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Original Paper

The Management of Cervical Intra-epithelial Neoplasia (CIN): Extensiveness and Costs in The Netherlands

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In order to provide greater insight into both the extensiveness and the medical costs of the diagnosis and treatment of screen-detected cervical intra-epithelial neoplasia (CIN) in general medical practice in The Netherlands, data from national registries and gynaecology departments were retrieved, and experts were interviewed. Of the 5060 women diagnosed with CIN in 1988, more than 50% were treated in hospital with conisation or hysterectomy, which on average took 5.5 days stay per admission. The assessed average duration of the total pre- and post-treatment period is 4.6 years. The average total medical costs in women with detected CIN III are Dfl 3700 per woman. The diagnosis of CIN I and II involves more medical procedures and time than CIN III, but fewer women have conisation or hysterectomy, resulting in lower total medical costs (Dfl 2572). The overall extent and costs of the management of CIN should be accounted for when balancing the benefits, unfavourable effects and costs of cervical cancer screening.

Key words: cervical intra-epithelial neoplasia, costs of treatment, mass screening
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INTRODUCTION

THE AIM of this study was to provide greater insight into the extent and the medical costs of the diagnosis and treatment of screen-detected cervical intra-epithelial neoplasia (CIN) in general medical practice. Such knowledge is most important for assessing the balance between costs and favourable and unfavourable effects of screening for cervical cancer. Part of the unfavourable effects is caused by detection of non-progressive lesions. The number of women involved is increasing because the cut-off point in cytology for colposcopic follow-up has been shifting to lower grade abnormalities.

It is often stressed that the management of CIN is quick, safe and cheap. Even if this were true in an ideal situation, such a statement should be verified for general medical practice. Available literature refers to data from one or two selected treatment centres per study [1–3]. We studied the number of the various diagnostic and treatment procedures from national data, and when this was not possible, from a number of gynaecological departments covering 25% of the population. Data from the Dutch national hospital admission registration (coverage over 99%) were combined with centrally collected data from at least 85% of the cytopathology laboratories (PALGA, Pathological National Automated Archive, The Netherlands). Currently, The Netherlands is one of the few countries for which these data are available on a national scale.

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MATERIALS AND METHODS

The study concerns women with histologically confirmed CIN: the episode studied starts with the first visit to the gynaecology department for follow-up after an abnormal Pap smear and ends after the woman is referred back to normal screening practice. The situation for women having invasive cervical cancer has been considered elsewhere [4]. This study concentrates on pre-invasive disease, cervical intra-epithelial neoplasia: CIN I/II and III.

The annual number of women in whom CIN I, II and III has been diagnosed in The Netherlands was retrieved from PALGA, which is connected to the cytopathology laboratories. All women with histologically confirmed CIN in the period 1987–1990 were selected [5]. For each of these women, the maximal diagnosis within this period was established. The population coverage rate of PALGA was 70%, 85%, 98% and 99.6% in 1987, 1988, 1989 and 1990, respectively. The annual total numbers (corrected for incomplete coverage) of women detected with CIN I/II and CIN III for 1988 were 2590 and 2570, respectively, and for 1990, 3410 and 3420, respectively.

The annual number of conisations (2180), hysterectomies (425) and days of hospitalisation (15 780) associated with the

diagnosis and treatment of CIN (see Table 1), were retrieved from national data on hospital admissions, selecting admissions with dysplasia or carcinoma *in situ* of the cervix uteri (ICD-9 codes 622.1 and 233.1, respectively) as the main diagnosis [6]. Some of the cases with hysterectomy also had a secondary diagnosis, but there were also hysterectomy cases with dysplasia or carcinoma *in situ* in the secondary diagnoses, which were not included in our figures. Together with the retrieved annual number of women with CIN, the hospital data enabled us to compute an average number of medical procedures per woman with CIN (Table 1).

In the search for CIN grade-specific data and data on outpatient procedures (particularly conservative treatments), all gynaecology departments in The Netherlands were sent a request for annual figures on diagnostic and treatment procedures in the management of CIN. Gynaecologists from 10% of the hospitals responded with relevant data, mostly by sending annual reports, data on treatment of women with CIN III (there are hardly any data on CIN I and II), annual number of conisations, conserving treatments and colposcopies, covering the period 1984–1989. These hospitals cover 25% [7] of the Dutch population. In these data, 33% of the women with CIN III had conservative treatment (cryocoagulation, laser evaporation and hot loop diathermy are widely used in The Netherlands), 56% had conisation and 11% hysterectomy. These fractions were accepted as our estimates. In the 50% of responding hospitals with the highest frequency of conservative treatment, these percentages summated to 58%, 35% and 7%, respectively. In addition, we assumed that 15% of all women treated will need retreatment at least once [8], 75% of whom will receive conservative treatment and 25% of whom will receive conisation, amounting to 0.44 ($0.33 + 0.75 \times 0.15$) conservative treatments and 0.60 ($0.56 + 0.25 \times 0.15$) conisations.

