

Surveys of Italian cervical cancer screening programmes: assessing implementation and quality

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Introduction

Screening with Pap smear remains the best currently evaluated method of reducing the incidence and mortality from invasive cervical cancer. Organised programmes have shown to be the most effective, in particular because of a more rational distribution of smears in the population. Nation-wide programmes have been set up in several countries of Northern Europe.

So far in Italy no nation-wide programme has been implemented, but in the past years several organised programmes have been set-up on a local basis and, more recently, on a regional level. In 1966 an Italian Group for Cervical Cancer Screening (GISCI) was founded in order to promote the implementation of mass screening and to evaluate the on-going programmes. Within the group a

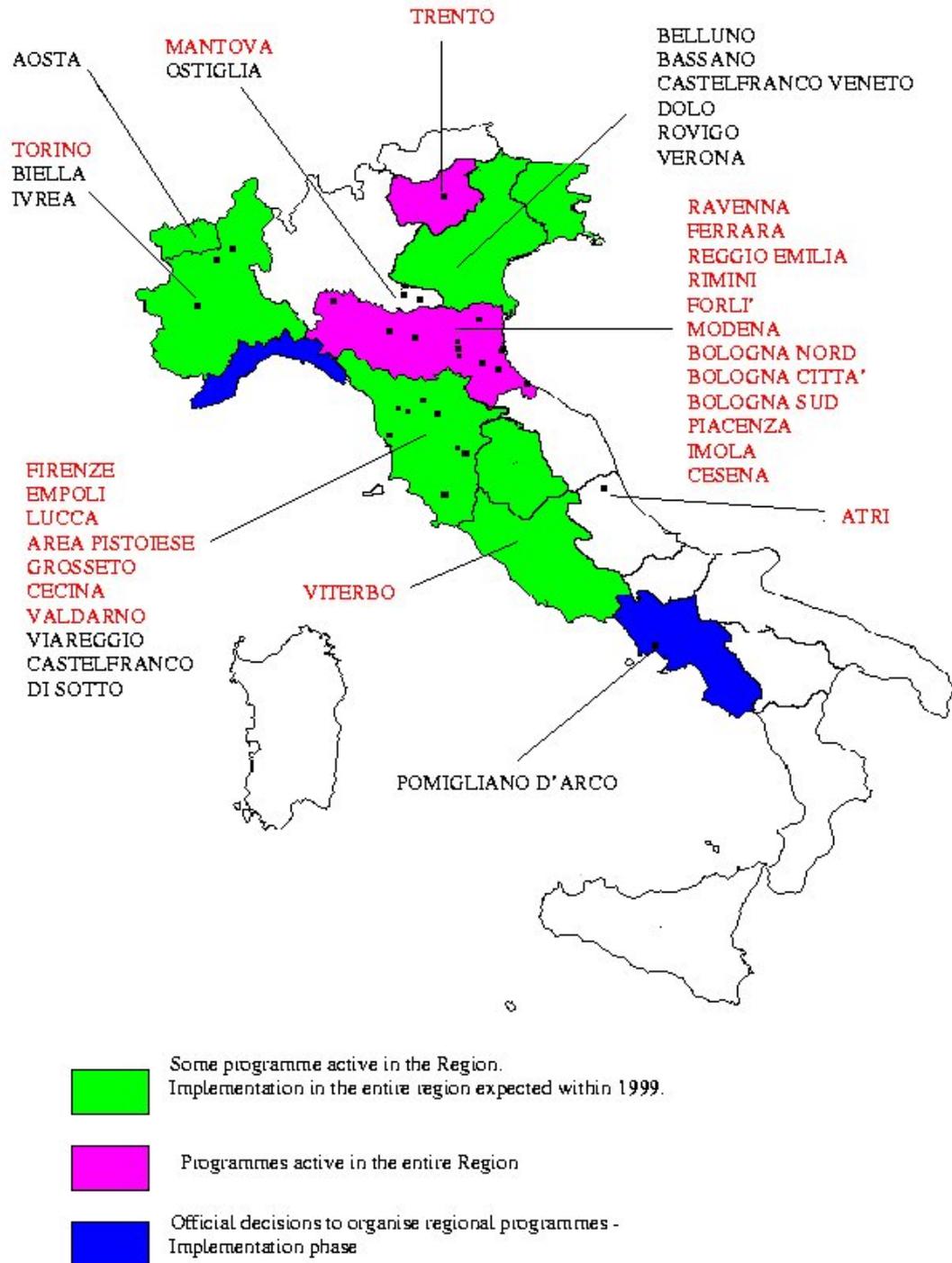
standardised questionnaire was mailed to collect information on the main features of the programmes. The first survey (Ronco et al. Tumori 84:624-630;1998) identified 33 organised programmes that covered more than two million women in the age range 25-64 years (13.5% of the Italian population of the same age).

