Cost of screening and treatment of cervical dyskaryosis in Germany

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Summary

Human papillomavirus (HPV) infection is the principal cause of cervical cancer. Clinical trials with HPV vaccines have shown high efficacy against HPV-induced precancerous cervical lesions. Before implementing a vaccination programme, up-to-date data on cervical dyskaryosis, incidence and annual treatment costs are needed. We assessed resource use and costs for 12 months following diagnosis for women with abnormal Pap smears in Germany based on a sample of 138 women who had received abnormal results on Pap smears taken during March and April of 2004. Most women had a Pap IIID (57%) vs Pap III (20%) or Pap IV (23%). Women with a Pap IV consulted their gynaecologist more frequently than those with a Pap III or Pap IIID (5.6 visits vs 4.2 and 4.6 visits, respectively). Only 9% of patients underwent colposcopy plus biopsy; this may be due to the lack of histological assessment by colposcopy and biopsy done currently in Germany. More women in the Pap IV group had a cold knife conisation, compared with those in the Pap IIID group, (84% vs 27%) hysterectomy (22% vs 4%) and laser coagulation (12.5% vs 4%). Median treatment duration was shorter for women with a Pap III than for those with Pap IIID and IV (3 vs 5 months, respectively). Overall, 28.3% of the women were hospitalised (median 5; range 1-33 days). The estimated average annual cost per patient was € 1,055, € 943 and € 3,174 for Pap III, IIID and IV, respectively. The cost of managing precancerous cervical lesions in Germany was shown to be high.

Key words: Human papillomavirus; Cervical cancer; Cervical cancer screening; Cervical dyskaryosis; Retrospective study; Resource use; Treatment cost.

Introduction

Human papillomavirus (HPV) infection is the primary cause of cervical cancer [1, 2]. Approximately 200 HPV types have been identified, and 35 of these have been shown to infect the genital tract epithelium [3]. They are classified into high-risk and low-risk HPV types, based on their oncogenic potential [4]. High-risk types 16 and 18 are associated with an estimated 70% of high-grade cervical lesions and cervical cancer, while other high risk types, e.g. 45, 31, 33, 52 and 58, account for only 19.6% of these conditions [5]. Low risk HPV types are associated with anogenital condylomata (i.e., genital warts) and mild dyskaryosis. HPV types 6 and 11 are associated with 90% of genital warts and also with low-grade cervical lesions [6, 7].

HPV infection is responsible for the development of the precursor lesions leading to cervical cancer. Cervical screening programmes enable the early detection and treatment of these precursor lesions or cervical dyskaryosis. Cytological screening using the conventional Papanicolaou tests (Pap smears) is currently the recommended method for cervical cancer screening in most countries. In Germany, cytologically-identified lesions are classified according to the modified Munich Cytological Classification, a variation of the most common Pap reporting convention (Table 1). In the Munich system, both Pap I and Pap II classifications correspond to a normal Pap smear, and the Pap IIw or Pap IIk classification normally requires additional follow-up. The Pap III to IVb classifications correspond to the precancerous stages of cervical cancer, and matches with LSIL (low-grade squamous intraepithelial lesion - Pap IIID) up to HSIL, possible neoplasia (high-grade squamous intraepithelial lesion - Pap IVb) according to the Bethesda classification.

After abnormal Pap smear results further procedures, including colposcopy and biopsy, may be performed to determine the CIN (cervical intraepithelial neoplasia) grade of the lesion. CIN lesions are treated by a variety of techniques including laser coagulation, leep excision or cold knife conisation.

Information regarding the actual costs related to cervical cancer screening exists in some European countries, such as France and the UK, but no such information is available for Germany. As healthcare systems are not uniform across Europe and healthcare pathways differ widely between countries, costs related to cervical cancer screening are likely to be different. Hence, it is necessary to collect and analyse country-specific data on the cost burden of HPN-related diseases. The aim of this study was to collect data on healthcare resource use and costs for the management of women with cervical dyskaryosis (Pap III, IIID and IV) in Germany.

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Table 1. — *Comparison of classifications used in abnormal cytological reportings*.

