Endometrial cancer diagnoses prompted by routine cervical cytology: a retrospective case study

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ABSTRACT

AIMS: Endometrial cancer is the commonest gynaecological cancer in New Zealand. Some women have their diagnosis of endometrial cancer prompted by an abnormal cervical cytology screening test. When high-risk human papillomavirus (hr-HPV) testing becomes the primary test for cervical screening, this avenue of incidental diagnosis will be reduced. Therefore, our aims were to estimate the proportion of women whose diagnosis of endometrial cancer follows incidental detection on routine cervical cytology, and to understand the clinicopathologic characteristics of these cases.

METHODS: Retrospective analysis of patient medical records from women of cervical screening age diagnosed with endometrial cancer between 2015–2019 in the South Island of New Zealand.

RESULTS: Of 334 women, 26 (7.8%) had endometrial cancer diagnosis prompted by abnormal cervical cytology. Most women had low-grade (17/26, 65.4%), low-stage (18/26, 69.2%) disease of endometrioid histologic subtype (21/26, 80.8%). The small cohort prevented significant correlations with clinicopathologic characteristics and outcomes. Overall, cervical cytology had low sensitivity (32.3%) for the detection of endometrial cancer in the 6 months before diagnosis.

CONCLUSIONS: A small number of women currently have diagnoses of endometrial cancer prompted by routine cervical screening with cytology. However, the undefined clinical benefit from and poor sensitivity of cervical cytology for detecting endometrial cancer does not justify its use in screening, or opposition to hr-HPV cervical screening.

Endometrial cancer is the fifth most common cancer among New Zealand women overall, and is the most common gynaecological malignancy.[1,2] Its incidence is further increasing with rates of obesity, diabetes and an aging population.[1,3,4] The current and projected burden of endometrial cancer hence emphasises an unmet need in its early diagnosis: to date, no specific and cost-effective screening method has been established. Rather, diagnosis depends on reporting of clinical symptoms or incidental detection. Clinical symptoms include abnormal uterine bleeding, discharge and pain. Symptomatic reporting is certainly unreliable in its timeliness, and delayed diagnosis predisposes to worse clinical outcomes.[5]

The purpose of the New Zealand National Cervical Screening Programme (NCSP) is to detect abnormalities of the cervix by 3-yearly screening utilising liquid-based cytology. However, it has also had a role in the incidental diagnosis of endometrial cancer. Three types of endometrial cells can be reported: normal endometrial cells (NEMCs), atypical endometrial cells (AEMCs) and endometrial carcinoma cells (EMCCs).[6,7] As NEMCs may reflect physiological exfoliation related to menstruation, they are only reported in women older than 40 years, for whom the likelihood of malignant endometrial pathology is significant.[7]

Compared with cytology, high-risk human papillomavirus (hr-HPV) testing has been shown to offer greater protection against cervical cancer.[8–10] The NCSP therefore plans to action routine utilisation of primary hr-HPV testing in place of cytology. This change to primary hr-HPV testing will reduce routine cervical cytology as an incidental diagnostic avenue for endometrial cancer. Only women who have a positive hr-HPV result will go on to have cytology. Existing literature confirms that cervical cytology can detect abnormal endometrial cells in women with endometrial cancer, albeit with low sensitivity and predictive value.[11–17] Presence of abnormal endometrial cells on cervical cytology has also been correlated with unfavourable clinicopathologic disease characteristics.[17,18] Nevertheless, there is a dearth of evidence specifically addressing the role of routine cervical cytology in prompting diagnoses of endometrial cancer.

This retrospective observational study

reviewed the cervical cytology histories of women in the South Island of New Zealand who were diagnosed with endometrial cancers between 2015 and 2019. The primary aim of the study was to quantify the proportion of women with endometrial cancer that were diagnosed following incidental finding on routine cervical screening by cytology. Secondary aims were to determine whether ethnicity, grade and stage of disease at diagnosis, histological tumour type and 12-month mortality differed significantly for women diagnosed following routine cervical cytology, compared with women who presented symptomatically.

