Resource use and cost analysis of managing abnormal Pap smears: a retrospective study in five countries

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Summary

Objective: To evaluate and compare treatment patterns and related resource use and costs in women with abnormal cervical smears in five countries. *Methods:* Data from patient charts were collected for a minimum of 24 months, starting from the first recorded abnormal cervical smear. Costs, from the public health perspective, were calculated based on country-specific unit costs per procedure and expressed in euros. *Results:* A total of 3,380 patient charts were reviewed. Subjects with suspected or detectable cervical cancer were excluded from the analysis (n = 380). A significant age difference of 1.8-2.6 years was observed between the lowest and highest severity of cytological and histological types ($p < 0.05$). The correlation between cytology and histology results was weak overall (35.8%) and varied widely between countries (ranging from 48% for Australia to 29.7% for the UK). As expected, countries with an organised screening programme (UK, Australia) diagnosed and initiated treatment at earlier disease stages. These countries demonstrated a much lower and narrower cost band for more advanced histological types. In contrast, other countries (Germany, Italy, Spain) followed an opportunistic screening programme in which advanced disease was diagnosed and treated at much higher and more varied costs. Histological, not cytological, results were the main factor underlying the cost differences per type. *Conclusion*: Costs and treatment patterns in women with abnormal cervical smears differ among countries due to the type of screening programme (organised versus opportunistic) and, consequently, the histological type. These results need to be taken into consideration when designing cost-effectiveness studies which include cervical cancer screening data.

Key words: Cervical cytology; Screening; HPV; Cervical cancer; Cost analysis; Pap smear.

Introduction

A proven way to effectively reduce the public health burden caused by cervical cancer is through the implementation of a regular screening programme designed for the early detection of abnormal cytology of the cervix [1]. The screening is carried out with pap smears taken from the cervix in which abnormal cervical squamous cells are searched with a microscope [2]. Several cytological classifications of squamous cells have been developed to grade cell abnormality [3, 4]. Depending on the level of abnormality further examination of the cervix, which may include a biopsy of the cervix, is undertaken followed by appropriate treatment if necessary. The whole process is perceived as cumbersome by the individual undergoing the screening [5-7].

An organised screening programme requires an extensive infrastructure and a large labour force for taking the pap smears, analysing the cytology, setting up a follow-up, and implementing an appropriate and consistent treatment scheme. Countries with the most sophisticated programmes have observed the highest reduction in cancer incidence such as the Netherlands, the UK and the Nordic region in Europe since their implementation [8]. Other countries with a less aggressive systematic screening programme, also termed "opportunistic" screening, have seen changes in cancer incidence but to a lesser extent. To maintain or enhance an efficient screening programme with a high sensitivity and specificity rate, a quality assurance programme needs to be established at each level of the screening process which again requires an increase in manpower for controlling and adjusting procedures where necessary [9].

Different screening management models have been developed to define the best screening frequency, the best start- and end-age for screening in order to achieve the most efficient reduction in cervical cancer incidence and mortality over time [10, 11]. Subsequent to these initial models, country-specific screening and treatment guidelines have been developed taking into account the characteristics of the country [12].

The cost of developing and organising screening as well as the cost of treating cervical cancer has been well documented [13]. However, the cost implications for the management of abnormal pap smears, representing about 5% of all the Pap smears taken, are a poorly explored domain [14-16].

Because different countries apply different methods of cytological analysis and follow-up, an evaluation of several countries would be helpful to better highlight the

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diversity of the cost implications. Five countries were selected, four in Europe (UK, Germany, Spain and Italy) and one outside (Australia) in which a retrospective patient chart review was conducted and analysed. The period of investigation was consistent across all five countries (2002-2005) and all resource use and associated costs related to the different aspects of management of abnormal pap smears were collected.

Obtaining exact cost information is crucial in light of cost-effectiveness models reporting the value of cervical cancer vaccines where often cost estimates for the management of abnormal pap smears are imputed based on treatment guidelines [17].

