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Compliance with Follow up Cytology after Discharge from the Colposcopy Clinic

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Abstract
Cervical cancer represents the second common cancer in women and is a major public health issue in Ireland and worldwide. Despite appropriate treatment of precancerous lesions, women with dysplasia are at relatively increased risk, and require follow up. We aimed to evaluate the compliance rate with follow up cytology advice given to patients discharged from the colposcopy clinic and to identify predictive factors for poor compliance. This is a retrospective cohort study of patients initially managed in our institution in 2001. Patients were evaluated for adherence with the recommendations received at the time of discharge from the clinic. Of the116 women that were initially contacted, 100 agreed to participate in the study (86% response rate). Sixty women (60%) were entirely compliant. While older patients (>40 years) were significantly less likely to show complete compliance (OR: 0.12; 95% CI: 0.02-0.58; p=0.009).

Introduction
The incidence of cervical cancer has been dramatically reduced in the UK since the introduction of cervical screening programme. Nonetheless 493,000 new cases and 273,000 deaths still occur annually worldwide[1]. Effective methods of treatment commonly used for CINs (cervical intraepithelial neoplasia) are LLETZ (large loop excision of the transformation zone)[2,3], cold knife cone (CKC), laser conisation and other destructive techniques such as laser vaporization and cold coagulation. With the exception of CKC, all represent simple and quick procedures, mostly performed under local analgesia. To date, no difference in efficacy among the available conservative methods of treatment has been demonstrated[4,5] though the evidence is not conclusive[7]. Despite appropriate treatment, women with pre-malignant cervical disease are at increased risk of residual or recurrent disease[4,6,7].

Several tools for post-CIN treatment surveillance are available such as cytology, colposcopy, and more recently HPV testing[8,12]. Despite robust evidence that HPV testing represents the best stand-alone test of cure[13,15]. It is neither universally available nor affordable yet. The use of cytological cervical smears still represents the most common follow up test, patients often being asked to have a yearly smear for 5 to 10 years before returning to routine screening recall. However such a follow up policy is crucially dependent on patient compliance. The objective of this study was to evaluate the compliance rate of women discharged from the colposcopy clinic with follow up cytology advice and to identify predictive indices of poor compliance.

Methods
Data from 660 patients who attended the colposcopy service at the CWH (Coombe Women's Hospital) during 2001 was reviewed. A total of 326 "new" patients (first-ever attendees in a colposcopy clinic) with proven CINs in 2001 who were then discharged before 2007 were initially eligible. At the time universal practice following a LLETZ treatment was that a patient should have two normal smears to return to yearly cytology follow-up for 10 years; the smears could be either obtained at the GP or at CWH smear clinic. If only biopsies were obtained, then two or three consecutive smears at CWH in six month intervals were essential for returning to community cytology screening; if an abnormal smear was obtained, the patient returned to the colposcopy clinic. Patients who had a subsequent hysterectomy were excluded from the study (n=8). Patients' data such as the grade of the initial referral smear, final colposcopic diagnosis, number of visits and duration of follow up, details of possible intervention and the histology diagnosis were documented. In addition, the patients' age, smoking status and parity were systematically recorded.

Of the 318 eligible patients 116 patients were successfully contacted by telephone and asked to participate in the study, 212 patients were lost to follow up (moved from their previous address or changed telephone number). No statistical differences observed regarding age, parity, smoking, referral smear, diagnosis and procedure performed (LLETZ / Biopsy) or grade of CIN between patients who could not be contacted and others. A Research Assistant conducted the telephone survey using a series of identical questions to each patient. Participating patients were asked about the number, dates and results of cervical smears since they were discharged from the colposcopy clinic. Subsequently their cytology was confirmed by checking their medical record & GP letters. Women who had regular cervical smears as recommended were considered as entirely compliant. Women who had sporadic cervical smears were considered as poorly compliant while those who had no smears were considered as non compliant. This study was approved by the hospital's Research Ethics committee. Data were analyzed using the Fischer's exact test, the Chi-square test and logistic regression. Median values were compared using the Anova test. All reported p values are two-sided and are not adjusted for multiple testing. A value of $p < 0.05$ was considered as significant.

Table 1 Overall patients' characteristics and according to their compliance to the cytology guidelines (n=100).

