the characteristics of women who present symptomatically with cervical cancer.

Methods: A retrospective study of all cervical cancer cases diagnosed over a 4-year period. Details of mode of presentation, stage at diagnosis and cytological/gynaecological history were collated.

Results: In total, 148 cases were identified with a median age of 46 years (range, 20–91 years). In this population, 112 (75.7%) women were within the screening age range. Forty-eight (33.6%) were asymptomatic at diagnosis and presented through the colposcopy clinic. All asymptomatic women (100%) had stage I disease at diagnosis, compared with 37.2% of the symptomatic group ($P < 0.001$). Postmenopausal bleeding was the most common presenting symptom (33%), followed by postcoital bleeding (14.2%), intermenstrual bleeding (12.2%) and increased vaginal discharge (3.4%). The majority of symptomatic women presented through colposcopy, gynaecological oncology or gynaecology clinics (87.6%); however, 6.5% presented through the emergency department. Women who presented symptomatically were significantly older than asymptomatic women (54.9 versus 38.1 years, $P < 0.001$). Women at risk of social isolation (non-English speakers, alcohol abusers, heavy smokers, receiving treatment for psychiatric disease) were more likely to present with symptoms, through the emergency department and with advanced disease at diagnosis (stage II+) ($P < 0.001$).

Conclusions: A review of local cervical cancer cases can highlight areas of weakness in a screening programme and can identify populations who are at risk in presenting symptomatically with advanced disease.

Keywords: cervical cancer, screening, symptoms, emergency presentation, postmenopausal bleeding

Introduction

Cervical cancer is largely viewed as a preventable disease in the UK because of the success of the National Health Service cervical screening programme (NHSCSP). Despite an initial fall in the number of cases following the introduction of the NHSCSP in 1988, the number of cases over recent years has been static and has even risen in certain populations.[1,2] The National Invasive Cervical Cancer Audit[3] has been collecting details on all cervical cancer cases diagnosed in the UK since April 2007. The 2007–2010 report[4] showed that, although the majority (75.1% of the national average) of cervical cancers diagnosed in women of screening age were FIGO (International Federation of Gynecology and Obstetrics) stage I, almost one-quarter (24.9% of the national average) were stage II+ at presentation, and therefore more likely to be associated with an increased disease-specific mortality and treatment-related morbidity compared with early-stage disease. The down-staging of cervical cancers by earlier diagnosis could potentially have a significant impact on morbidity and mortality;

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hence, it is imperative to identify the reasons why women present with late-stage disease.

Previous studies have investigated cervical cancer presentation in the light of the National Audit of Invasive Cervical Cancer,[5] but have not looked at the mode of presentation and patient factors that may have contributed towards a delay in diagnosis. The objective of this study was to examine in depth the association between cervical cancer presentation, screening behaviour, stage of disease and patient factors.

Methods

A retrospective review was conducted of all cases of cervical cancer diagnosed in a 4-year period (January 2007 to December 2010) at the University Hospitals of Leicester, a regional cancer centre covering a population of approximately 1 100 000. Cases were identified through the pathology database and Gynaecological Oncology Multidisciplinary Team (MDT) weekly meeting records. Institutional approval was granted from the Departmental Clinical Audit Team for the service evaluation. Data collection included patient demographics, ethnicity and language, co-morbidities, obstetric/gynaecological/cytological history and symptoms, stage at diagnosis and histological subtype. Women were classified as being at risk of 'social isolation' if they had at least one of the following criteria: non-English speaker, alcohol or illicit drug abuse, heavy smokers (more than 20 cigarettes/day) or were receiving treatment for a psychiatric illness (schizophrenia, anxiety, depression, anorexia nervosa). The time from the development of symptoms to presentation at the gynaecological service was identified and classified as delayed if symptoms were present more than 3 months before review. With regard to screening history, women were classified according to their age as eligible for screening in the UK (25–65 years old) or ineligible for screening (less than 25 years or over 65 years old). Those within the screening age were categorised as being compliant or non-compliant with the screening programme according to the NHSCSP Audit of Invasive Cervical Cancer[4]; the 'never attender', 'lost to follow-up' and 'defaulter' groups were collectively termed as 'non-compliant'.

Data were collated and analysed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Missing data were excluded from the analysis. Descriptive statistics were used to analyse patient characteristics. Pro-portional differences were compared using non-parametric tests (chi-squared, Mann–Whitney) for categorical variables and non-normal distributions and Student's t-tests for mean differences of continuous variables and normally distributed data.