Most of these programmes followed Italian and European recommendations as regards age limits, interval between screening rounds, presence of fail-safe system for women referred for colposcopy, presence of protocols for diagnostic work-up and treatment, and presence of referral centres for such phases.

Many organised programmes are in a phase of implementation, as a result of the guidelines delivered from the National Oncologic Commission in 1996. Within 1999 the 44.3% of the female Italian population 25-64 years old is expected to be included in the target population of organised programmes (Figure 1). In 1999 funds for the implementation of a nation-wide programme in regional basis have been granted.

Here the results of the second Italian survey are be presented. The aim of this survey was collecting data on process activity of the above mentioned programmes and measuring a first list of indicators for process evaluation, focusing on those aspects that determine more directly the effectiveness and costs of screening.

FIGURE 1
ORGANISED CERVICAL CANCER SCREENING
PROGRAMMES ACTIVE IN ITALY IN DECEMBER 1998.
PROGRAMMES IN RED INCLUDED IN THE PRESENT SURVEY



Materials and methods

A standardised questionnaire was prepared and mailed on June 1998 to collect aggregated data in a standard format on:

- Target population (by 5-year age class)
- Women invited in 1997 and among them those who performed the test within April 1998 (by 5-year age class)
- Achieved coverage (i.e. % of the target population having a smear within the last 3 years, either in the organised programme or spontaneously)
- Population screened (in some cases only women screened after invitation could be included, in others all screened women; by 5-year age class)
- Distribution of their smear results (including unsatisfactory)
- Women in the screened population referred to colposcopy and among them those who actually underwent it (by 5-year age class and index cytology)
- Their histological diagnoses (by 5-year age class) and correlation with previous cytology

In addition variables possibly useful in order to interpret differences were collected.

Collection of data on interval cancers was not considered feasible and of limited significance in most programmes, given recent start.

Not all centres were able to provide the requested information, due mainly to insufficiencies in the computerisation of data and in some cases to lack of referral centres for colposcopy.

The Positive Predictive Value (PPV) was calculated taking into account only women who actually underwent colposcopy. PPV was computed on three levels of cytological result (HSIL, LSIL, and ASCUS) and in respect of two different histological results (CIN2+ AND CIN1+). We modelled it by a logistic model, including the logit of detection rate as an offset, in order to control for different disease prevalence.

Determinants of the Detection Rate were studied by Poisson regression.

Results

Questionnaires were mailed to all 29 programmes identified as active in 1997 according to the first systematic survey of organised cervical cancer screening programmes in Italy. Among them 24 (73%) filled the questionnaires of the present survey. They were mainly located in Northern and Central Italy (Figure 1). Overall in 1997 these programmes covered 1,870,000 women, with a wide range of target populations (5,200 to 278,000; median 56,600).

Most programmes started very recently (13 after October 1995).

The overall screened population was 351,567 women, with a wide variability among centres (range 2,000 to 40,000).

