

Human papillomavirus DNA test positivity: a clinical finding without evidence of disease

Editorial

Cervical cancer is a relatively common disease that affects women of all ages. The main risk factors are cigarette smoking and sexual promiscuity. Over the past 30 years, it has been shown that cervical cancer has a viral origin, due to the persistence of the Human Papillomavirus (HPV).¹ This virus is very common and is transmitted by sexual contact, its presence does not bring disorder, and it is harmless. Most people come into contact and become carriers of the virus without being aware: usually, the body eliminates it spontaneously over several months, as it happens with other viruses such as, for example, those that cause flu. Part of the population does not eliminate the virus: its persistence, associated with other risk factors, such as those mentioned above, favors the development of precancerous lesions that if untreated can, over time and in a very small percentage of cases, evolve in cervical cancer.² We know more than 100 different types of HPV, 13 of which, referred to as high-risk (HR-HPV), are closely linked to the onset of cervical cancer. Other types of HPV, those at low risk (LR-HPV), are responsible for the appearance of genital warts. The persistence of HR-HPV can cause in some people the onset of genital dysplasia, which over time can develop into cancer.³ The consequence of this new information is that the presence of HPV deoxy-ribonucleic acid (DNA) is a necessary condition for the development of lesions: for this reason, it has been introduced the identification of HPV DNA (HPV-DNA test) together with Papanicolaou (Pap) test.⁴ In fact, the absence of the virus gives greater security, compared to the simple Pap test, to have no lesions and not to develop them in the immediate future. HPV test can, in fact, detect the presence of HR-HPV even before the cervical cells develop visible changes to Pap test. Since the presence of HPV is an absolutely necessary condition for the development of cervical cancer, this test helps to identify with greater anticipation women at risk of developing this disease. On the other hand, a positive HPV test does not necessarily mean that a woman will develop cervical cancer, but it allows the physician to identify which women are at risk, and so must be checked more carefully. Finally, for this reason vaccination against HPV has recently been introduced for women under 26 years old, so we can better prevent precancerous lesions and cervical cancers.⁵ The introduction of Pap smear has decreased mortality from this cancer, because the test is able to identify not only tumors when they are still small and therefore curable, but also and especially benign lesions that can transform over time into malignant tumors. As a result of this new knowledge, who is not a carrier of the virus has a very low risk of developing these lesions. In order to fully exploit its potential, Pap test should be repeated at regular intervals: in case of negativity, security is so high that the next check can be made three years later.

HPV is the main cause of cervical cancer in women, and can also cause various other cancers (anus, penis, throat, etc.), as well as genital warts. Prevention is the best weapon we have at our disposal to defend ourselves against this threat and until a few years ago, the only option in this regard was offered by Pap test. HPV test, which has a higher sensitivity, represents a big step forward for early diagnosis, allowing to detect a HPV infection. For this, it is gradually replacing Pap test, especially in women more than 30 years old, because it allows a

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Franco Borruto,¹ Ciro Comparetto²¹Department of Obstetrics and Gynecology, Monaco²Division of Obstetrics and Gynecology, City Hospital, Italy

Correspondence: Ciro Comparetto, Division of Obstetrics and Gynecology, City Hospital, Azienda USL Toscana Centro, Via Suor Niccolina 20, 59100 Prato, Italy, Tel +393474856799, Fax +390574802955, Email cicomp@tin.it

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lower frequency of screening, arriving to be repeated every five years. For HPV-positive and Pap test-negative patients, it is recommended the annual execution of both tests, as the simple positivity is not synonymous of the presence of injury. Compared to Pap test, this test is able to detect a greater number of positive cases, then it is considered more sensitive, but from a different point of view it exposes to a higher risk of positive reports that turn out not dangerous. Because in young girls HPV infections are particularly common, but usually regress spontaneously without complications, most of the scientific societies recommend to undergo the examination only after 30-35 years. HPV infection is a very common condition in young women and is not a pathological event per se, although it is frequent. In most cases, in fact, there is the spontaneous regression of the virus. The occasional presence of HPV at the genital level is a transient event that does not constitute a pathological event and, therefore, does not necessarily require treatment but periodic monitoring.⁶ Treatment is however required when this condition is accompanied by cytological abnormalities at Pap test and abnormal images on colposcopy, a test that allows the visual examination of the cervix through a special lens. In this case, the biopsy on abnormal areas is the test that makes the diagnosis and which possibly indicates the need for therapies. In fact, almost all women sooner or later take HPV, high or low risk that it is, and the great majority of them eliminates it spontaneously, without need to do anything. Among the few women in which the virus persists, changes occur that with age can (but not always) result in a cervical cancer. Importantly, Pap test and HPV test can only identify tumors and precancerous lesions of the cervix. A disease that affects the body of the uterus or ovaries cannot be identified through these tests. Therefore, cervical screening DOES NOT REPLACE gynecological examination. In most cases of positive Pap test there is not, however, a tumor, but a precancerous lesion that can be eliminated with a simple outpatient surgical operation. In addition, there is the possibility that it could be a false alarm (false positive). This possibility increases when the test indicates very slight alterations, such as "atypical squamous cells of undetermined significance (ASC-US)", or "low-grade squamous intraepithelial lesion (L-SIL)", or medium alterations, such as "atypical glandular cells (AGC)"⁷ in these cases, the probability that there are no injuries may be higher than 50% and it can be indicated to associate HPV test.⁸ If Pap test is negative, however, it remains the possibility that there is a cervical