Results

In total, all 148 new cervical cancer cases that were diagnosed in the review period were included in our analysis (Table 1). The median age at diagnosis was 46 years (range 20–91 years) and displayed a bimodal distribution, with peaks at 40 and 70 years of age. The majority of women, 90 cases (61.6%), were pre-menopausal, three women (2%) were diagnosed with cervical cancer during pregnancy and the remainder were postmenopausal. Ten (6.8%) women had been treated previously with a local cervical excision for abnormal cytology and/or colposcopy.

Details of patient ethnicity and place of birth were available in every case. The majority of women, 127 (85.8%), were white British, five (3.4%) were UK born, but from a non-white ethnic group, and 16 (10.8%) women were born outside of the UK. Of the non-UK-born women, six had migrated to the UK from South Asia (India, Pakistan), five were from Eastern Europe (Poland, Ukraine, Russia), three were from a sub-Saharan African country and two were from North America. Eleven of the 16 non-UK-born women (68.8%) were unable to speak English fluently and required an interpreter. Seven women were reported to have a high alcohol intake, but none of the women admitted to illicit drug use. Of all cases, 19 women were heavy smokers (more than 20 cigarettes daily) and seven were on treatment for schizophrenia, depression, anxiety or anorexia nervosa. In total, 33 (22.3%) women had at least one risk factor for potential social isolation.

Overall, 48 (33.6%) of the cervical cancer cases were asymptomatic at diagnosis. Of the 95 (66.9%) patients who experienced symptoms, postmenopausal bleeding was the most common presenting symptom (33%), followed by postcoital bleeding (14.2%), intermenstrual bleeding (12.2%) and increased vaginal discharge (3.4%). In addition, six (4.1%) women presented with acute renal failure, ureteric obstruction, lymphoedema, a pelvic mass and/or ascites. The duration of symptoms had been recorded for 52 women and, of these, 26 (49.1%) had symptoms for more than 3 months prior to their presentation to a gynaecological service. There was

Table 1. Demographics of the study population ($n = 148$)

	n/total of each category (%)
Demographics	
Age, median (range) in years	46 (20–91)
Non UK born/total	16/148 (10.8%)
Multiparous	111/132 (84%)
Nulliparous	21/132 (16%)
Menopausal status	
Postmenopausal	56/146 (38.4%)
Premenopausal	90/146 (61.6%)
Hormone use	
Hormone replacement therapy usage (users/postmenopausal)	6/54 (11.1%)
Contraception (users/pre-menopausal)	55/79 (69.6%)
Pregnant (cases/pre-menopausal)	3/81 (0.37%)
Risk factors for social isolation	
Non-English speaker	11/148 (7.4%)
Alcohol abuse	7/137 (5.1%)
Heavy smokers >20 cigarettes/day	19/138 (13.8%)
On treatment for depression, schizophrenia, anxiety, anorexia	7/140 (5.0%)
Presentation	
Colposcopy clinic	84/139 (60.4%)
Gynaecology clinic	44/139 (31.7%)
Emergency department	9/139 (6.5%)
Other (general surgery/urology)	2/139 (1.4%)
Symptoms	
Asymptomatic	48/143 (33.6%)
Symptomatic	95/143 (66.9%)
Screening information	
Eligible, compliant	45/131 (34.4%)
Eligible, non-compliant	51/131 (38.9%)
Ineligible	35/131 (26.7%)
Cervical cancer stage	
Stage I	81/143 (56.6%)
Stage IA1	42/143 (29.4%)
Stage IA2	4/143 (2.8%)
Stage IB1	31/143 (21.7%)
Stage IB2	4/143 (2.8%)
Stage II	31/143 (21.7%)
Stage III	19/143 (13.3%)
Stage IV	12/143 (8.4%)
Histology	
Squamous cell carcinoma	114/145 (78.6%)
Adenocarcinoma	27/145 (18.6%)
Other (adenosquamous, neuroendocrine, etc.)	4/145 (2.8%)

no significant difference in the mean age at diagnosis between women who presented within 3 months of becoming symptomatic and women who delayed presentation (56.5 versus 52.7 years, $P > 0.05$).