Methods

A retrospective review of hospital clinical records was conducted for women with endometrial cancer diagnosed between 2015–2019, who were managed by New Zealand southern regional gynaecological cancer services and retained in their clinical databases. Inclusion required confirmed histological diagnosis between January 2015–December 2019, and being of cervical screening age (25–69 years) at the time of diagnosis. Data relevant to the primary and secondary outcomes were obtained through manual review of electronic clinical records and transcribed to a Microsoft Excel database. Ethical approval for the study was obtained from the University of Otago Human Research Ethics Committee (approved 23 September 2020, reference number: HD20/076).

Prompt for diagnosis was reported as any one of: abnormal cervical cytology, clinical symptoms, other incidental or unclear. Where the prompt for diagnosis was abnormal routine cervical cytology, this was usually specified in a referral letter to specialist services. A prompt for diagnosis was unclear if there was an absence of clarifying clinical information in the hospital record.

Results of cervical cytology in the 36 months preceding endometrial cancer diagnosis were recorded to a maximum of the 3 most recent results prior to diagnosis date. Endometrial abnormalities were reported as NEMCs, AEMCs and EMCCs, as per NCSP and Bethesda system resources for cytologic diagnoses.[6,7] The sensitivity of cervical cytology for the detection of endometrial cancer was estimated from those cytology results in the 6 months pre-diagnosis.

A cervical cytology sample taken in the 6 months prior to diagnosis was classified as routine if it was taken at, or just beyond, the routine screening interval for that person (i.e., 12 months or 3 years, depending on what was advised on the preceding cervical cytology result), and there were no coincident clinical symptoms. If clinical symptoms were explicitly reported prior to cytology (i.e., not reported after an abnormal result), the investigation was considered to have been done for clinical work-up of symptoms. A cytology sample taken earlier than required for routine screening, and/or by a specialist, and/or in conjunction with other investigations (e.g., high vaginal or endocervical swabs, pipelle biopsy) was also classified as being part of clinical work-up. The indication for cytology was categorised as unclear when a cervical cytology sample was taken in a primary care facility, its timing fell at or beyond a woman's routine screening window and there were no available notes to confirm or refute its use in work-up of coincident symptoms. From this categorisation, the proportion of women participated in routine cervical screening was estimated.

Ethnicity was reported as total response ethnicity, whereby every ethnicity recorded for a woman is counted independently. Hence, numbers of ethnicity-related events exceed the number of women in the study cohort.

12-month mortality was measured using date of death, cause of death (if available on electronic record, otherwise deemed unclear) and date of last contact with any medical service.

Data were analysed using STATA (nptrend StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StatCorp LP).

Results

From 512 women identified with a diagnosis of endometrial cancer between 2015 and 2019, the final study population comprised 334 women (Figure 1). The median age at diagnosis for the cohort was 60 years (range 36–69). Eighty-seven percent of women identified as NZ European. And, most had low-grade, low-stage endometrioid disease: 69.8% had grade 1, 65.3% FIGO stage 1A and 90.1% had endometrioid type disease.

The prompt for diagnosis was abnormal routine cervical cytology for 26/334 women (7.8%). The majority of diagnoses were prompted by presentation with clinical symptoms (283/334, 84.7%), or other incidental findings (19/334, 5.7%). Diagnostic prompts for six women were unclear (1.8%).

Figure 1: Study cohort after eligibility criteria applied, and their diagnostic prompts.

