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Elimination of HPV–associated oropharyngeal cancers in Nordic countries

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ABSTRACT

Incidence of human papillomavirus (HPV, most notably HPV type 16) associated oropharyngeal squamous cell carcinoma (OPSCC) among middle-aged (50–69 year-old) males has tripled in four high income Nordic countries (Denmark, Finland, Norway and Sweden) over the last 30 years. In Finland and Sweden, this increase was preceded by an HPV16 epidemic in fertile-aged populations in the 1980's. The recent implementation of school-based prophylactic HPV vaccination in early adolescent boys and girls will gradually decrease the incidence, and eventually eliminate the HPV-associated OPSCCs (especially tonsillar and base of tongue carcinomas) in the Nordic countries. However, beyond the adolescent and young adult birth cohorts vaccinated, there are approximately 50 birth cohorts (born in 1995 or before) that would benefit from screening for HPV-associated OPSCC. This article reviews the need, prerequisites, proof-of-concept trial and prospects of preventing HPV-associated OPSCC in the Nordic countries.

1. Introduction

The WHO campaign for the elimination of cervical cancer, the necessary cause of which is human papillomavirus (HPV) (Walboomers et al., 1999), has raised questions as to whether or not such elimination would also be possible for other HPV-associated cancers? While cervical cancers are linked with two to five high-risk HPV types (primarily types 16/31/33 and 18/45 for squamous cell carcinomas and adenocarcinomas, respectively) (Lagheden et al., 2018), HPV-associated oropharyngeal squamous cell carcinomas (OPSCCs) are mainly (up to 90%) positive for HPV16. This fits with the epidemic increase of OPSCC incidence in Sweden and Finland, and the USA approximately 10–20 years after HPV16 epidemics in these high- income countries (Hansen et al., 2018; Hansen et al., 2020), and probably will facilitate the elimination of HPV-associated OPSCCs by current gender-neutral vaccination programs that are predicted to eliminate HPV16 infections from the countries with organized vaccination of reasonable coverage. After HPV16 is no longer circulating there will still exist prevalent, persistent HPV16 infections that may cause OPSCC. This calls for HPV-based screening of OPSCC to tackle the epidemic in birth cohorts not offered vaccination. While both serological (Beachler et al., 2016a; Lang Kuhs et al., 2016, 2017; Holzinger et al., 2017) and DNA-detection (Haeggblom et al., 2017) based tools for versatile combinations of screening steps are available, difficulties in the identification of pre-cancerous lesions or latent/early cancerous lesions are a challange for the ENT doctors responsible for diagnosis of occult OPSCC. In the following we review prospects for the elimination of HPV-associated OPSCCs via the synchronized implementation of HPV vaccination and screening over time.

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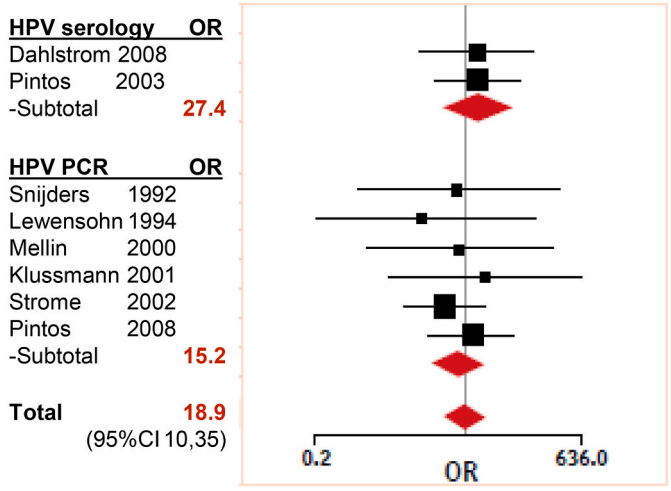

Fig. 1. Meta-analysis on human papillomavirus (HPV) associated relative risk (odds ratio, OR with 95% confidence interval, CI, logarithmic scale) of tonsillar cancer.

