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Why Do We Go on Screening?

As healthcare rules are becoming better organized and as vaccination against Human Papillomavirus (HPV) infections is arising, the conditions of cytological screening for cervical carcinoma may have to be modified in the near future. After reminding the Quality Control constraints of the Pap test and the technical and epidemiological conditions for the HPV detection as a precursor of cervical carcinoma, the present paper wishes to discuss the possible role of vaccine on the screening strategy.

1. Pap test Quality Control

All the steps of the Pap test sampling, whether with a conventional smear or a fluid-based method, have to be controlled, as well as all the laboratory technical procedures (staining, fluid-based procedure…).

As usual, screening and morphological study by cytotechnicians and final diagnosis by pathologists are performed with the aid of all the necessary technical, theoretical and computerized devices, such as books, CD-Rooms, panels, teletransmission of images for consultation… However, the most common possible errors are the following:

– atypical cells are not seen;
– atypical cells are seen but not classified as so;
– atypical cells are classified but report is not clear (the Bethesda terminology is now accepted all over the world but the recent terms ASC-US and ASC-H may be confusing);
– report is clear but, for some reason, it does not reach the clinician or the clinician is not well informed of the patient's history and follow up.

Final report (and signature), taking into account the patient's clinical background, is always under the responsibility of a pathologist. It must be kept in mind that a so-called "negative smear" may host a very small group of atypical cells, the omission of which may represent the loss of several years of life.

Recently, has raised a question about the opportunity of adding a HPV test to the conventional Pap test, inducing several social and economical problems. Which question is the Pap test supposed to answer to? Presence/absence of cancer cells? Or of any other sexual transmitted disease?

2. Morphological strategy

A question arises: what are we screening for? The relationship between cervical carcinoma and HPV is now well established: cervical carcinoma is an HPV-induced tumour and the HPV infection is a sexually transmitted disease (the main one). 25–40% of the patients are young people. But it is generally attested that the presence of the HPV is a more a label of sexual activity than a real disease and its natural evolution is recovery.

However, some viruses are oncogenic ones and associated factors enhancing the risk exist such as smoking, traumas, immunity troubles (AIDS?). HPV-DNA has been detected in 90.7 per cent of cancerous patients and there are no cancerous patients without HPV. Unfortunately, on the cytological point, we have yet no means of detecting the oncogenic viruses, for the cell is expressed by no morphological features that we might be able to identify. There stops our morphological accuracy.

For that reason, the recent scientific meetings and organizations have claimed that epidemiological informations might be useful, as an aid to morphological questions.

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3. Epidemiological strategy

The 500,000 new cases of cervical carcinoma/year are related to the most common HPV oncogenic viruses, in descending order of frequency the 16, 18, 35 types. The cell infection has no specific morphological features and the virus typing cannot be performed through morphological reliable procedures applied to conventional smears, so that, even when typical HPV is visible, for instance the koilocytic pattern, one does not know whether the infectious agent is an oncogenic one or not. The risk factors are not identified and, of course, HPV specific detection can not be added to all conventional Pap tests!

Public health policy rules require a new management of risk factors. Risk evaluation has to appreciate the incidence of the disease, to quantify the risk factors thanks to randomized studies and to develop strategies so as to decrease them, for instance proficiency adequacy, information of populations and clear recommendations.

However, most of the images classified as LGSIL, ASC-US and ASC-H, according to the ancient and recent Bethesda nomenclatures (Table 1), are in fact related to HPV. As a consequence, they may be considered as alarm indicators, so that it is not unreasonable to consider the Pap smear detection of cervical carcinoma as an adequate ***triage system***. Nevertheless, the system has to be organized.

In western countries, public health disasters have taught health authorities how to focus risk problems; they have led to emerging caution rules; as a consequence, cytology has moved gently towards epidemiology and expert groups, national/international programs, cancer registers have been created. During the last decades, the incidence of invasive carcinoma in France decreased from 15.6/100,000 in 1978 to 8.6/100,000 in 1992 (~33.5%). The standardised level of the invasive carcinoma is now lower than that of the in-situ carcinoma. The age decrease is significant for the 45-69 yrs groups and the incidence of cervical cancer has moved from the 3rd row amongst the female cancers in 1975 down to the 7-8th row in 1998. Finally, the mortality has revealed a decrease of 70%.