Methods

Study design

A retrospective study was conducted in five countries (UK, Germany, Spain, Italy and Australia) from June 2005 through May 2006 of clinical records of women who had been referred to a gynaecology or a colposcopy clinic by the patient's general practitioner (GP) following a confirmed abnormal smear two to three years before (2002-2003). Between six and eight specialised centres were selected per country with the aim of gathering an adequate number of patients and ensuring a reasonable geographic spread in each selected country. Each centre contributed approximately 100 randomly selected patients to the study, producing a total of 600 to 800 patients per country or approximately 3,400 subjects in total. In most of the countries studied the primary cervical screening is carried out by the GP, while further evaluation and follow-up treatment is carried out in specialised clinics. Referral from the GP might occur immediately after an abnormal smear or the GP might choose to repeat the test to first confirm the results.

The requirement of ethics approval for the study was reviewed in each of the countries selected. However, as the study was retrospective in nature and therefore no direct contact with patients was required. Out of the five countries, two countries (UK & Australia) asked for ethics approval. All data was collected and maintained anonymously by patient and by centre. This formulation was approved by all the authors.

Selection of study centres

Recruitment of a random sample of the centres at country level was not considered feasible, due to the low response and study acceptance rates with such a procedure. Specific centres with a published service level of follow-up and treatment of women with cervical abnormalities detected by a smear test were identified and contacted by mail or phone to determine their interest to participate in the study. At the same time, data were collected about the centre and its physicians (e.g., number of women treated each year). From this information, those centres were selected to be representative of the management of women with abnormal smear tests in each country. Additionally, consideration was given in each country to ensure that appropriate regional representation was given to identify any potential management variances that might occur.

Data collection

Within each centre, the objective was to identify an adequate number of patients to ensure a sufficient number of patients from each cytological diagnostic group: mild (approximately equivalent to ASCUS and atypia), moderate (equivalent to low-grade squamous intraepithelial lesions [LSIL]), and severe dyskaryosis (equivalent to high-grade squamous intraepithelial lesions [HSIL]), and cancer. Each selected country has its own cytological classification system of pap smears: the Bethesda (Spain & Italy) [18], the British Society of Clinical Cytology (BSCC) (UK) [19], the Munich II (Germany) [20], or the AMBS (Australia) [21] classification system. The various classifications were compared and standardised to allow an overall evaluation as well as a cross-country comparison.

Clinical data of all the selected women were reviewed for a minimum of 24 months from the date of the first confirmed and recorded abnormal cervical smear which resulted in the referral to the gynaecological clinic. This first screen was designated as the 'referral smear'. Details of the clinic visits, tests and procedures during that period were collected. If a woman returned to a 'normal' pap smear within the 2-year period, no further medical activities were recorded. If the patient continued to receive treatment after the minimum 2-year review period, all further medical activities were recorded until the most recent one or until a 'normal' result was reported.

Data collection forms were developed, which defined the minimum data set to be collected for each subject. These forms served as the basis for the review of the patient charts. Data from these forms were then transferred to a central database in MS Access. Three separate databases were extracted from the central database, all linked by patient identifiers: a master database which included demographic data for all subjects; a procedure database which recorded details of each test/procedure and outcomes for all subjects; and a cancer database which included only those patients with a confirmed histological diagnosis of cervical cancer.

Calculation of costs

All costs were applied from the payer perspective (i.e., the national health authorities) and only patients that were treated under the national health system were included (i.e., no privately insured patients). Unit costs for all resource use were determined from national country specific references on reimbursed prices, and in the absence of having a well-defined reference cost, from discussions with the purchasing departments of the participating sites. These unit costs were assigned to each procedure in the database (Table 1). They were converted into 2005 € values and adjusted by country with the health specific purchasing power parity exchange rates from the OECD, 2005 to allow cross-country comparison [22]. For those patients with a cytological or histological diagnosis of cancer it was difficult to collect complete information on costs related to cancer treatment (both acute and long-term). Resource use and costs associated with treating cervical cancer are in a different order of magnitude than those associated with the management of abnormal cytology and vary widely depending upon the cancer grade. A separate study, with more cancer cases and of longer duration would be required, therefore for this study patients with cervical cancer were excluded.

The detailed database was used to create a summary file which contained the cytology result of the referral smear, the time of first and last intervention post referral smear expressed in days, the first and the maximum histological diagnoses during the observation period, and the related total cost for each patient excluding the cost of cancer treatment. This file allowed for the calculation per country of the average cost associated with the management of women per cytology or histology stage of precancerous lesions.

