Time to strengthen the struggle against cervical cancer with primary and secondary prevention

The follow-up of a previous entry into this blog intends to enhance interest in cervical cancer by reporting about a new WHO initiative and proof that vaccination against the tumor works.

Particularly tragic is the death of young females and women in the prime of their life. The females are the core of the family and often with children in need of their mother (1). The tremendous loss of life of young- and middle-aged women happened for hundreds and hundreds of years, related to pregnancy and birth. Within the Age of Enlightenment, in the middle of the 18th century, attempts to reduce maternal and child mortality in Europe slowly started to be addressed (2). Finally, an overall improvement in mother and child health (MCH), also in low and middle-income countries (LMICs), was achieved during the decades of Primary Health Care (PCH) (3). In this context, Thailand was recognized to be at the forefront of developments (4).

Females are a vulnerable group in times of NCDs

The epidemiological transition followed PCH. Non-communicable diseases (NCDs) extended the burden of low- and middle-income countries (LMICs). Again, young and middle-aged women must be recognized as a particularly vulnerable group, suffering and dying from cancer attacking females. Death of females, because of breast and cervical cancer, by no means is of the same magnitude as death formerly linked to the role of females in reproduction. But still, cervical cancer is one of the primary malignancies for women below 45 years of age (5).

Thailand again cares and aims to reduce the incidence of cervical cancer. In 2005 the country launched a National Cervical Cancer Screening Program in most provinces, using Pap smear and the Visual Inspection with Acetic acid (VIA) (6). On trial phasis, the new technology of a high-risk herpes virus assay (hrHPV assay) was tested (7) and waits to be implemented after the Covid-19 calamity is over (personnel communication). Activities are within the global strategy to reduce cervical cancer as a public health problem, initiated recently by the World Health Organization.

Targets set by WHO to fight cervical cancer

The WHO initiative concentrates on the fight against cervical cancer in LMICs. In need of action against cervical cancer are not only countries in Eastern- and Southern Africa, but the situation there is especially difficult. The mortality rate accounts for over 40 cases of cervical cancer per 100.000 women (ASMR - world age-standardized mortality rate), and cervical cancer occupies the first rank of all types of cancer for women and those within the age range 15 to 44 years (5). Southeastern Asia is faring better with an ASMR of 10. However, cancer still is a significant risk to die for women, being of the second rank of all cancers and accounting for 12.6% of the total cancer mortality. Thailand is probably in a better position than several neighboring countries, but annual cervical cancer cases still include 9.158 unfortunate women as estimated for the year 2020, and 4.705 died. The situation justifies all efforts to reduce this female cancer incidence further. In Latin America and the Caribbean, the problem of cervical cancer is comparable to Thailand and Southeast Asia (8).

Targets set by WHO

The prospects for Latin America and Southeast Asia might be better than Africa to curb the number of cases to reach the 90-70-90 target set by WHO. The targets refer to 90% of girls being vaccinated by the age of 15, 70% should be screened by the age of 35 and again at 45 years of age, and 90% of women with precancer should be treated, and 90% with invasive cancer cared for within the medical sector. The dateline is set for 2030, and cervical cancer then should more or less vanish during the next decade.

Vaccination needs more promotion

Even given the steady falling incidence rates for cervical cancer, such as in Thailand and Latin America (6, 8), there are still issues waiting to be addressed. In a preceding entry to this blog, various aspects of cervical cancer, from the history of the Pap smear up to the opportunity for vaccination, were discussed. On the HPV Information Centre website, Thailand, the HPV vaccination is mentioned to have reached 76% of women being targeted in receiving a first dose and 66% a second dose in 2019. The IOC/IARC data given by the HPV center are contradicted from the result of a self-administered questionnaire obtained from 520 undergraduate students (77% females) from the South of Thailand. It seems that the chance of immunization is not to be used as it should be (9).

Only 1.9% of the female students admitted to being vaccinated, and only 30.3% intended to be vaccinated later (9). Knowledge about the vaccination was "low-to-moderate", and the main reasons for not being vaccinated were high costs and the "perception of no need due to low-risk behavior."

No need for vaccination because of "low-risk behavior"!?

The perception probably should be questioned, at least for other parts of Thailand. The study was conducted among university students at a university in the South of Thailand. Female university students are supposed to belong to a more privileged and guarded group of young people. A high proportion of the population in the south of the country are Muslims, which might explain the somehow naïve perception of not needing prevention from HPV infection because of no sexual intercourse by the study participants.