lesion that the test has not identified (false negative): in fact, no test is 100% safe.⁹ Repeat at regular intervals of Pap test is a method to overcome the problem of false negative test. The HPV test/Pap test combination allows to increase security. The negativity of the two tests gives a higher than 98% security.¹⁰ In the presence of symptoms, the patient should consider the necessity to consult the family doctor or the gynecologist. As already said, the positivity of the viral test does not imply the presence of disease, but is only an indication of the presence of a risk factor. For this, both tests will be repeated one year later. These exams are harmless and painless, and are executed in a single operation: the midwife or the gynecologist inserts a vaginal retractor and takes some cells from the outer surface of the cervix with a spatula and from the inside of the cervical canal with a small brush. The cells for the two tests are dispersed in a test tube containing a liquid, and then sent to the laboratory to be analyzed.¹¹ The developing of the tumor is usually a slow process: it may take up to 20years, a long enough time to enable women who undergo regular screening to interrupt the development of the cancer in its early stages.

Pap test is a well-established screening program with a long history behind it. The first applications date back to the Fifties of the last century and, since its use has emerged on a large scale, it has enabled us to obtain important results against this tumor. It is sufficient to say that the mortality rate for cervical cancer is steadily decreasing in Italy over the past two decades thanks to the start of organized screening programs. Cervical cancer screening in Italy, according to the indications of the National Observatory of Screenings (ONS), involves performing a Pap test every three years for women aged between 25 and 65years. It is not indicated to perform a Pap test before the age of 25.¹² HPV infections are in fact more frequent in younger age groups, but in almost all cases they regress spontaneously. Undergoing the examination would therefore unnecessarily expose the girls to further testing not without risks. Similarly, for a woman who is negative to Pap test at the age of 65, we can exclude this cancer also for years to come, given the very slow time of growth. If Pap test is positive, screening includes the performance of colposcopy that can allow the execution of a biopsy. If the histological examination confirms the presence of a precancerous lesion, the treatment consists in its removal through micro-surgical techniques performed on an outpatient basis under local anesthesia. Not all precancerous lesions, however, require treatment: this is advisable only for those in more advanced stage, since the simplest ones may spontaneously regress.¹³ HPV test then began to be used in some areas of the country instead of Pap test, within organized screening programs.¹⁴ For women, the methods of examination are identical: the sample, however, instead of being examined under a microscope, is submitted to a genetic test. For women that are positive, the reading of the sample under a microscope is performed, as is the case with the traditional Pap smear. If this examination confirms the positivity, then we can proceed to colposcopy. Otherwise, we can avoid this assessment, but one year later we have to repeat HPV test. If this turns positive again, we proceed directly with the colposcopy. Screening with HPV test in place of Pap test finds more lesions of the cervix than Pap test and is therefore more protective, while exposing to a greater risk of false positives, that is lesions considered suspicious that subsequent investigations instead prove harmless, as we have said before. HPV test use changes the times and ways of cervical cancer screening: since this test finds an early injury, it should be repeated every five years instead of every three years as Pap smear. Also, since in younger

women HPV infections are very frequent, but in most cases, they spontaneously regress, the examination is recommended only starting from 30-35years (in Italy from 34years).¹⁵

The tests for the molecular diagnosis of HPV infection are now available since several years, during which it was collected an enormous amount of data about the reliability and the diagnostic utility of these investigations.¹⁶ Only in recent years, we have begun to put these tests in cervical cancer screening programs. The American Cancer Society (ACS) and the American College of Obstetricians and Gynecologists (ACOG) recently revised the guidelines for cervical cancer screening, including, for women over 30years, combining HPV test with Pap test as an alternative to Pap test alone.¹⁷ From the “operative” point of view, the molecular analysis is performed with the same mode of Pap test: the patient must undergo the removal of cervical material using special tools (see above). For this reason, and also for its best diagnostic significance, a positive HPV test is followed by the conventional cytology (Pap test). In general, HPV test performed in association with Pap test allows to:

