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The incidence of cervical cancer in women with postcoital bleeding and abnormal appearance of the cervix referred through the 2-week wait pathway in the United Kingdom: A retrospective cohort study

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Abstract

Aim: To determine the incidence of cervical cancer in women referred through the 2-week-wait pathway for postcoital bleeding and abnormal appearance of the cervix.

Methods: A retrospective cohort study was conducted of women with postcoital bleeding, or abnormal appearance of the cervix referred to colposcopy clinics through the 2-week-wait pathway for suspected cervical cancer at Cambridge University Hospitals in the United Kingdom over 5 years. Women were identified from a departmental database. Clinical and demographic data were collected. Categorical data was analyzed with chi-squared or Fisher's exact tests and predictive values were calculated.

Results: Of the 604 women referred, 1.16% were diagnosed with cervical cancer. None of the women who were up-to-date with cervical screening were diagnosed with cervical cancer, while 6.25% of women out-of-date with cervical screening or outside the screening age group were diagnosed with cervical cancer ($p < 0.001$). The positive predictive value for diagnosing cervical cancer was 1.70% for postcoital bleeding (95% confidence interval [CI] 0.64–3.7) and 0.31% for abnormal appearance of the cervix (95% CI 0.0008–1.7).

Conclusions: The incidence of cervical cancer in women referred through the 2-week-wait pathway for postcoital bleeding and abnormal appearance of the cervix is low. These referrals have considerable implications for both patients and clinicians, and have a low predictive value for diagnosing cervical cancer. In light of emerging evidence and changing practices, referral guidelines should be reviewed based on up-to-date data and current practices.

Key words: cervical intraepithelial neoplasia, colposcopy, incidence, referral and consultation, uterine cervical neoplasms.

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Introduction

Clinical indications of cervical abnormalities constitute 27.2% of referrals to colposcopy.[1] Six percent of women of menstruating age in the United Kingdom experience postcoital bleeding,[2] mostly due to benign etiologies (cervical polyps, cervical ectropion), infection or inflammation (vaginitis, cervicitis),[3] and less commonly (~3%) due to cervical cancer.[4] Similarly, referrals for abnormal appearance of the cervix are often due to benign etiologies including Nabothian cysts, cervical ectropion, and cervical polyps.[5,6]

As part of the National Health Service (NHS) Cervical Screening Programme (CSP) women aged 24.5 to 64 years are offered cervical screening at regular intervals.[7–9] Women outside the screening age (over 65 years), should be screened if a recent cervical cytology sample is abnormal, or if they have not had a screening test since 50 years of age.[8] Samples are now primarily tested for human papilloma virus (HPV) and cytology is only examined for those that are HPV positive.[10–12] The 2-week-wait (2WW) referral system for urgent suspected cancer referrals to specialist care (such as gynecological oncology) was designed to reduce the incidence of and mortality from cancer.[13,14] 2WW referrals are usually sent by general practitioners in primary care, and ensure that these patients are seen by a specialist as soon as possible within 2 weeks of referral.[13] Abnormal cervical cytology (such as high-grade dyskaryosis or suspected invasive carcinoma), abnormal appearance of the cervix, and postcoital bleeding are common indications for a 2WW referral for suspected cervical cancer.[1,7] However, there are discrepancies in the current advice between the National Institute for Health and Care Excellence (NICE) guidelines[13] and NHS CSP[7] regarding whether symptoms including postcoital bleeding should be assessed in 2WW colposcopy clinics. During our study period 2014–2019, both the 2010[14] and updated 2016[7] NHS CSP guidelines recommended 2WW referral for women with symptoms suspicious of cervical cancer such as postcoital bleeding. However, the NICE guideline makes no reference to 2WW referrals for symptoms suspicious of cervical cancer.[13] In light of these discrepancies, further research and congruous guidelines are required to ensure the appropriateness of 2WW referrals when cervical cancer is suspected.

The objective of this study was to determine the incidence of cervical cancer in women referred through the 2WW pathway for postcoital bleeding and abnormal appearance of the cervix. This study aims to contribute to the growing body of research in support of refining national referral guidelines for suspected cervical cancer in a well-screened population.

