

## Cervical cancer screening strategies: not the test you take, but the decision you make

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Starting from May 1, 2017 in Australia the National Cervical Screening Program will shift from cervical cytology every two years, to HPV DNA testing as the sole primary screening test every five years in women aged 25 to 74 years, together with the implementation of an active HPV vaccination program [1]. Conversely in Japan cervical screening using cytology every two years is still being recommended for population-based and opportunistic screening [2]. While Canadian guidelines also recommend cervical screening with cytology every 3 years [3], in Europe cervical cytology is recommended for women under 30-35 years, and HPV testing as the sole primary screening test every 5-10 years for women above 30-35 years [4].

Actually, guidelines do not represent the real situation in each European country. In the Netherlands, screening is well organised and relies on primary HPV testing every 5 years until 40 years of age and every 10 years for women aged 40 and beyond: no screening is provided for women under 30, nor over 60 years of age [5]. Other countries recommend cytology or HPV testing, and differences are marked even within the same country and sometimes within the same region. As a matter of fact in Italy there are regions employing cytology, other regions employing HPV DNA testing, and one local health unit employing HPV mRNA testing as the sole test, while some regions still do not implement organized screening programs [6]. In the U.S. guidelines for cervical cancer screening are well-structured and - in their effort to reach maximum cost-effectiveness - are articulated into several scenarios. Briefly, cytology alone every 3 years is recommended for women under 30 years, while women aged 30 to 65 years may either continue screening with cervical cytology every 3 years, or offered cotesting (cytology + HPV testing) if they want to be screened less frequently [7-9]. Interestingly, European guidelines insist that only one primary test (either cytology or HPV testing) should be used at any given age in cervical cancer screening. In the U.S. until more data and algorithm development will be available, it is judged premature to use HPV testing alone as a valid screening approach [10]. This is the

reason why the latest edition of the CDC guidelines published in June 2015 state that HPV testing should not be performed in screening for cervical cancer as a stand-alone test (i.e., without a concurrent Pap test) [11].

In terms of the age at which to begin screening, screening in the teens is associated with a high number of colposcopies but small gains in life expectancy. In addition, a large percentage of high-grade lesions are estimated to be CIN2, which is more likely to regress in younger women. As such, detection of CIN2-3 in this population may result in overdiagnosis and treatment. This is important because studies of cone or loop electrosurgical excision procedure treatments for CIN in reproductive-aged women have been associated with an increased risk of adverse pregnancy outcomes.<sup>62-63</sup> If the age at first screening is delayed past age 21 years, there is an increasing risk of cancer for each year that screening is delayed. Although these findings are relatively robust, it should be noted that the measure of colposcopies per life-year gained may be misleading in terms of the burden of screening, as well as resource use, when applied to adolescents, since the latest ASCCP guidelines recommend repeated screening prior to referral for colposcopy in women younger than age 21 years.<sup>64</sup> If a measure of screening cytology tests per life-year is used, screening beginning at age 21 years and conducted at least every 3 years, as currently recommended by the USPSTF, is also identified as a strategy that provides a reasonable trade-off between the burden and benefits of screening.

As we can see, there is considerable disagreement worldwide about cervical cancer screening strategies between countries that have similar population characteristics. The main problem employing HPV testing based strategies in cervical cancer screening is the fact that both positive and negative HPV results are often misinterpreted or overestimated. An HPV positive, cytology negative woman, should repeat both tests after one year interval. Actually, patients too often tend to undergo immediate colposcopic examination, increasing health care costs and patients' anxiety, without benefit and potentially resulting in overtreatments. Not rarely

clinicians start treating HPV infections detected with molecular tests with surgery, laser, cryotherapy, interferon, 5-fluorouracil. Then multiple preventive, diagnostic, and therapeutic activities are initiated, both in women and their partners, with strict follow up programs, more tests and more interventions. What many health professionals actually do is test women under 30 years of age; re-screen every 1-2 years; test for low risk HPV types; test anal, vulvar, penile, oral sites; test male partners; test to screen for sexually transmitted infections [12]. All these indications are not recommended and may lead to wrong decisions, with well documented but poorly recognized ill effects. On the other side, a false negative HPV result can occur not infrequently, so that extending rescreening intervals should not be considered safe. In 2009 Kitchener and coll. found that co-testing with HPV test and Pap test was not able to detect a higher rate of high grade lesions than Pap test (ARTISTIC trial) [13].

