Review Article

Colette Marsan

Cervical Carcinoma: Conventional Screening Methods Efficient Enough?*

Quai du Marche Neuf, Paris, France

Organized screening for cervical carcinoma has already demonstrated its efficiency in industrial countries but it still has to be better organized, particularly in developing countries. In the European Union, results may be improved thanks to more cooperation with Health authorities, enabling the pathologists to focus the risk evaluation and to broadcast recommendations about prevention on a population level.

Until recent days, it was usually admitted that screening for cervical carcinoma could be considered as an efficient method when screening programs had been established and when the PAP test procedure was controlled. But, when screening programs became better organized, it was stressed that, if incidence and mortality from cervical cancer were effectively decreasing, incidence and mortality were not decreasing as fast as it could have been expected. Perhaps, other conditions should be taken into account, related in particular to screening strategy and to national health organization [11, 16, 17].

In this paper we intend to study the following points:
1. Is PAP test procedure controlled?
2. Screening strategy: what is new?
3. Associate HPV detection.
4. Recommendations.

1. Is PAP test procedure controlled?

Of course, all the technical steps have to be controlled, including sampling, whether by conventional smear or fluid-based method [13] and laboratory technical procedures (ancillary staining methods, fluid-based procedure or possible other methods).

Screening and definitive diagnosis have to be as reliable as possible. External and internal quality controls of screening by numerous methods have been thoroughly described by many authors. Training, teaching and testing by all existing methods have to remain currently applied (books, CD-rooms, panels...), so as to make morphological analysis as precise as possible.

Final diagnosis, i.e. taking into account clinical background, report and signature is upon the pathologist's responsibility.

Several series of errors have to be searched for [14], according to the following circumstances:
- atypical cells are not seen;
- atypical cells are seen but not classified as so;
- atypical cells are classified but report is not clear (Bethesda);
- report is clear but there is no follow-up.

Patient's follow-up, although uneasy, is considered as a part of the pathologist's workload, including mailing and, if ever, any new information about patient's clinical history. This means that all possible Quality Control Tests are recommended.

Altogether, it may be admitted that the management of the different steps of the technical procedure is usually conveniently applied.

2. Screening strategy: what's new?

Several schemes exist worldwide and in the European Union, according to organized/non-organized status of screening on a national level. An organized screening can reduce the mortality rate up to 90% "*in the screened population*". But it remains rather unclear to appreciate who is, in one particular country, the "screened population" and it is well known that most cervical carcinomas develop in not screened or underscreened populations.

In many developing countries, screening is not yet organized on a national level. The percentage of invasive carcinomas remains quite impressive, for instance in Latin

* Conference in the Dept of Pathology, Pomeranian University – Prof. W. Domagała, Prof. M. Chosia, Szczecin, September 2004.

America where the incidence rate may reach 55/100,000 cases [1, 2, 5, 6, 12, 18], compared to 3–14/100,000 in industrialized countries. Reports mention that most of deaths from female cancers are due to cervical carcinoma (sometimes before breast cancer) and that practically all the cases of cancer develop in non-screened females. Lifestyle, poverty and perhaps smearing procedure may be partly responsible for such a situation but the main reasons seem to be encountered in the following circumstances:

– when there is poor population coverage, more than 65% of the cases develop in not screened or underscreened females;
– when resources are not well employed. For instance, in Mexico City, a few years ago, although huge amounts of money were spent for sampling and screening, the incidence of invasive cervical carcinoma remained quite as high as it was before, even in very young females, not infrequently under 20; patients with positive smears were not treated, for it was extremely difficult to contact them, due to the lack of organization of the mail; in fact, the young women had their first smear on the occasion of their first pregnancy, and they would not be informed about an abnormal smear, if ever, and consequently looked after, before they would attend another consultation, usually several months – or years – later, on the occasion of another pregnancy!
– when, due to the lack of information, the patients are not aware of cervical carcinoma being a sexually transmitted diseases and know nothing about prevention (in Congo, the spreading of AIDS is related to sexual violence and the incidence of cervical carcinoma may be higher in AIDS-positive patients).