	Total	Compliance with cytology advice		p
		None or poor (n=40)	Perfect (n=60)	
Age (years)				
Median	26	30	26	0.001†
Range	17-64	17-64	(17-64)	
Parity				
Median	0	0	0	0.217†
Range	0-6	0-6	0-6	
Current smoker	46 (46)	17 (42.5)	29 (48.3)	0.357¥
Initial referral smear				
Normal / Clinical indication*	2 (2)	0 (0)	2 (3.3)	0.608†
BNA	13 (13)	7 (17.5)	6 (10)	
CIN1	44 (44)	16 (40)	28 (46.7)	
CIN2-3	41 (41)	17 (42.5)	24 (40)	
Cervical biopsy	34 (34)	13 (32.5)	21 (35)	0.832¥
LLETZ	63 (63)	24 (60)	39 (65)	0.675¥
Number of visits to the colposcopy clinic				
Median	4	3	4	0.263†
Range	2-8	2-6	2-8	
Duration of management (months) **				
Median	26.2	25.2	27	0.553†
Range	0.6-63.3	0.6-63.3	3.2-53.3	
DNA***	10 (10)	5 (12.5)	5 (8.3)	0.515¥
Final diagnosis				
CIN1	45 (45)	18 (45)	27 (45)	1
CIN2-3	55 (55)	22 (55)	33 (55)	

Data are expressed as numbers with percentages in brackets (%) unless otherwise indicated.

BNA: Borderline Nuclear Abnormality; CIN: Cervical Intraepithelial Neoplasia; DNA: Did Not Attend; LLETZ: Large Loop Excision of the Transformation Zone.

* Suspicious looking cervix or post-coital bleeding

** Duration of the clinical and colposcopic management in our institution before discharge

*** Did Not Attend to at least one of their appointment during the time they were followed-up in our institution

† Anova test

‡ Chi-square test

¥ Fisher's exact test

Results

Of the 116 patients contacted by telephone, 100 women were interviewed and answered the questionnaire (86.2% response rate); among those 45 presented with mild dyskaryosis (CIN1) and 55 with severe dyskaryosis (CIN2-3). Patients' characteristics are summarised in Table 1. Cervical biopsies had been performed in 34 cases. A total of 63 women underwent a LLETZ procedure. Spontaneous regression of CIN1 to normal was observed in 34 (75.6%) women. LLETZ was performed in the remaining 11 (24.4%) who had persistent CIN1 after a median follow up of 15.8 months (range 3.8 - 45.8 months). Fifty-two patients with CIN2-3 (94.5%) had LLETZ. Two women with cytology and a colposcopic impression of CIN2 spontaneously regressed to normal after 17.1 and 26.5 months of follow up respectively. One woman with a smear and biopsy of CIN 2 regressed spontaneously after 10.6 months.

Among the respondents, 60 women had regular cervical smears as recommended and were considered entirely compliant. One of these was referred back to the colposcopy clinic after receiving two consecutive CIN3 smears; she was subsequently treated. Two women had CIN1 in their recent smear tests. One with a persistently abnormal smear was referred by her GP to another colposcopy clinic. A total of 4 women out of 60 were diagnosed with residual or recurrent CIN.

Figure 1: Odds ratios for age as an effect on patient compliance with cytological follow up advice after the management of CIN (n=100).

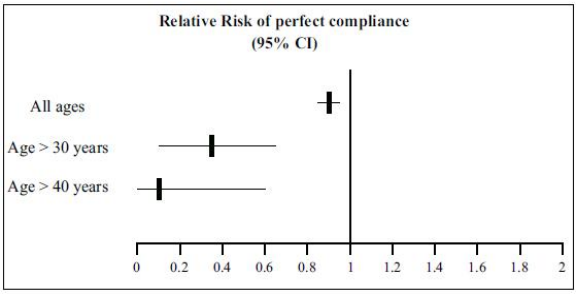

Table 2 Effect of different variables on compliance with cytological follow up advice (n=100).			
	OR	95% CI	p
Age	0.92	0.87-0.97	0.004
> 30 years	0.27	0.12-0.64	0.003
> 40 years	0.12	0.02-0.58	0.009
Parity	0.84	0.64-1.1	0.22
Current smoker	0.79	0.35-1.77	0.57
Patient had a cervical biopsy	0.89	0.38-2.08	0.8
Patient had a LLETZ	0.81	0.35-1.84	0.61
Number of visits to the colposcopy clinic	1.19	0.87-1.64	0.28
Duration of follow-up*	1	0.99-1.01	0.685
DNA**	1.65	0.44-6.2	0.460
Final diagnosis†	1	0.45-2.24	1

Data are expressed as numbers with percentages in brackets (%) unless otherwise indicated.
BNA: Borderline Nuclear Abnormality; CIN: Cervical Intraepithelial Neoplasia; DNA: Did Not Attend; LLETZ: Large Loop Excision of the Transformation Zone.
* Suspicious looking cervix or post-coital bleeding
** Duration of the clinical and colposcopic management in our institution before discharge
*** Did Not Attend to at least one of their appointment during the time they were followed-up in our institution
† Anova test
‡ Chi-square test
¥ Fisher's exact test