Table 1. — *Unit cost for the different interventions occurring after a positive pap smear expressed in 2005 euros and adjusted using PPP exchange rates (2005).*

	UK	Aus	G	It	Sp
Pap smear	20.0 €	48.3 €	10.9 €	26.3 €	98.6 €
HPV test	n/a	n/a	66.6 €	71.4 €	36.7 €
Cervical Biopsy	30.7€	85.5 €	13.7 €	79.0 €	51.2 €
Colposcopy	119.1€	273.2 €	27.3 €	47.6 €	118.5 €
Conisation	300.9 €	307.7 €	599.8 €	678.3 €	429.9 €
LEEP/LLETZ	300.9 €	317.4 €	599.8 €	657.9 €	405.4 €
Hysterectomy	2,121.7 €	4,581.6 €	3,616.3 €	3,257.2 €	3,020.2 €

PPP: exchange rate; UK: 0.627; Aus: 1.38; G: 0.913; It: 0.85; Sp: 0.765.
UK: United Kingdom; Aus: Australia; G: Germany; It: Italy; Sp: Spain.

Resource use and associated cost results were analysed from the perspective of both baseline cytology and the histology result. Both perspectives are important as many of the cytology results that suggested the presence of a precancerous lesion appeared to be negative by histology and/or observation of the cervix. The histology result therefore became the starting point for new assessments and treatments that may be different from those indicated by the initial cytology.

Statistical analyses

All statistical analyses were undertaken using SPSS software version 14.0 (Chicago, IL, USA) and BestFit® 4.5 from Palisade (Ithaca, NY, USA) to estimate the appropriate distributions. First analyses were descriptive in nature, including mean, median, standard deviation (SD), minimum and maximum value for continuous variables and absolute numbers and percentages for categorical variables. Where comparisons were made, the statistical significance of any differences was evaluated using rank tests or parametric tests depending on the variables selected and their spread in values, with $p < 0.05$ indicating statistical significance. The strength of association between the cytological and histological findings was measured using Kappa statistics expressing mainly the level of agreement.

Results

Study population

A total of 3,380 women with the first abnormal pap smear were initially enrolled in the study. Three hundred and eighty women suspected by cytology or with confirmed histological invasive cancer were excluded from further analysis.

Table 3. — *Age distribution by cytology and histology type (years).*

	N	Mean	SD	Min	Max	Median
Cytology result						
Mild	942	34.3	11.8	16	75	31
Moderate	1,095	34.4	11.1	17	72	33
Severe	963	36.1	10.4	16	90	35
Histology result						
Negative	814	36.2	12.5	18	90	34
CIN-1	587	33.3	11	16	74	31
CIN-2	620	33.3	10.2	17	72	31
CIN-3	979	35.9	10.3	16	79	35
Total	3,000					

Table 4. — *Number of subjects enrolled per country with age structure (years).*

	N	Mean Age	SD	Min	Max	Median
UK	538	30.1	10.3	17	72	26
Aus	500	31.9	9.9	16	73	29
G	583	35.9	11.8	16	90	34
It	624	38.1	10.8	18	78	37
Sp	755	36.9	10.6	17	78	36
Total	3,000	34.9	11.1	16	90	33

UK: United Kingdom; Aus: Australia; G: Germany; It: Italy; Sp: Spain.

Table 5. — *Cross tabulation between cytology and histology result.*

	Cytology			
Histology	Mild	Moderate	Severe	Total
Negative	425	313	76	814
CIN-1	208	290	89	587
CIN-2	191	248	181	620
CIN-3	118	244	617	979
Total	942	1,095	963	3,000

An analysis by country, by cytology and histology result of the remaining women indicates that the UK and Australia enrolled significantly more early subjects (mild/CIN-1 disease) than Germany, Spain or Italy (Table 2 and Figures 1A and B).

The age distribution was skewed according to the baseline cytology result as well as according to the histology grade, as illustrated in Table 3 and Figures 2A and B. There was a significant difference of a few years for women with a more advanced disease stage (suspected by cytology and confirmed by histology) (ANOVA-testing, p

Table 2. — *Number of subjects in each cytology and histology category by country with %.*

	UK	%	Aus	%	G	%	It	%	Sp	%	Total	%
Cytology result												
Mild	275	51%	244	49%	153	26%	123	20%	147	19%	942	31%
Moderate	155	29%	136	27%	291	50%	249	40%	264	35%	1095	37%
Severe	108	20%	120	24%	139	24%	252	40%	344	46%	963	32%
Histology result												
Negative	199	37%	83	17%	200	34%	136	22%	196	37%	814	27%
CIN-1	87	16%	107	21%	90	16%	144	23%	159	16%	587	20%
CIN-2	130	24%	164	33%	93	16%	115	18%	118	24%	620	21%
CIN-3	122	23%	146	29%	200	34%	229	37%	282	23%	979	33%
Total	538		500		583		624		755		3000	

UK: United Kingdom; Aus: Australia; G: Germany; It: Italy; Sp: Spain.