In most industrialized countries, screening is more or less organized, but not always on the national level. A decreased mortality of more than 70% has been mentioned [3, 7, 8, 16]. The incidence of invasive carcinoma decreased up to 4.6/year in several Latin countries such as France, Switzerland, Italy, Spain. In France, according to several epidemiological studies [15], the level of standardized incidence for invasive carcinoma decreased from 15.6/100,000 in 1978 to 8.6/100,000 in 1992 (33.5% decrease) and standardized levels of invasive carcinoma became lower than those of *in situ* carcinoma.

The age decrease was significant for the 45–69 years old patients and the cervical cancer, the 3rd amongst female cancers in 1975, went backwards to the 7–8th range in 1998.

It is necessary to evaluate risk factors and to deliver adequate information on the national level. Recent public health disasters have focused the risk problems in the centre of health policy and have led to emerging caution rules. Public health policy goals require a new management of risk factors. Risk evaluation has to appreciate the incidence of the disease, to quantify risk factors thanks to randomized studies, and to develop strategies in view to decrease them. Consequently, there is a need for proficiency adequacy, better information of population and clear recommendations. When the rules started to be applied to screening, during the recent years, several Expert Groups were created and a number of national/international programs were settled, including the 1996-funded "Europe against cancer" program [3].

Countries may have to aim at different goals

They must find how to get more people to enter screening programs. For instance, in France, the test is free since February 2004 for all patients with a previous ASC-US or ASC-H (according to Bethesda terminology) and the screening HPV-test is reimbursed since May 1st, 2004. On the other hand, an adequate management of health resources should limit overscreening in rich or anxious categories. The pathologists may have to change slightly their attitude, to move gently from a merely morphological behavior (i.e. "*my Lab is a good one, there are very few diagnostic errors"*) to a more managing attitude ("*where are the unscreened patients, what can I do to build a screening program?"*), that is to add epidemiological needs to cytology daily workload. Pathologists have not been trained in that direction. They have to learn, working together with Health authorities. They also have to undertake a more efficient use of health resources.

Cytology is thus slowly moving to less morphological programs in which pathologists and cytopathologists are not the only ones to be involved.

3. Associate Human Papillomavirus detection

Cervical carcinoma is now admitted to be an HPV-induced tumor, as HPV infection is a sexually transmitted disease. From 25% to 40% are young people. Usually, the infection is considered more as a label of sexual activity than as a real disease and its natural evolution tends towards recovery. But some viruses are oncogenic ones and some events are supposed to act as associated factors: smoking, traumas, immunity troubles (AIDS?). Setting up a strategy for HPV screening and evaluation, several European Institutes for women health were created recently (Paris, London, Dublin, Brussels, Rome, Berlin), the aim of which is women's information [9, 10].

Then, HPV detection should be added to the conventional Pap test: if not conclusive (i.e. neither positive nor

negative), the viral test would enable an ASCUS triage. In France, the HPV test was recommended by the National Agency for Health Accreditation and Evaluation [10] and is partly reimbursed since February 2004 in cases of ASC-US and ASC-H.

Vaccination is thoroughly expected to be possible in the near future. It should be available within 3–5 years. It would save 500,000 new worldwide cases every year, cutting out at least 70% of the cases of cervical carcinoma.

4. Recommendations

The screening recommendations are mentioned in the so-called EUROPEAN CODE AGAINST CANCER [3], in which the 9th item (out of the 10) mentions that every woman should have regular screening tests. The arising question is the following: what can be done?

– For all state members, cervical smear should be the referring method for screening for women aged from 30 to 60, once every 3–5 years and ***programs have to be organized.***
– For European Community, a ***common histocytology terminology has to be adopted*** and Quality Control has to be settled on the national level.

Of course, new methods have to be evaluated so as to reduce overscreening and reach disadvantaged people. Quality control and follow-up must be set up with epidemiological indicators monitoring. New methods have to be evaluated (++HPV/DNA), screening focused on 30–60s when resources are limited and cost/efficiency measured.

Conclusion

Screening for cytological abnormalities in gynecological smears is probably moving towards less morphological criteria and it is difficult to imagine what it will look like within a few years. Nevertheless, all European countries will have to associate their efforts for evident economical and public health reasons.