2. Relative risk and attributable fractions of HPV in oropharyngeal cancers

Cross-sectional studies on the HPV-associated relative risk (RR) of OPSCC yield highly increased risk estimates worldwide, irrespectively whether oral HPV DNA or HPV antibodies have been used for exposure assessment (for meta-analyses/systematic review see Haeggblom et al., 2017). As for tonsillar cancer, the serology-based RR-estimates are, however, 1.5 times higher than the HPV DNA -based RR estimates (Fig. 1) which is opposite to comparable risk estimates linking HPV exposure and cervical cancer even in longitudinal studies (Lehtinen et al., 1996; Wallin et al., 1999). This is most likely due to the HPV infection focus in the oropharynx being in or close to the Waldeyer's ring which facilitates accessibility of HPV antigens to immune cells and antibody production. These apparently optimal prerequisites for serological diagnosis of HPV infections in the oropharynx pave the way for serological screening for HPV-associated OPSCCs. The fact that HPV is a necessary cause of all cervical cancers (Walboomers et al., 1999) but present in varying proportions (30–70%) of OPSCCs (Haeggblom et al., 2017), however, makes it important to understand what type(s) of HPV-associated OPSCC(s) could be/should be screened.

Population attributable fraction (PAF) estimates of HPV in OPSCC differ depending on whether A) HPV prevalence (P) in the cases (P_{cases}) is exploited: PAF = P_{cases} × (1–1/RR), or B) HPV prevalence in the population (P_{pop}) is exploited: B) PAF = P_{pop} × (RR-1)/ [P_{pop} × (RR-1) + 1] (Greenland, 2015) As noted above, the former (A) is prone to misclassification biases when data on HPV DNA identified in heterogenic tumour material are applied. In the latter (B), exposure assessment in the population can be biased by suboptimal serology. While the HPV DNA-based PAF estimation is also prone to calendar time-dependent changes in the abundance of oral HPV DNA and incidence of HPV DNA-positive OPC-cases, longitudinal seroepidemiological HPV studies can rely on matching and the seroprevalence being an indicator of cumulative incidence that are not sensitive to temporal changes.

The only longitudinal nested case-control study, which originally estimated the relative risk of 14.4 for HPV16 in OPSCC, can be used to elaborate on the difficulties in obtaining the correct HPV PAF in OPSCC. The above equations result in a PAF of 46.5% when a HPV DNA prevalence in the cases of 50% is used: A) PAF = 0.5 × (1–1/14.4) = 46.5%), and B) up to PAF of 73.2% when the population HPV16 seroprevalence P_{pop} = 0.1 [P_{pop} = 0.2 when corrected for suboptimal 50% sensitivity of serology] is used: PAF = 0.1 × (14.4–1)/ [0.1×(14.4–1) +1] = 57.7% [73.2%]. With the best available, epidemiological evidence on the HPV OPSCC association the above exercise exemplifies later difficulties we then face when trying to understand the preventable fractions of OPSCC that are within reach by HPV vaccination followed by screening, and associated cost-efficiency of pertinent preventive efforts.

3. Oropharyngeal squamous cell carcinoma incidence trends

OPSCC incidence in high-income countries has risen in the last 30 years, especially in males. An increase in OPSCC incidence is also seen in females. These changes may be in part due to the changes in sexual practices and a rise in sexually-transmitted infections including OPSCC-related HPV infections (Hansen et al., 2020). This rise in OPSCC was first observed in the Stockholm region. Over the last 25 years similar changes in the OPSCC incidence can be seen in the capitals of four Nordic countries: Denmark (Copenhagen)/Finland (Helsinki)/Norway (Oslo)/ Sweden (Stockholm) between 1991 and 2016 (Fig. 2), and in these countries overall (www.nordcan.fi). Using data from the highly reliable cancer registries (www.nordcan.fi) the changes have been estimated to be 2–4-fold.

