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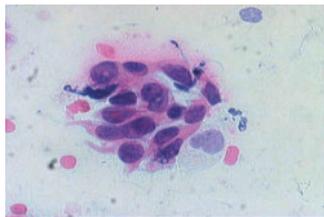
# Time for a paradigm shift in the prevention of cervical cancer?

Congress report of “Eurogin” in Monte Carlo, February 17th–20th, 2010

**The Eurogin Congress in Monte Carlo in 2010 showed overwhelming scientific and clinical data that HPV testing is a better screen for cervical cancer prevention in women, than the traditional Papanikolaou smear test (Pap) which is currently used in Switzerland and in many other developed countries. This is due to significantly greater sensitivity. The advantages, disadvantages and the open questions that are linked to a possible paradigm shift in changing from Pap to HPV as the primary screening test are discussed in this article.**

## Detection and Prevention of Cervical Cancer (CC)

CC is one of the most frequent neoplastic diseases in women worldwide [1]. In developed countries, the toll due to this cancer has fortunately reduced markedly in recent years. This is due to the introduction of a CC prevention and screening program with the help of a cytological examination: cells of the cervix (fig. 1) are taken from women by a swab and are screened for degenerated cells under the microscope (this is the so-called “Pap-Test” or “Pap-Smear”). Any detected cell irregularities are recorded and categorised into different pre-cancerous and cancerous stages.



**Figure 1**  
Microscopic picture of human cells from a Pap smear.

This test had been established by a Greek-American pathologist, Georgios Papanikolaou, in 1923, but was not accepted by the medical community until during World War II [2].

CC is a particular neoplasia, because – since its detection [3] by Harald zur Hausen, a German virologist, in the 1970s – it is clear that CC follows, in almost every case, an infection with the human papilloma virus (HPV)

that is transmitted by sexual contact and may become chronic. This opened the area for a new diagnostic procedure and prevention of CC, namely by testing for (chronic) HPV infection. Gradually in the subsequent years after the introduction of Pap, the medical communities in most countries – as it was also the case in Switzerland – agreed on the following CC prevention program: women at a certain age were encouraged by their gynaecologists to undergo regular “CC prevention screening”. The onset and time periods between those regular examinations varied from country to country but the method was more or less uniform: the primary screen should be based on a Pap test. If this test was negative, everything was clear and there was no apparent risk for the particular women. If the test was “positive” (i.e., (pre-)cancerous cells were present), the woman was normally transferred for further examinations (colposcopy) and treatment (surgery). In the case that the Pap test was equivocal, an HPV test on the swab material was performed and if it was positive for a high risk HPV type (sometimes also a full virus typing was done), further examinations and closer surveillance was initiated. This procedure is called “triage” and it is the current practice in this country.

## New scientific data and common sense at Eurogin 2010 [4]

Overwhelming clinical data, which were presented in Monte Carlo, showed that HPV is a better and more sensitive (see below) test than Pap for primary detection of pre-cancer and cancer in women. As a consequence,

there was a consensus that it is now the time to consider a new regimen of CC prevention programs: HPV testing should play a stronger role in the detection and management of pre-cancerous and cancerous stages. This was the basic message throughout the congress but there are still some open questions in this context that were debated with an, as yet, open outcome. This article will list those questions and the arguments from all sides, to determine how to find the relevant answers. The following section starts with a comparison of the advantages and disadvantages for Pap and HPV testing, respectively, and will thus explain why the vast majority of the Eurogin delegates came to the conclusion that time is ripe for a paradigm shift.

## Strengths and weaknesses of the Pap test

Strengths:

- This test is well established and has been used for decades.
- Every gynaecologist and pathologist knows this test.
- There is no doubt that this test was, and is still, beneficial in preventing CC.
- The test looks for degenerated cells and is thus highly specific.
- In most countries (also the case in Switzerland) the test is relatively cheap.

Weaknesses:

- The analysis of the test is subjective.
- Some specimens give an equivocal result.
- Full automation in the laboratory is not possible.
- The test is poor for the detection of

<sup>1</sup> Conflict of interest: The author is employed by Roche Diagnostics (Switzerland) AG.

adenoma cancer of the cervix (due to the kind of sampling).