Fig. 1A

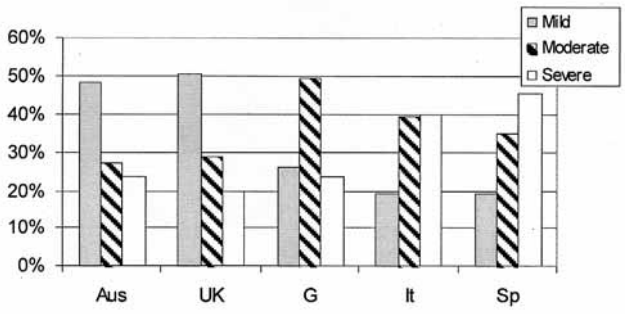


Fig. 1B

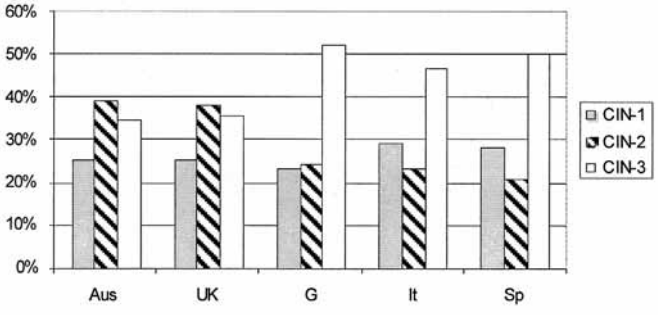


Fig. 2A

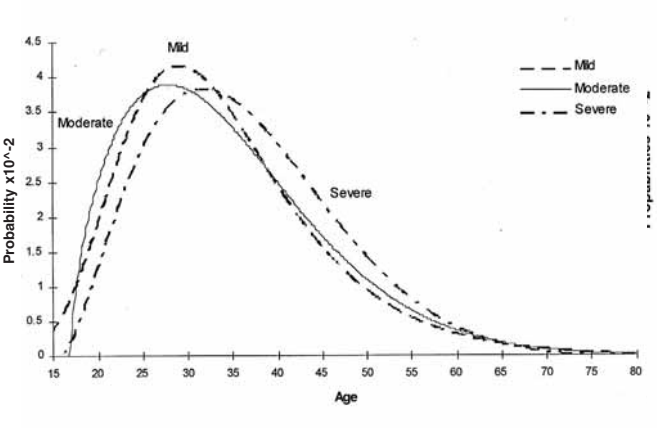


Fig. 2B

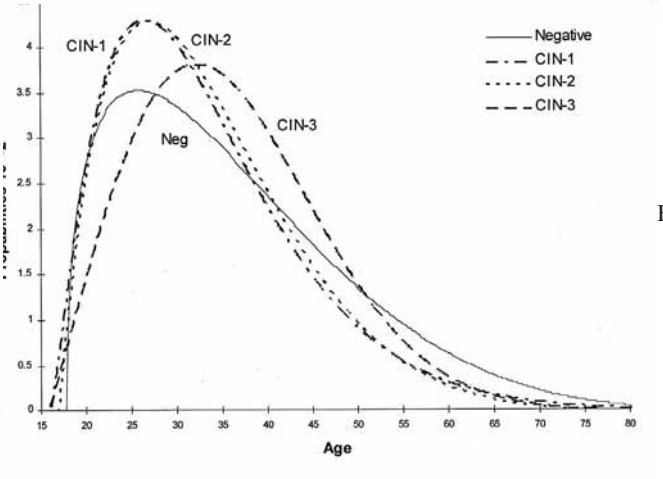


Fig. 3

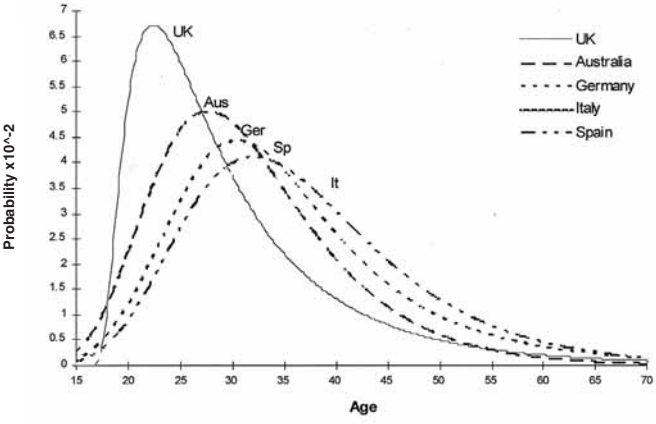


Figure 1. — Disease distribution (expressed as % of patients) as evaluated by cytology (A) or histology (B) in each country.

Figure 2. — Age distribution of different disease stages as determined by cytology (A) or histology (B).

Figure 3. — Country-specific and overall age distribution of women included in the analysis.

< 0.05). As a consequence of the above, the age distribution of the 3,000 remaining women in the study was not only slightly skewed to the right overall but was significantly different between the countries (Table 4 and Figure 3).

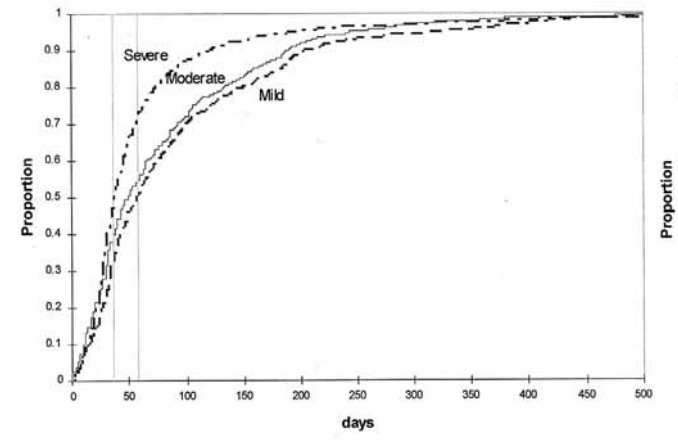
Time before taking action

An analysis by cytology type indicates that the time from the referral smear to first intervention expressed in days was significantly different between the three