However, the following items may summarize our comments:

– Non-organized screening is better than nothing.
– Efficiency of organized programs is demonstrated.
– One cervical smear every 3 years prevents 90% of cervical cancers when all women join the program.
– Benefit is only obtained if population coverage is high.
– Risk factors have to be evaluated.

And, prevention can change the historical course of the disease.

References

1. *Ako S, Fokoua S, Tchanan Sinou M, Leke R, Campana A:* Reproductive Health in Cameroon. Matweb 2000. Available from: http://www.matweb.hcuge.ch.
2. *Boon ME, Schwinghammer H, van der Veen G:* Analysis of lifestyle data and cytologic findings in a pilot cervical screening project in Rural Vietnam. Acta Cytol 1999, 43(5), 786–793.
3. "Europe against cancer program" – Internet.
4. *Godin I, Masset C:* Cervical cancer screening in the Frameries community, Belgium. Arch Public Health 2001, 59, 181–192.
5. *Hernandez-Avila M, Lazcano-Ponce EC, Alonso de Ruiz P, Romieu I:* Evaluation of the cervical cancer screening programme in Mexico: a population-based case-control study. Int J Epidemiol 1998, 27(3), 370–376.
6. *Luthra UK:* Screening for cervical cancer in developing countries; need for new thinking. Cytopathology 1995, 6(2), 71–74.
7. *Mégevand E, Van Wyk W, Knight B, Bloch B:* Can cervical cancer be prevented by a see, screen and treat program? A pilot study. Am J Obstet Gynecol 1996, 174(3), 923–928.
8. *Miller A, Nazeer S, Fonn S, Brandup-Lukanow A, Rehman R, Cronje H, Sankaranarayanan R, Koroltchouk V, Syrjänen K, Singer A, Onsrud M:* Report on consensus conference on cervical cancer screening and management. Int J Cancer 2000, 86, 440–447.
9. *Munoz M et al:* Cancer du col utérin: une classification du risque associé aux différents papillomavirus. NEJM 2003, 348, 518–527.
10. National Agency for Health Accreditation and Evaluation (ANAES). Évaluation de l'intérêt de la recherche des Papillomavirus humains (HPV) dans le dépistage des lésions précancéreuses et cancéreuses du col de l'utérus – Mai 2004.
11. *Raymond L, Menegoz F, Fioretta G et al:* Recent trends in incidence of cervical cancer in several regions of South-Western Europe. Rev épidem et Santé publ 1995, 43, 122–126.
12. *Sankaranarayanan R, Budukh AM, Rajkumar R:* Effective screening programmes for cervical cancer in low- and middle-income developing countries. Bull World Health Organisation 2001, 79(10), 954–962.
13. *Schneider V, Henry M, Jimenez-Ayala M, Turnbull L, Carr Wright T:* Cervical cancer screening, screening errors and reporting. Acta Cytol 2000, 45, 493–498.
14. *Vassilakos P, De Marval F, Muńoz M:* Dépistage du cancer du col utérin. Les frottis faux-négatifs. Acta Cytol 1998, 43, 65–68.
15. *Weidmann C, Schaffer P, Hedelin G et al:* L'incidence du cancer du col de l'utérus régresse régulièrement en France. Bulletin épidémiologique hebdomadaire (BEH), réseau Francim des registres de cancer. 1998, 5, 1–5.
16. *Wilson S, Woodman C:* Assessing the effectiveness of cervical screening. Clin Obstet Gynecol 1995, 38(3), 577–584.
17. World Health Organisation. Cervical Cancer Control in Developing Countries: Memorandum from a WHO Meeting. Bull World Health Organisation 1996, 74(4), 345–351.
18. *Woto-Gaye G, Critchlow C, Kiviat N, Ndiaye PD:* Le dépistage cytologique des cancers du col utérin en Afrique noire: quelles prespectives? Bull Cancer 1996, 83(5), 407–409.

Address for correspondence and reprint requests to:
Madame Colette Marsan, M.D., FIAC
4. Quai du Marche Neuf
75004 Paris
France