Of the 131 cases (88.5%) in which cervical smear screening history data were available, 96 (73.3%) women were eligible, 45 (36.4%) were compliant with their attendances and 51 (38.9%) were non-compliant. Within the non-compliant group, there were 10 (7.6%) patients who had never attended screening. Thirty-five women (26.7%) were ineligible for screening as they were outside of the UK screening age range. Thirty-one of these 35 women were over 65 years of age and all presented symptomatically, with postmenopausal bleeding being the leading symptom. The remaining four cases were under 25 years of age and presented with either postcoital or intermenstrual bleeding.

The majority of symptomatic women presented through the colposcopy service (34 cases, 38.2%), gynaecological oncology (25 cases, 28.1%) or gynaecological (19 cases, 21.3%) clinic; however, nine (10.1%) women presented through the emergency department. All 48 (100%) asymptomatic patients were of screening age, diagnosed through the colposcopy clinic and all were stage I at diagnosis. This was in contrast with the symptomatic group in which 65 women (60.9%) were of screening age and only 29 women (37.2%) were stage I at diagnosis ($P < 0.001$). Adenocarcinoma was equally diagnosed in women experiencing symptoms or not (22.1% versus 14.6%, $P > 0.05$). There was no statistically significant difference in the distribution of squamous cell cancers versus adenocarcinomas among symptomatic and asymptomatic patients at presentation. In addition, there was no difference in the distribution of adenocarcinomas versus squamous cell cancers among women compliant and non-compliant with screening ($P > 0.05$). Asymptomatic patients were significantly younger [mean age, 38.1 years; standard deviation (SD), 8.6 years] than symptomatic patients (mean age, 54.9 years; SD, 17.6 years) ($P < 0.001$) (Table 2). A significantly greater number of women presenting symptomatically were postmenopausal (55.3% versus 6.3%) and ineligible for screening (39.1% versus 0%) in comparison with asymptomatic women ($P < 0.001$).

All nine women who presented via the emergency route were symptomatic with advanced disease (three stage II, two stage III and four stage IV cases). All (100%) who presented as an emergency were diagnosed with stage II+ disease, in comparison with 32.2% of those who presented electively ($P < 0.001$). Six of the nine women who presented through the emergency department had at least one

Table 2. Comparison of demographics between women presenting with symptoms and asymptomatic women

	Symptomatic (n = 95) n/total n of each category (%)	Asymptomatic (n = 48)n/total n of each category (%)	$P*$
Demographics			
Age in years, mean (standard deviation, SD)	54.9 (SD 17.6)	38.1 (SD 8.6)	<0.001
Postmenopausal	52/94 (55.3%)	3/48 (6.3%)	<0.001
Socially isolated (substance abuse, psychiatric illness, no English)	27/90 (30%)	6/48 (12.5%)	0.022
Screening status			
Compliant	23/87 (26.4%)	23/42 (47.6%)	<0.001
Non-compliant	30/87 (34.5%)	19/42 (45.2%)	<0.001
Ineligible	34/87 (39.1%)	0/42 (0%)	<0.001
Presentation site			
Colposcopy	34/89 (38.2%)	48/48 (100%)	<0.001
Emergency department	9/89 (10.1%)	0/48 (0%)	<0.001
Tumour characteristics			
Stage I	29/78 (37.2%)	48/48 (100%)	<0.001
Stage II+	49/78 (62.8%)	0/48 (0%)	<0.001
Adenocarcinoma	21/95 (22.1%)	7/48 (14.6%)	NS 0.423
Squamous cell carcinoma	71/95 (74.7%)	40/48 (83.3%)	NS 0.423
Other histological subtype	3/95 (3.2%)	1/48 (2.1%)	NS 0.341

NS, not significant.

risk factor for social isolation, significantly greater than the 24 of 125 women who presented through various clinics (66.7% versus 19.2%, $P < 0.001$).

Discussion

The NHSCSP was officially launched in the UK in 1988 and, since then, has been shown to have had an impact on cervical cancer incidence and mortality.[6,7] This study has shown that, despite this open-access, financially free, structured national cervical screening programme, a significant proportion of women are still presenting symptomatically with advanced cervical cancer. We have identified that factors associated with social isolation appear to be contributing to this finding, in particular with non-English speakers and alcohol abusers more likely to present symptomatically via the emergency department.

