Cervical cancer - vaccination, modern diagnostic technology, and HPV self-sampling reduces incidence and mortality

Replacement of the traditional Pap smear for cervical cancer screening by newly advanced technologies might work well in Thailand.

An initial entry to this blog questioned the dichotomy of infectious diseases versus non-communicable diseases (NCDs). The prevailing example of the role infectious agents may play in the development of NCDs is the human papillomavirus (HPV) and its part in cervical cancer occurrence. Against long-time skepticism, it could be proved that HPV 16 and HPV 18 are cofactors for cervical cancer development (1). October 2008, Harald zur Hausen, former Chairman and Scientific Director of the German Research Centre, Heidelberg, received the Nobel Prize for Physiology and Medicine for this discovery*.

HPV and risks

Actually, besides HPV 16 and 18, there are more than 170 types of the HPV virus (2). Not all of them are at high risk of causing disease. The virus is widespread worldwide and the most common viral infection of the reproductive tract. Contamination is highest among adolescents while starting sexual activities. Coition, but even only skin-to-skin contact, transmit the virus. Most infections are more or less asymptomatic, and the immune system overcomes about 90%. But sometimes, infection resists and causes several severe diseases at various locations, particularly in the anogenital region. Conventionally one distinguishes between low- and on the other hand, high-risk HPV (hrHPV) types. The high-risk types HPV 16 and 18 cause approximately 70% of cervical cancer worldwide (3, 4). Other high-risk types such as 31, 33 are also linked to cancers of the anus, vulva, vagina, penis, and oropharynx. The low-risk types HPV 6 and 11 cause 90% of anogenital warts (5).

Among the cancers for females, cervical cancer is the second most common one with an estimated age-adjusted incidence rate of 13.3 per 100.000 (IARC). Breast cancer is the most common one woman is suffering from, with an incidence rate of 47.8 per 100.000. However, for cervical cancer, not only screening but also vaccination is available to reduce the mortality of the malignancy.

HPV vaccination

There are three vaccines against various types of the HPV virus available. The HPV is a non-enveloped DNA virus. The bivalent vaccine Cervarix® (GlaxoSmith Kline) works against the types 16 and 18, while the quadrivalent vaccine Gardasil® (Merck) protects against HPV 6, 11, 16, and 18. (6). The immune response for both types of vaccines is induced by L1 virus-like particles (VLPs) based on the L1 capsid protein of the HPV virus (7). For the production of Cervarix, the Baculovirus infecting Trichoplusia ni cell lines are functional. Baculoviruses are DNA viruses infecting insects, in this case, a medium-sized moth called Cabbage looper. To increase immune response, an adjuvant, ASo4, is added to the vaccine. To produce Gardasil, the quadrivalent vaccine, the yeast Saccharomyces cerevisiae is used. This is true for Gardasil 9®, made available by Merck against the HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The immune response for both Gardasil vaccines is enhanced by the adjuvant AAHS (6).

Children of both sexes could be vaccinated from the age of nine years onwards. For girls within the age range of 9 to 14 years, two shots are recommended (6). Adolescents should be protected before exposed to the virus and therefore be vaccinated at 11 to 12 years of age (Centre for Disease Control and Prevention (CDC)). Children being vaccinated before the age of 15 should receive two doses of the vaccine. Those 15 years and older 'with certain immunocompromising conditions' (probably means infected with HIV) need three doses. Those above the age of 26 won't benefit from the vaccines.

The majority of women benefiting from vaccination live in high-income countries. Around the year 2006, many countries introduced HPV vaccination, paid for by public funds. Up to 2014, 118 million women were 'targeted' from all the vaccination programs, but only 1% were from low-and middle-income countries (8). The total population coverage with a full course of vaccine shots amounted to 1.4%, while 1.7% got at least one dose. It seems that those with the highest incidence and mortality are grossly disadvantaged.

HPV vaccination in Thailand

Thailand doesn't follow the general trend of low- and middle-income countries. Here, the burden for cervical cancer seems to decline. Based on cancer registry data, breast and colon cancer increased while cervical cancer decreased from 2000 to 2012 (9, 10). The decrease of cervical cancer in Thailand probably is not due to HPV vaccination, although Cervarix and Gardasil are available. Recommendations for vaccination are similar as described above for the USA. In Thailand, girls should be vaccinated within the age of 9 to 26 and males from 13 to 21. Men aged up to 26 could be vaccinated in having sex with men, transgender individuals, and those infected with HIV. A recent investigation in the vaccine status and knowledge of students in the South of Thailand concluded that both being immunized and knowing about the opportunity to participate was relatively low. Barriers were high cost and the opinion that there was no need for injection because of low-risk behavior (11).