The largest increase in age-specific OPSCC incidence in the four Nordic countries can be seen in 50–69 year old males (Fig. 2). As mentioned this is associated with the rise of HPV16 infection numbers since the 1980s documented in Finland, and in the other Nordic countries (Hansen et al., 2020). A recent increase can also be seen in the incidence of female OPSCC among the 70–85+ year age group in Helsinki (Fig. 2) which fits with a longer lag between the incidence peaks of HPV16 infection and OPSCC (approx. 45 years) as compared to that between HPV16 infection and cervical cancer (approx. 25 years).

Due to the long delay from chronic infection to cancer the changes in HPV-associated OPSCC are seen decades later. In oral cavity cancer (negligible 3% HPV positivity) similar changes are not seen. In the Nordic countries, the numbers of HPV-associated OPSCC have increased from 150 to 500 new annual cases in males annually. The prognosis of HPV-associated OPSCC is better than those of HPV-negative OPSCC, which further underlines the importance of HPV-specific screening and diagnostics. In population-based studies it has been possible to demonstrate the improved overall survival over decades which supports the factual increase in the proportions of HPV-associated OPSCC, and makes their early identification important.

4. Prophylactic HPV vaccines against oropharyngeal infections

The HPV VLP L1 vaccine appears to readily produce oral and systemic immune responses: HPV vaccine induced specific antibodies have been observed in oral gargle and serum samples and sera both in animal models (Ahn et al., 2018) and in males.

In males the quadrivalent vaccine has been shown to have good efficacy against anogenital HPV infections (Giuliano et al., 2011). The HPV prevalence in urine samples was lower four years post vaccination in males vaccinated with the bivalent vaccine, but no randomized efficacy studies against anogenital infections have been published. For the nonavalent vaccine no studies on the vaccine efficacy against anogenital infections in males have been published.

In females all the licensed HPV vaccines are highly efficacious against anogenital HPV infections (for reviews see Lehtinen and Dillner, 2013). Against oropharyngeal HPV infections both the bivalent and the quadrivalent HPV vaccines have shown high efficacies (with overlapping 95% confidence intervals, Table 1) in the females. In a randomized Finnish trial, the bivalent vaccine had 81.3% efficacy against oropharyngeal HPV16 infection after four years of follow up. In post hoc analysis of the Costa-Rica Vacination trial the bivalent vaccine efficacy against oropharyngeal HPV16 infection was 91.6% after four years of follow up (Herrero et al., 2013) in line with findings on the high bivalent vaccine efficacy against multisite (cervical, anal or oral) HPV infection (Beachler et al., 2016b).