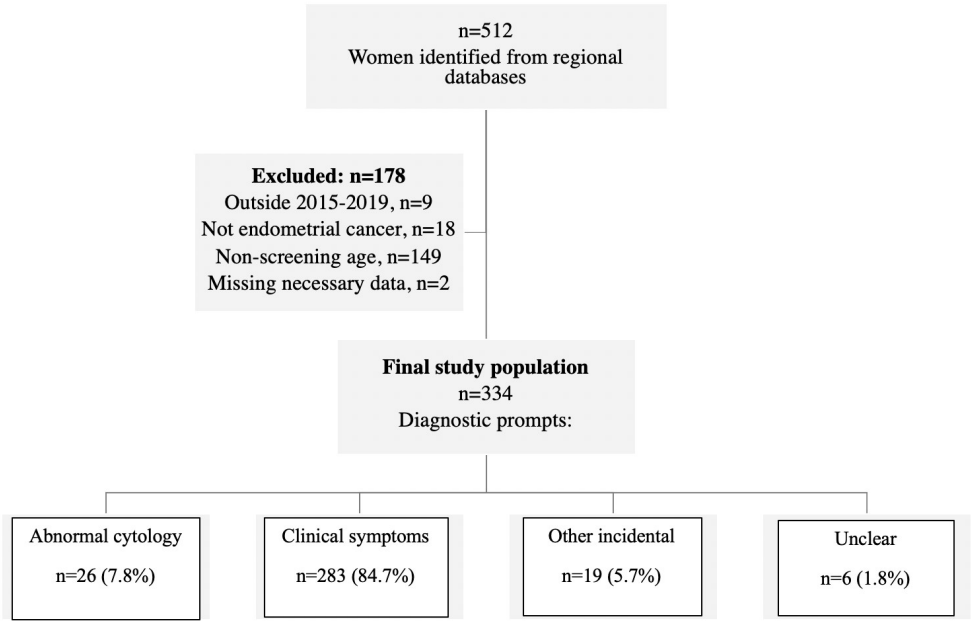

Table 1 shows disease characteristics by diagnostic prompt. Low-grade and low-stage disease was present in >65% and >57% of cases across all diagnostic groups. Seventeen out of 26 (65.4%) women diagnosed following abnormal routine cervical cytology had FIGO grade 1 disease, and 18/26 (69.2%) had FIGO stage <IA disease. This was comparable to proportions of low-grade (198/283, 70.0%) and low-stage disease (185/283, 65.4%) in the group of women whose diagnostic prompt was clinical symptomatology.

For analytic purposes, all endometrial carcinomas were classified as either endometrioid or non-endometrioid histologic subtypes. Non-endometrioid carcinomas included serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, mixed type and carcinosarcomas. Most carcinomas were of endometrioid histologic subtype (301/334, 90.1%) as compared with their non-endometrioid counterparts. This was true across all diagnostic prompts. Twenty-one (80.8%) of the abnormal routine cervical cytology group and 258 (91.2%) of the clinical symptoms group had endometrioid endometrial carcinomas. However, 15% (5/33) of women with non-endometrioid tumours, as opposed to 7% (21/301) of women with endometrioid type, had abnormal cytology as a diagnostic prompt.

Data pertaining to age and ethnicity are not shown. There was no substantial deviation of median diagnostic age for any diagnostic prompt group. The median age at diagnosis was 60 years (range 47–65) for the abnormal cytology group, 59 years (range 31–69) for the clinical symptoms group, 65 years (range 36–69) for the other incidental group and 62.5 years (range 41–66) for the group whose diagnostic prompt was unclear.

For every total response ethnicity group, clinical symptomatology most frequently prompted diagnosis (248/292 [84.9%] Europeans, 15/19 [79.2%] Māori, 12/12 [100%] Pacific, 19/24 [79.2%] Asian, 22/25 [88%] Other). Twenty-three European (7.9%), three Māori (15.8%), two Asian (8.3%) and two Other (8.0%) were diagnosed following abnormal cytology. Fifteen (5.1%) European, one (5.3%) Māori, three (12.5%) Asian and one (4.0%) Other had other incidental diagnostic prompts. Only six (2.1%) Europeans had an unclear diagnostic prompt.