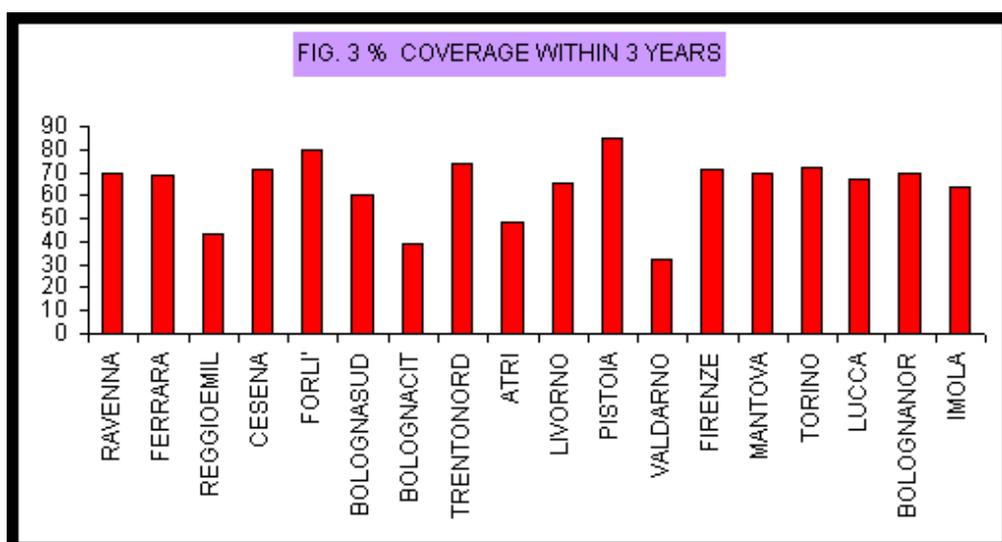
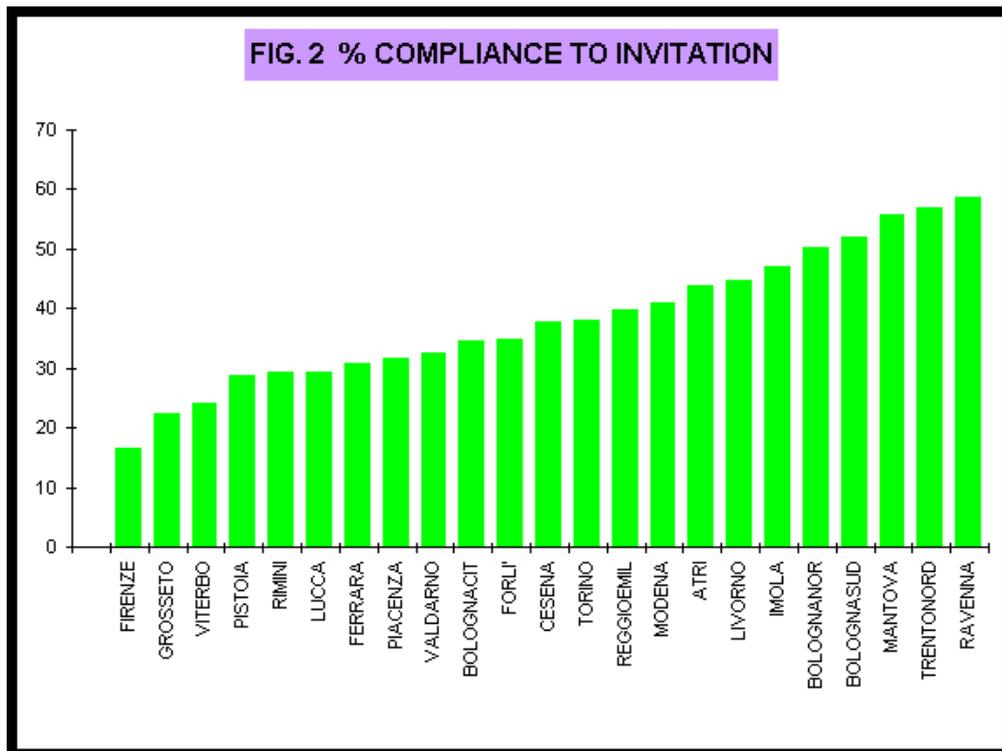
Compliance to invitation and coverage

Overall 636,638 women were invited and among them 229,928 (36.12%) accepted. There was a large variability in compliance to invitation, ranging from 17% to 58%. It depended largely on the type of organization. The lowest value (17%) was found in a programme that, each year invites women resulting not to have performed a test in the last 3 years. In programmes inviting only women spontaneously uncovered in the last 3 years the (weighted) average coverage was 26,7 vs. 39.9 in programmes inviting all women in the target population ($p < 0.001$). A higher compliance

was also found in programmes inviting at a pre-fixed appointment vs. those with a free one (43.4% vs. 23.8%, $p < 0.01$). However there is a high correlation between type of women invited and type of invitation.

Only part of programmes (19 out of 24) provided data on coverage, failure being mainly caused by lack of information on spontaneous activity. Data ranged from 32% to 85%. However in centres with the lowest values estimates are based on largely incomplete information on spontaneous activity, leading to severe underestimation.