Cervical cancer screening and a little bit of history

Despite the declining incidence and mortality rate of cervical cancer over the years, the malignancy remains a public health problem. Almost 30 Million women 15 years and older are at risk. Over 8.600 cases occur annually, and 5000 women die suffering from this cancer. The crude incidence rate amounts to 24.3 per 100.000 and year (HPV and Related Diseases, Thailand). Thailand concentrated on secondary prevention of cervical cancer. From 2005 until 2019, almost 16 Million females were screened.

For screening, similar to other countries, Thailand used the conventual Pap smear method. The method was published in 1928 by George Papanicolaou (1883-1962). With the Pap smear, it was possible, by viewing swaps smeared on microscopic slides, to differentiate normal from malignant cervical cells (12).

The Greek medical doctor found his way into the USA in 1939 and became a pioneer in concentrating on the female reproductive system's physiology and cytology. His first publication had no real impact. Only after the book 'Diagnosis of uterine cancer by the vaginal smear', published in collaboration with the gynecological pathologist Herbert Traut in 1943, the method became widely known. In Romania**, the technique is called the Babes-Papanicolaou method, since Aurel Babes used platinum loops to collect cells from the cervix in 1927.

Lead-time bias

Screening will detect the malignancy in its early stage. Surgical intervention at this stage is supposed to prevent the further development of the disease. The patient might have a longer survival time than a similar case, who turns up at the hospital with an advantaged cancer stage. The longer survival time is thought to indicate that screening is useful. But this view is challenged. Malignant cells might have occurred for both cases at the same time. Screening might detect tumorous cells early, but the women might die from cervical cancer around the same time as the one coming into the hospital with the advanced tumor. So, the advantage of screening is hampered by the 'lead time bias'. Verification of the usefulness of screening would be a reduction in the overall mortality of cervical cancer. There are indications that this actually might happen. For instance, in England and Wales, cervical cancer mortality rose three-fold from 1967 to 1987' in women younger than 35 years. It was the highest cervical cancer mortality in the world even though screening was offered voluntarily. In 1988 a national screening program got underway and intensified, and the rising trend was reversed (13).

Cervical cancer screening now and in future

Besides using the Pap smear technique, Thailand occasionally also applied visual inspection with acetic acid (VIA) and the self-sampling cytology/HPV test (9). (The latter is explained below). Females should be screened every five years (National Cancer Institute (NCIT)). In case of an abnormal screening test result, a colposcopy is done. To continue the Pap smear screening programs seems not to be suitable. Especially in low- and middle-income countries, cytology screening was not as successful as one would have wished. Lack of coverage, low sensitivity, and insufficient quality assurance slowed down the reduction of cervical cancer occurrence (14). According to the guidelines to further enhance cervical cancer prevention as given for Asia and Oceania (15), an HPV/DNA test as an advanced primary screening technique is now available (16) and could be used. For instance, the method was tested in Sri Lanka (17) and the guidelines also will be followed in the future in Thailand*** (NCIT). Here the accuracy of the HPV screening had been tested against the Pap smear method at the Ubon Ratchatani province. Especially the hrHPV testing (HPV 16 and HPV 18) was much more sensitive than the Pap smear screening (18).

An endocervical brush (such as THINPREP® or Cytobrush®) collects the cells. The brush is then rinsed and placed in a vial containing PreservCyt solution. The vial can be stored and transported at room temperature. The cervical specimen is automatically tested by a PCR (Polymerase chain reaction) machine (Cobas 4800x® instrument and analyzer). The analyzer simultaneously detects the hrHPV 16 and 18. Colposcopy will be applied in these cases to rule out or confirm a pathological status. The detection of one or more other hrHPV types (i.e. 31,33,35,39,45,51,52,56,58,59,66,68) will be indicated by the machine results. To detect a pathological alteration of cells due to one or the other of those hrHPV types listed above, a liquid-based cytology (LBC) check will be done.