Methods

We conducted a retrospective cohort study of women with postcoital bleeding, or abnormal appearance of the cervix referred to colposcopy clinics through the 2WW pathway at Cambridge University Hospitals (CUH) in the United Kingdom between November 1, 2014 to November 1, 2019. This clinical audit was registered at the Cambridge University Hospitals audit and clinical research department (Reference number PRN8641).

CUH is located within the Cambridgeshire and Peterborough Care Commissioning Group (CCG) and serves 5.8 million people throughout various hospitals in Bedfordshire, Hertfordshire, Cambridgeshire, Peterborough, Norfolk, Suffolk, and Essex.

Women referred for suspected cervical cancer with postcoital bleeding or abnormal appearance of the cervix through the 2WW pathway were identified from a departmental computerized database of women who attended colposcopy clinics. The clinical records of these women were inspected for the indication for referral, cervical screening test results, biopsy results, and diagnosis. Demographic variables were also recorded including age, menopausal status, parity, smoking status, and contraception use.

Descriptive statistics were reported as mean and standard deviation (SD) for normally distributed continuous data, median and interquartile range (IQR) for non-normally distributed data and frequencies and percentages for categorical data. Continuous data were tested for normality using the Shapiro–Wilk test and analyzed using the t test. Categorical data were analyzed using either a Mann–Whitney U test, chi-squared, or Fisher's exact test where appropriate. Positive predictive values (PPV) and 95% confidence intervals were calculated. p-values < 0.05 were considered significant. All analyses were conducted using R statistical software.

Results

Cambridge University Hospitals saw 10 722 women in colposcopy clinics between November 1, 2014 and November 1, 2019. Of these women, 1041 were referred

for suspected cervical cancer through the 2WW pathway. Our target population was 604 women referred for postcoital bleeding, abnormal appearance of the cervix, or both (Table 1). The indication for 2WW referral included 47.5% of women referred for postcoital bleeding, 42.7% for abnormal appearance of the cervix, and 9.8% for both referral indications. The median age of women referred was 42 years (SD 12.2, range 17–91). There were 65 women (10.7%) who were outside the routine screening age for cervical cancer. Most women (81.5%) were up-to-date with their cervical screening tests, while 7.8% were out-of-date or overdue for their cervical screening. Of the 604 women, 24.3% were current or ex-smokers, 78.5% were premenopausal, and 72.5% were multiparous.

TABLE 1 Study cohort demographic variables

Demographic	*n*	%
Indication for 2-week-wait referral		
Postcoital bleeding (PCB)	287	47.5
Abnormal appearance of cervix (AAC)	258	42.7
Both PCB and AAC	59	9.8
Age		
Range 17–91 years, median 42, SD 12.2		
Cervical screening program status		
Cervical screening up-to-date	492	81.5
Cervical screening out-of-date	47	7.8
Age below screening criteria (<24.5 years)	42	6.9
Age above screening criteria (>64 years)	23	3.8
Smoking status		
Nonsmoker	438	72.5
Current smoker	100	16.6
Ex-smoker	47	7.8
Unknown	19	3.1
Menopausal status		
Premenopausal	497	82.3
Postmenopausal	107	17.7
Parity		
Multiparous	438	72.5
Nulliparous	145	24.0
Unknown	21	3.5
Contraception		
No contraception	242	40.1
Condoms	83	13.7
Oral contraceptive pill (COCP and POP)	118	19.5
Intrauterine device	66	10.9
Progesterone depot (injection and implant)	27	4.5
Sterilization (female and male)	49	8.1
Other	3	0.5
Unknown	16	2.7

Seven women (1.16%) were diagnosed with cervical cancer and two women (0.33%) were incidentally diagnosed with other cancers (Figure 1). Six out of the seven women diagnosed with cervical cancer had squamous cell carcinoma of the cervix ($n = 6$, 0.99%), and one woman was diagnosed with neuroendocrine carcinoma of the cervix ($n = 1$, 0.17%). As per The International Federation of Gynecology and Obstetrics (FIGO), the women diagnosed with cervical cancer ranged from stage IB1 to IVB.[15] Three women (0.50%) were diagnosed with cervical intraepithelial neoplasia (CIN) III, and all were out-of-date with routine cervical screening. Furthermore, seven women (1.16%) were diagnosed with CIN II, and all but one woman (6/7, 85.71%) were out-of-date with routine cervical screening. Most women (91.22%) either had no pathology, variations of normal (including Nabothian cysts and cervical ectropion), or benign pathology diagnosed (including cervicitis, cervical endometriosis, and benign cervical polyps).