Modified Munich Cytological Classification	World Health Organization	Bethesda System	Papanicolaou class system
PAPI	Normal	Normal	Class I
PAP II	Reactive inflamation	Reactive inflammation	Class II
PAP III /PAP IIId	Mild dysplasia Moderate displasia	Low-grade SIL High-grade SIL	Class III
PAP IVa	Severe dysplasia		
PAP IVb	Carcinoma in situ	High-grade SIL in favour of neoplasia	Class IV
PAP V	Invasive carcinoma	Invasive carcinoma	Class V

Methods

Gynaecologists were selected using the ACNielsen regions database [8]. This database divides Germany into eight regions and defines the number of physicians to be recruited from each region to obtain a representative geographical distribution of gynaecologists. Between March and April 2005 a total of 50 gynaecologists were recruited for the study. Each gynaecologist was asked to provide data for the first three patients aged over 21 years, consulted during this period, who had been diagnosed with Pap III, IIID or IV in March or April 2004, and were living in Germany.

For each patient, information on socio-demographic data, clinical data (medical history, diagnosis, and outcome), healthcare resources used (specialists visits, diagnostics, medications, interventions, adverse events, hospitalisations) and work days lost were collected. Healthcare resources used and work days lost were recorded from the date of diagnosis (March/April 2004) for a follow-up period of up to one year from diagnosis. At each visit the Pap stage was reevaluated and if the Pap stage had regressed to a stage other than Pap III, IIID or IV, the resource use data were not collected for that particular visit.

The costs per patient were calculated by combining the healthcare resources used with the associated unit costs. Units costs were based on national sources [9, 10] and are expressed in euros (€) for the year 2005 (Table 2). For procedures (leep excision, laser coagulation, cold knife conisation, curettage, biopsy and haemostasis), office-based unit costs and hospital-based unit costs were applied. These latter include hospitalisation costs, as well as costs for laboratory tests. Hospitalisation costs were based on the German diagnostic related groups (DRG) system, which incorporates the mean length of stay [11]. Since colposcopy is currently not reimbursed, its cost was not considered in this cost analysis.

We estimated the cost of productivity loss by multiplying the mean number of work days lost per patient by the Gross Domestic Product (GDP) per person per working day. In 2004, the GDP per person per working day for Germany was € 119 [12]. In the estimation of the costs due to productivity loss, it was assumed that patients for whom data were missing had not taken sick leave. For the healthcare payer perspective, only direct costs related to treatment and management of women with Pap III, IIID and IV were analysed, whereas for the societal perspective direct and indirect costs were taken into account. The total cost of detection and treatment of precancerous cervical lesions for the German population in 2005 was estimated by multiplying the mean screening cost per patient by the number of women screened by Pap stage per year.

Statistics

Demographic, clinical, resource use and cost data were analysed using SAS® version 8 (SAS Institute INC). As the distribution of resource use and cost data was expected to be skewed, 95% confidence intervals (95% CI) were obtained using non-parametric bootstrapping techniques [13]. To identify patient characteristics that had a significant impact on overall costs, we used a multivariable model based on analysis of the variance (ANOVA) of the overall costs taking into account different patient characteristics as cofactors. The F-statistic was used to assess the overall significance of the model. The significance of each co-factor of the model was assessed by a *t*-test.

Table 2. — *Unit cost of healthcare resources used*.

Resource	Cost per unit (e)
Outpatient visits[a]	
Gynaecologists	19.37
Diagnostics[a]	
Biopsy	86.59
Curettage	86.59
Pap smear	5.42
HPV DNA test - PCR	16.40
Office-based procedures[a]	
Cold knife conisation	86.59
Cryotherapy	19.37
Laser coagulation	34.97
Haemostasis	19.37
Hospital-based procedures[b]	
Biopsy	1,061.40
Cold knife conisation	1,464.50
Curettage	1,061.40
Hysterectomy	3,485.80
Laser coagulation	1,464.50
Leep excision	1,464.50
Haemostasis	852.60

[a] Kassenärztliche Bundesvereinigung Einheitlicher Bewertungsmaßstab für ärztliche Leistungen. http://www.kbv.de/ebm2000plus/EBMGesamt.htm. Date accessed: 22 November 2006 [9].

[b] Hospital-based procedures include all costs (e.g., hospitalisation, laboratory testing). German Drug Related Groups. Available at: http://www.g-drg.de/. Date accessed 15 February 2007 [10].

Results

Seventy-four gynaecologists were asked to participate in this study; 67 agreed and 50 gynaecologists provided patient data. Most gynaecologists were office-based (80%) and worked in private practice (68%). These gynaecologists were a representative sample in terms of the geographical distribution of gynaecologists in Germany except for the region of Schleswig-Holstein, which was under-represented; gynaecologists in this region represent 16% of all gynaecologists in Germany, but they represented only 10% of those in the study.