The LBC technique

The LBC technique is an improvement of the conventional Pap smear. Cells collected by an endocervical brush, rinsed, and placed into a vial with PreservCyt solution are further processed for cytological evaluation. In the laboratory, the PreservCyt sample is inserted into

a ThinPrep processor. Within the processor, blood, mucus, and non-diagnostic debris are removed, and the cells are collected on a ThinPrep Pap test filter, designed to collect cells for the diagnosis (Hologic Inc.®). The risk for malignancy is given following the Bethesda system, differentiating between CIN 1 up to CIN 3 and invasive cancer. CIN 1 means that a mild dysplasia of the cells had been detected, whereas CIN 2 and 3 indicates 'higher grades of squamous intraepithelial lesions'. The detection of CIN 2 and CIN 3 is followed by colposcopy and a biopsy 'to sample or remove the dysplastic tissue. Also, 'atypical squamous cells of uncertain significance (ASCUS) are found. In this case, a colposcopy is done to exclude that a malignancy had been missed. Normal LBC findings should be followed up in 12 months. In case HPV testing was negative, screening should be done again in 5 years.

The self-sampling method

The best set-up for cervical cancer screening is useless if women don't turn up for the examination. Campaigns to motivate females to participate might work reasonably well in the rural area of low- and middle-income countries through Primary Health Care initiatives. In urban and semi-urban areas, motivation to be tested in the intimate area without actually having any reason to see a medical doctor is much more difficult. Common reasons not to participate are lack of control, fear of pain, embarrassment, no time, and the belief that testing is 'not relevant for me' (19). Additionally, women of specific subgroups are 'hard-to-reach'. This includes lesbians, very young and older females, aboriginals, those within the low socio-economic fraction of the population, and migrants. Self-sampling methods for collecting cells from the cervix were developed and introduced to motivate women to participate in screening programs.

Even at times of Pap smear screening, several projects tried to initiate self-sampling for cervical cancer. Most of the studies were conducted in Europe and North America (20), but some also in low- and middle-income countries such as Cameroon (21) and Thailand (22). Generally, there seems to be a high perception and positive attitude towards self-sampling. This also applies to HPV self-sampling, as a recent report from Hong Kong indicates (19). The study used an HPV self-sampling kit (the Evalyn® Brush) produced by a Netherlands company. Detailed instructions on using the device were provided, and the sample was mailed back or given in person to the study group. For HPV Detection and genotyping, modern equipment is used as described above. It was concluded from the Hong Kong trial that participating in the study improved health awareness on top of 'promoting cervical cancer screening uptake'. Self-sampling could not only reach the under-screened population but also 'overcome the perceived barriers in clinicians-based screening.

Outlook

The hrHPV types 16 and 18 are the striking example that infection can trigger the occurrence of cancer. In this case, a virus causes the second most frequent cancer affecting women. A sizeable fraction of women dying from this cancer are young- or middle-aged females. Their loss causes great sadness to the families and has a significant social impact on society because they lose the mothers' and wives' vital support (23). A remarkable decline in the incidence of cervical cancer for Thailand from 23.4 to 11.7 per 100.000 is reported from the National Cancer Institute and elsewhere (9, 10). That seems, at least partly, accountable for as a remarkable achievement of Thailand's health delivery system. The notion, however, that 'the eradication of cervical cancer from Thailand is within the near future an achievable goal' might be an over-optimistic view (9). As long as hrHPV types circulate within the population,

it is hard to believe that cervical cancer will disappear. However, the current development will be an encouragement to further strengthen the efforts for prevention using available means. Besides concentrating on screening, including self-sampling, investigation on risk factors might be very useful. It means to detect how the infection with hrHPV is acquired. To assess risk factors for cervical cancer and concentrate predominantly on woman's behavior might be short-sided. The action of men is of importance as well. Males having unprotected intercourse with commercial sex workers can transmit the papillomavirus to their wives (24, 25). Bisexual behavior, by 'men having sex with men' and having sexual contact with females, might contribute to an unfavorable epidemiological situation as far as HPV distribution is concerned. A spillover of the West's attitude, in that sexual orientation, is a 'social construct', and the LGBTQ**** movement might cause unforeseen risk patterns for Thai women in the future.

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*Additional Nobel Prize laureates were Françoise Barré-Sinoussi and Luc Montagnier for the discovery of the human immunodeficiency virus (HIV).
**Romania, a southeastern European country, is known to those interested in the origin of the Dracula stories.
*** For Thai readers, the issue of HPV vaccination and HPV testing is nicely summarized on the website of the NCIT. Because of frequent inclusions of technical terms in English, the website is also useful for those who cannot read Thai.
****LGBTQ – Lesbian, Gay, Bisexual, Transgender, Queer.

The manuscript was written by Frank P. Schelp. Points of view expressed are those from the author and might not reflect the stance and policy of the Faculty of Public Health, Khon Kaen University, Thailand.