Most programmes provided a similar estimate of about 70% and we are confident that this can be considered as a true estimate of the actual situation.



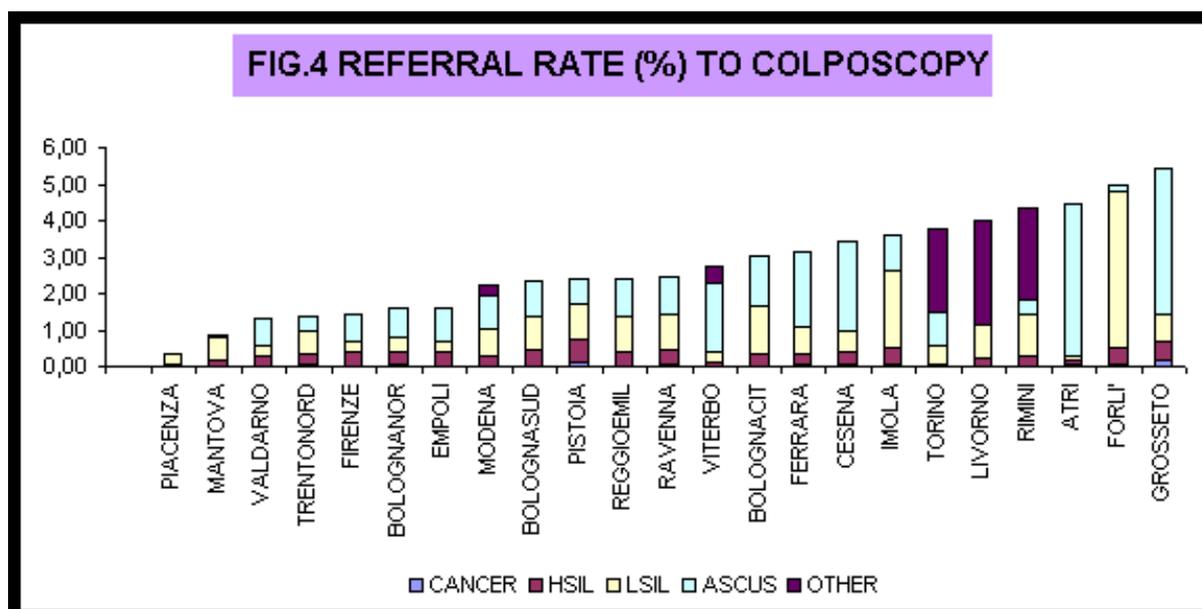
Referral rate and compliance to colposcopy