Eleven women (11%) had no follow up smear since discharge. Another eleven women (11%) had at least 2 smears and were aware of the normal results. The remaining 18 women (18%) had only one smear performed for variable reasons, the results have not been communicated to several of them; most however had arbitrary assumed it was normal. Despite advice given on discharge, a significant proportion of women (40%) were unaware of the importance of compliance and four women (3%) assumed that once they were discharged from the colposcopy clinic there was no need for further follow up. The mean time of follow up after discharge from our clinic was 42.3 months (range, 8-74.9), with no significant difference between women who achieved perfect compliance and those with poor or non compliance: 42 months (range 18.4-71.8) and 42.8 months (range, 8-74.9) respectively (p=0.774). Older women were significantly less likely to be entirely compliant with cytology follow up advice OR=0.92; 95% CI=0.87-0.97; p=0.004 (Table 2). The proportion of entirely compliant women diminished significantly with age. Women above 30 and 40 years were less likely to achieve perfect compliance: OR=0.27, 95% CI=0.12-0.64; p=0.003 and OR=0.12, 95% CI=0.02-0.58; p=0.009, respectively (Figure 1). No association observed between the compliance rate and parity, smoking status, number of visits to the clinic, type of procedure or grade of CIN.

Discussion

Only 60% of patients proved entirely compliant. Poor compliance following discharge from the colposcopy clinic is not without implications. According to Soutter et al's analysis of pooled data on women 8 years after treatment, the risk of invasive disease after conservative treatment of CIN is 4 to 5 times higher than in the general population[16] and this risk does not appear to reduce over time[8]. Being at a relatively increased risk these patients should be cognizant of their need for regular and prolonged follow up. Yearly cytology post discharge from colposcopy for 5 to 10 years is commonly recommended. The addition of colposcopy in the patient work-up after the initial post treatment review has been debated[9,17,18] and is not universally employed, possibly because of its poor specificity[8].

To date, very little data on patient compliance and behaviour after CIN management has been published. Besides changing time-trends in surveillance guidelines, poor patients' adherence to the advised follow up protocol represents a common issue also documented in other publications. Cristiani et al. reported a 21% rate of patients who defaulted from follow-up; in their study 43% were suboptimally followed-up[19]. Greenspan et al recently reported an overall compliance rate as low as 55.6% for the very first year[20]. Cristiani et al. reported that patients living in urban areas as well as those treated in private clinics were considerably more likely to achieve incomplete follow up or to be lost for follow up[19]. The findings of this study have several possible implications. As far as we are aware, this is the first study to report an association between age and compliance. It was not surprising to us that younger patients appeared to be relatively more compliant as younger individuals have better access to internet resources and are usually concerned about fertility issues. But, as our advice at the time was largely verbal, this might be also explained by differences in physicians' attitudes, and their approach while counselling younger women. The introduction of leaflets in CWH's colposcopy clinics with concise information written in lay terms in the mid-2000's partially addressed this issue. Older women's relative inability to clear HPV infection as age advances, as well as fundamental changes in the transformation zone that parallel estrogen decline, multiply cancer risk in this very group that is more likely to default.

There is an urge to improve the awareness of patients regarding their risk of recurrence and the need for follow up compliance. A number of strategies for ensuring better compliance could be considered, for example reminder letters, telephone calls or short message service (SMS)[21,24]. The use of information's leaflets has been conclusively shown to improve women's knowledge of abnormal smears and colposcopy services[25]. The National screening programme is currently in place with the ability to remind women of their next smear due date indeed helps contextualise the findings. Finally, our study is limited by standard biases inherent to retrospective analysis and by the limitation of our small study sample. Moreover, since our study took place in a single clinical setting it is possible that characteristics of our population directly influenced our results. Minor variations in the management of patients and the information provided to the patients among different physicians in the colposcopy clinic should have minor impact as all adhered to the current BSCCP guidelines of the time.

The use of high risk or oncogenic HPV testing as part of post-CIN treatment follow up has been currently shown to be the most effective strategy for the recognition of post treatment residual CIN . In the context of post treatment surveillance, a positive HPV test is associated with an increased risk of residual disease[10]. In its ability to rule out residual and/or recurrent disease, HPV testing is also more accurate than follow up cytology, colposcopy or the histological recognition of resection margin positivity at the time of excision[10,11,14]. With close to 100% negative predictive value[5], a negative HPV test (like hybrid capture 2 - HC2) virtually eliminates the risk of recurrent disease after treatment for CIN[11,18]. The use of high risk HPV testing as a test of cure is well established and should be universally implemented in clinical practice. Recent results from Kitchener et al. suggest that a single negative HPV testing eliminates the risk of recurrence over a 5-year period[5]. This has obvious implications for cost effective post treatment protocols. Compliance with advice given at the time of discharge to patients treated for CIN is unpredictable and might be limited. Specific attention should be paid to older patients. Physicians should provide women with appropriate comprehensive verbal as well as written information on the necessity for follow-up. Proposed strategies for improving compliance should be further investigated. The realization of poor compliance to cytology surveillance adds strength to the argument in favour of oncogenic HPV testing as the definitive test of cure.

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