Of the 334 women who met inclusion criteria, 299 (89.5%) had cervical cytology results from the 36 months antecedent to their endometrial cancer diagnosis. Total cytologic results are summarised in Table 2. One hundred and sixty-nine out of 299 (56.5%) women had one documented cytologic result in the 36-month pre-diagnosis period, 115 (38.5%) had two results and 15 (5.0%) had three

Table 1: Pathologic disease characteristics by diagnostic prompt.

Diagnostic prompt						
Disease characteristic		**Abnormal cervical cytology (n=26) n (%)**	**Clinical symptoms (n=283) n (%)**	**Other incidental (n=19) n (%)**	**Unclear (n=6) n (%)**	**All (n=334) n (%)**
FIGO grade	1	17 (65.4)	198 (70.0)	14 (73.7)	4 (66.7)	233 (69.8)
	2	3 (11.5)	33 (11.6)	2 (10.5)	1 (16.7)	39 (11.7)
	3	6 (23.1)	52 (18.4)	3 (15.8)	1 (16.7)	62 (18.6)
FIGO stage	≤IA	18 (69.2)	185 (65.4)	11 (57.9)	4 (66.7)	218 (65.3)
	≥IB	8 (30.8)	98 (34.6)	8 (24.1)	2 (33.3)	116 (34.7)
Histological type	Endometrioid	21 (80.8)	258 (91.2)	17 (89.5)	5 (83.3)	301 (90.1)
	Non-endometrioid	5 (19.2)	25 (8.8)	2 (10.5)	1 (16.7)	33 (9.9)

Table 2: All cytology results (to a maximum of three) for 299/334 women with endometrial cancer that had available cytology in the 36 months before their diagnosis.

Cytologic result	No. (%) results from 0–36 months before diagnosis
Abnormal cytology	
Glandular (n=83, 18.7%)	
NEMC≥40	16 (3.6%)
AEMC	45 (10.1%)
EMCC	21 (4.7%)
AGC	1 (0.2%)
Squamous (n=14, 3.2%)	
HSIL	3 (0.7%)
LSIL	3 (0.7%)
ASC-US	8 (1.8%)
ASC-H	0 (0%)
NILM (n=347, 78.2%)	
Normal	341 (76.8%)
Reactive cellular change	3 (0.7%)
Unsatisfactory	3 (0.7%)
Total	444 (100%)

NEMC≥40 = normal endometrial cells in woman over 40 years; AEMC = atypical endometrial cells; EMCC = endometrial carcinoma cells; AGC = atypical glandular cells; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells – cannot exclude high-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy.

Table 3: Corresponding disease characteristics (FIGO grade and stage, histological type) for cervical cytology results nearest cancer diagnosis for those sampled.

Cytology result nearest diagnosis		Disease characteristic						
		FIGO grade			FIGO stage		Histological type	
		1 (n=213) n (%)	2 (n=34) n (%)	3 (n=52) n (%)	≤IA (n=200) n (%)	≥IB (n=99) n (%)	Endometrioid (n=270) n (%)	Non-endometrioid (n=29) n (%)
Glandular	NEMC≥40 (n=14)	12 (5.6)	2 (5.9)	0 (0)	11 (5.5)	3 (3.0)	14 (5.2)	0 (0)
	AEMC (n=41)	29 (13.6)	7 (20.6)	5 (9.6)	27 (13.5)	14 (14.1)	39 (14.4)	2 (6.9)
	EMCC (n=21)	7 (3.3)	5 (14.7)	9 (17.3)	7 (3.5)	14 (14.1)	13 (4.8)	8 (27.6)
	AGC (n=1)	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (0.4)	0 (0)
	Any glandular (n=77)	49 (23.0)	14 (41.2)	14 (26.9)	45 (22.5)	32 (32.3)	67 (24.8)	10 (34.5)
Quamous (n=6)		3 (1.4)	1 (2.9)	2 (3.8)	2 (1.0)	4 (4.0)	6 (2.2)	0 (0)
NILM (n=216)		161 (75.6)	19 (55.9)	36 (69.2)	153 (76.5)	63 (63.6)	197 (73.0)	19 (65.5)

or more. Most women that had a cytology sample taken in this period only yielded results negative for abnormality (211/299, 70.6%). Two hundred and thirty-two out of 299 (77.6%) women had at least one cervical cytology sample taken in the 6 months preceding diagnosis. Among these 232 women, 159 (68.5%) had cytology samples taken for clinical work-up for symptoms, while 66 had samples taken for routine screening. Seven had an unclear indication.