groups as illustrated in Figure 4A. The difference is mainly observed between the severe cases (50% seen within 36 days) versus the other cases (mild and moderate, 50% seen within 57 days). This is also reflected in an analysis by country where not much difference is seen between the first 50% of the subjects in whom a first intervention occurred within 42-44 days, but subsequent subjects are seen at a different rate by country depending on how many mild and moderate subjects were in each country (Figure 4B).

Correlation between cytology and histology results

Cytology classifications were regrouped into a uniformed classification, as reported in Table 5, allowing comparison across countries. Cytological classes were regrouped into three and the histological grades into four categories. The overall level of agreement between cytological and histological findings was 35.8%. This result

Fig. 4A



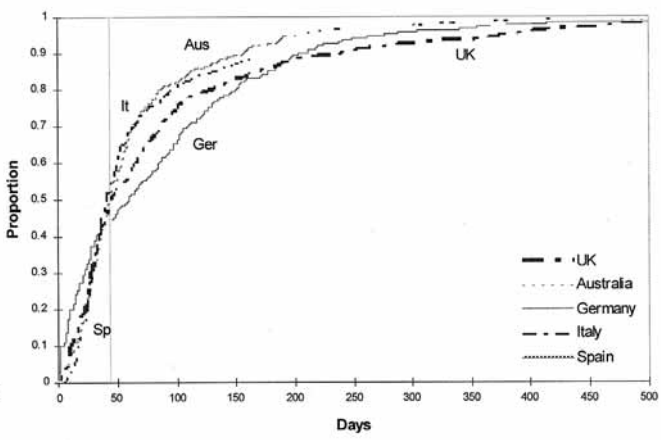


Fig. 4B

Figure 4. — Time to first intervention by cytology type (A) and by country (B)