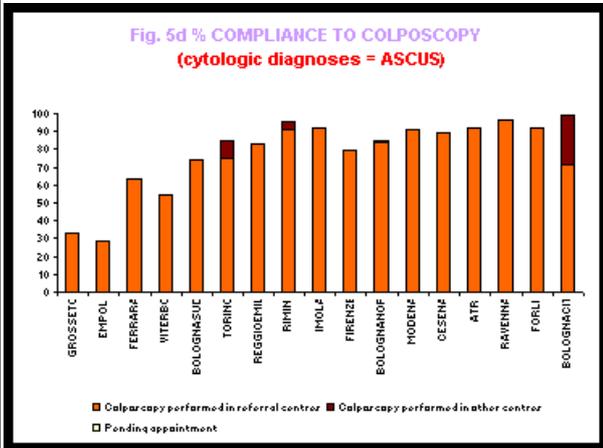
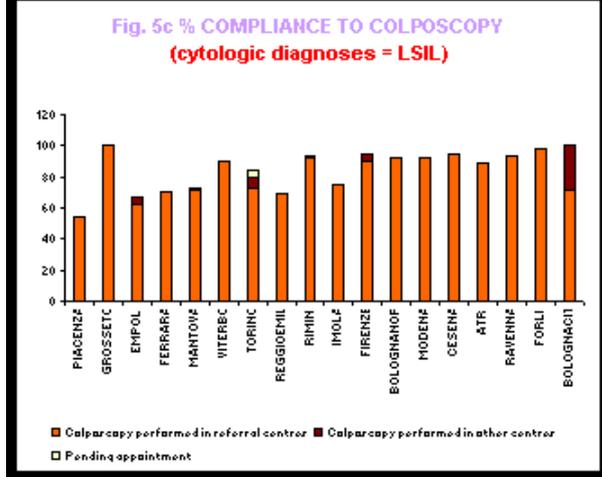
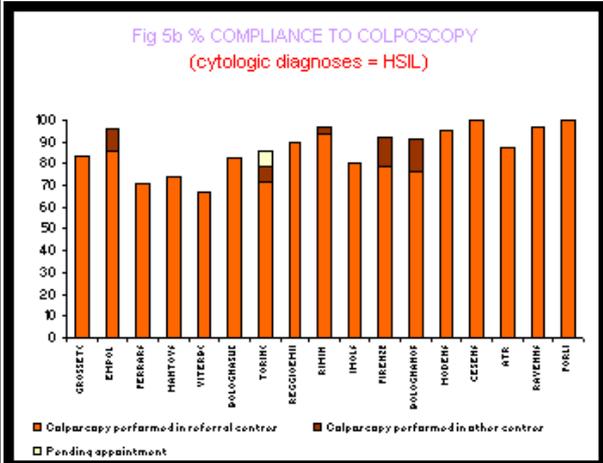
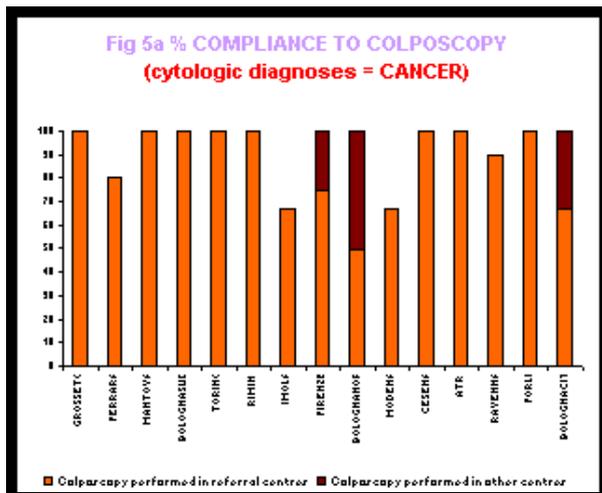
Figure 4 reports the percentage of women referred for colposcopy by each centre, according to the cytological report. Variability was large, ranging from 0.4% to 5.4%. These figures did not change after standardisation for 5-year age class (range: 0.4%-5.1%). In most programmes (14 out of 24) referral rate was below 3%.

Differences partly reflect variation in the Positive Predictive Value of cytology but also the variability in the detection rate of histologically confirmed lesions (see below).

They were also partly due to differences in protocol: indeed the highest values were observed in centres where women with ASCUS cytology are immediately referred for colposcopy. In one programme, at that time, women were invited to colposcopy at the second consecutive smear to be repeated.

Compliance to colposcopy ranged from 67% to 100% when the index cytology was invasive cancer or HSIL, from 55% to 100% when it was LSIL and from 28% to 71% when the index cytology was ASCUS. Overall 86.3% of women with LSIL or more severe cytology attended (82.5% considering only women having colposcopy in referral centres). This is less would be advisable. However it has to be taken into account that in many programmes data about colposcopies performed outside referral centres are lacking or incomplete and that in some cases these are plausibly a substantial proportion.





Positive Predictive Value (PPV)