England had a 5-yearly screening coverage of 78.9% in 2009/10,[8] and Leicestershire coverage for the study period of 2006/7 to 2010/2011 ranged from 83.2% to 84.4%; in particular, Leicester City coverage ranged from 75.3% to 76.9%.[9,10] Despite the high screening coverage of our population,

39.7% of cervical cancer cases were diagnosed at an advanced stage (stage II+). We have identified that, in our local population, postmenopausal women outside screening age, never attenders or women who were not compliant with screening were more likely to be diagnosed with advanced disease (stage II+). This is in keeping with many previously published reports, including the National Invasive Audit Report,[3] which showed that stage II+ disease was diagnosed in 43.2% of cancer cases among women aged 50–64 years and 65.9% of cases among women older than 65 years.[3] In the group of women aged 25–50 years, stage II+ disease was diagnosed in 17 of 85 (20%) cases, which is in accordance with the 19.4–21.9% reported in the National Audit of Invasive Cervical Cancer for the years 2007–2010 in the UK.[3] It is a great achievement, however, that 100% of asymptomatic women were diagnosed as a result of attending for screening, and all were stage I at diagnosis. This reinforces the pivotal role of screening in identifying asymptomatic women with early-stage disease.

Although the majority of cervical cancer cases (60.4%) were diagnosed through colposcopy clinics, a significant 31.7% were diagnosed through gynae-

cological outpatient clinics. This reflects the local practice of assessing referrals of 'suspicious looking cervix' and intermenstrual/postcoital bleeding initially by a gynaecologist because of the high volume of these types of referrals from primary care. This is in accordance with the guidance for the management of bleeding in young women, from the Department of Health, England.[11] The postmenopausal women referred with vaginal bleeding were standardly seen in a gynaecological clinic initially, as the more frequent diagnosis in this population is an endometrial malignancy.

The population uptake of a screening programme is key to reducing disease burden. Adherence to national screening programmes is very important to ensure their success in the prevention of invasive cervical cancer. Education programmes, access to health care and multimedia publicity are aimed at encouraging and engaging women to attend cervical screening.[12] Intervention studies, using an invitation letter to patients, have shown a limited increase in cervical screening uptake in the short term, but the effect was small overall.[13] The influence of the media and multimedia educational strategies in engaging more women within a screening programme is supported by the outcomes of a multisite qualitative study in the USA by Cooper et al.[14] In the UK, there was a 2.23-fold increase in the diagnosis of high-grade disease [cervical intraepithelial neoplasia (CIN) II–III] in women not previously screened following the diagnosis of the television celebrity Jade Goody, but again this was short lived.[15]

Late diagnosis has been associated with illiteracy or low educational level, older age, marital status (widowed, divorced or single women) and low socio-economic status. These factors have been consistently identified in many studies internationally, in different health care settings in both rural and low resource countries, but also in higher economic income countries with structured cervical screening programmes.[16–20] Brookfield et al.[21] showed that insurance status is an independent predictor for poorer survival outcome, as it is related to late-stage presentation and under-treatment in the USA. Low socio-economic and educational status are important factors, as compliance with cancer screening is significantly lower in this population, even in the UK, where screening is free to all irrespective of insurance status.[22,23] Reasons for non-compliance when access and finance are not an issue could be a lack

of understanding of the natural history of cervical cancer and the role of screening, or because patient focus is more on prominent daily life issues and concerns rather than attending smear test invitations. Practical barriers were raised more often by younger women, whereas older women had more negative attitudes to screening.[24] Defaulters or never-attenders are more likely to present symptomatically with stage II+ disease and occasionally in non-gynaecological settings, as we have again confirmed in this study.

In our study, ethnicity was not identified as an independent statistically significant factor for symptomatic presentation, as long as the women were able to speak English, which implies that not speaking the language is a continued barrier to accessing health care. New strategies to reach non-English-speaking women need to be considered and may involve engagement with their communities and social leaders in order to increase education and the availability of screening programmes.

In our study, we have identified that a significant proportion of women who had at least one risk factor for potential social isolation, e.g. substance abuse (alcohol, drugs or smoking) or psychiatric disease (psychosis, bipolar disorder, mania or depression), were more likely to present symptomatically with advanced disease. Weiderpass et al.[25] identified that alcoholic women are at high risk for in situ and invasive cervical cancer and vaginal cancer, which was attributed to their poor adherence to cervical screening programmes and lifestyle-related reasons, such as smoking and dietary deficiencies. The evidence in the literature that HPV viral load and alcohol consumption are associated with the risk of CIN I among high-risk, HPV-positive women further supports these findings. Alcohol consumption was an independent and combined risk factor for CIN.[26] Jensen et al.[27] have shown that, among high-risk, HPV-positive women, an increased risk for CIN III+ was associated with long-term smoking (≥10 years) and heavy smoking (≥20 cigarettes/day). Although cigarette smoking itself is not a factor for social isolation, heavy smoking can be associated with the abuse of other substances or mental health disease.[28] In addition, women who smoke heavily may feel reluctant to engage with health care services as they may fear that they will be criticised and advised to stop smoking. Substantial evidence in the medical literature confirms disparities in breast and cervical cancer screening rates among women with mental