Fig. 5

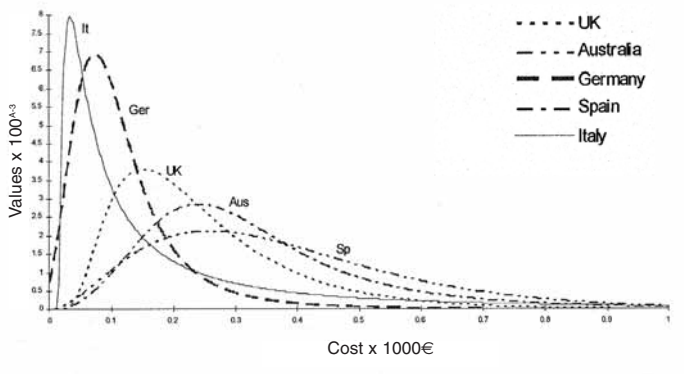


Figure 5. — Cost distribution of negative histology results by country.

is not overwhelming and two elements highlight the poor association: 1) false-positive data (814 negative results on 3,000 subjects (27%)); and 2) under- or overvaluing the histological disease stage (25% in any direction (553 subjects undervalued and 560 overvalued)).

Resource use and cost estimates

Resource use and cost data are reported by cytology and histology type and by country in Table 6. An overall result has not been constructed because the resource use and cost is very country specific as well as the number of subjects per category per country. The former is demonstrated for the negative histological results in Figure 5 as an example with quite different cost distributions per country.

From Table 6, two trends from the above analysis can be highlighted. First, those countries with a programmed screening such as the UK and Australia have a much lower cost per advanced cytology and histology type compared to the countries with an opportunistic screening process such as Spain and Italy. This is well illustrated in Figures 6A and B comparing the UK and Italy in their average cost distribution per histology type as an example. Related to that, the standard deviations in the UK figures are much smaller compared to the results for Italy.

Second, the histology results demonstrate a gradual increase in cost from CIN-1 to CIN-3 which is less the case for the cytological data. The histological data therefore better determine the cost figures than the cytological results as seen in the example for the UK and Italy (Figures 7A and B).

Discussion

It is clearly demonstrated that countries with an organised screening programme are doing better regarding cost outcome. It can be hypothesised that they are less expensive as they detect earlier cases on which less costly interventions are applied and they act under more comfortable conditions [23]. There is less urgency to intervene because of the very early disease stages detected. Hence the longer period to start any intervention observed in the UK compared to other countries (Figure 4b).

A second observation is the low performance of the screening results expressed by the poor level of agreement found between the cytology and histology data independent as to whether an organised or an opportunistic screening has been put into place [24-27].

Using the same study protocol to investigate resource use and cost data for a medical intervention in different countries, it will eventually lead to the observation of dramatic cost differences as we have shown here. Many reasons explain the differences such as treatment guidelines that are country specific, as well as the health care system with its reimbursement processes for interven-

Table 6. — *Average cost per histology and cytology type and by country.*

Histology *Negative*	N	Mean	Median	SE	Min	Max
UK	199	249.0	199.7	14.0	50.4	2138.1
Aus	83	375.7	276.3	24.8	46.6	1154.2
G	200	200.7	106.3	37.6	11.0	4243.4
It	136	265.9	140.0	24.6	21.8	1163.9
Sp	196	392.9	319.9	33.5	66.2	5927.2
Total	814					
CIN-1						
UK	87	381.3	329.8	22.7	19.7	774.1
Aus	107	606.4	649.1	24.5	266.3	1191.6
G	90	353.4	170.5	66.6	11.0	4257.0
It	144	550.7	459.2	26.0	48.2	1632.8
Sp	159	1090.4	1052.4	59.4	159.1	6168.2
Total	587					
CIN-2						
UK	130	520.3	529.5	14.8	148.9	964.6
Aus	164	760.4	718.1	22.1	266.3	1702.6
G	93	510.8	613.4	28.9	41.0	1308.8
It	115	1007.0	970.0	24.2	246.7	2214.4
Sp	118	1570.9	1309.5	96.6	318.1	6729.4
Total	620					
CIN-3						
UK	122	550.9	529.5	19.3	148.9	2188.5
Aus	146	766.5	695.7	22.2	382.8	1503.7
G	200	1215.9	691.0	94.4	54.6	7859.8
It	229	1092.0	982.9	45.2	279.1	7295.2
Sp	282	1640.6	1254.5	83.5	439.7	13137.1
Total	979					
Cytology *Mild*						
UK	275	371.8	318.8	13.6	19.7	1006.3
Aus	244	630.1	671.5	19.2	46.6	1680.9
G	153	177.5	107.6	17.8	11.0	1290.9
It	123	736.7	863.3	37.7	21.8	2063.4
Sp	147	1023.3	576.2	123.0	66.2	13137.1
Total	942					
Moderate						
UK	155	416.9	448.0	19.5	50.4	2138.1
Aus	136	646.0	649.1	22.5	139.0	1446.3
G	291	561.6	278.2	46.6	11.0	4310.1
It	249	621.5	472.8	39.3	21.8	6796.3
Sp	264	1003.2	986.2	63.4	66.2	6795.6
Total	1095					
Severe						
UK	108	469.4	529.5	23.0	148.9	2188.5
Aus	120	759.0	695.7	29.3	229.7	1702.6
G	139	1237.8	662.5	123.6	41.0	7859.8
It	252	936.4	898.6	35.9	21.8	7295.2
Sp	344	1404.4	1229.4	56.8	159.1	7549.1
Total	963					