Approximately 228/334 (68%) women underwent routine cervical screening in the 36 months before their diagnosis. The proportion of screened women whose diagnosis was prompted in the same way was 11.4% (26/228).

AEMCs were detected on 16/26 (61.5%) cervical cytology samples that prompted a diagnosis of endometrial cancer. EMCCs were detected in 5/26 (19.2%), as were NEMCs≥40 (5/26, 19.2%). The sensitivity of cervical cytology for the detection of endometrial cancer based on results most antecedent to diagnosis in the 6-month pre-diagnosis was 32.3%, given 75/232 women returned an abnormal related result (40 AEMC, 21 EMCC, 13 NEMC ≥40, one AGC) in this interval.

Cervical cytology results most antecedent to diagnosis (and not exceeding 36 months) (n=299) were analysed with regard to the pathologic characteristics of a corresponding woman's disease (Table 3). Irrespective of the FIGO grade, FIGO stage and histological type of disease, >55% of cytology results nearest diagnosis were negative for intraepithelial lesion or malignancy (NILM). Fourteen out of 52 (26.9%) women with grade 3 disease, and 49/213 (23.0%) women with grade 1 disease, had a glandular abnormality on cervical cytology prior to their diagnosis. Thirty-two out of 99 (32.3%) women with ≥IB stage disease returned a glandular abnormality, as did 45/200 (22.5%) women with ≤IA stage disease. Glandular abnormalities on cervical cytology ahead of diagnosis were recorded for 10/29 (34.5%) women with non-endometrioid type cancers, and for 67/270 (24.8%) those with endometrioid types.

14 women died in the 12 months following their diagnosis of endometrial cancer. All deaths were ascribed to end-stage endometrial cancer, or were of unclear cause (none definitely died from an unrelated cause). No women for whom cytology prompted diagnosis died within 12 months.

Discussion

This retrospective study is important as it quantifies the active role of cervical cytology in incidental diagnoses of endometrial cancer, which appears not to have been previously estimated. In this study, at least 7.8% (26/334) of women eligible for cervical screening had their endometrial cancer diagnoses prompted in this way. Excluding women who appear not to have taken part in cervical screening, the proportion of women whose diagnostic prompt was abnormal cervical cytology becomes 11.4%.

In terms of diagnostic accuracy, cervical cytology has already been designated an overall poor sensitivity for the detection of endometrial cancer.[12–17] Discordant estimates range between 28.1–88.3%, reflecting the heterogeneity of the studies producing them.[12–17] Thirty-two point three percent of women who had cervical cytology within 6 months of their diagnosis had an abnormal result in this study. This aligns with that of past literature, which deems cervical cytology an unreliable screening test for endometrial cancer.[12–17]

Glandular abnormalities on cervical cytology have previously been correlated with endometrial cancer of higher grade, higher stage and worse prognoses.[14,17,18] When considering cytology nearest to cancer diagnosis irrespective of diagnostic prompt, the results of the present study were consistent with those of preceding studies. Specifically, glandular abnormalities (AEMC, EMCC, NEMC ≥40, AGC) were more often detected by cervical cytology nearest to cancer diagnosis in women with higher FIGO grade (14/52, 26.9% grade 3 vs 49/213, 23.0% grade 1) and stage (32/99, 32.3% stage ≥IB vs 45/200, 22.5% stage ≤IA) of disease. Glandular abnormalities were also detected more often in women with non-endometrioid histological tumour types (10/29, 34.5% vs 67/270, 24.8% endometrioid). However, diagnoses prompted by abnormal glandular results on cervical cytology were not correlated with worse clinicopathologic characteristics of disease: most had low FIGO grade (17/26, 65.4%) and stage (18/26, 69.2%) disease, and endometrioid tumour histologies (21/26, 80.8%). This is likely because the majority of women in the study had low-grade and low-stage disease, regardless of diagnostic prompt. Due to the small study size, correlation with worse disease characteristics cannot be excluded.