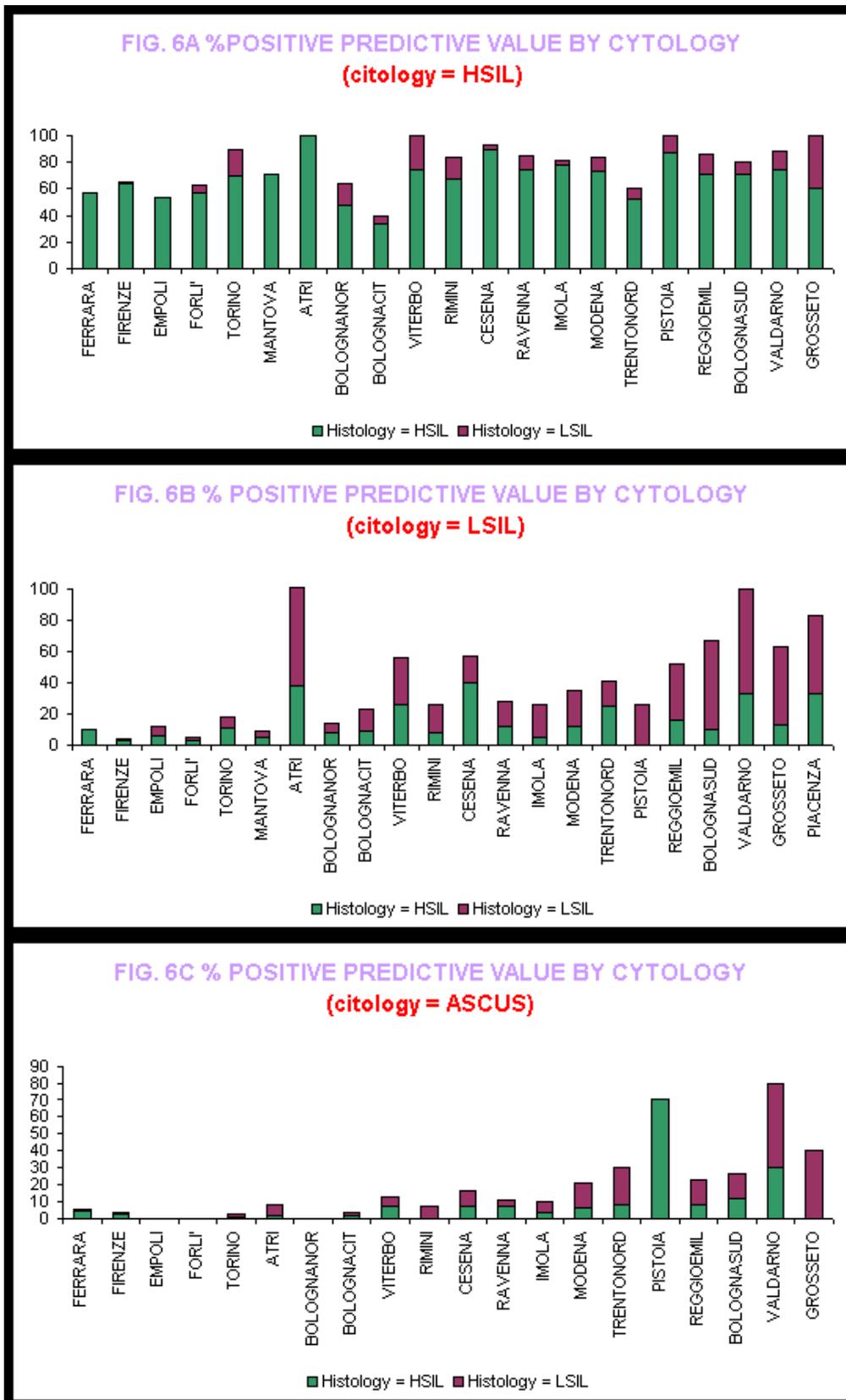
Figure 6 shows, for each programme, the Positive Predictive Value to have a histologically confirmed CIN2+ or CIN1+ according to the smear's result.

In all the 22 programmes, which were able to provide such an indicator, the PPV of cytology of carcinoma for CIN2+ was near 100%; anyway such cytological reports are quite rare. As far as HSIL smear is concerned the PPV for CIN2+ ranged from 34% to 100%, but in most centres it was higher than 60%. In the case of LSIL the PPV was rather low for CIN2+ but it tended to increase substantially when CIN1+ histologies were considered. For ASCUS smears the PPV for CIN1+ ranged from 2% to 80%. In some programmes the PPV of such diagnosis was very low. In some programmes ASCUS cases are referred for colposcopy only after smear repeat.

Variability in PPV partly depends on different criteria of interpretation of cytology but also, as well known, on prevalence of disease. In addition random variation can be remarkable in some case, given small numbers. In order to control these factors we computed Likelihood Ratios of a positive test ($LR+ = \text{post-test odd of disease} / \text{pre-test odd}$). $LR+$ does not depend on disease prevalence. As an example, Table 1 reports, for each programme, the PPV of a cytology ASCUS or more severe in predicting histologically confirmed CIN+, its expected value in the hypothesis of constant $LR+$, and the corresponding $LR+$. Some programmes have high $LR+$ values despite a low PPV, showing that the latter was the result of low disease prevalence. However, variability remains high: in 6 programmes the observed values were significantly different from those predicted. This confirms that large differences in interpretation of cytology exist.