In the next step, the fraction of conisations was multiplied by the total number of women diagnosed with CIN III, resulting in the number of conisations which should be attributed to women with CIN III ($0.60 \times 2570 = 1542$). The number of conisations which should be attributed to women with CIN I or II was calculated by subtraction ($2180 - 1542 = 638$), and the fraction of women with CIN I or II having conisation was determined ($638/2590 = 0.25$). The same procedure was followed to calculate the number of hysterectomies and conservative treatments in women with CIN I/II. The total annual number of conservative treatments was calculated from the ratio between conservative treatments and conisations in the reporting gynaecology departments and the total annual number of conisations ($1.273 \times 2180 = 2775$). The fraction—for which no data were available—of women with CIN I/II without conservative treatment, conisation, or hysterectomy was calculated as the residue after subtracting the total fraction of treatment procedures from 1 plus the fraction of retreatments (1.15–0.63–0.25–0.05, see Table 1). The annual number of colposcopies reported from the gynaecology departments was extrapolated to the national level (15 466 colposcopies).

Table 1. Estimated average number of diagnostic and treatment procedures, and days in hospital in women with screen-detected CIN

	CIN I/II Number per woman *a*	CIN III Number per woman *b*	All CIN Annual members *c*
Treatment procedures			
No treatment	0.21	0.00	544
Conservative treatment	0.63	0.44	2775
Conisation	0.25	0.60	2180
Hysterectomy	0.05	0.11	425
Hospital days*			
Conisation	1.1	2.7	9810
Hysterectomy	0.7	1.3	5100
Other	0.1	0.2	870
Total	1.9	4.3	15 780
Hospital admissions			
Conisation	0.25	0.60	2180
Hysterectomy	0.05	0.11	425
Other	0.03	0.08	285
Total	0.33	0.79	2890
Assessment procedures			
Pap smears	8.7	7.3	41 383
Colposcopy	6.0	4.6	27 200
Biopsy	2.4	1.8	10 799
Number of consultations and duration of total period studied			
Consultations	9.0	7.6	42 680
Years	4.9	4.3	23 851

$c = a \times 2590 + b \times 2570$, in which 2590 and 2570 are the annual number of women with CIN I/II and CIN III, respectively. *Example: 1.1 days for conisations per woman with CIN I/II = 0.25 conisations × 4.5 days (Table 2). Women were diagnosed in 1988.

To collect information on aspects for which no detailed large scale data were available—number of consultations at the gynaecology department, Pap smears, colposcopies and (ecto- or endocervical) biopsies, and the duration of the total period studied—four gynaecologist-colposcopists from different hospitals (three university hospitals and one regional hospital) were interviewed in a standardised way. From these interviews, we could assess which aspects show variation in practice, and consequently, since large scale data are missing, remain uncertain. The possible influences of these uncertainties were studied in a sensitivity analysis.

A cost-effectiveness analysis was the goal of the cost part of this study and the costs were assessed from the viewpoint of society. An analysis of the true resource costs of all relevant procedures was, however, beyond the scope of this study. Apart from the cost per colposcopy and per hospital day, which reflect an assessment of the true resource costs, the costs of diagnosis and treatment have been approximated by tariffs charged (1993) in The Netherlands (Table 2). The cost per colposcopy was assessed by interviewing colposcopists for time investment, by reviewing financial accounts of gynaecology departments, and by cost analysis of the equipment. The cost per hospital day is an estimate of the average cost per day (weighted average for the general and teaching hospitals, and of general and intensive care), including "hotel" costs, nursing and medical staff, standard medical equipment, medication and overhead costs. We performed a sensitivity analysis on a lower cost per hospital day (see Discussion). The costs are presented in Dutch guilders (Dfl) in Table 3. In 1993, the exchange rate for the British pound sterling was Dfl 2.8 and for the U.S. dollar Dfl 1.85.

RESULTS

The resulting numbers of treatments and days of hospitalisation are summarised in Table 1. As expected, the fraction of women treated with hysterectomy or conisation was much lower in CIN I/II than in CIN III. Important differences in practice occurred in the management of low grade lesions. The gynaecologists interviewed confirmed that in some of the gynaecology departments in The Netherlands, women with CIN I and, to a lesser extent, CIN II were treated only if there was persistence or progression in the first 2 years after diagnosis. In our calculation, the fraction of women with diagnosed CIN I/II who have no treatment was 21%. Assuming that half the women with CIN I/II show regression within 2 years, this would mean that approximately 40% of the women diagnosed with this condition were initially followed-up with cytology and colposcopy only. In a sensitivity analysis, we examined the effect of all women with CIN I/II being treated immediately after diagnosis, other than by conisation or hysterectomy. We also examined the effect of all these women being initially followed up with cytology and colposcopy (Table 4).

