**Increase In Cervical Cancer Incidence Among Swedish Women Below Age 50: The Role of Human Papillomavirus (HPV) Vaccination**

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***Abstract***   
The Centre for Cervix Cancer Prevention in Sweden has in a year-report (1) noted a large increased incidence of invasive cervical cancer, especially during the two last recorded years, 2014 and 2015. I have subgrouped the data according to age, using the same statistical database of the National Board of Health and Welfare as the authors of the above-mentioned report. The increase in cervical cancer incidence was shown to be most prominent in women 20-49 years-of-age while no apparent increase was observed in women above 50 years-of-age. It has earlier been noted by the FDA that women exposed to the human papilloma virus (HPV) prior to vaccination had an increase in premalignant cell changes compared with placebo controls. The possibility that HPV vaccination could play a role for the increase in cervical cancer incidence by causing instead of preventing cervical cancer disease in women previously exposed to HPV is discussed. There is a time relationship between start of vaccination and the increase in cervical cancer incidence. The HPV vaccines were approved in 2006 and 2007 respectively. In 2012-2013 most young girls were vaccinated.

***Introduction***  
The Centre for Cervix Cancer Prevention in Sweden has in a year-report (1) noted a large increased incidence of invasive cervical cancer, especially during the two last recorded years, 2014 and 2015. An English translation of the increase in cervical cancer incidence in this report (page 45) is presented in Table 1.

**Table 1. Age-standardised Incidence of Invasive Cervical Cancer (Per 100,000 Women)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **County** | **2006-2009** | **2010-2013** | **2014-2015** | **Average change 2005-2015 expressed as percentage** | **p-value for trend** |
| **Sweden, total** | **9,71** | **9,56** | **11,49** | **1,7** | **0,03** |
| Stockholm | 11,59 | 9,87 | 10,59 | -0,8 | 0,51 |
| Uppsala | 11,16 | 14,17 | 16,02 | 3,8 | 0,20 |
| Södermanland | 8,45 | 12,43 | 10,57 | 2,3 | 0,40 |
| Östergötland | 8,87 | 14,47 | 15,04 | 7,3 | <0,05 |
| Jönköping | 5,33 | 8,38 | 11,17 | 6,4 | 0,04 |
| Kronoberg | 8,99 | 6,14 | 13,15 | 1,1 | 0,78 |
| Kalmar | 12,78 | 7,39 | 11,83 | -2,4 | 0,50 |
| Gotland | 8,00 | 6,47 | 14,18 | 6,5 | 0,32 |
| Blekinge | 13,47 | 14,16 | 17,00 | 8,2 | <0,05 |
| Skåne | 9,50 | 9,21 | 9,48 | -1,6 | 0,22 |
| Halland | 8,84 | 10,78 | 11,47 | 7,4 | 0,04 |
| Västra Götaland | 8,96 | 7,98 | 11,04 | 1,4 | 0,55 |
| Värmland | 6,81 | 9,23 | 13,61 | 8,1 | <0,01 |
| Örebro | 8,22 | 9,51 | 12,29 | 8,3 | <0,05 |
| Västmanland | 9,19 | 10,60 | 11,31 | 4,1 | 0,07 |
| Dalarna | 8,08 | 8,70 | 13,93 | 7,8 | 0,01 |
| Gävleborg | 11,68 | 11,04 | 14,28 | 1,9 | 0,24 |
| Västernorrland | 7,61 | 5,57 | 11,59 | -1,9 | 0,66 |
| Jämtland | 9,74 | 9,80 | 9,85 | 0,0 | 0,99 |
| Västerbotten | 7,39 | 9,36 | 8,94 | 4,0 | 0,06 |
| Norrbotten | 13,60 | 8,34 | 14,24 | -0,6 | 0,86 |

From the report (translation): “The age-standardised incidence of invasive cervical cancer in Sweden has increased substantially the last two years (20 %) and for the whole period 2005-2015 there is a statistically significant increase. The incidence in Sweden for 2014-2015 is 11.5 per 100,000 women. The increase the last two years can be seen in all counties except Södermanland, Skåne, Jämtland and Västerbotten. Substantial and statistically significant increases are seen for Östergötland, Jönköping, Blekinge, Halland, Värmland, Örebro and Dalarna, with an average increase of 7 % - 8 %. Tendencies to substantial increases are also seen for Uppsala, Gotland, Västmanland and Västerbotten with yearly average increases of 4 % or more.”