Data for 138 patients out of the 152 patients initially included were analysed. Data for 14 patients were not analysed because either the protocol was not respected or the treatment duration was > 12 months. The mean age of the patients included in the study was 39 ± 11 years. Most patients were married (or living with their partner) (61%), had at least a high school degree (52%), were employed full-time (52%), and had had at least one pregnancy (65%). Twenty-eight percent of the patients had never smoked before, 9% were ex-smokers and 49.2% were current smokers. For 61% of the patients (n = 84) infor-

mation on new sexual partners in the last 12 months was available. The median number of new sexual partners < 12 months was one; about 20% of the women had no new sexual partner < 12 months, while 7.2% had two or three < 12 months. Lastly, most women used hormonal contraceptives (38%) followed by intrauterine devices (13%); 30% said they did not use contraceptives.

Of the 138 patients analysed, 27 patients (20%) had Pap III diagnosis, 79 (57%) had a Pap IIID diagnosis, and 32 (23%) had Pap IV diagnosis. The overall mean treatment duration was 5.1 ± 3.7 months: for Pap III, 4.4 ± 3.8 months; for Pap IIID 5.5 ± 3.1 months and for Pap IV 4.9 ± 3.7 months. The mean number of consultations was 4.7 ± 1.9. This was higher for the patients with Pap IV (5.6 ± 1.4) than for patients with Pap IIID (4.6 ± 2.0) and those with Pap III (4.2 ± 2.0).

Only a minority of the patients (9%) underwent colposcopy with biopsy, which was not frequently performed as a diagnostic procedure (Table 3). More women with Pap IV (59%) underwent curettage compared with those with Pap III (19%) or Pap IIID (14%). During the study period, 47% of all patients underwent surgery (Table 4). Women with Pap IV underwent surgery more frequently than those with a Pap III or a Pap IIID; 96.9% compared with 26% and 34%, respectively. Cold knife conisation was the most frequent surgical intervention (Table 4). Adverse events related to the treatment of cervical lesions were reported by eight patients (four in the Pap IIID group and four in the Pap IV group): pelvic pain, (1 patient), severe bleeding (3 patients), infection (1 patient) and three patients had other adverse events (unspecified). Two of these patients had additional visits to the gynaecologist due to adverse events.

Overall, 39 (28.3%) women were hospitalised for a median duration of five days (range 1-33 days). More patients in the Pap IV group were hospitalised: 19 (59%) versus six (22%) and 14 (18%) in the Pap III and Pap IIID groups, respectively. The median duration of hospitalisation was 5.5, 5.0 and 3.5 days for the Pap III, Pap IIID and Pap IV groups, respectively.

Information on sick leave was available for only 93 patients of whom 47 (51%) took sick leave. The median duration of leave was 12 days (range 2-64 days), with 22 of the 26 women in the Pap IV group having sick leave compared with six out of 17 and 19 out of 50 in the Pap III and IIID groups, respectively.

The average direct costs per patient and the costs related to gynaecologist visits were significantly higher for patients in the Pap IV group compared with those in the Pap III group and Pap IIID patients (Table 5). Although curettage was infrequently used, it accounted for more of the costs than did coloposcopy; it is mainly performed in hospital and is therefore more costly. The mean costs for medical interventions were statistically significantly higher in the Pap IV group than in the other groups due to the more frequent use of cold knife conisations and hysterectomies in patients in the Pap IV group (Table 4).

The mean indirect costs per patient due to sick leave were significantly higher in the Pap IV group compared with the Pap III and IIID groups (Table 5). The contribution of indirect costs to total costs was similar in all three Pap groups (40-45%); these costs were € 442, € 430 and € 1,293 in the Pap III, IIID and IV groups, respectively. It was assumed that patients for whom data were missing had not taken sick leave. From the societal perspective, the mean total costs per patient were significantly higher for women in the Pap IV group than those for women in the Pap III and IIID groups (Table 5).

The effect of patient characteristics on the costs was estimated using a multivariable analysis using data available from 118 patients. The model included Pap stage, age, smoking habits and pregnancy status but the type of setting was not included since the majority of patients were from office-based, private practices. The Pap type had a significant effect on total costs ($p < 0.0001$), whereas age group, smoking habits and pregnancy status did not.