On average $LR+$ values were around 50, i.e. the frequency of histologically proved CIN2+ is

roughly 50 times greater in women with ASCUS+ cytology than in the average of screened women. The same value for cytology LSIL+ is around 100.



Repeated ASCUS

TABLE 1**PPV AND LR+ OF ALL CASES ASCUS OR MORE SEVERE IN PREDICTING A HISTOLOGY OF CIN2 OR MORE SEVERE**

PROGRAMME	% OBSERVED PPV	OBSERVED/ PREDICTED* PPV (1)	LR+
FORLI'	8.24	0.48**	21.99
FERRARA	12.48	0.75**	36.09
IMOLA	14.74	0.69**	32.12
CESENA	23.61	0.81	38.00
GROSSETO	20.00	0.56	22.67
BOLOGNA CITY	9.09	0.99	50.03
RIMINI	16.48	0.99	50.30
RAVENNA	21.53	1.01	51.33
BOLOGNA-SOUTH	23.14	1.05	53.90
REGGIO EMILIA	22.79	1.05	53.74
VITERBO	13.51	1.24	64.50
EMPOLI	22.58	1.39	76.50
BOLOGNA-NORTH	16.54	1.39	74.16
MODENA	19.07	1.18	62.19
TORINO	8.02	1.47	76.36
ATRI	19.40	1.99	113.14
PIACENZA	33.33	5.65*	404.40
MANTOVA	21.92	2.61**	155.08
FIRENZE	18.99	1.63**	90.29

1. Predicted values were computed by a logistic model having the logit of PPV for CIN2+ as dependent variable, just an intercept as explanatory variable and the logit of the detection rate of CIN2+ as an offset variable. Therefore it assumes a constant LR+.

* | standardised deviance residual | ≥ 1.96

**| standardised deviance residual | ≥ 2.56

Detection rate (DR)

The weighted average DR of histologically confirmed CIN2+ lesions was 3.10 per thousand screened women. Programmes that started from less than 3 years (therefore all screened women are at the first round within the organised programme) had a significantly higher detection rate (rate ratio 1.82 $p < 0.0001$). This could be expected "a priori" but these programmes largely correspond to a specific region (Emilia Romagna). Therefore some possible confounding with local factors is possible.

Table 2 reports the observed number of histologically confirmed CIN2 or more severe lesions and that predicted by a model assuming an equal DR for all programmes started from at least 3 years and another one for those started more recently.

Part of variability can be explained by random fluctuations of rates due to the small number of screened women in some centres. Nevertheless out of 19 programmes with valid data 10 had a value significantly different from that predicted.

Differences seem to be too large to reflect real differences between the considered geographic areas. A possible confounding due to a different age distribution of the screened populations (potentially relevant given the remarkable age variability of pre-invasive lesions) was controlled by standardisation, resulting in a very limited effect. Also correction for a possible loss, due to incomplete compliance to follow-up, showed a limited effect. In principle differences in detection rate could reflect differences in sensitivity but the observed variation is too large to admit this as the only explanation. In addition a very low incidence of interval cancers was observed in some of the programmes showing the lowest detection rates, like in Turin.

TABLE 2

OBSERVED AND EXPECTED CIN2+ CASES

PROGRAMME	OBSERVED CIN2+	PREDICTED CIN2+ (1)	OBSERVED/ PREDICTED
BOLOGNA-CITY	27	60.21	0.45**
TORINO	20	42.90	0.47**
VITERBO	20	36.81	0.54**
BOLOGNA-NORTH	22	36.71	0.60**
PIACENZA	2	7.20	0.28*
MODENA	78	91.91	0.85
MANTOVA	16	21.64	0.73
FERRARA	76	85.90	0.88
RIMINI	32	36.42	0.88
ATRI	13	14.97	0.87

FORLI'	36	36.55	0.98
FIRENZE	91	85.90	1.06
EMPOLI	15	9.66	1.55
GROSSETO	6	2.45	2.45
RAVENNA	146	122.10	1.20*
REGGIO EMILIA	134	109.11	1.22*
BOLOGNA-SOUTH	118	94.50	1.25*
CESENA	51	28.12	1.81**
IMOLA	37	16.90	2.19**

1. From a Poisson model having the number of screened women as an offset variable and intercept and a term for recent (< 3 years before survey) start as explanatory variables.
* | standardised deviance residual | ≥ 1.96
**| standardised deviance residual | ≥ 2.56

In Grosseto, Cesena, Forli and Modena only uncovered women are invited; only women screened after invitation included in study population. In Turin all women are invited; only women screened after invitation included in study population. In all other cases all screened women were included in the study population.