- The test is not very sensitive; broad and variable ranges between 50% and 82% have been reported (one example report under five).

This last point is actually the Achilles' heel of the Pap screen: For a cancer screening program, a test procedure should be as sensitive as possible, because with an insensitive test the chance of not detecting people at high risk is great.

In contrast, if one looks at the strengths and weaknesses of an HPV test, we can state the following facts.

#### **Strengths and weaknesses of the HPV tests (there are different formats on the market, see below)**

Strengths:

- The tests are very sensitive ( $\geq 97\%$ ) and thus clearly superior to the Pap test [6].
- The tests are totally objective.
- The tests are suitable for all HPV associated CC, and for HPV subtype 18 induced adenoma cancer.
- Solutions with full automation are on the market.

Weaknesses:

- The tests are relatively new and up to now have been established for triage only.
- The test looks for the virus and not for the cancer (might be unspecific).
- The test is more expensive in many countries (in Switzerland: much higher reimbursement figure [7]).

Since there are various HPV test formats on the market, the following question is often asked:

#### **Which HPV test is the best?**

The following alternatives are offered by commercial diagnostic companies:

1. Detection of all high risk (HR) HPV subtypes in one test.
2. Test that allow an extensive typing of high risk (and some low risk) HPVs.
3. A (partial) combination of (1) and (2), namely high risk bulk test and differentiation of HPV types 16 and 18.
4. Tests that look for HPV E6 and E7 gene expression (m-RNA).

The reason for separately identifying HPV 16 and 18, in addition to the other high risk HPV types, is that those two types are known to be very

aggressive [8]. Therefore, if a woman is chronically infected by one of those two types, she has a higher risk to develop CC than in the case of an infection with another HR type. As a consequence, in some countries (like the USA), there is a different follow-up/surveillance of women with HPV 16 and/or 18 than in women infected with other HR types. In addition, HPV 16 is by far the most prevalent subtype in most countries (as is the case in Switzerland [9]).

The expression testing of viral E6 and E7 genes was also proposed, since those gene products are involved in the transformation of the human cell [10]. It is now hoped that testing the m-RNA would make the HPV test more specific for the detection of cancer and pre-cancerous lesions, but up to now the scientific data does not strongly support this claim. In addition, the inclusion of those markers compromised the overall detection of HR HPV in some commercial tests, since the number of detectable different HR subtypes was reduced – a feature that does not render such a test really suitable for a primary screen.

The problem of an “unspecific” (for pre-cancer and cancer) HPV test result has already been debated for a long time and was again a discussion point at Eurogin 2010. The author of this article, however, is convinced that this issue could be solved by two measures: firstly by appropriate selection of women to be tested by age (see below) and secondly by calibration of the test sensitivity against the clinical outcome (CIN 2+ or greater) which has now been done by most manufacturers.

In summary, many experts think that a HR bulk test combined with an immediate typing of HPV 16 and 18 is the best strategy, because these two types deserve special attention due to their aggressiveness. Commercial tests from Roche Diagnostics (fig. 2) and Abbott Diagnostics offer this testing strategy.

#### **Which CC prevention strategy is the best?**

As already pointed out, the current regimen is that first line screening performed with Pap is done in women aged 15 years old and over, and that

an HPV test is used as triage in unclear/equivocal cytology. During Eurogin 2010, there was, however, a consensus by most experts that the time is now ready for a paradigm shift and that the HPV test should be used as the first line screen. The reason for this shift is very clear and very well documented by an overwhelming amount of clinical data, as this new strategy will detect more women at risk and will hence prevent more CC cases. However, there was some discussion regarding how this shift should be executed. The more radical opinion, that was defended by some European experts, was to exclusively use HPV testing for primary screening and to use Pap testing for triage only, which would be the opposite to the existing regimen. The less radical opinion, which was defended by some US experts, was to use both Pap and HPV testing in parallel for a screening and CC prevention program, at least for a certain time for a transmission phase. The arguments for the first procedure was that Pap in addition to HPV testing shows (almost) no benefit but makes the new screening more costly than it was in the past. The arguments for the second procedure were historical and psychological reasons and medico-legal considerations, which are of particular importance in the USA.