Table 3. — *Frequency of the use of procedures. Values are reported as number of women (percentages).*

Procedure	All patients (n = 138)	Pap III group (n = 27)	Pap IIID (n = 79)	Pap IV group (n = 32)
Colposcopy	106 (77%)	24 (89%)	58 (73%)	24 (75%)
HPV-DNA	41 (30%)	5 (19%)	30 (38%)	6 (19%)
Curettage	35 (25%)	5 (19%)	11 (14%)	19 (59%)
Biopsy	13 (9%)	1 (4%)	6 (8%)	6 (19%)

Table 4. — *Frequency and type of surgical interventions. Values are reported as number of women (percentages).*

Intervention	All patients (n = 138)	Pap III group (n = 27)	Pap IIID (n = 79)	Pap IV group (n = 32)
Cold knife conisation	54 (29%)	6 (22%)	21 (27%)	27 (84%)
Hysterectomy	12 (9%)	1 (4%)	4 (5%)	7 (22%)
Laser coagulation	7 (5%)	0	3 (4%)	4 (13%)
Leep excision	5 (4%)	2 (7%)	1 (1%)	2 (6%)
Cryotherapy	1 (1%)	0	1 (1%)	0
Haemostasis	2 (2%)	0	1 (1%)	1 (3%)
No intervention	73 (53%)	20 (74%)	52 (66%)	1 (3%)

Table 5. — *Mean costs per patient (€) and 95% confidence intervals for healthcare resource use for treatment of Pap and for productivity loss over 12 months.*

Resource	Pap III group (n = 27)	Pap IIID (n = 79)	Pap IV group (n = 32)
Gynaecologist visits	81.59 (68.15-96.13)	89.53 (80.67-98.08)	109.10 (99.88-117.43)
Diagnostic tests	161.65 (30.25-412.26)	82.66 (49.55-127.70)	273.90 (146.26-410.77)
Interventions	369.50 (28.86-824.44)	342.00 (142.34-589.16)	1,498.04 (991.12-2,108.12)
Total mean direct costs	**612.75 (197.44-1117.78)**	**514.19 (299.19-768.30)**	**1,881.03 (1,325.19-2,545.37)**
Mean number of sick days	3.8	3.6	10.9
Total mean indirect costs	**442.23 (55.09-932.17)**	**430.17 (221.43-707.97)**	**1,292.71 (792.09-1,857.52)**
Total mean costs	**1,054.98 (441.62-1,819.15)**	**944.36 (564.69-1,403.31)**	**3,173.75 (2,393.98-4,050.70)**

Table 6. — *Estimated annual costs of detection and treatment of precancerous cervical lesions in Germany.*

Pap Stage	Number of women screened*	Direct costs		Societal costs	
		Mean cost/ woman (€)	Total cost for German population (€)	Mean cost/ woman (€)	Total cost for German population (€)
Pap I & II	16,241,538	26.28**	426,872,556	26.27	426,872,556
Pap III	32,941	612.74	20,184,268	1,054.97	34,751,767
Pap IIID	172,940	513.22	88,756,267	943.39	163,149,867
Pap IV	22,235	1,881.04	41,824,927	3,172.75	70,568,109
Total	16,470,478		577,592,856		695,297,361

* Previously reported distribution of Pap types in Germany [18-20].

** It was assumed that women with a Pap I and II undergo 1.06 Pap smears each year (unit cost € 24.79). This number has been calculated based on the fact that there are 18 million Pap smears performed annually, [22], and that our study reported a mean number of Pap smears of 2.7, 3.6 and 3.1 respectively for Pap III, Pap IIId and Pap IV.

Discussion

Our results show that most women enrolled in the study had a Pap IIID (57%) vs Pap III (20%) or Pap IV (n = 23%) diagnosis. Patients in the Pap IV group consulted a gynaecologist more often than those in the Pap III or Pap IIID groups (5.6 visits compared with 4.2 and 4.6 visits, respectively). The most common intervention was colposcopy (77%). Patient management, including treatment, was initiated on the basis of Pap-smear-detected cytological abnormalities, although diagnostics such as biopsy and coloscopy are recommended [14, 15]. Cold knife conisation was the most often prescribed surgical procedure, regardless of Pap stage. The median treatment duration was five months for women in the Pap IIID and IV groups compared with three months for those in the Pap III group. Overall, 28.3% of the women were hospitalised for a median of five days (range 1-33 days). The estimated mean annual cost (direct and indirect) per patient associated with the screening and treatment of women with Pap III, IIID and IV results were € 1,055, € 943 and € 3,174, respectively.

These data can be used to estimate the total annual cost for screening and treatment of pre-cancerous lesions in the German population. Assuming that 50% of women aged between 20 and 84 years old have a Pap smear annually, the number of women screened annually in 2005 was estimated to be 16,470,478 [16, 17]. Using the previously reported distribution of Pap types in Germany, the number of women diagnosed with a Pap I, II, III or IV can be calculated (Table 6) [18-20]. Assuming that women with Pap I or II have on average 1.06 Pap smears annually (Table 6) the mean cost per women with Pap I or II is € 26.28. Thus, the annual costs associated with the screening and management of all Pap stages can be estimated at € 578 million from the healthcare provider perspective, and € 695 million from the societal perspective. Total costs for Pap III, IIID and IV represent 26% (€ 150.8 million) and 39% (€ 268.5 million) of these costs, respectively.

