An overview of cervical cancer epidemiology and prevention in Scandinavia

Running headline: Cervical cancer in Scandinavia

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ABSTRACT

New technologies such as human papillomavirus (HPV) testing and vaccination necessitates comprehensive policy analyses to optimize cervical cancer prevention. To inform future Scandinavian-specific policy analyses, we aimed to provide an overview of cervical cancer epidemiology and existing prevention efforts in Denmark, Norway and Sweden. We compiled and summarized data on current prevention strategies, population demography, and epidemiology (e.g. age-specific HPV prevalence and cervical cancer incidence over time) for each Scandinavian country by reviewing published literature and official guidelines, performing registry-based analyses using primary data, and discussions with experts in each country. In Scandinavia, opportunistic screening occurred as early as the 1950s, and by 1996, all countries had implemented nationwide organized cytology-based screening. Prior to implementation of widespread screening and during years 1960-1966, cervical cancer incidence was considerably higher in Denmark than in Norway and Sweden. Decades of cytology-based screening later (i.e., years 2010-14), cervical cancer incidence has considerably been reduced and has converged across the countries since the 1960s, yet remains lowest in Sweden. Generally, Scandinavian countries face similar cervical cancer burden and utilize similar prevention approaches; however, important differences remain. Future policy analyses will need to evaluate whether these differences warrant differential prevention policies, or whether efforts can be streamlined across Scandinavia.

Key message: Cervical cancer prevention efforts and epidemiology in the Scandinavian countries are similar, yet the disease burden remains lowest in Sweden. Future policy analyses should evaluate whether these differences warrant differential prevention policies or whether efforts can be streamlined across Scandinavia.

Key words: cervical cancer, human papillomavirus, mass screening, prevention, Scandinavia

Abbreviations: ADC; adenocarcinoma, CIN3; cervical intraepithelial neoplasia grade 3, HPV; human papillomavirus, SCC; squamous cell carcinoma.

INTRODUCTION

Persistent infection with carcinogenic genotypes of human papillomavirus (HPV) is the cause of nearly all cervical cancers (1). Organized screening programs aiming to detect and treat cervical precancers before they progress to cancer have contributed to reducing the cervical cancer burden (2). For example, it has been estimated that in the Scandinavian countries of Denmark, Norway and Sweden, introduction of cytology-based screening has almost halved the number of cervical cancer cases over the period 1961 to 2010, and incidence rates would have been between three to five times higher than observed rates for the more recent period 2006 to 2010, compared to no screening (3). Similar audits of the Swedish screening program found that attending screening reduced the risk of developing cervical cancer (4) and improved prognosis (5). However, cervical cancer remains the third most common cancer among women aged 15-44 years (6-8). In addition, these programs require considerable monetary and non-monetary resources (9, 10), and in some cases, unnecessary screening procedures stemming from false positive screening results, motivating initiatives to improve cervical cancer prevention.

Application of novel technologies, such as the first- and second-generation prophylactic vaccines, may eliminate most carcinogenic HPV infections and prevent between 70% and 90% of all cervical cancers (11). In addition, new screening technologies such as home-based HPV testing and novel biomarkers may improve the effectiveness and efficiency of screening (12-14). Comprehensive policy analyses are needed to evaluate forthcoming prevention policies that utilize new technologies. While randomized trials are essential in informing decisions about whether and how to adopt emerging technologies in clinical practice, no single trial can capture all the short and long-term health and resource consequences of alternative prevention policies. Mathematical simulation modeling is an alternative approach for evidence acquisition, which involves synthesizing best available evidence from multiple sources of data and extrapolating consequences beyond the time horizon of the empirical data. These models have been broadly applied to inform decisions about cervical cancer prevention policies in Scandinavia (12, 13, 15-18) and elsewhere (19). Such analyses require comprehensive data of cervical cancer prevention and HPV epidemiology, including both long-term data on cervical cancer incidence available from databases such as cancer registries (e.g. NORDCAN) (20) and other epidemiologic outcomes (e.g. risk factor exposure) provided in empirical studies. To inform future policy analyses, our objective was to provide an overview of cervical cancer epidemiology and prevention approaches across the three Scandinavian countries.

MATERIAL AND METHODS

We performed a state-of-the-art review of cervical cancer epidemiology and prevention efforts in Scandinavia. Anticipating the use of mathematical simulation models to inform future policy analyses, we reviewed an existing mathematical simulation model of HPV and cervical carcinogenesis (21) to identify analytic components required to contextualize the model to a specific country. We identified current prevention strategies and behavior, population demography, and epidemiology (e.g., HPV prevalence and cervical cancer incidence) as vital pieces of evidence of modeling. Consequently, we reviewed published literature and official guidelines, performed registry-based analyses using primary data, and held discussions with experts in each country in order to summarize these data for each Scandinavian country.