Population-based observations on approximately 90% reduction of

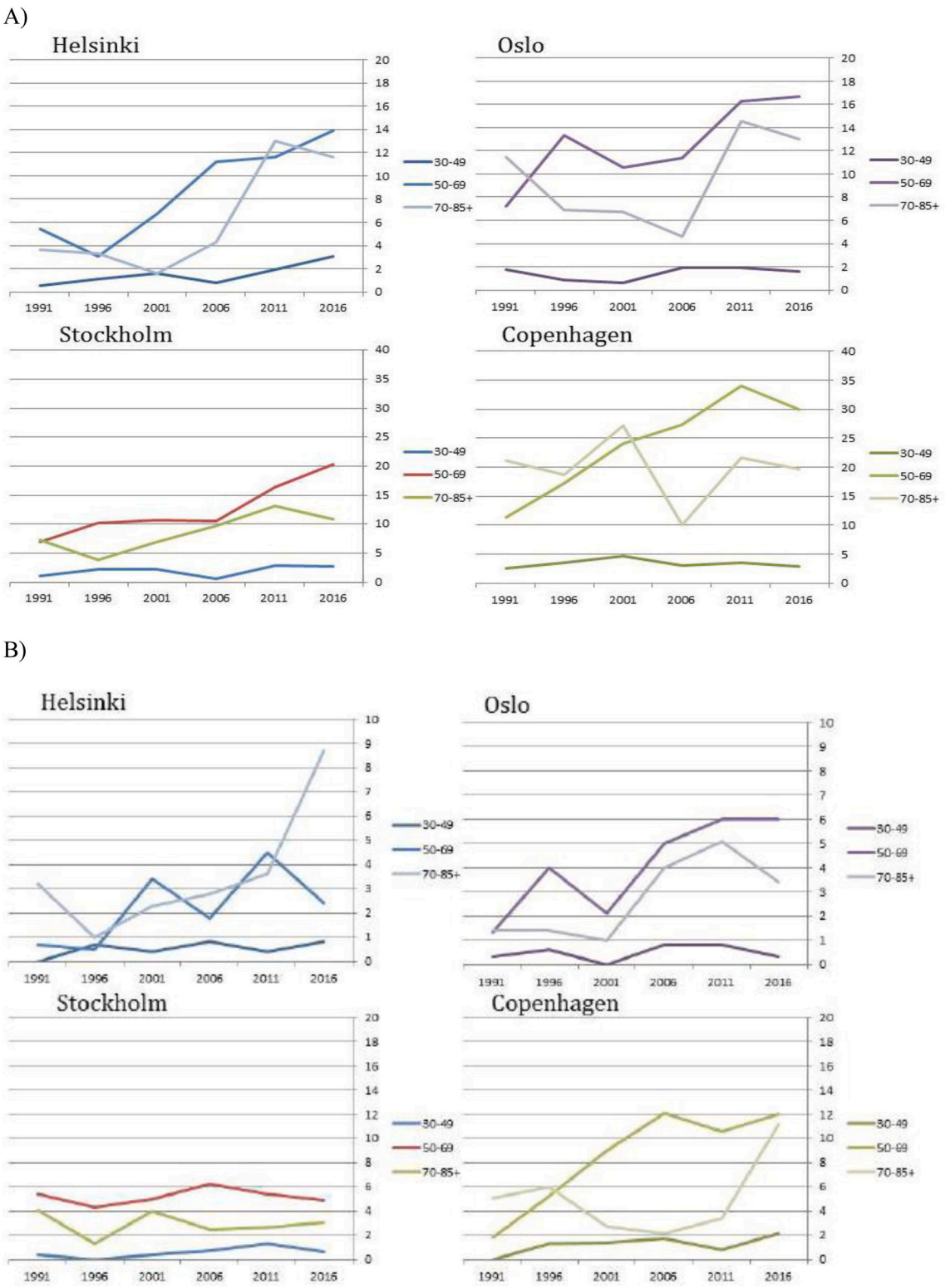

Fig. 2. Age-specific incidence (/10^5 person years) of oropharyngeal squamous cell cancer between 1991 and 2016 in the Nordic capitals: Helsinki, Oslo, Stockholm, Copenhagen. A) males, B) females.

oral HPV16 and all HPV vaccine type (6/11/16/18) prevalence following vaccination with the quadrivalent vaccine would probably have provided borderline significant vaccine efficacy estimates if properly analysed. The suggestive results concerning the quadrivalent vaccine will soon be confirmed in a randomized setting by Giuliano et al. (NCT01432574).

5. Step-wise prevention of HPV-associated OPSCC, proof-of-concept trial in the Nordic countries

In the following, the characteristics of preventive interventions: A1) Vaccination, A2) Serological E6 screening, and A3) DNA screening, and their B) step-wise combination for OPSCC screening in a proof-of-

Table 1
Efficacy of the bivalent human papillomavirus (HPV) vaccine against incident oropharyngeal HPV infections by type in Finland (A), and in Costa-Rica (B).