This estimate for the healthcare provider is higher than that recently reported in the UK of £ 138.5 million (about € 206.4 million, with £1 = € 1.49, exchange rate 23 February 2007). This difference can be explained partly by the different screening programmes in these two countries. In Germany, women covered by statutory health insurance and aged over 20 years are eligible for a yearly consultation with their gynaecologist, which includes a Pap test every year, whereas in the UK national guidelines recommend screening women aged 25 to 49 years every three years and women aged 50 to 64 years every five years [21]. In Germany it is estimated that there are 18 million Pap tests performed every year [22], whereas in the UK it was estimated that in 2003 there were 4.8 million tests, which is nearly four times fewer [23]. In France, where screening is opportunistic, as in Germany, it was estimated that 6,111,787 Pap tests were performed in 2004 giving an estimated uptake of 27% in women between 20 and 69 years old [24]. The costs associated with the detection and treatment of cervical dyskaryosis in 2004 in France was estimated at € 174.2 million from the healthcare payer's perspective and € 336 million from the societal perspective [25]. This estimate is lower than we report here for Germany. The difference in costs can mainly be attributed to the number of Pap smears performed annually in each country: 6,111,787 in France versus 18,000,000 in Germany (almost three times more). This difference is directly related to the difference in the current screening intervals for women with normal Pap smears in both countries: recommendation for annual screening in Germany versus every three years in France. However attributing the whole cost for the annual visit to the costs of Pap smear screening does not reflect the reality since in Germany women have an annual consultation with their gynaecologist which includes a physical examination and health advice. Women are advised about colposcopy, mammography and other examinations during this consultation with their gynaecologists. Despite this consideration, irrespective of the fee being totally or partially attributed to Pap smear screening, the German screening costs still exceed that of France and the UK.

The study has several limitations. There were few patients in the Pap III and IV groups giving a skewed distribution of the patients over the three Pap stages. Moreover, as we only evaluated the resource use and costs of Pap III, Pap IIID and Pap IV stages, and not for Pap I and II, the average resource use and costs for patients who changed to another stage may have been underestimated. However, if we assume that change to another stage would mainly involve changing to Pap II, the impact on the average costs would be limited as the costs for this stage are low. Curettage was often performed, and cold knife conisation was the preferred type of treatment.The high cost of managing precancerous cervical lesions may be related to histological assessment by cold knife conisation instead of colposcopy with biopsy. This specific management of cytological smears in Germany differs from corresponding algorithms in neighbouring countries.

It is difficult to say whether the treatment of the 138 patients in this study reflects that which German women with abnormal Pap smears would undergo; however it is a necessary first step in evaluating the costs in Germany. Despite these limitations, this is the first study in Germany to report on how women with abnormal Pap smears are managed. Our results show that the majority

of women with abnormal Pap smears are treated without histological confirmation of the lesions in Germany. This practice is in contrast with the UK and the US and could be partly due to the lack of national guidelines for the management of abnormal Pap smears in Germany, a lack of coloposcopy clinics, and the fact that coloposcopy is not a reimbursed health care procedure in Germany.

The results from recent clinical trials of prophylactic immunisation of young women with a quadrivalent HPV L1 virus-like particle vaccine (types 6, 11 16 and 18) show an efficacy of 100% (95% CI: 55.3% to 100%) in preventing type-specific HPV-associated disease and 95.8% (95% CI: 83.8% to 99.5%) in the reduction of the combined incidence of HPV infection and disease [26]. Thus, although this vaccine will not protect against all HPV infections, it has been shown to prevent 98% (95.89% CI: 86% to 100%) of HPV-16/18 related CIN grades 2, 3 and adenocarcinoma *in situ* in uninfected women. This same study, which followed the women for an average of three years post-vaccination, also reported 44% (95% CI: 26% to 58%) efficacy in preventing high-grade cervical lesions in women who were infected prior to vaccination. This reduction of lesions will dramatically reduce the costs associated with the treatment of HPV-related cervical disease [27].

In conclusion, the total cost of detecting and treating atypical Pap smears in Germany is high, estimated at € 268.5 million per year from the societal perspective. The introduction of a HPV vaccine preventing cervical dyskaryosis, in combination with the cervical cancer screening programme, will result in a significant reduction of the burden of disease.

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