The required numbers of Pap smears, colposcopies, and biopsies per women reported by the colposcopists interviewed showed little variation with primary diagnosis. We assumed 1 Pap smear, 1.2 colposcopies and 1.4 biopsies per women during 1.2 consultations over a period of 0.3 years. In women initially followed up with cytology and colposcopy only, but treated eventually (in our calculations 21% of the women with CIN I/II), these numbers were doubled because a second diagnosis is required. In treated women, the numbers were increased by 30% for (suspected) recurrence. During follow-up without treatment, one colposcopy and Pap smear per 6 months was added.

Finally, for all women with CIN, we accounted for consultations, Pap smears and colposcopies during the follow-up after primary management. This follow-up ends when a woman is referred for routine screening. The different kinds of schedules used in this period are:

– 5 years of follow-up with both cytology and colposcopy; – 5 years of follow-up with only cytology; – 3 years of colposcopy followed by 2 years of cytology;	eight consultations in total
– 1 year with one colposcopic and two cytologic evaluations	two consultations in total.

We basically assumed an intermediate schedule with six consultations, six Pap smears, three colposcopies and a duration of 4 years. In a sensitivity analysis we accounted for more and less intensive schedules (Table 4). The resulting numbers of diagnostic procedures during the total period studied are shown in Table 1.

Table 2 presents the cost per procedure. In Table 3, the estimated costs for diagnosis and treatment of CIN are presented. The costs of the medical procedures were approximately Dfl 1600 for all grades of CIN. The total costs in CIN III were 45% higher than in CIN I/II, due to the larger number of hospital days. The costs of hospitalisation accounted for more than half of the total costs of Dfl 3727 of the diagnosis, treatment and after treatment follow-up per woman with CIN III.

DISCUSSION

Multiplication of the estimated numbers of colposcopies per women with the estimated annual number of cases results in the

Table 2. Costs (in Dutch guilders) per medical procedure in the management of CIN

	Cost per procedure	Days in hospital	Total costs*
Visit	67	0	67
Pap smear	52	0	52
Primary colposcopy	145	0	145
Secondary colposcopy	106	0	106
Biopsy	87	0	87
Cryocoagulation etc.	123	0	123
Conisation	401†	4.5	2622
Hysterectomy	2536†	12	8458

*Cost per procedure plus Dfl 494 per day in hospital; † Including Dfl 165 for presurgery laboratory procedures and chest X-ray.

Table 3. Estimated average medical costs (in Dutch guilders) per woman with screen-detected CIN

	CIN I/II		CIN III	
Consultation*	201	7.8%	201	5.4%
Pap smear	454	17.7%	380	10.2%
Colposcopy†	673	26.2%	522	14.0%
Biopsy	206	8.0%	158	4.2%
Conservative treatment	78	3.0%	54	1.4%
Conisation	646	25.1%	1573	42.1%
Hysterectomy	465	18.1%	930	24.9%
Other days in hospital	51	2.0%	109	3.1%
Total costs	2572	100.0%	3727	100.0%
Of which:				
Costs for procedures	1649	64.1%	1634	43.8%
Costs of hospitalisation‡	923	35.9%	2093	56.2%

*Only consultations without colposcopy are charged; † One "primary colposcopy", all others "secondary colposcopy" (see Table 2); ‡Dfl 494 per day in hospital.

Table 4. Sensitivity analysis on average medical practice

Assumptions	Colposcopies	Consultations	Number of women in follow-up	Total costs (MLN)
Baseline assumptions	35 977	56 467	31 559	21.5
Initial management of women with CIN I and CIN II				
Immediate treatment in all cases	−14%	−9%	−7%	−4.2%
Initial cyto-/colposcopic follow-up in all cases*	+19%	+12%	+9%	+5.6%
Follow-up schedule after treatment				
1 year, colposcopy	−38%	−48%	−65%	−13%
5 years, colposcopy during the whole period	+95%	+24%	+22%	+20%

*In which we assume that 50% of the followed-up women are treated eventually because regression is not observed within 2 years.
Percentage changes in annual total number of colposcopies, consultations, length of follow-up period and costs of the management of screen-detected CIN in The Netherlands (calculations for 1990).

total number of colposcopies (27 200) (see Table 1) which seems to be (80%) too high compared with the annual number of 15 466 estimated from the data from the gynaecology department. This could partly be due to the cervical cancer screening programme reintroduced in The Netherlands since 1987. The total number of smears in 1988 was 20% higher than in 1987 [5]. A substantial number of the colposcopies induced by screening in 1988 will only be incorporated in later years and are not present in the reports of 1988. Moreover, the gynaecologists interviewed suggested that there had been substantial underregistration of colposcopies in their departments.

