QUEST DIAGNOSTICS STUDY 2020

Référence : Harvey W Kaufman, MD, Damian P Alagia, MD, Zhen Chen, MS, Agnieszka Onisko, PhD, R Marshall Austin, MD, PhD, Contributions of Liquid-Based (Papanicolaou) Cytology and Human Papillomavirus Testing in Cotesting for Detection of Cervical Cancer and Precancer in the United States, *American Journal of Clinical Pathology*, Volume 154, Issue 4, 1 October 2020, Pages 510–516, https://doi.org/10.1093/ajcp/aqaa074

Among women subsequently diagnosed with cervical cancer within 1 year (including all types of cervical cancer – classified as SCC, ADC and others), 85,1% were identified by LBC whereas 77,5% were HPV positive. Hence, if we use a screening strategy based on a primary HPV test, 22,5% of these cases would be missed. Thanks to co-testing, 13,1% were actually missed (when co-testing result is negative for both HPV test and LBC). These results confirm another very large Quest Diagnostics study published in 2015[1] where 87,8% of the detected cancers (within 1 year of the screening test) were LBC positive whereas 81,4% were HPV positive.

Study Presentation

Between 2010 and 2018, Quest Diagnostics database includes nearly 19 millions of co-testing results realized on 13.5 millions of women over 30 years old. So, this study and its conclusions are based on the biggest and most diversified US population sample regarding cervical cancer screening.

This study analyzes the link between co-testing results (liquid based cytology and HPV testing) realized to screen the population and the following diagnoses obtained through histology. The diagnosed cancer and precancers cases are included in this study and distributed regarding their histology grade:

- Regarding cancers (SCC, ADC and others), 1,259 cancer cases were preceded by 1,615 co-testing results.
- Regarding precancers (CIN3 or high-grade squamous intraepithelial and AIS), 8,048 precancers cases were preceded by 11,164 co-testing results.

In the study, the authors recall that the goal of screening program is to minimize the cervical cancer incidence rate and the mortality associated to it. Hence the screening tests results have to be analyzed from a cancer diagnosis standpoint instead of precancer (CIN3 and AIS). These analyses are too often biased by the importance given to precancers leading to advantages for HPV tests. It is probably a mistake because regarding CIN3 cases, long-term studies[2] (realized over 30 years) reveal that only 30% of these CIN3 lesions will become invasive cancer. In other words, comparative studies on cytology and HPV testing draw conclusions on the detection of non-cancerous lesions and, for the 2/3, they will never become a cancer. Detection of these nonprogressive lesions has been even termed by some

[1] Blatt AJ, Kennedy R, Luff RD, et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015;123:282-288

[2] McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9:425-434.

epidemiologists as "over-diagnosis."[3]. By the way, overdiagnosis is associated with additional procedures but does not lower cancer risks (and these procedures are costly… I add here this personal comment because in France it is a purely economic vision that was prevailed when the policy using primary HPV testing was chosen).

As a summary, HPV testing is more sensitive for the detection of precancerous lesions detection but only 30% of these lesions are progressive (evolve in an invasive cancer) whereas liquid based cytology (LBC) using nowadays technology is more sensitive for the cancer detection.

Focus on cancer detection results

We are focusing here on the 1,615 co-testing results preceding the 1,259 cancer cases included in the study. Those are divided in two groups: cases diagnosed with cervical cancer within 1 year after the co-test and more than 1 year after.

Co-tests prior to a cancer diagnosis within 1 year (74% of the co-testing results included in this study)

We can see here that LBC is more sensitive than the HPV test in a statistically significant way (Table 3 – P-value < 0.0001). On these co-tests only 5.9% missed a cancer case that will be diagnosed within 1 year.

Co-tests in a period of time over 12 months of the diagnosis (26% of the co-testing results included in this study)

The missed cases rate strongly increases on this part and reach 33.6%. This time the HPV test is more sensitive when compared to LBC. Here the study conclusions emphasize that the performance drop-off of HPV test and cytology should be the focus of research and not this drop-off on the CIN3 detection. One of the reasons is the reduction of the lesions size and the difficulty to get a sample containing infected cells.

Cytology improvement using AI-assisted slides reading

Co-testing is surely the best strategy when you look for a high-quality screening tool where the unique goal is to maximize the chances to be diagnosed and cured. We know that cytology performance can be improved in order to increase the co-testing sensitivity rate. In our study we compared our AI solution to read slides to the market leader system using 1,352 cases[4] (see https://datexim.ai/fr/library_document/cytoprocessortm-un-nouveau-systeme-de-depistage-du-cancer-du-col-uterin-pour-le-diagnostic-a-distance-2/). We demonstrated a 10% increase in sensitivity and the number of false negative cases was divided by 2.6. We can easily imagine the improvement our technology can bring to the screening even with co-testing (the target would be here the 13% false negatives before cancer cases). Moreover, this assisted reading solution is comfortable and ensures a reliable and reproducible diagnosis even when screeners read pap smears all day at a high speed.

In the studies, liquid based cytology is compared to HPV testing but there is no study yet where it is compared to an « augmented LBC » based on slides reading using our AI solution

[3] Hakama M, Pokhrel A, Malila N, et al. Sensitivity, effect and overdiagnosis in screening for cancers with detectable pre- invasive phase. Int J Cancer. 2015;136:928-935.

[4] Crowell E, F, Bazin C, Saunier F, Brixtel R, Caillot Y, Lesner B, Toutain M, Ferreri C, Garcia I, Mathieu M, -C, Vaussanvin J, Depardon J, Renouf A: CytoProcessor^{TM}: A New Cervical Cancer Screening System for Remote Diagnosis. Acta Cytologica 2019;63:215-223. doi: 10.1159/000497111

CytoProcessor. It would be really interesting to look at its impact on co-testing that is, once again, the best strategy for women healthcare.

Quick reminder on cervical cancer data in France

In France, each year 3,000 new invasive cervical cancers are diagnosed leading to more than 1,000 deaths. 75% of these diagnoses are related to women between 25 and 64 years old[5]. One of the main problems to be tackled is the population coverage that is only 60% at the moment in our screening programs.

[5] www.has-sante.fr