Mortality was the clinical outcome of interest in this study, but was also a rare outcome (14/334). This was probably augmented by the short 12-month follow-up period. Although there were no cases of 12-month mortality in the group diagnosed following abnormal cytology, the study is again too underpowered for correlation.

The incidence of endometrial cancer is 19.6 per 100,000 Māori women and 40.9 per 100,000 Pacific women, notably higher than for non-Māori/non-Pacific women (12.6 per 100,000 women).[4] Compared with non-Māori, Māori women are also nearly twice as likely to present with advanced stage endometrial tumours[22] and have a 56% higher mortality rate (age- and sex-adjusted cancer-specific excess mortality).[23] Again, small numbers of Māori and Pacific women in this study deem correlations with ethnicity unreliable. However, matters of equity in relation to endometrial cancer are evidently of utmost importance. Further research including more Māori and Pacific women is required to better postulate the impact of the NCSP change on these groups.

Results of this study indicate that with the introduction of cervical hr-HPV screening, diagnosis for at least a small proportion of women with endometrial cancer may be delayed. In 2019, there were 686 women diagnosed with endometrial cancer in New Zealand.[24] By extrapolation of figures from this study, approximately 35 women a year would therefore have their diagnosis of endometrial cancer delayed by the change in NCSP policy. Here, the impact of delay is undefined, as the interval between incidental detection on cytology and onset of symptoms cannot be studied outside of real practice. Concern is reduced by this study, as the majority of women detected by cytology had low-grade disease, such that delay may not result in a significantly worse outcome.

The increasing burden of endometrial cancer is well documented. This study identifies that endometrial cancer can be detected in some asymptomatic women. Respondent to this are efforts to develop screening tests with the necessary elements of early detection and easy dissemination across clinical contexts. Some progress has been made with combining molecular testing and non-invasive sampling techniques. Genomic, epigenomic and proteomic approaches have shown potential in leveraging the sensitivity of numerous specimens (e.g., cervical cytology, cervical scrapings, cervicovaginal secretions, tampons) for detection of endometrial cancer, to 70–90%.[25–27] These approaches may meet the growing diagnostic need in this area, but research is ongoing. For disenfranchised Indigenous Māori and Pacific populations in New Zealand that have higher incidence of endometrial cancer, culturally sensitive and equitable screening strategies are needed.

This research is most limited by its retrospective design and small regional cohort. Although the cohort is a relatively complete representation of women with endometrial cancer in the Southern Region of New Zealand, it has reduced applicability to other populations. For example, Māori and Pacific populations were significantly under-represented in this study. Small cohorts also undermine statistical power, which has not been formally analysed in this study.

In conclusion, endometrial cancer can be detected in asymptomatic women by cervical cytology. Seven point eight percent of women eligible for cervical screening in this study had their endometrial cancer diagnoses prompted this way. The implementation of hr-HPV screening will reduce this pathway to diagnosis. It is important to acknowledge the women who will consequently have their diagnoses delayed, as the true clinical impact of these delays is undetermined. The poor sensitivity of cervical cytology for endometrial cancer does not justify its continued use as the primary cervical screening test in New Zealand; nor does it support a potential role in endometrial cancer screening. Research exploring screening modalities and potential benefits for endometrial screening in asymptomatic and disenfranchised Indigenous women is justified.

COMPETING INTERESTS
The authors of this paper have no conflicts of interest (relational, financial or otherwise) to report.

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