Cervical cancer prevention policies and demographic data

We compared historic, current, and future cervical cancer prevention strategies and screening coverage across the Scandinavian countries. We reviewed the literature to identify the timing of implementation of opportunistic and organized screening in each country, as well as to identify current and future prevention strategies in each country, including cervical cancer screening and HPV vaccination policies. We also reviewed official documents and quality assurance reports from the screening program managers (22-24) as well as consulted with experts. For demographic data, we extracted data on the size of the female population eligible for screening, the size of the annual female birth cohort, and life expectancy for each woman in each Scandinavian country from national databases (25-27).

Epidemiologic data

HPV epidemiology

To identify studies that reported age- and HPV genotype-specific prevalence of high-risk HPV infections, and HPV genotype distribution in cervical high-grade precancers (i.e. cervical intraepithelial neoplasia grade 3 (CIN3)) and cancers (stratified by squamous cell carcinoma (SCC) and adenocarcinoma (ADC)), we reviewed the literature for published studies as well as reviewed country-specific reports from the ICO (Institut Català d'Oncologia) Information Centre on HPV and Cancer (herein referred to as 'ICO') for all countries (6, 7, 28), and

consulted with experts. We subsequently summarized age- and HPV genotype-specific prevalence of high-risk HPV infections (i.e. ages 14-24, 25-34, 35-44 and 45-54 for Denmark, which slightly differed from those reported for Norway and Sweden; i.e. ages 18-24, 25-34, 35-44, and 45-49 years) and HPV genotype distribution in CIN3, SCC and ADC across the selected studies (15, 29-34). Details for identification, selection and characteristics of relevant studies are available in the **Supporting Information**.

Cervical cancer incidence

For each country, we compiled data on cervical cancer incidence per 100,000 women-years by age (five-year age-groups) for all available years from the NORDCAN database (20). We used years 1960-66 to represent the historic period, as this was a common period prior to initiation of organized or opportunistic cervical cancer screening for which data were available for all Scandinavian countries. We used years 2010-2014 to represent current cervical cancer incidence, and presented recent incidence for all cervical cancers, as well as SCC and ADC histologies separately. The recent incidence rates for all cervical cancers were extracted from the NORDCAN database; however, we did not have access to histology-specific incidence rates in Denmark, therefore these were calculated by adjusting the NORDCAN data (years 2010-2014) using age-specific proportions of SCC for years 1997-2011 from a published study (35). For Norway, SCC and ADC incidence rates were available from the Cancer Registry of Norway (36) and extracted for a previous model-based analysis (18). For Sweden, SCC and ADC incidence rates were available from the National Board of Health and Welfare (37).

Statistical analysis

For the estimates of age-specific HPV prevalence and genotype-distributions of HPV in CIN3 and cancer (stratified by SCC and ADC), we calculated exact binomial 95% confidence intervals (CIs) and assessed country-specific variation using Fisher's exact test and logistic regression. For age-specific cervical cancer incidence estimates, we calculated exact Poisson 95% CIs and used Poisson regression with indicators for each five-year age-group (ages 20-84 years) and for each country. For cumulative incidence, we calculated the variance assuming that the observed counts were Poisson distributed. All analyses were performed using STATA statistical software version 14.

RESULTS

Cervical cancer prevention

Although opportunistic screening activities occurred earlier, organized cytology-based screening reached nationwide coverage for all Scandinavian countries by 1996; however, implementation varied widely across the countries **(Table 1)**. In Denmark, organized cervical cancer screening was first introduced in a single municipality in 1962, and expanded to other counties starting in 1967 until reaching nationwide coverage in 1996 (38). In Norway, organized cervical cancer screening was also first introduced in a single county (Østfold) in 1959 (39), followed by a pilot program in two counties in 1992 (40), and implementation of nationwide organized cervical cancer screening was in 1995. In Sweden, a nationwide organized program was rolled-out between 1967 and 1973 (41).