	Vaccinated		Control		Vaccine efficacy
	N	n (%)	N	n (%)	(95% confidence)
A)					
Type					
HPV16	3192	6 (0.2)	1679	19 (1.1)	81.3% (25.8, 95.3)
HPV18	3192	4 (0.1)	1679	10 (0.6)	78.9% (32.3, 93.4)
HPV16/18	3192	9 (0.3)	1679	27 (1.6)	82.4% (47.3, 97.1)
HPV31/33/45	3192	9 (0.3)	1679	16 (1.0)	69.9% (29.6, 87.3)
B[a])					
Type					
HPV16	2910	1 (0.0)	2924	12 (0.4)	91.6% (51.7, 99.6)
HPV18	2910	0 (0.0)	2924	4 (0.1)	100% (−12.0, 100)
HPV16/18	2910	1 (0.0)	2924	15 (0.5)	98.3% (62.5, 99.7)
HPV31/33/45	n.a.		n.a.		n.a.

N = number of subjects, n = number of HPV DNA positives.
[a] Herrero et al., 2013; Beachler et al., 2016b.

concept trial are described assuming that HPV PAF in OPSCC is 55%.

5.1. Vaccination

Gender-neutral use of HPV vaccines in vaccination programs has a high impact and can lead to eradication (Lehtinen et al., 2018). Even if HPV vaccination does not cure established infections it can prevent re-infection/recurrence of associated lesions in 45% to 65% of individuals with anal or cervical intraepithelial neoplasia (Joura et al., 2012; Kang et al., 2013; Hildesheim et al., 2016; Ghelardi et al., 2018). These facts, together with the observational, post hoc (Herrero et al., 2013; Beachler et al., 2016b) and randomized trial evidence on the high VE against oropharyngeal HPV infections are notable. Moreover, the observed clustering of HPV-cancer risks in spouses: a 10-fold relative risk of tonsillar and base of tongue cancers in spouses of women diagnosed with invasive anogenital cancer (Lehtinen et al., 2020) underlines the importance of breaking genito-oral transmission chains (Du et al., 2012) by HPV vaccination. The impetus to start a stepwise OPSCC prevention trial with baseline HPV vaccination of consenting middle-aged trial participants has obvious advantages.

5.2. Serological screening

HPV seroprevalence in the general population and in diseased individuals varies by the antigens that are being used for antibody determination. HPV type 16 oncoprotein E6 antibodies are found in 0.5% of healthy controls and in 3% of males with persistent oral HPV infection (Kreimer et al., 2013; Beachler et al., 2016b). Due to recent epidemics, E6 seroprevalence among OPSCC cases is between 30 and 65% with yielding an OPSCC RR of 270 (Kreimer et al., 2013, 2019). Most E6 antibody positive OPSCC cases seroconvert already 30 years before the cancer diagnosis (Kreimer et al., 2019). While 5–25% of the general population is HPV16 (L1) seropositive, about half of HPV16 E6 antibody-positive OPSCC patients have HPV16 L1 antibodies which confers an OPSCC RR of 15 Between 65 and 85% of the E6 antibody-positives have HPV16 E2 and E7 antibodies (Holzinger et al., 2017) but screening can be based on the HPV16 E6 antibodies determination alone.

5.3. DNA screening

Compared to other HPV types clearance of HPV16 infection is slow both in the uterine cervix (18–23 months, Lehtinen and Dillner, 2013) and in the oropharynx (20–22 months) in comparable Finnish females. Type-specific persistence of HPV DNA (most notably HPV16) positivity for at least four years results in a 20-fold risk to develop invasive cervical cancer during the next 20 years (Wallin et al., 1999). Corresponding