illness.[29] For women with major mental illness, the odds of cancer screening and related acute care visits are greater and, for women with substance use disorders, participation in a structured screening programme is reduced.[27]

Postcoital and intermenstrual bleeding are the two most common presenting symptoms of cervical cancer. In a systematic review performed by Shapley et al.,[30] the prevalence of postcoital bleeding in women with cervical cancer ranged from 0.7 to 39%, but the actual incidence of an invasive malignancy with postcoital bleeding was reported to be as low as 0.5–1.6%. Although the chance of cancer in young women with abnormal vaginal bleeding is very small, visualisation of the cervix is appropriate and postcoital bleeding should remain an indication for referral for gynaecological assessment and colposcopy.[31,32] Cervical cytology can give a false negative result in non-squamous histology, such as neuroendocrine cancers, which have been shown not to be detected through routine cervical cytology.

The number of women over 65 years of age being diagnosed with cervical cancer is increasing.[1] Cervical cancer can present as postmenopausal bleeding, and gynaecologists should be aware and exclude cervical pathology in women who present with postmenopausal bleeding. In our cohort, 38.6% (56/145) of patients were postmenopausal and 89.3% (50/56) of them experienced postmenopausal bleeding. Kamineni et al.[33] investigated the efficacy of screening in older women, and concluded that, for women aged 55–79 years, 5-yearly cytology is highly efficacious, although it has been shown that coverage for older age groups, for example 60–64 years, is as low as 44%.[34] In addition, recent data from the screening of older women in the USA and Sweden have suggested that there are substantial reductions in cervical cancer incidence and mortality, even among previously screened women.[35] The practical and economic implications of extending screening over the age of 65 years would need to be considered, especially as postmenopausal women have higher rates of inadequate cytology sampling.

In England, women under the age of 25 years are not invited to participate in cervical screening because of the rarity of invasive cancer in this age group, and the potential implications of unnecessary over-treatment.[36,37] Castanon et al.,[38] extrapolating data from the UK National Cervical Cancer audit registry, identified that cancer in women aged 20– 24 years was rare, but tended to be more advanced and more often of a rare histological subtype. As this population does not receive an invitation for screening, the need for careful assessment and investigation of women who do experience symptoms that could be suggestive of cervical cancer should be emphasised to both the general public and medical practitioners.

Raising the awareness of the symptoms associated with advanced cervical cancer, in particular renal failure as a result of ureteric obstruction, with non-gynaecologists is important, especially amongst doctors working in emergency departments, such that, when women present via this route, their path to a diagnosis can be short. Unfortunately, patients who present as an emergency experience high short-term mortality in all cancer types and, for cervical cancer, mortality rate ratios are as high as 7.5 times greater than those of non-emergency presentation.[39]

The limitations of this study include the retrospective nature of data collection and missing data. It is possible that the data may not be complete as patients might not have fully disclosed substance abuse or the diagnosis of psychiatric diseases; however, the information was obtained from multiple sources, including hospital case notes, nursing records and primary care referrals, in order to make the dataset as complete as possible.

Conclusions

An in-depth review of cervical cancer cases can help to identify areas of weakness in a screening programme and referral pathways, and highlight where improvements can be made. Adherence to screening programme protocols was associated with the diagnosis of cervical cancer at an early stage and therefore a good long-term prognosis. Gynaecologists should be aware of the need to exclude cervical pathology in women aged over 65 years who present with postmenopausal bleeding. Doctors working in all medical specialities should be aware of the symptoms associated with cervical cancer, as women may present to non-gynaecologists, potentially resulting in a delay in diagnosis and treatment.

Conflict of interest

None.

Contribution to authorship

ELM and EM designed the study. EM and LB performed the data collection. EM and NP performed statistical analysis. NP reviewed the statistics. EM, ELM, QD and NP wrote and revised the manuscript. All authors approved the final manuscript.

Ethical approval

Ethical approval was not required for this study.

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