Until 2017, all countries recommended cytology-based cervical screening, but varied by screening target ages and follow-up management **(Table 1)**. In Denmark and Sweden, screening with cytology was recommended for women aged 23-59 and 23-60 years, respectively (23, 24), while the screening target population in Norway was older (i.e., women aged 25-69 years) (22). For younger women, the primary screening interval was consistently three years for all countries, while Denmark and Sweden recommend an extended 5-year interval for women older than age 50 years (since 2007 in Denmark (42) and since 1998 in Sweden (43)). Since 2012, Denmark implemented an "exit" HPV DNA test for women aged 60-64 years with continued surveillance for HPV-positive women. All countries recommended reflex HPV testing for women with minor cervical lesions; however, management of HPV-positive women differed (i.e., direct colposcopy referral in Denmark and Sweden versus repeat HPV and cytology co-testing 6-12 months later in Norway). In addition, in Denmark, there are regional differences in triage and follow-up guidelines, and reflex HPV DNA testing is only recommended for women aged >30 years (23). The use of HPV testing to triage women with minor cervical lesions was first recommended in official guidelines in 2007 in Denmark (42), in 2005 in Norway (44), and in 2010 in Sweden (45), although application in clinical practice began earlier in some areas.

As of 2014, screening coverage, defined as the proportion of women in the screening target age who have attended screening within the recommended screening interval (i.e., the

last 3.5 years for triennial screening and the last 5.5 years for 5-yearly screening), was higher in Denmark (76%) (46) and Sweden (81%) (47) than in Norway (67%) (22).

Beginning in January 2017, Sweden implemented new guidelines recommending primary HPV testing for women aged 30 years and older at three-year intervals, with extension to seven-year intervals for women aged 50-64 years. In Sweden, only a few counties have adopted the new guidelines; the majority of these utilize HPV DNA testing while the remaining utilize HPV mRNA testing. HPV testing is currently under consideration in both Denmark and Norway. Although guidelines have not yet been outlined in Denmark, switching to HPV testing at age 50 years has been suggested in previous recommendations (23). From February 2015, the controlled implementation of primary HPV testing at five-yearly intervals starting at age 34 years was initiated in four Norwegian counties. Women aged 34-69 years and living in these counties (covering approximately 25% of the screening target population) were randomized into triennial cytology (i.e. the current guidelines) and primary HPV DNA testing. Nationwide primary HPV testing for all women aged 25-69 years is expected within the next few years following a gradual scale-up implementation process. (48). In addition to primary HPV testing, other prevention policies are also emerging; for example, Denmark was the first Scandinavian country to implement HPV self-sampling for non-attenders in Copenhagen in January 2017 (49). Finally, HPV vaccination for 12-year old girls was introduced in 2009 in Denmark and Norway (girls born in 1996) (50) and in 2012 in Sweden (girls born in 1999) (51), while catch-up vaccination programs have been offered in all countries, although roll-out of these programs varied in each country **(Table 1)**.

Population demography

The size of the female population in screening age and annual female birth cohorts were similar in Denmark and Norway, and almost twice the size in Sweden. The female population life expectancy was slightly lower in Denmark than in Norway and Sweden, but was greater than 82 years in all countries (**Table 1**).

HPV epidemiology

In general, HPV prevalence peaked at ages 14-24 years (18-24 years for Norway and Sweden) and decreased by age for all genotypes in all countries **(Figure 1)**. The most prevalent genotypes, HPV16, 18, and 31, were the same across Scandinavia; however the magnitude differed. The reported HPV prevalence was considerably (and often significantly) lower for specific age-groups and genotypes in Sweden compared to Denmark and Norway. For example, at ages 14-24 (ages 18-24 in Norway and Sweden), the prevalence of HPV16 (95% CI) was 13.7% (12.3-15.3%) in Denmark, 15.2% (12.7-18.0%) in Norway, and 5.9% (4.0-8.2%) in Sweden. For this age-group, the reported prevalence was also significantly lower in Sweden than in Denmark and Norway for HPV18, 31, 45, and 52 infections.

The reported HPV genotype distributions in CIN3, SCC and ADC were generally similar across the Scandinavian countries (**Figure 2**). HPV16 was the most prevalent genotype in both CIN3 and SCC for all countries, ranging from 52-59% in CIN3 and from 54-68% in SCC, and was the most prevalent genotype in ADC in Norway (46%). However, HPV18 was the most prevalent genotype in ADC in Denmark and Sweden (43% and 49%, respectively). In addition, 18% (95% CI: 16-21%) of CIN3 were positive for HPV31 in Denmark, while the corresponding proportions were 8% (95% CI: 4-13%) in Norway and 10% (95% CI: 7-14%) in Sweden.

Cervical cancer epidemiology

Prior to implementation of organized screening (i.e., years 1960-1966), the incidence of cervical cancer peaked at ages 40-49 years and thereafter decreased with age in all three Scandinavian countries **(Figure 3)**. Norway had the lowest cervical cancer incidence; in comparison, Sweden had rates that were on average 11% higher (age-adjusted rate ratio=1.11, 95% CI: 1.06-1.17) and Denmark had rates that were appreciably higher (rate ratio=1.99, 95% CI: 1.90-2.09). The incidence peaked at 94 cases per 100,000 woman-years for ages 45-49 years in Denmark, while it peaked at ages 40-44 years in Norway and Sweden, at 52 and 45 cases per 100,000 woman-years, respectively.