As shown in Table 1, the ages of the seven women diagnosed with cervical cancer ranged from 24 to 91 years (median 48 years, SD 23.2). Six women were referred for postcoital bleeding and one woman was referred for abnormal appearance of the cervix. Of the women diagnosed with cervical cancer, 57.1% were current or ex-smokers compared to 24.3% of the total study cohort ($p = 0.07$). At colposcopy, the clinical impression was documented by the specialist as "clinically evident cancer" for two out of the seven women (28.57%), "suspicious for cervical cancer" for four out of the seven women (57.14%) who were diagnosed with cervical cancer. The clinical impression of the remaining one woman (14.23%) was "suspected high-grade CIN."

None of the women (0/492) who were up-to-date with the recommended cervical screening were diagnosed with cervical cancer, while 6.25% (7/112) of women out-of-date or outside the screening age for cervical screening were diagnosed with cervical cancer ($p < 0.001$). Two of the women diagnosed with cervical cancer were aged 75 and 91, considerably outside the routine screening age and had unknown previous cervical screening history. Four women were out-of-date for routine cervical screening, ranging from 5 to 19 years since their last cervical screening test. A 24.5-year-old woman was diagnosed with cervical cancer whose first cervical screening result was pending at the time of referral and was later returned as abnormal (Table 2).