In many developing countries, screening is not yet well organized. There is poor population coverage and more than 65% of cases develop in not screened or underscreened patients. Resources not well employed and there is a tremendous lack of information of the population. As a consequence, up to 80% of female cancer mortality is due to cervical cancer and about 80% of cancers develop in non screened females.

But it has been proved that ONE cervical smear every 3 years prevents 90% of cervical cancers when ALL women join the program.

TABLE 1
Bethesda

Squamous	*Cells*
Bethesda 1991	Bethesda 2001
Atypical squamous cells undetermined significance: ASC-US	Atypical squamous cells undetermined significance: ASC-US Cannot exclude HGSIL: ASC-H

4. Vaccination soon?

Vaccination soon may not be a dream [4], as it has been stressed that vaccination could cut out at least 70% of the 500,000 new worldwide cases of cervical cancer.

Different possible windows have been studied enhancing ***whether a prophylactic or a "therapeutic" vaccination system.***

The ancillary vaccination method is that of a *prophylactic vaccination*, as infection prevention may be conferred when antibodies are neutralized after immunization with virus-like particles. If such a method is performed on human beings in the future, clinical trials will need the vaccine to demonstrate its safety and its immunogenicity. But, obviously, waiting for the evidence of absence of CIN and, later on, of invasive carcinoma would require a long follow-up.

Recently, a *therapeutic vaccination method* has been proposed: the immune cells are taught how to kill already infected cells. Briefly, several viruses are known to resist to an immune answer (AIDS, HPV), as some of their proteins induce an immunosuppression and prevent an efficient answer of T-lymphocytes. This new technology is based on a vaccine permitting patient to develop antiviral antibodies against these viral immunosuppressive proteins. It is called a *therapeutic* vaccine as it stimulates the altered defences against a tumoral antigen.

In the present case, one of the proteins, considered as oncogen, of the HPV 16 was linked to an immunogen protein of *Borderella pertussi*. The authors have invented a transport system able to send the viral protein to the dendritic cells which will activate T-lymphocytes. On an animal model of the human tumor they observed a 100% regression [6].

Several authors have studied the vaccine acceptability according to different scenarios: age of patients, efficiency of vaccine. According to the ACOG study [7], gynecologists are willing to include the vaccine in their office practice. To examine the potential health and economic effects of the vaccine in a setting of existing screening, a mathematical model (Markov model) was used to estimate the lifetime cost and life expectancy of a hypothetic cohort of women

screened for cervical cancer in US. Three strategies were compared: (1) Vaccination only; (2) conventional cytology screening only and (3) vaccination followed by screening. The author concluded that vaccination in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence. Identifying the optimal age for vaccination should be a top research priority [3]. According to others, any program of vaccination that would permit a later age of screening initiation and a less frequent screening interval is likely to be a cost-effective use of health care resources [1].

If the method is demonstrated as an efficient one, vaccine may become ***a routine part of office gynecology*** [7]. However several other problems will then arise and ethical, social and religious questions will have to be debated.

5. Conclusions

In a recent paper [5] we had insisted upon the following proposals:

– efficiency of organized programs was proven but benefit was only obtained when population coverage was high;
– optimal organization had to include a reliable technical Quality Control although non organized screening might be better than nothing;
– prevention could change the historical course of the disease.

Taking into account the probable new healthcare behaviour related to the emerging vaccine, our present conclusions would like to highlight the fact that vaccination will probably modify the conditions of the cytological screening. The Pap test will be aimed differently, as it will be no more a lesion detection test but a control test of the efficiency of the vaccine and it is evident that the need for highly qualified cytotechnicians (screening 7000 slides per year) [2] and cytopathologists will remain a priority for many years.

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