UK: United Kingdom; Aus: Australia; G: Germany; It: Italy; Sp: Spain.

tions, the unit costs, the incentives to intervene, and finally the culture of practicing medicine. It is therefore risky to pool and analyse resource use and cost data from different countries and to report an overall cost result and an overall statement about the management of the disease. This was avoided by not reporting any overall cost result per cytology or histology class as selection bias at country and/or disease stage level heavily impacted those cost results. Moreover there is no demand for that kind of information as cost decision makers in health care remain at the level of a country.

Based on the results, a number of important observations were made. Firstly, cytology results do not drive differences in intervention type or costs. One could classify the cytology result into essentially two outcomes: suspected and non-suspected subjects. Additional subclassification leads to a different urgency of intervention as seen and reported in Figure 4a, but will not lead to a different use of diagnostics and treatment. The correlation with the biopsy result is therefore too weak. Secondly, a negative histology result or a false-positive cytology result leads to a much lower cost than subsequent histology stages as reported in Table 6 and Figures 6A and B. Thirdly, the cost distribution per histology type is not normal but skewed with a tail to the right for every histology type (Figures 6 and 7). In addition, the cost distribution per histology type has a wider spread in early versus late histological stages for obvious reasons (more exploration at start, better defined intervention pattern at later stages). Furthermore, countries such as the UK and Australia with their organised screening programmes show a more distinct cost difference by histology type. They are cheaper in each histology type excepted for the false-positive results compared to the other countries like Spain and Italy. The standard deviations of their cost distributions are smaller indicating a narrower spread of their cost figures (Figure 6 as an example). A reason for that could be that the treatment guidelines are better defined and followed by histological type for both countries. Lastly, hysterectomy is quite often done in women independent from the disease stage of cervical abnormality as there are other reasons within a certain age-group to do hysterectomies. A financial bias in the cost analysis by histology type could therefore appear so it was excluded from our analysis up to CIN-3.

There are limitations with the retrospective design and methodology used in this study. The retrospective design of the study may lead to an underestimation of the resource use and cost. The observational period, limited to two years post-referral screen, was difficult to extend over a longer period due to local, logistic problems as well as to the potential bias of change in management of a same case definition over a longer observation period. In addition, due to time and financial constraints, the selection of countries enrolled in the study as well as the site selection per country was not performed following a rigorous, scientific randomisation process to avoid selection bias.

Previous studies that have published cost results on the management of abnormal pap smears indicated a clear cost increase per higher histology as well as per higher cytology type [16]. The study methods used by these studies used different data sources for resource use and costs and may therefore claim to report ‘best estimates’. Our analysis has tried to be as close to the data sources as possible and may therefore better reflect reality. The

