Cervical cancer & older women
- why is the incidence so high when HPV prevalence is low?

Anne Hammer Lauridsen, PhD dissertation defended 12 February 2016

Abstract

Cervical cancer ranks as the fourth most common cancer among women in the world, accounting for > 500,000 cases every year. Cervical cancer is caused by an infection with human papillomavirus (HPV), which is one of the most common sexually transmitted diseases. The prevalence of HPV is highest in women aged 20 years (50%) and lowest in women > 60 years (5–10%). An HPV infection is usually cleared within a year or two; however, in 10–20% of women a persistent infection is established. A persistent high risk HPV infection might cause development of dyskariotic cells and eventually progression to cervical cancer. In Denmark, approximately 370 women are diagnosed with cervical cancer annually. The age-specific cervical cancer incidence is bimodal, with peaks at ages 35 and 75 years. While women aged 30–40 years are more likely to be diagnosed with early stage disease, women > 60 years are more commonly diagnosed with advanced stage disease and their mortality is therefore high. Since the introduction of cervical cancer screening in Denmark in the 1960s, the incidence of cervical cancer has decreased markedly. Today, Danish women aged 23–64 years are invited to cervical cancer screening.

The main objective of this thesis was to explore why the cervical cancer incidence is so high in Danish older women even though the prevalence of HPV, the causal factor, is low in this age group. This thesis is based on two published papers, two submitted papers, and a manuscript in preparation.

Papers 1 and 2: In a systematic review and meta-analysis we found that the prevalence of HPV 16/18 in cervical cancer declined significantly with age from 74.8% in women aged 30–39 years to 56.8% in women ≥ 70 years. These results might indicate that the burden of cervical cancer may shift to older ages in fully vaccinated cohorts. In paper 2 we found that HPV16/18 prevalence decreased with age in Danish women with cervical cancer, whereas the prevalence of HPV genotypes included in the nonavalent HPV vaccine (i.e. HPV16/18/31/33/45/52/58)

remained stable around 85% until age 75 years, after which the prevalence dropped to 65%. This was merely because women ≥ 75 years were more likely infected with genotypes not included in the nonavalent vaccine and were more commonly HPV negative.

Paper 3

Paper 3 was based on a population-based cohort study in which we described the cervical cancer incidence over time and by age in Denmark before and after correction for hysterectomy. We found that correction for hysterectomy resulted in an 8.4% increased overall cervical cancer incidence, a shift in the peak incidence from 35 years to 75 years, and that women ≥ 60 years were, in general, at highest risk over time.

Paper 4

This paper was a retrospective cohort study in which we investigated whether the high burden of cervical cancers in women over the age of 64 years could be attributed to a lack of screening. We found that ~50% of women diagnosed with cervical cancer during 1990-2013 had never been screened; however, the vast majority (> 90%) of unscreened women had presumably never had the opportunity to be screened, as they were too old when screening was implemented nationally. The proportion of never-screened women declined over calendar time. Of the women who had been screened within 5 years of cervical cancer diagnosis, > 80% had a normal cytology result, which indicates that screening by cytology may not be suitable in older women.

Paper 5

This paper was a methodological study that aimed to explore the ability of commercial HPV assays to detect a low copy number HPV infection in formalin-fixated and paraffin-embedded specimens. Using a commercial HPV assay, such as the HPV Sign Genotyping test, we found that it is possible to detect 50 HPV18 copies among 1,000,000 non-infected cells and 1-5 HPV16 copies among 100,000 non-infected cells. Thus, using a PCR-based HPV assay it may be possible to detect a latent HPV infection in future studies on HPV latency in the human uterine cervix.

In conclusion, the results reported in this thesis indicate that older women are at highest risk of cervical cancer. The high incidence is likely due to several factors such as a lack of screening, low sensitivity of the screening method applied, or perhaps because cervical cancer in older women, in part, may arise as a result of somatic mutations. However, cervical cancer in older women could also arise following a viral reactivation of a latent HPV infection or possibly due to a viral re-infection.