- I. Identify a greater number of HPV infections compared to those seen with just Pap test, which in some circumstances can miss up to a subject at risk out of ten (false negative result).
- II. Better quantify the risk of developing cervical cancer, with the ability to identify the high oncogenic risk serotypes.
- III. Strengthen, in case of negativity, the diagnostic value of a negative Pap test, classifying the patient as low-risk, with possibly delaying the subsequent control surveys (in other words, a negative HPV test gives more guarantees that the disease is not present and that it will not be in the short period); and
- IV. Add important diagnostic information to Pap tests of uncertain outcome, allowing to distinguish positive patients to the virus from negative ones, directing them, in the event of a further positivity, to colposcopy.¹⁸

As for the use of HPV test as a primary screening tool to replace Pap test, we can reasonably say that the search for HR-HPV has a higher sensitivity than Pap test, but it is burdened by a lower specificity, especially in younger women: therefore, given the frequent reversibility of the infection, a positive result would subject a greater number of young patients to unnecessary apprehensions, investigations, and treatments.¹⁹ HPV test acquires specificity, and can therefore be used as a primary screening tool starting from the ages of 30-35 years, with cytological triage (Pap test) only in case of positive HPV tests in women over 30years. In general, collecting the views of the various associations and guidelines, constantly updated, we can reasonably say that:

HPV test as a primary screening tool IS NOT indicated in women aged less than 30years, given the high incidence and reversibility of the infection in this age group;

- I. Within three years of sexual activity but not before the age of 21, or from the age of 25 according to other sources, it is advisable to undergo a Pap test every three years (old sources, however, advised more frequent checks, every one-two years: in this regard, importantly, also women who undergo vaccination against HPV SHOULD TAKE a Pap smear screening).²⁰

- II. In women younger than 30 years who have abnormal Pap test results of ASC-US type, it is possible to use HPV test as a follow-up survey to monitor the evolving situation and determine whether or not to undergo colposcopy, thus as a triage test.
- III. From ages 30-35 years, screening via Pap test every three years may be replaced by HPV test every five years.
- IV. In women higher than 30-35 years of age, the joint execution of cytology and HPV testing is advisable only in case of Pap smear positivity (or vice versa).²¹

If we opt for Pap test as the screening method, in case of a negative result and in the absence of other risk factors, such as Human Immune-deficiency Virus (HIV), sexual promiscuity, previous history of cervical cancer, smoking, etc., the test should be repeated every three years. But if we choose HPV test, in case of a negative result and in the absence of other risk factors, the test should be repeated every five years until the age of 65 years. In fact, the peak incidence of cervical HPV infections is between the ages of 15 and 25 years, and the increase of incidence of precancerous and neoplastic lesions occurs after 25 years of age, expression both of the considerable body's ability to fight infections, and of the latency between HPV infection and the onset of cervical cancer: this last point, in particular, allows secondary prevention through screening.²² As anticipated, to perform HPV test a sample of cells from the cervix is taken exactly as for a normal Pap smear. In view of the examination, the patient is required strict compliance of these rules: undergo HPV testing at least five days before menstruation or at least five days after they are finished, abstain from sexual intercourse for at least two days, and avoid the application of creams, pessaries, and vaginal irrigators in the five days preceding the examination.²³

In summary, the first point is that cervical cancer screening does not look for tumors, but for precancerous abnormalities, i.e. benign abnormalities that precede the development of cancer: the elimination of these alterations allows PREVENTION of the tumor.²⁴ Mammography screening allows an early diagnosis: breast cancer is not avoided, but diagnosed when it is small and we can take better care, cervical cancer is avoided, because we identify the alterations that come before cancer. These alterations are identified by Pap test, and are due to HPV: if there is no HPV, there are no changes. So, today we have HPV test: it guarantees the negative users more security of Pap test and more of colposcopy. For this reason, we use HPV test: for its high negative predictive value (NPV). A positive HPV test means that the woman may have a transient infection, that has recently arrived and soon will disappear by itself, or that this infection will persist over time, or that she has HPV infection since many years. For this reason, once Pap test is performed and with a negative result, she is advised to repeat it: the repetition allows us to see if the infection is persistent or transient. The positive test predicts the occurrence of any abnormalities detectable by colposcopy even many months after, therefore the positive HPV test reminds her to check the uterine cervix most frequently, waiting for the infection resolves spontaneously, as it happens in most cases.^{25,26}

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Conflict of interest

The author declares no conflict of interest.

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