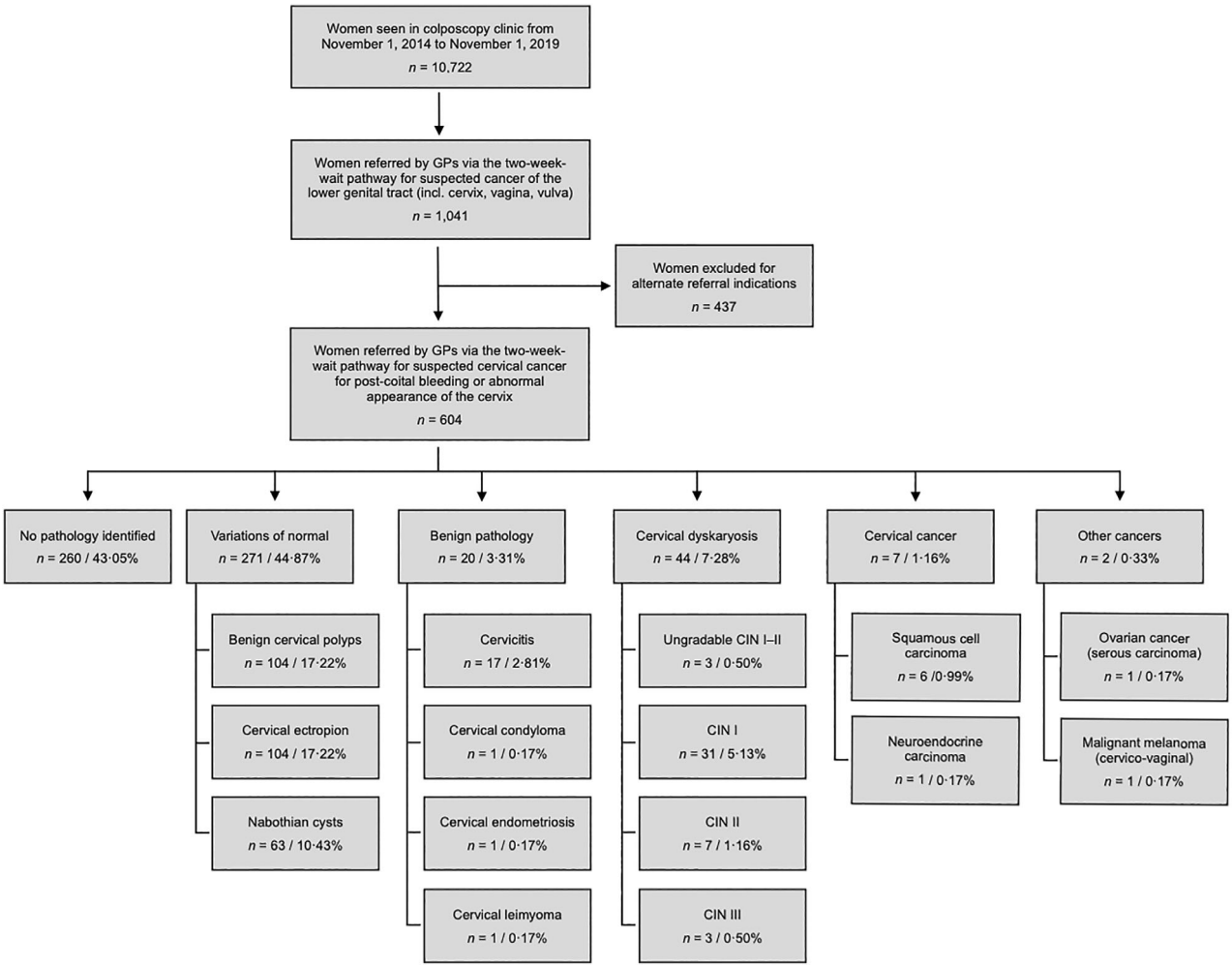

FIGURE 1 Flow diagram of study design and gynecological pathology diagnosed

The PPV for diagnosing cervical cancer in the 2WW referral pathway was 1.70% for postcoital bleeding (95% confidence interval (95% CI 0.64–3.7) and 0.31% for abnormal appearance of the cervix (95% CI 0.0008–1.7). In women who were up-to-date with cervical screening and within the screening age, the PPV of postcoital bleeding and abnormal appearance of the cervix for diagnosing cervical cancer was 0.00%.

Discussion

Main findings

In this study, the incidence of cervical cancer was 1.16% in women referred through the 2WW pathway for suspected cervical cancer with postcoital bleeding and abnormal appearance of the cervix (Figure 1). This value is consistent with other authors who report a comparably low incidence of cervical cancer for these referral indications.[4,16] Of the seven women diagnosed with cervical cancer, none were up-to-date with the recommended cervical screening either due to not accepting an invitation to screening or due to their age being outside of the routine screening ages of 24.5 to 64 years. Though symptomatic referrals are not aimed at detecting CIN, three women in our study population were diagnosed with CIN III, however, these women were all out-of-date with their recommended cervical screening. In contrast, in a well-screened population of women who were up-to-date with regular cervical screening and within the routine screening age, no women were diagnosed with cervical cancer or CIN III (Figure 1).

TABLE 2 Cervical cancers diagnosed in women through the 2-week-wait pathway

Diagnosis and FIGO stage	Referral indication	Age	Smoking status	Last cervical screening	Cervical screening program status
Cervical cancer stage IB1 (neuroendocrine carcinoma)	PCB	24.5	Current smoker	Never had	Diagnosis via abnormal cervical screening test, at time of referral
Cervical cancer stage IB1 (squamous cell carcinoma)	PCB	28	Current smoker	Abnormal	Cervical screening out-of-date (last cervical screening 5 years)
Cervical cancer stage IVB (squamous cell carcinoma)	PCB	35	Ex-smoker	Unknown	Cervical screening out-of-date (last cervical screening 17 years)
Cervical cancer stage IB1 (squamous cell carcinoma)	PCB	39	Non-smoker	Normal	Cervical screening out-of-date (last cervical screening 10 years)
Cervical cancer stage IIB (squamous cell carcinoma)	PCB	48	Ex-smoker	Normal	Cervical screening out-of-date (last cervical screening 19 years)
Cervical cancer stage IVA (squamous cell carcinoma)	PCB	75	Non-smoker	Unknown	Age above screening criteria[a]
Cervical cancer stage IVA (squamous cell carcinoma)	AAC	91	Non-smoker	Unknown	Age above screening criteria[a]

Abbreviations: AAC, abnormal appearance of the cervix; PCB, postcoital bleeding. and [a]Cervical screening program criteria: routine cervical screening offered to women aged 24.5 to 64 years.