The information above was based on data from the statistical database managed by the National Board of Health and Welfare in Sweden. The author of the report suggested that it is important to track the causes of the increase in cervical cancer incidence. However, at present no explanations were given for the increase in cervical cancer incidence by the Centre of Cervix Cancer in their year-report.

To better understand possible reasons for the increase in cervical cancer incidence, I have subgrouped the data according to age, using the statistical database of the National Board of Health and Welfare (by using the same database used by the authors in reference [1]). In addition, a relevant literature survey was made to put the current data into perspective.

***Results***

The increase in cervical cancer incidence was shown to be most prominent in women 20-49 years-of-age while no apparent increase was observed in women above 50 years-of-age (Figure 1). The number of cases in the 20-49-year-group increased from 202 cases in 2006 up to 317 cases in 2015. The absolute increase was 115 cases corresponding to an increase of 50 % in this younger age group. In Sweden, there are 1.9 million women between 20-49 years-of-age according to Statistics Sweden in 2015 (2). The incidence of cervical cancer is therefore 0.17 ‰ for women in the 20-49-year-group (317 cases per 1.9 million women). In Figure 2 the relative change between 2006 and 2015 is given for each 10-year-age-group cohort, further illustrating the more pronounced increased cancer incidence of the younger age groups.

*Figure 1. Increase in incidence of cervical cancer in younger women (<50 years-of-age) as compared with women ≥50 year-of-age. The number of cases/100 000 women from 2006 to 2015 is shown.*

*Figure 2. The relative change in percent of invasive cervical cancer incidence in Sweden between 2006 and 2015 in different age groups. The figure is based on data from the statistical database of the National Board of Health and Welfare in Sweden. The cancer incidence is age-adjusted according to the standard Swedish population in 2000.*

***Discussion***

Possible explanations for the increase in cervical cancer incidence among young women are discussed.

A change in routines or other technical or methodological changes during this period may affect the reported incidence of cervical cancer due to a change in the sensitivity of the diagnostic tools. The selective change in younger women and the fact that the increase was noted in most counties in Sweden argue against this explanation. Neither was such an explanation given by the Centre for Cervix Cancer Prevention in Sweden in their Year-report (1).

Another possibility is that HPV vaccination could play a role for the increase in cervical cancer incidence. The efficacy of HPV-vaccines has been evaluated by studying premalignant cell changes in the cervix called CIN 2/3 and cervical adenocarcinoma in situ or worse (3). The efficacy was calculated for individuals who have not been exposed to HPV 16 and 18. These individuals are called naïve. The vaccine is only efficacious in individuals not previously exposed to HPV 16 and 18 (naïve individuals). If an individual already has been exposed to HPV 16 and 18, no new antibodies are made. Therefore, the vaccine will not work for non-naïve individuals. HPV 16 and 18 are responsible for about 70 % of all cervical cancers (3). It is therefore crucial to give the vaccine to naïve individuals. During their review of Gardasil by the FDA the efficacy of the vaccine was also evaluated on individuals which were exposed to the oncogenic HPV strains before vaccination since individuals which are non-naïve will also receive the vaccination. A concern was raised for disease enhancement (increase in CIN 2/3, cervical adenocarcinoma in situ or worse) in this subgroup (3). In these individuals, the efficacy was -25.8 % (95 % CI: -76.4, 10.1 %) (3). Thus, vaccination with Gardasil of non-naïve individuals which had HPV 16/18 oncogenes before vaccination showed a higher level of in premalignant cell changes than did placebo. The FDA statisticians could not draw any firm conclusions. In their analysis, the FDA included only cases with HPV 16/18. If cases with other HPV oncogenes than HPV 16/18 had been included in the analysis, the efficacy data could have been even more unfavourable.