Following decades of opportunistic and organized cytology-based screening, current cervical cancer incidence rates (i.e., years 2010-2014) are more similar across the countries and substantially lower than for the period 1960-1966 in all Scandinavian countries, peaking at an earlier age (i.e., at ages 35-39 years with 27, 29 and 21 cases (all histologies) per 100,000

woman-years for Denmark, Norway and Sweden, respectively) **(Figures 4 and 5)**. For years 2010-2014, cervical cancer incidence begins to plateau at ages 50-54 with small increases until ages 80-84 years **(Figure 4a)**. These trends were similar for SCC and ADC incidence **(Figure 4b-c)**. Differences in cancer incidence are worth noting; Compared to Sweden, which faced the lowest cervical cancer incidence rate, Norway and Denmark continue to have a higher burden of cervical cancer (age-adjusted incidence rate ratio of 1.28 (95% CI: 1.20-1.37) and 1.36 (95% CI: 1.28-1.45), respectively). In addition, Sweden had significantly lower incidence rates than Denmark and Norway between ages 35-69 years.

The cumulative incidence of cervical cancer by age 75 years for Denmark, Norway and Sweden was 0.94% (95% CI: 0.84-1.04), 0.90% (95% CI: 0.79-1.01) and 0.69% (95% CI: 0.62-0.75), respectively **(Table 1)**. Cervical cancer survival was similar for all countries, with 1-year and 5-year relative survival of 88-89% and 69-72%, respectively (20) **(Table 1)**.

DISCUSSION

By synthesizing evidence from Denmark, Norway and Sweden, we found that cervical cancer epidemiology and prevention efforts (i.e., screening guidelines and HPV vaccination programs) in the Scandinavian countries are similar. Although cervical cancer incidence was higher in Denmark than in Norway and Sweden in the early 1960s, decades of cytology-based screening likely contribute to the converging incidence rates across Scandinavia; however, cervical cancer incidence remains the lowest in Sweden. Importantly, until 2017, cervical cancer screening guidelines were similar in Denmark and Sweden, differing slightly from the Norwegian guidelines, yet these policy differences did not reflect baseline epidemiologic differences (e.g. HPV prevalence). Interestingly, and despite the lower HPV prevalence in Sweden observed in this study, a previous study found that sexual behavior today was similar across the Scandinavian countries (52). The lower reported HPV prevalence in Sweden might be due to lack of published studies presenting reliable HPV prevalence estimates. The differences observed in the cervical cancer burden may be caused by historical differences in background risk, earlier introduction of nation-wide screening in Sweden, different screening history of the respective birth cohorts (53), and a range of other factors, such as compliance to screening and follow-up procedures, colposcopy performance, treatment guidelines and follow-up after treatment, some of which have not been presented in this study.

Although the current HPV prevalence does not influence the current cervical cancer incidence, it may do so in the future. As primary HPV testing was implemented in Sweden in 2017 and is underway in Denmark and Norway, there may be a need to revisit prevention efforts. In addition, in all Scandinavian countries, HPV16 was the most prevalent genotype among women (with or without precancer or cancer). As all currently available HPV vaccines target HPV16, a considerable reduction in cervical precancers and cancers can be expected following the introduction of HPV vaccination programs in all Scandinavian countries. Consequently, adapting cervical cancer screening policies for women vaccinated against HPV infections may be important to maintain high-value prevention approaches.

This study is, to our knowledge, the first to summarize cervical cancer prevention efforts as well as HPV and cervical cancer epidemiology in Scandinavia. A major strength of this study is that all data are based on evidence from primary and/or published sources and have been extensively evaluated and discussed with experts prior to inclusion. This review can inform policy analyses to guide future prevention of cervical cancer in Scandinavia. Specifically, the information on prevention efforts and HPV and cervical cancer epidemiology can be used to inform policy analyses that utilize mathematical simulation models, similar to those performed previously within a Scandinavian setting (12, 13, 15-18).

Defining screening target ages is an important part of organized screening programs. Interestingly, screening starts at age 23 years in Denmark and Sweden, while it starts at age 25 years in Norway; however, there were no significant differences in the current cervical cancer incidence rates for women younger than age 35 years. Furthermore, while the incidence curve plateaus after age 65 years in Norway, where screening is recommended to stop at age 69 years, incidence rates tend to increase after age 65 years in both Denmark and Sweden, where screening is recommended to stop earlier (age 60-64 years). The bipolar pattern in the current age-specific cervical cancer incidence was examined in a previous study which concluded that the pattern is probably not a biological phenomenon, but more a result of different screening histories in the different birth cohorts contributing to the different age-groups (53). Future studies, including simulation modeling, may further elucidate which factors contribute to these similarities and discrepancies, and evaluate the optimal age to start and stop screening in the Scandinavian countries.