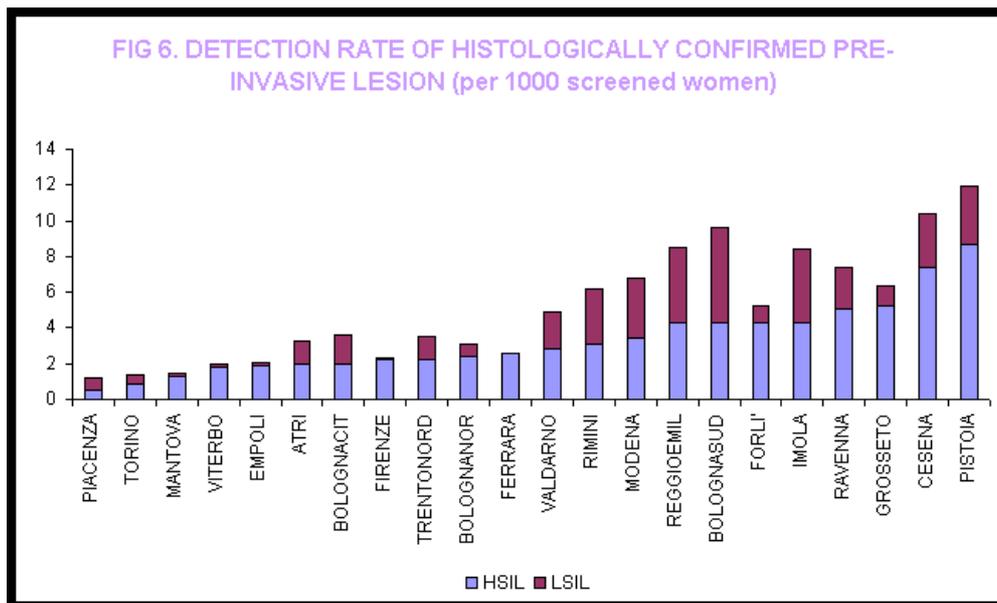
In our judgement the largest determinant of such variability is in selection processes for the study populations, resulting in different histories of prior Pap-testing.

Such different histories are only partially approximated by a recent start of the organised programme, since spontaneous activity was already present everywhere. Selection plausibly depends on different approaches to integration with spontaneous activity (in some programme only women not spontaneously covered are invited while others invite all women, independently of previous screening history) and in criteria of inclusion in the study population (some programme could include only women screened in the organised programme while others included all).

However modelling these factors is difficult given the small number of observations.

Unfortunately a reliable measure of previous screening history of the study population was not available.

In addition selection for risk factors of the study population can be present, especially in programmes in a starting phase. Finally local differences in histology interpretation can play a role.



Discussion

This is the first survey carried out among Italian programmes in order to evaluate process indicators for cervical cancer screening.

Variability was actually found to be high for most indicators. Part of it is likely to be an artifact, due to difficulties of some programmes in collecting data. Furthermore many of the more extreme values were based on a small number of screened women (either because the programme was in a starting phase or because it was very small). However large differences are still present, even when taking into account such a problem.

In some programme data showed atypical situations that need local in-depth investigation and correction, if needed.

In general data show relevant differences in cytological reporting criteria. These differences clearly resulted in a remarkable variation of predictive values and, therefore, of human and economic costs of screening. They surely require actions for homogenisation.

It is difficult to assess if these differences resulted in different sensitivity.

Unfortunately, in cervical screening evaluation, Detection Rate showed not to be usable as an indicator of sensitivity in absence of data that allow standardising for previous screening history. These data clearly show the need that good information systems are implemented in organised screening programmes, in order to produce data in a standardised way, so that comparison of programmes can be done.