NICE guidelines recommend a PPV of at least 3.00% for suspected cancer referrals, given the clinical and financial costs associated with these referrals.[13] In our study, the PPV of postcoital bleeding for diagnosing cervical cancer was 1.70%, and the PPV of abnormal appearance of the cervix for diagnosing cervical cancer was 0.31%. Furthermore, women who were well-screened for cervical cancer, the PPV of postcoital bleeding and abnormal appearance of the cervix for diagnosing cervical cancer was 0.00%, as there was no cervical cancer diagnosed in these women. One study from 2017 of 117 women referred through the 2WW pathway for suspected cervical cancer had a PPV of 5.98% for diagnosing cervical cancer.[17] Another study from 2011 of 25 women had a PPV of 12.00% for diagnosing cervical cancer.[18] This is underscored by the NHS CSP guideline, which also states "evidence for the precise predictive value of postcoital for cervical cancer is poor."[7] Our study is the first to calculate the PPV for the 2WW referral indications of postcoital bleeding and abnormal appearance of the cervix in diagnosing cervical cancer and included a larger cohort of women.

Strengths and limitations

Our study examined all 2WW referrals to colposcopy for postcoital bleeding and abnormal appearance of the cervix over a 5-year period at a tertiary cancer centrer which receives a large volume of referrals annually. To our knowledge, this is the first paper to calculate the PPV of abnormal appearance of the cervix for diagnosing cervical cancer. We did not exclude women based on their age or pregnancy status to comprehensively illustrate the women being referred through the 2WW pathway for suspected cervical cancer. Our study is limited by the fact it is a retrospective observational analysis and data was collected from a single centre.

Interpretation and implications for practice

We believe the low incidence of cervical cancer diagnosed in women with postcoital bleeding and abnormal appearance of the cervix as demonstrated in this study and others are convincing evidence to support a review in referral guidelines which may reduce 2WW referrals for suspected cervical cancer. If 2WW referrals were reduced, it would greatly decrease the time burden 2WW referrals impose on clinicians, particularly time in specialist clinics,[19] given 98.84% of women referred for suspected cervical cancer in our study were not diagnosed with cervical cancer (Figure 1). Women receiving 2WW referrals for suspected cancer inflicts a significant psychological, social, and emotional burden[20,21] with a minimum 2-week period of stress considering a potential cancer

diagnosis. This burden should not be understated and reducing 2WW referrals may help alleviate this.

The introduction of the HPV vaccination program in 2008 and primary HPV testing from 2019[22] will further decrease the incidence of precancerous changes[23] and increase the sensitivity and thus effectiveness[24] of screening, respectively. These factors are likely to further reduce the predictive value of postcoital bleeding and abnormal appearance of the cervix for diagnosing cervical cancer via the 2WW pathway.[22] Furthermore, HPV tests have a national turnaround time of less than 14 days,[9] thus results are delivered much faster than the conventional cytology tests. Additional research examining the effects of HPV screening and HPV vaccination on the incidence of cervical cancer in the United Kingdom would be of great interest. Local and national cost analysis of colposcopy for clinical indications was outside the scope of this study but would be highly informative.

The incidence of cervical cancer in women referred through the 2WW pathway for postcoital bleeding and abnormal appearance of the cervix is low. In a well-screened population, including regular cervical screening and within the routine screening age of 24.5 to 64 years, no women were diagnosed with cervical cancer. Given the population of women vaccinated against HPV now entering routine cervical screening and the change to primary HPV cervical screening, the incidence of cervical cancer will likely continue to decline. Based on the findings of our study and others, we propose the NHS CSP[7] guideline should be consistent with the NICE guideline.[13] We agree with the advice as per the NICE guideline, in that women with symptoms should be referred via the 2WW pathway only if on examination, the appearance of the cervix is consistent with cervical cancer, and not for symptoms such as postcoital bleeding alone.

Two-week-wait referrals for postcoital bleeding and abnormal appearance of the cervix have a low predictive value for diagnosing cervical cancer. National 2WW referral guidelines should be reviewed and congruous throughout to ensure a high-quality referral system.

Author contributions

Conception: Brittany Jasper and Emma Thorley. Planning and development: Brittany Jasper, Emma Thorley, Krishnayan Haldar. Data analysis: Brittany Jasper, Emma Thorley, Filipe Correia Martins, Krishnayan Haldar. Initial draft of manuscript: Brittany Jasper and Emma Thorley. Manuscript writing, review, and approval: Brittany Jasper, Emma Thorley, Filipe Correia Martins, Krishnayan Haldar.

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Conflict of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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