The increase in premalignant cell changes in non-naïve individuals as suggested by the FDA is consistent with the knowledge that vaccination can cause reactivation of both target and non-target viruses (4-10). For Gardasil the HPV types 16 and 18 are called target HPVs since the vaccine contains antigens for these two HPV types. Other HPV types for which the vaccine does not contain any antigens are called non-target HPVs. For individuals exposed to Gardasil, evidence of a selective and significant reactivation of the oncogenic non-target HPV types 52 and 56 was reported in the genital tract for all women (11). In this article, women 13-22 and 23-40 years-of-age from 2008 to 2013 were studied. The target HVPs 16 and 18 decreased only in the younger age group but oncogenic non-target HPVs increased in both groups, 20-40 % and 8-30 %, respectively. The increase in the total burden of non-target oncogenic HPVs for vaccinated individuals may be consistent with the findings in the FDA report where the efficacy of the HPV-vaccine was less favourable for non-naïve women compared with placebo. A possible mechanism to explain the increased incidence of cervical cancer may therefore be virus reactivation as described above.

In the evaluation of Gardasil by the FDA it was found that about 25% of all individuals were non-naïve in the pivotal trial (3). There are more than 200 types of HPVs, of which 12 are currently classified as high-risk cancer types (12). HPV may be found in non-sexually active girls (13). It may be transmitted through non-sexual means, either by way of mother to child, fomites, self-inoculation or nosocomial infection (13), or via blood (15-16). The virus can lie latent in any tissue and escape detection by standard techniques (17). It can also be redistributed systemically during the lytic cycle into previous virus-free tissues (auto-inoculation), for example infecting an earlier virus-free cervix. Recently, it was shown that previous HPV positive women with normal cytology remained at increased risk of preneoplasia (CIN3) despite two follow-up HPV-negative tests (18). “*Proving that HPV is absolutely gone is, of course, impossible*”, states Brown and Weaver in an Editorial from 2013 (19). Therefore, non-naïve-individuals can be seen among females at all ages. Sometimes these individuals have measurable HPV-virus and sometimes not. When taking these results into account, the proportion of non-naïve individuals may be underestimated in the studies.

Since the vaccine is recommended up to 45 years in the European Economic Area, it is possible that the vaccination has facilitated the development of new or existing cervical cancer among women who were non-naïve at the time of vaccination. Vaccination against HPV has started in Sweden during the study period. Gardasil, the vaccine mostly used in Sweden, was approved in September 2006. There are no statistics for the over-all use of Gardasil in Sweden. For young girls (12-13 years-of-age) there are special programmes for vaccination. About 75-80% of all girls are vaccinated in this age group (20). For older girls there are catch-up programmes. For older girls/women who will be vaccinated on-demand, data on vaccination frequency are missing. The increase in incidence of cervical cancer between 2006 and 2015 was 50 % (corresponding to 115 absolute cases). Therefore, the vaccination coverage of the Swedish population does not need to be very high to explain a role for the vaccine. The findings could be consistent with on-demand vaccination of women above 18. In Sweden there were 702,946 cervical cell screenings made on women aged 23-60 years-of-age in 2016 (1).

Could the HPV-vaccination cause an increase in invasive cervical cancer instead of preventing it among already infected females and thereby explain the increased cancer incidence reported by the Centre for Cervix Cancer Prevention in Sweden? The increased incidence in young females, the possibility of virus reactivation after vaccination, the increase in premalignant cell changes shown by the FDA for women who were already exposed to oncogenic HPV types and the time relationship between start of vaccination and the increase in cervical cancer in Sweden could support this view. The answer to this question is vital for correctly estimating the benefit-risk of this vaccine. More studies focused on already HPV-infected individuals are needed solve this question.

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