European Journal of Cancer 91 (2018) 68–75

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines

Kine Pedersen [a,*], Emily A. Burger [a,b], Mari Nygård [c], Ivar S. Kristiansen [a], Jane J. Kim [b]

[a] *Department of Health Management and Health Economics, Institute of Health and Society, University of Oslo, P.O. Box 1089 Blindern, 0317, Oslo, Norway*
[b] *Center for Health Decision Science, Harvard T.H. Chan School of Public Health, 718 Huntington Ave, 2nd Floor, Boston, MA, 02115, USA*
[c] *Department of Research, Cancer Registry of Norway, P.O. Box 5313 Majorstuen, 0304, Oslo, Norway*

Received 23 June 2017; received in revised form 6 December 2017; accepted 13 December 2017

KEYWORDS
Cervical cancer;
Mass screening;
Cost-effectiveness analysis;
Mathematical model;
Human papillomavirus

Abstract ***Background:*** Several countries have implemented vaccination against human papillomavirus (HPV) for adolescent girls and must decide whether and how to adapt cervical cancer (CC) screening for these low-risk women. We aimed to identify the optimal screening strategies for women vaccinated against HPV infections and quantify the amount that could be spent to identify vaccination status among women and stratify CC screening guidelines accordingly.

Methods: We used a mathematical model reflecting HPV-induced CC in Norway to project the long-term health benefits, resources and costs associated with 74 candidate-screening strategies that varied by screening test, start age and frequency. Strategies were considered separately for women vaccinated with the bivalent/quadrivalent (2/4vHPV) and nonavalent (9vHPV) vaccines. We used a cost-effectiveness framework (i.e. incremental cost-effectiveness ratios and net monetary benefit) and a commonly-cited Norwegian willingness-to-pay threshold of €75,000 per quality-adjusted life-year gained.

Results: The most cost-effective screening strategy for 9vHPV- and 2/4vHPV-vaccinated women involved HPV testing once and twice per lifetime, respectively. The value of stratifying guidelines by vaccination status was €599 (2/4vHPV) and €725 (9vHPV) per vaccinated woman. Consequently, for the first birth cohort of ~22,000 women who were vaccinated in adolescence in Norway, between €10.5–13.2 million over their lifetime could be spent on identifying individual vaccination status and stratify screening while remaining cost-effective.

* *Corresponding author*:
E-mail address: Kine.pedersen@medisin.uio.no (K. Pedersen).

https://doi.org/10.1016/j.ejca.2017.12.018

Conclusion: Less intensive strategies are required for CC screening to remain cost-effective in HPV-vaccinated women. Moreover, screening can remain cost-effective even if large investments are made to identify individual vaccination status and stratify screening guidelines accordingly.

1. Introduction

Cervical cancer (CC) is the fourth most common cancer in women worldwide, with the greatest burden in low- and middle-income countries [1]. Following the implementation of prophylactic human papillomavirus (HPV) vaccination, the risk of developing CC in vaccinated women is expected to decrease considerably, which will increase the heterogeneity of CC risk in the population. Currently available vaccines include the first-generation bivalent and quadrivalent HPV vaccines (2/4vHPV), targeting HPV-16 and -18 high-risk infections (with or without the addition of HPV-6 and -11 low-risk infections) that contribute to ~75% of all CCs, and the second-generation nonavalent vaccine (9vHPV), targeting HPV-6/11/16/18/31/33/45/52/58 infections that cumulatively contribute to ~90% of all CCs [2]. In clinical trials, the vaccines have demonstrated >90% efficacy against persistent HPV infections and precancers among HPV-negative individuals who completed the three-dose schedule [3–6]. The vaccines are most effective when administered to young individuals prior to HPV exposure [7], and national immunisation programmes for adolescent girls have been implemented in most developed countries. In Norway, all three HPV vaccines are available, and the 2vHPV was recently selected to replace the 4vHPV in the vaccination programme [8]. To prevent CC caused by non-vaccine-targeted genotypes, screening may still be required for HPV-vaccinated women. The first cohort of Norwegian girls vaccinated with the 4vHPV at age 12 years in 2009 will become eligible for CC screening in 2022; however, no countries have yet adapted CC screening guidelines according to individual vaccination status, which may be required for screening to remain cost-effective and balance benefit-harm trade-offs for these low-risk women.

Previous model-based analyses have indicated that cost-effective CC screening strategies for HPV-vaccinated women involve primary HPV testing starting at later ages and occurring less frequently [9–13], and that cost-effective guidelines may differ between settings [10]. Within the context of Norway, we aimed to identify the most cost-effective CC screening strategy for women vaccinated against HPV infections in adolescence. Moreover, as stratifying guidelines based on vaccination status may require additional resources (e.g. registry linkage to identify individual vaccination status) we enumerated the maximum amount of money that could be spent to obtain individual vaccination status and stratify guidelines while remaining cost-effective.

2. Materials and methods

2.1. Analytic overview

We used a previously developed mathematical simulation model of HPV-induced CC [14], adapted to reflect Norwegian epidemiologic data using 50 good-fitting parameter sets (described previously [11,15,16], Supplementary Appendix), to project the health and economic consequences of candidate CC prevention strategies for women vaccinated against HPV infections at age 12 years. The model simulates and tracks the disease history, clinical events and resource use for a hypothetical cohort of four million individual women from age 9 years until death. Women progress through the model at monthly transitions between health states, including HPV infection status, precancer and CC (by stage). Analyses were considered separately for women vaccinated with the 2/4vHPV and the 9vHPV vaccines. In addition to 'no intervention' and 'vaccination only' scenarios, we considered 74 candidate screening strategies that varied by the primary screening test (cytology or HPV), age to start screening (ages 25–34 years) and screening frequency (once/twice per lifetime and 3-yearly to 20-yearly). We also evaluated Norwegian-specific guidelines currently in use, including triennial cytology for women aged 25–69 years ('current guidelines') and a strategy under consideration in a pilot study [17] ('proposed guidelines') involving five-yearly HPV testing, starting at age 34 years (with triennial cytology for ages 25–33 years).

Using a societal analytic perspective, we projected the lifetime risk of developing CC compared to no intervention, the number of colposcopy referrals and screening (cytology and HPV) tests per 1000 women screened over their lifetime, the quality-adjusted life-years (QALYs), life expectancy and the total lifetime cost (expressed in 2014 Euros [€EUR 1.00 = NOK 8.35] [18]) per woman associated with each strategy. Costs and QALYs were discounted by 4% per year as recommended in Norway [19]. We also considered a 0% discount rate as a lower bound for discount rates across European countries.