As can be seen from Table 4, the length of the follow-up period after treatment is important both for the extent of the management for the women involved and for the costs. It also affects the number of colposcopies, which is important in terms of the capacity of the gynaecology departments. The considerable variety in practice shows the need for more evidence on how long a woman treated for CIN should be followed-up colposcopically. How much information colposcopy after treatment adds to cytology is questionable [9]. When only cytology is required, the women can be referred to the general practitioner.

Other important cost factors are the number of women with CIN having conisation and hysterectomy, respectively. For the Dutch situation, we found that the number of hysterectomies in women with CIN III differs considerably (from 10% to almost 50%) between hospitals [10]. The use of hysterectomy for the treatment of CIN has been decreasing over recent decades. In a literature search for data from 1980 onwards we found three studies from British hospitals, in which 15–40% of the women with CIN had conisation and 1–7% hysterectomy [1–3]. This compares favourably with the 41% and 8%, respectively, (retreatments included) recorded in this study. Each of these studies, however, came from one treatment centre, and quality bias (towards more conservative treatment) cannot be ruled out in data from publishing (= selected) centres. Our estimates on the use of conisation and hysterectomy are based on national data. Furthermore, in two of the studies from the United Kingdom [1, 2] conservative treatment was performed as an in-hospital treatment and under general anaesthesia. Conservative treatment in The Netherlands is performed as an out-patient treatment, under local (if any) anaesthesia.

Current Dutch data, only the distribution of the conisations (and hysterectomies) over the different grades of CIN was based on less complete data (although coverage was much higher than in one-centre studies). The responding 10% of the gynaecology departments represent the larger hospitals, possibly causing an overestimation of the use of conservative treatment in CIN III.

Correction of such an overestimation in our assessment would shift part of the conisations and hysterectomies from women with CIN I or II to women with CIN III, without affecting the total number of these treatment modalities used.

Data from Loizzi and associates [11], also obtained from one treatment centre, show 73% conisations in women with CIN. Goodwin and colleagues [12], who performed a population-based study on all women from New Mexico with diagnosed carcinoma *in situ* of the cervix in 1982–1985, found 44% hysterectomies. (In The Netherlands, 40% of the CIN III diagnosis concerns carcinoma *in situ*.) These figures reflect more aggressive treatment strategies and probably large differences in gynaecological practice between regions or countries.

In The Netherlands, a conisation on average takes 4.5 days in hospital. If we hypothetically assume only one hospital day per conisation, this would reduce the total number of hospital days by 29%, and the total costs for the management of screen-detected CIN by 14% (calculations for 1990). As far as the cost per hospital day is concerned, women hospitalised for the treatment of CIN are probably more healthy than the average hospital population, and consequently, even having general anaesthesia, they might need less general care. If we arbitrarily decrease the cost per hospital day from Dfl 494 to Dfl 400, the total costs of the management of CIN would decrease by 9%.

The evidence as to whether women with CIN I and II should be followed-up initially, to give regression a chance, or should be treated immediately, is inconclusive. Immediate treatment is less costly than the "wait and see" management, but the difference is rather small (see Table 4). Treatment without delay saves 2 years of follow-up maximum, at the expense of treating more women. The difference in the psychological burden to the women involved might be important, but this has hardly been quantified: on the one hand, anxiety may occur as long as no treatment has been given, on the other hand women in whom CIN regresses have the psychological advantage of not needing treatment for a condition associated with cancer. The gynaecologist's counselling strategy and attitude probably plays a major role in these psychological effects.

Total costs for the management of woman with detected CIN amounted to 21.5 million guilders in The Netherlands in 1990 (Table 4). This is almost as much as the sum of the assessed costs for the diagnosis and primary treatment of women with invasive cervical cancer (757 women in 1990, *National Cancer Registration*) of 14 million, and for advanced disease (288 women died from cervical cancer in 1990, *Central Bureau of Statistics*) of 9 million [13].

In conclusion, the extent of the overall management of CIN is greater and the costs higher than might be expected. Although there has been a trend towards more conservative treatment, in The Netherlands half of the cases are treated with conisation or hysterectomy. The costs are substantial and the effect on the well-being of the women may be considerable. It is this overall practice that should be accounted for when balancing the benefits, unfavourable effects and costs of cervical cancer screening. A further trend towards less aggressive treatment in the near future from LEEP (Loop Electrosectional Excision Procedures) combined with "see and treat" strategies, and specific treatments for human oncogene, papillomavirus positive women, is controversial. Expectations will have to be reconciled not only with data from excellent treatment centres, but also with data reflecting overall practice.

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