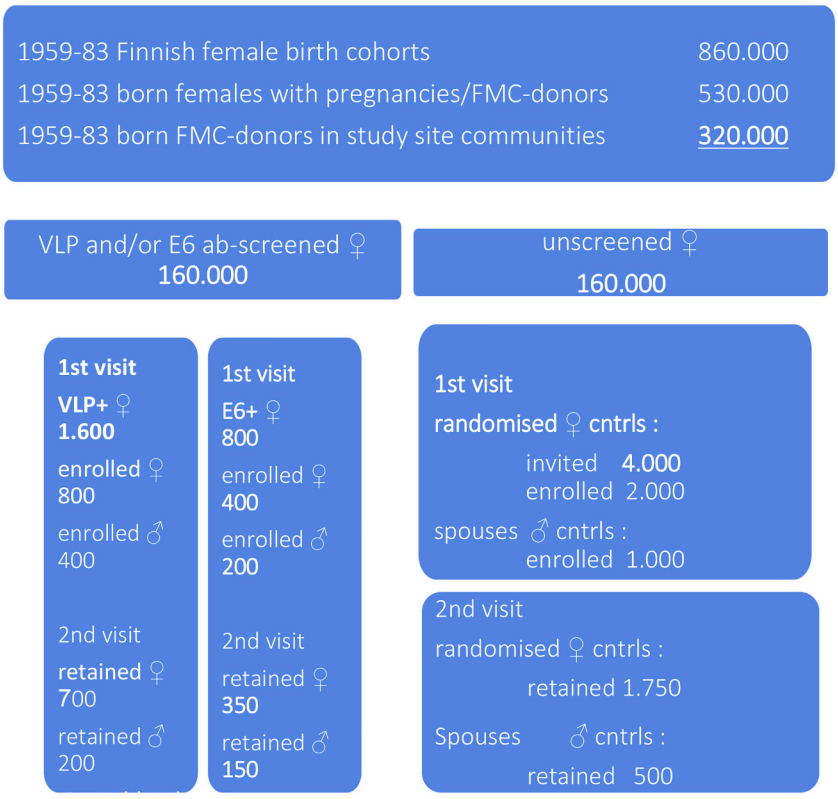

Fig. 3. Proof-of-concept study on step-wise screening of oropharyngeal HPV-cancers in Finland.
Setting and design with eventual sample sizes of the involved individuals in bold.

Table 2
Power to identify oncogenic HPV exposure predisposing to oropharyngeal cancer by various (stepwise) combinations of screening methods with sample sizes of 350/150 E6- antibody screen-positive women and men/women vs 1750/500 unscreened women and men/ women assuming different joint relative risks (RR) and combined prevalence rates (%).

RR	HPV16 E6 antibody and HPV16 DNA prevalence					
	0.02%		0.1%		0.5%	
	350/1750	150/500	350/1750	150/500	350/1750	150/500
30	45.8%	19.5%	100%	85%	100%	100%
60	45.8%	19.9%	100%	99.9%	100%	100%
300	100%	99.9%	100%	100%	100%	100%

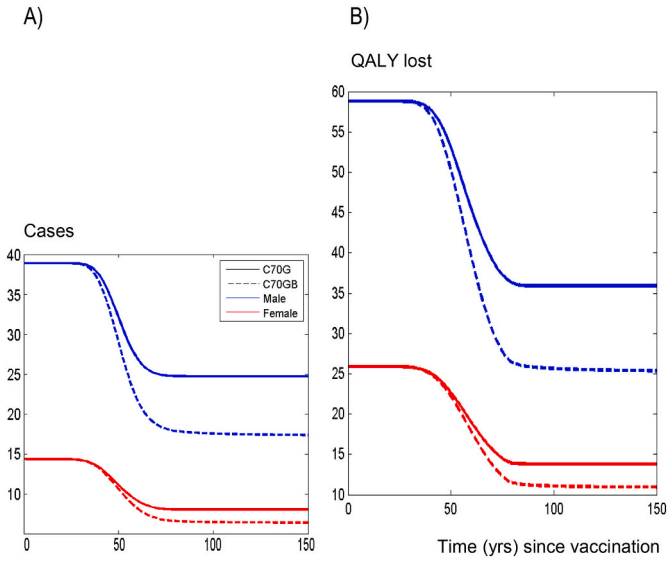

Fig. 4. Estimates on human papillomavirus vaccination preventable tonsillar cancer cases (A) and quality adjusted life years (QALY, B) lost over time in Finland. (70% coverage girls, C70G; 70% coverage girls and boys, C70GB).