Fig. 6A

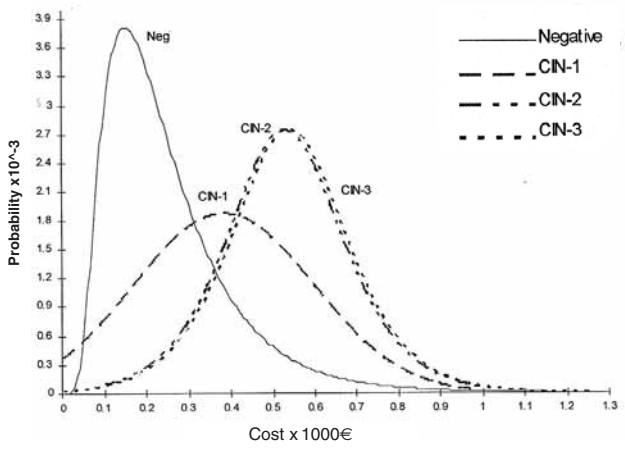


Fig. 6B

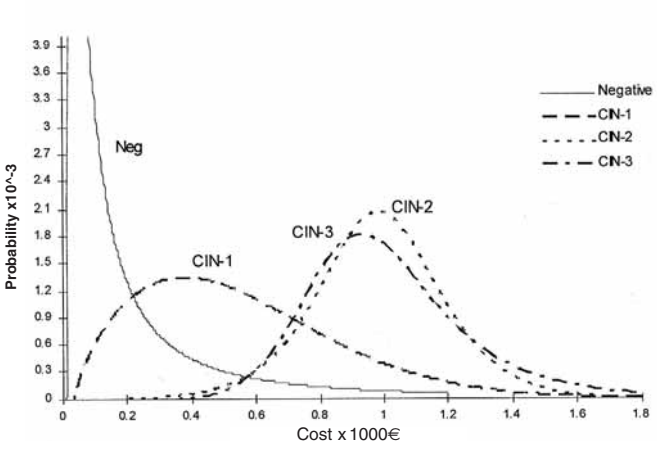


Fig. 7A

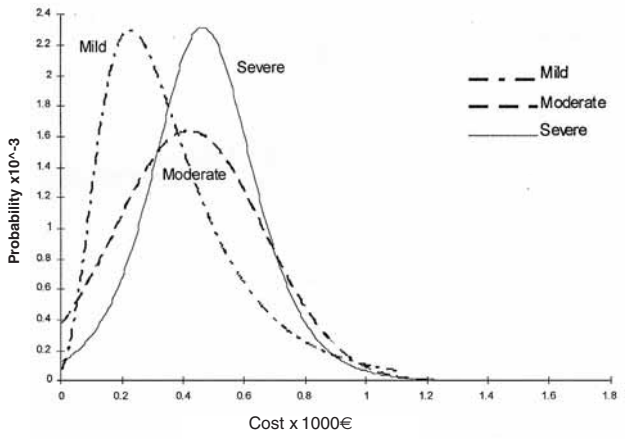


Fig. 7B

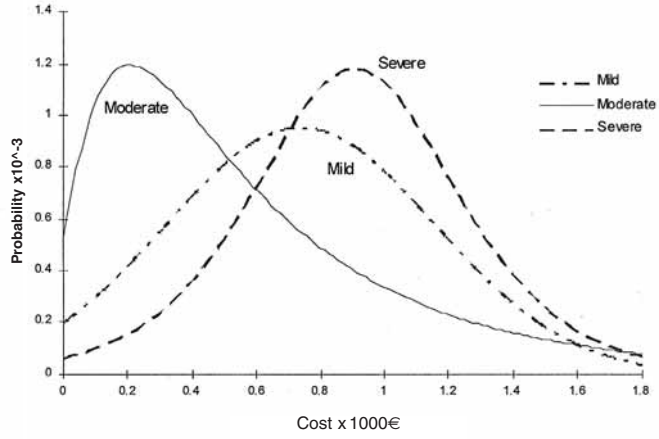


Figure 6. — Comparison of the cost distribution by histology type for the UK (A) and Italy (B).
Figure 7. — Comparison of the cost distribution by cytology type for the UK (A) and Italy (B).

results show a level of consistency in the data analysis given the premises that countries having a different screening programme, may have different treatment guidelines and have a poor correlation between cytology and histology results. Meanwhile there is an urgency to reassess the exact value of the cytology and to redefine a precise algorithm for screening given that HPV-testing is now available as well as vaccination against cervical cancer [28-30].

Conclusion

In conclusion, resource use and cost estimates for managing different cytology and histology types in abnormal cervical lesions should be reported by country. There are limitations in presenting a pooled cost analysis because of the expected big differences in types and costs per type between countries. Moreover it is likely that using treatment guidelines as a reference to resource use and cost estimates for the management of cervical precancer lesions are not appropriate given the cost distribution observed that could be heavily skewed. Finally it is more important to consider the management cost per histology type of precancerous lesions instead of per cytology type given the poor correlation observed between both results.

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