In reality, when it comes to the Bangkok slums, female adolescents to 55.8% admitted to being sexually active, with 41.8% having vaginal sex without condoms (10). Similarly, 40.6% of 106 female teenagers from the Ubon Ratchathani Province had sexual intercourse, with the first experience at the mean age of 17 years (11). Regardless of the validity of the data, it is safe to conclude that a substantial proportion of teenagers are at risk of being infected with hrHPV presently and in the future. That justifies intensifying primary prevention against cervical cancer. For those skeptical about the benefit of vaccination, new evidence emerged that vaccination reduces the risk of suffering from cervical cancer.

Vaccination works

A short notice on the 12th November 2021 in Science, announcing "HPV jabs ward off cervical cancer", alerted various media spreading the news further on. Unfortunately, the original publication in Lancet is hidden behind a rather expensive fee barrier (12). However, the essentials of the findings are disclosed in an editorial with comments and are freely accessible (13). Before going through the study results published in the Lancet, the editorial mentions that a Cochrane review in 2018 concluded that the bivalent vaccine prevents cervical cancer precursors (14). The bivalent vaccine Cervarix® protects from the two most dangerous HPV types 16 and 18. The vaccine's effectiveness in the studies reviewed was usually assessed through "cervical cancer precursors" and "surrogate markers" such as infection with the virus and cervical cytology results. The selection of outcome variables was justified because it takes long before cancer develops. But then, the use of proxy indicators was taken as an argument from vaccination opponents, saying that cervical cancer in the populations was not prevented.

The more recently published study in Lancet used the availability of HPV immunization in the UK since 2008 and data of the English cancer registry to estimate the "relative reduction" of cervical cancer based on CIN3 and the actual detection of the malignancy (12). The vaccination program available from 2008 was meant for girls aged 12 to 13 years. From 2008 to 2010, a "catch-up program" for those 18 years old was offered.

For three HPV-vaccinated cohorts, the relative risk was assessed in comparing the vaccinated with earlier cohorts of females not having the opportunity to be vaccinated. For the assessment, 13.7 million years of follow-up from women aged 20 and those younger than 30 years were evaluated. For the group vaccinated at the age of 16 to 18 years, the relative reduction in cervical cancer manifestation was 34% (95% CI 25-41), for the age group 14 to 16 years, the reduction was 62% (95% CI 52-71), and for the 12 to 13 years old girls at vaccination the reduction was 87% (95% CI 72-94). CIN3 cytological findings reduced to 39% (95% CI 36-41) for the age group at vaccination 16 to 17 years, and CIN3 findings in the younger age group of 12 to 13 years dropped by 97% (95% CI 96-98). The results indicate an increase in vaccination from the older to the younger cohorts from approximately 45% to 85% for the younger cohort. It also reflects the increase of relative risk of HPV exposure with age. The findings also justify a vaccination twice instead of three times, given that the first vaccination was provided to girls younger than 15 years.

Study bias and outlook

There is no epidemiological study without bias. The detection of cancer precursors and cancer depends on the female population taking part in screening. Unfortunately, in England, screening has lowered, and young women were especially reluctant to participate. Due to Covid-19, screening and colposcopy weren't done at the beginning of the spread of the infection, and vaccination was discontinued as well.

The accuracy of the extent of reduction to develop cervical cancer gained by vaccination might be questioned; however, the overall impression is that vaccination helps prevent getting the tumor. In further promoting screening, additional efforts should be given to vaccinating the young girls and probably the males. Although the cervix is the preferred site for HPV-caused

cancer, it is not the only location for the manifestation of the tumor. For women, the vulva and vagina, and the penis can be affected for males. At the same time, oropharyngeal cancer and cancer of the oral cavity due to HPV infection might attack both sexes.

As mentioned in the preceding entry about cervical cancer to this blog, to promote preventive measures against cervical cancer by concentrating predominantly on women might be shortsighted. Not only that hrHPV also attack males, but males transmit the virus to their wives or regular female partners by having unprotected sex. Still, advanced methods to enhance prevention, such as vaccination and screening, must be offered to women. Maybe there will be time to promote self-sampling practices to supplement screening. Once Covid-19 is gone, aspects of caring for the wellbeing of vulnerable groups of women within the health delivery system in Thailand are very promising.

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