data for OPSCC are missing due to the lack of detectable precancerous lesions. The predictive value of HPV DNA positivity in the OPSCC context is further complicated by the increasing occurrence of oral HPV DNA positivity by age in healthy individuals. In the head and neck cancers, however, it is 5-times more common to identify HPV DNA in the base-of-tongue carcinoma (BOTSCC) and (tonsillar carcinoma) TSCC tumors, than in other OPSCCs (Haeggblom et al., 2017).

HPV16 E6-antibody positive OPSCCs have a much better prognosis than antibody-negative OPSCC cases, which would indicate significant differences in the treatment and follow-up of the two entities (Lang Kuhs et al., 2016, 2017), an important screening prerequisite. Recently, a set of viral and non-viral serology patterns have been suggested to further improve the assessment of prognosis in the different OPSCC entities (Laban et al., 2019; Gangkofner et al., 2019).

5.4. Step-wise combination of the preventive measures

We propose a randomized proof-of-concept trial for the stepwise prevention of OPSCC embedded in the Finnish health care setting which is population-based and linkable due to unique personal identifiers. National health registers/biobanks and consent-based trial participation, with very high compliance, make the trial feasible (Lehtinen et al., 2015). The trial steps are (Fig. 3): 1) Stratification of the 320,000 Finnish Maternity Cohort participants by birth cohort (1959–1983) and residence in the HPV study site communities; 2) Randomization of E6 antibody screening into 160,000 screened and 160,000 unscreened women; 3) Invitation of the E6 antibody positive (800) and E6 antibody negative women, HPV16 antibody positive women (1600) and their spouses, for HPV vaccination and for two HPV DNA tests. In addition, 4000 unscreened women and their spouses will be invited as population-based controls. Assuming 50% participation and 50% to 90% compliance in the follow-up, the proposed stepwise screening is duly powered with either additive or multiplicative joint effects of the above-mentioned risk-indicators for the identification of occult OPSCC in screen-positive, middle-aged individuals (Table 2). The population-based controls will provide the desired screening test characteristics: sensitivity, specificity, and positive and negative predictive values for the identification of HPV-associated OPSCC in four years.

6. Cost-efficiency of OPSCC-prevention

It is most likely that the change of sexual risk-taking behaviour, the original cause of tonsillar and base of tongue epidemics in the high-income countries, resulted in increased occurrence of oral HPV infections in adolescent and young adults in the 1980's. The lag between oral HPV infection and diagnosis of HPV-associated OPSCCs is, however, probably more than twice as long than the lag (11 years) between epidemic acquisition of genital HPV16 infection and epidemics of invasive cervical cancer in fertile-aged women (Harper et al., 2010; Laukkanen, 2012). The impact of vaccinating early adolescent boys and girls on the numbers of incident OPSCC cases and associated quality-adjusted-life-years lost provides a cost-effective solution but slowly (Fig. 4). Even if gender-neutral vaccination results in rapid elimination of HPV circulation, the effects of persistent, prevalence HPV infections on the most HPV-associated tonsillar cancer will continue for decades after HPV circulation has stopped. Saving ≥50 unvaccinated adult birth cohorts from the ongoing OPSCC epidemic favours the suggested combined OPSCC prevention.

7. Conclusion

Annually, in Denmark, Finland, Norway and Sweden up to 1000 new OPSCC cases could be avoided in a population of 27 million people by implementing screening for HPV-associated OPSCC cases after accomplishing a successful, organized HPV vaccination program. A Finnish proof-of-concept trial is presented in a randomized, comparative effectiveness research setting for plausible implementation into public health policies of the Nordic countries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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