Some limitations are worth mentioning. Importantly, our estimates of HPV prevalence and HPV genotype-distribution in CIN3, SCC and ADC are based on data from different

sources and time periods, which may limit comparability across countries. For example, while HPV prevalence is estimated for women with normal cytology results using PCR-based HPV testing in Norway and Sweden, HPV prevalence estimates for Denmark are based on women in a general screening population (with any cytology result) and using Hybrid Capture II HPV DNA testing. Different HPV detection methods have difference performance characteristics (54) and should be taken into account when comparing results. However, the overall HPV prevalence estimates were similar to two other Danish studies using PCR-based testing (55, 56). In addition, the Danish estimates were presented for different age-groups than for Norway and Sweden, and the youngest age-group (i.e., ages 14-24 years in Denmark, ages 18-24 years in Norway and Sweden) may be subject to selection bias as these women are not within the target age groups of the screening programs. However, this did not prohibit general comparisons across ages. Population-based prevalence data were not available in any country; thus the higher prevalence observed in Denmark and Norway compared to Sweden could be partially explained by (i) a selected sample of women living in larger cities (versus six counties in Sweden) and (ii) that the Swedish data on prevalence was from an earlier calendar period. However, our estimates of HPV prevalence were generally comparable to those presented by ICO, except for the youngest age-group for Sweden (which is likely due to different ages of the sample populations). Furthermore, women with total (i.e., cervix-removing) hysterectomy are no longer at risk of developing cervical cancer, yet we did not adjust cervical cancer incidence rates for hysterectomy as population-based hysterectomy rates were not available in Norway. Although adjusting for hysterectomy rates influences cervical cancer incidence rates, such adjustment is more impactful on incidence rates among older age groups than on age-standardized incidence rates (57-59). Finally, the data presented in this study were outlined based on analytic components of an existing mathematical simulation model (60); other simulation models and policy analyses may require different data components. Nonetheless, we believe the data presented in this study may be useful for a wide range of analytic purposes.

In sum, among the Scandinavian countries, Sweden currently has the lowest HPV and cervical cancer burden, and is the first Scandinavian country to implement primary HPV testing for women older than 29 years. Future policy analyses (e.g., using mathematical simulation modelling) will need to evaluate whether different prevention policies are necessitated by differences in epidemiology, screening performance or other factors such as relative price differentials of input factors. In turn, these studies can use the data presented in this study to

project the lifetime health and economic consequences of alternative strategies and identify optimal prevention policies in Scandinavia.

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Figure Legends

Figure 1. HPV prevalence by genotype, age and country. Error bars represent 95% exact binomial confidence intervals. *Ages 18-24 years for Norway and Sweden. **Ages 24-34 years for Denmark. ***Ages 45-49 years for Norway and Sweden. Note that the y-axis range for the panel representing total hrHPV is expanded than for individual HPV genotypes. Total hrHPV reflects HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 for Norway and Sweden, while for Denmark, HPV53 and 66 are also included. Abbreviations: hrHPV; high-risk human papillomavirus.

Figure 2. . HPV genotype-distribution in cervical intraepithelial neoplasia grade 3 (CIN3), squamous cell carcinoma (SCC), and adenocarcinoma (ADC) by country. Error bars represent 95% exact binomial confidence intervals. Abbreviations: ADC, adenocarcinoma, CIN3; cervical intraepithelial neoplasia grade 3, HPV; human papillomavirus, SCC; squamous cell carcinoma.

Figure 3. Historic age-specific cervical cancer incidence (years 1960-1966) by country. Dotted lines represent 95% exact Poisson confidence intervals.

Figure 4. Current age-specific cervical cancer incidence (years 2010-2014) by histology, country and; a) all histologies, b) squamous cell carcinoma, and c) adenocarcinoma. For Denmark, the incidence of adenocarcinoma represents all cervical cancers other than SCC. Dotted lines represent 95% exact Poisson confidence intervals. Abbreviations: ADC; adenocarcinoma, SCC; squamous cell carcinoma.

Figure 5. Historic (years 1960-1966) and current (years 2010-2014) age-specific cervical cancer incidence by country; a) Denmark, b) Norway, and c) Sweden. Dotted lines represent 95% exact Poisson confidence intervals.