Surprisingly 3 out of 12 cervical cancers diagnosed in the first two rounds of the trial were preceded by negative HPV results (25%). At the same conclusions arrived Cotton and coll. showing a false negative rate of 22% in women with a high grade lesions or worse who tested HPV negative at baseline (TOMBOLA trial) [14]. Nevertheless, a study designed to evaluate the efficacy of HPV-based strategies in four European randomised controlled trials showed that HPV testing was supposed to provide 60-70% greater protection against cervical cancer compared with cytology [15]. This study has been criticized, because only 11 of 19 cervical cancers detected after enrolment were HPV-positive at baseline; and even among the presumed "prevalent" cases, 16% were HPV-negative at baseline [16], similarly to what we observed in our study showing a 14% false negative HPV testing rate in women treated for histologically confirmed high grade cervical lesions [17]. Another study evaluating the effectiveness of the cobas HPV test found that a total of 59.7% of women who had biopsies that showed abnormal cytology returned a negative result on the cobas HPV test: the authors concluded that the rates of false-negatives in patients with high-grade cervical lesions screened with the cobas HPV test were "unacceptably high" [18]. Eventually, in one study evaluating the concordance among four validated HPV assays, the disagreement was considerable. Among more than five thousand samples, only 29% of them tested positive on all four

tests in primary screening samples. In women with abnormal cytology the agreement was 68%, thus implying that referral to colposcopy would depend on which of the four assays has been used in 32% of the cases. In HPV positive, cytology negative women, who represent the vast majority of HPV positive cases, the disagreement was even larger [19].

An underestimated aspect is represented by the simplicity of the new algorithms introduced. Since they should be addressed to all health care providers, they need to be easily remembered and put into practice, in order to reduce waste in the health care system and avoid overtreatments and the downstream consequences they may produce in terms of anxiety, fertility outcomes, recurrence/persistence of the disease, overload of health care services. The sensitivity of cervical cytology - often reported as a little more than 50% - in well established settings is over 80% [20-22]. Both specificity and positive predictive value are higher for cytology than for HPV testing. One study claiming that over long term follow-up the cumulative incidence of high grade lesions was the same for HPV screening and for cytology, led the authors to conclude that the increased sensitivity of HPV test for high grade lesions reflects earlier detection rather than overdiagnosis [23]. Nevertheless they do not discuss the risks of overtreatment this strategy implies, and especially the ethics of communicating an information of a sexually transmitted infection which patients can't cope with. Concerns on sexual relationships are frequently reported, even after having provided detailed explanations. Besides, there is no urge to detect too early lesions that have a very slow progression rate, and might have been detected with repeat cytology a couple of years later.

Intricate algorithms are not easy to follow and poor adherence to guidelines recommendations affect the prerequisite upon which these new strategies are based. The decision making process can be unintentionally influenced by the test/tests taken, as well as by the patient's expectations. Both doctors' attitudes and women's expectations are difficult to meet with the widespread utilization of different molecular tests not applied consistently according to shared recommendations. The economic, social, and psychological impact of HPV screening seems to have outweighed presumed benefits: the risks are a waste of resources, raise in costs and anxiety, and under-

recognition of true disease. If we aim to furtherly reduce cervical cancer mortality, we need to: a) implement HPV vaccination programs (extending the target ages and including males as well as women); b) increase adhesion to screening programs (avoiding overtesting and

undertesting); c) implement cytology performance (for example, employing immunocytochemistry techniques); d) guarantee an adequate treatment and follow up to all women diagnosed with a high grade cervical lesion.