#### **What are the open questions?**

Since this debate and the proposals are considerably new, questions still remain that have to be solved on an international (European) or local level. Those questions are:

- **At what age should HPV testing be started?** A range of age between 25 and 35 years was discussed, and most experts recommended a start at 30–35 years of age.
- **At what age should HPV testing be stopped?** Here, too, a real consensus was not achieved. Most experts think that testing beyond an age of 65 is not justified, but studies in even older women exist.
- **What should the frequency of the testing be?** Again, opinions on this point were controversial: The maximum should be once in every three years, but longer intervals of 5 and even 10 years are under discussion.

### What are the advantages of such a paradigm shift?

The first and biggest advantage is for women. An HPV test instead of a Pap test will definitely detect more women at risk and will allow for more stringent surveillance and earlier interventions which should lead to a reduction in mortality because of CC. It is obvious that, as for any screening, the primary test should be as sensitive as possible in order not to miss any person at risk. It is true that in most diagnostic tests there is always a "battle" between sensitivity and specificity as is also the case here. However, with the Pap test as a triage, we do have the means to control specificity, as when an HPV test is positive, the Pap test is easy to do, relatively cheap and well established. One also has to bear in mind that with most of the new generation of HPV tests the issue with specificity (for detection of cancer and pre-cancerous stages) is more or less solved, since these tests were calibrated against the clinical outcome. There is probably also a benefit for the health care system in terms of costs. The new HPV tests must not be more expensive than a Pap test from the manufacturer's side. It is the matter of the re-imburement figure which is important here. Additionally, in the case of a negative HPV test for a particular woman, most experts agree that the test interval can be prolonged, as long as this woman is in a stable relationship with one partner. This can save money, because the number of necessary tests in those women will go down. Another benefit can lie in epidemiology and other prevention campaigns (like vaccination). Only HPV testing (together with typing) allows discrimination between a recurrent chronic infection and a new infection with a different HPV type. In addition, this kind of testing can monitor if there might be an "epidemiological shift" of different HPV subtypes that is induced by the HPV 16 and 18 vaccinations, and which was also discussed by several experts during the Eurogin congress.

### What are the obstacles for a paradigm shift?

The Eurogin delegates and the author

of this paper are well aware of the fact that such a "diagnostic revolution" will create some resistance in the general and medical populations in the health care community. In the opinion of the author, the following points have to be addressed:

- Pathologists and even gynaecologists might fear of seeing clients less frequently, or to lose them altogether.
- The differences in costs between the Pap and HPV test has to be minimal. This is less a question of the actual tests costs, but more a question of re-imburement. From working in the diagnostic industry, the author knows that HPV testing in terms of reagent costs and work load can be competitive with the costs created by a Pap examination.
- Pap is done in a doctor's office, whereas HPV testing officially requires a diagnostic laboratory under FAMH supervision.
- Many physicians (and lay women) do not know the real value of HPV testing, which is in contrast to Pap testing, and are confused by the number and variety of different tests offered.

As a consequence of these facts, I am convinced that a concerted action by all stake holders (physicians, health care authorities, insurances, diagnostic laboratories and diagnostic industry) is required to prepare Switzerland for this paradigm shift. In this context, the re-imburement for HPV testing as a primary screen scenario deserves some special attention. Here in Switzerland, we have to very carefully observe what is going on in this field in other European countries and not fall behind in this diagnostic (r)evolution. It would be a political and medical disaster, if Switzerland did not keep pace with the development in its neighbouring countries giving the impression that its female citizens are treated less diligently and less carefully than in other parts of Europe.

In addition, the scientific and medical community has to find answers for the open questions which remain. Clear guidelines (European or national) are required.

From my impression from Eurogin 2010 and discussions I had there with

some Swiss physicians and laboratory colleagues, I would like to finish with the following personal advice: Start the above mentioned action now and be prepared!

Note: A copy of the scientific abstracts of the Eurogin presentations is available from the author upon request.

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