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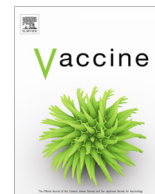
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Burden of HPV-caused cancers in Denmark and the potential effect of HPV-vaccination



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ABSTRACT

Background: Denmark is one of the countries where Human papillomavirus (HPV)-vaccination at present includes only girls. However, the burden of HPV-related cancer in men is increasing, which would argue for gender-neutral vaccination. The aim of this study was to examine the burden of HPV-caused cancers in women and men, and to evaluate the potential of HPV-vaccination in cancer control.

Methods: Data were retrieved from the literature on population prevalence of high risk (HR) HPV, on HR HPV-prevalence and genotypes in HPV-related cancers, and on number of cytology samples in cervical screening. Data on annual biopsies and conisations were retrieved from the Danish National Health Service Register and the Danish National Patient Register. Incidences of HPV-related cancers in Denmark were extracted from NORDCAN. Number of HPV-caused cancers was calculated from number of HPV-related cancers and the proportion known to be caused by high-risk (HR) HPV.

Results: In cross-sectional surveys in Denmark, one fifth of women and almost one third of men were found to be positive for HR HPV. Per year, 548 HPV-caused cancer cases were diagnosed in women and 234 in men, and twice as many cancers in women as in men were preventable with HPV vaccination. However, including screening prevented cervical cancers, the burden of cancers caused by HPV-infection would be 1300–2000 in women as compared to 234 in men.

Conclusion: Taking screening prevented cervical cancers into account, the cancer control potential of HPV-vaccination is considerably higher in women than in men. HPV-vaccination could reduce the burden of screening on women and on health care resources.

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1. Introduction

High-risk (HR) human papillomavirus (HPV) is involved in the pathogenesis of ano-genital and some head and neck cancers, and low risk (LR) HPV 6 and 11 in benign ano-genital conditions [1].

In September 2006 and 2007, respectively, the quadrivalent HPV-vaccine Gardasil[®] (Merck) and the two-valent HPV-vaccine Cervarix[®] (GSK) obtained license in the European Union for use in both men and women from the age of nine years. Both vaccines are recombinant and contain proteins from HPV 16 and 18, which cause 70% of cervical cancers [2]. In addition, Gardasil[®] contains proteins from HPV 6 and 11. Vaccine efficacy studies have shown that Gardasil[®] and Cervarix[®] are both highly protective against

HPV-vaccine-type infection and cervical intraepithelial neoplasia (CIN) in persons HPV-naïve at the time of vaccination [3,4]. Furthermore, Gardasil[®] protects against condyloma and perineal intraepithelial neoplasia (PIN) in men, though the evidence for the latter is based on small numbers [5]. In June 2015, the nine-valent HPV-vaccine Gardasil^{®9} obtained license in the European Union. This vaccine protects against the HR HPV 16, 18, 31, 33, 45, 52, and 58 besides HPV 6 and 11. The seven HR HPV-types cause 90% of cervical cancer [2], and Gardasil^{®9} is highly protective against HPV-vaccine type lesions in persons HPV-naïve at the time of vaccination [6].

National HPV-vaccination programs have been implemented in at least 64 countries [7], including all Nordic countries. In Denmark, HPV-vaccination became part of the child vaccination program for 12 year-old girls in 2009. Before and after there have been temporary catch-up programs for girls and women up to the age of 26 years [8]. In most countries, HPV-vaccination is recommended for girls only, and cost-effectiveness analyses generally conclude that HPV-vaccination of boys is not cost-effective [9]. However some countries, including Australia, the US, parts of

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Canada, Austria and Switzerland recommend gender neutral HPV-vaccination [10–14].

In Denmark, HPV-vaccination is at present offered to girls. But vaccination of boys has been debated, and the argument for vaccination has been supported by the recent observation of an increase in the burden of HPV-related cancers in men [15,16]. The aim of the present paper is to estimate the burden of cancers in Denmark in women and men caused by HPV-infection and to evaluate the impact of HPV-vaccination in cancer control.

2. Material and methods

For each cancer site, we tabulated number of HPV-related cases, defined as all cases with a given site-specific ICD-10 code. Furthermore, we calculated number of HPV-caused cases, defined as proportion of HPV-related cancers assumed to be caused by HPV-infection. We also calculated the number of cancers preventable by the two-/ quadrivalent and the nine-valent HPV-vaccines, respectively.

Cancers related to HPV-infection include cancers of the cervix, vulva, vagina, penis, anus and some head and neck cancers [1,17]. From NORDCAN [18], we retrieved data on incidence rate, number of incident cases, and number of deaths from these cancers in 2010–2014. For head and neck cancer, we focused on oropharyngeal cancer (OPC) because this is the subgroup most closely associated with HPV [1,15]. The following International Classification of Diseases (ICD)-10 codes were used: oropharynx (C01, C05.1–9, C09, C10.0, C10.2–9) and cervix (C53). Data on penile cancer (C60), vulvar cancer (C51), vaginal cancer (C52) and anal cancer (C21) were not specified in the publicly available version of NORDCAN, and these data were therefore retrieved from the web-page of the Danish Cancer Society [19].

Data on HPV-prevalence and genotype distribution in men [20] and women [21] as well as in the selected cancers were retrieved from the literature [2,16,17,22–24]. When available, Danish studies were used, otherwise European. Data on HPV-vaccination coverage was retrieved from Statens Serum Institute (SSI) [25]. Data on number of cervical cytology samples were retrieved from the annual report of the Danish Quality Database for Cervical Cancer Screening (DKLS) [26]. From the Danish National Health Service Register (NHSR) [27] and the Danish National Patient Register (NPR) [28] we obtained combined data from private gynaecologists and hospitals on number of cervical biopsies and conisations. NHSR holds information on service provided by private gynaecologists, and NPR holds information about in- and outpatient contacts to hospitals.

In order to assess the total burden of HPV caused cancer in women, we estimated the number of cervical cancer cases prevented by screening. We used three approaches. First, a previous estimate for Denmark found that one cervical cancer case was prevented for every 6–8 conisations [29]. Second, a study from New Zealand showed that 31.3% of CIN3 left untreated progressed to cervical cancer within 30 years [30]. Finally, it has been estimated that cervical cancer incidence in Denmark in the absence of screening would have been five times higher in 2006–2010 than observed; comparable with the highest incidence currently observed in low-income countries [31].

3. Results

3.1. HPV prevalence in the population

Two studies both used Hybrid capture 2 (HC2) and polymerase chain reaction (PCR) to estimate the HPV-prevalence and genotype distribution in the Danish population [20,21]. When testing 2436

men aged 18–65 years, 30% were positive for HR HPV, 5.8% for HPV-16, 4% for HPV-18, 3% for HPV-31, 1.5% for HPV-33, 1.5% for HPV-45, 3.4% for HPV-52 and 0.8% for HPV-58. In 40,382 women aged 14–95 years, the HR HPV prevalence was 20.5%, 5.4% were positive for HPV-16, 2.4% for HPV-18, 3.8% for HPV-31, 1.7% for HPV-33, 1.9% for HPV-45, 3.9% for HPV-52 and 1.2% for HPV-58.

3.2. Burden of HPV related cancers in men and women

On average, 376 women annually were diagnosed with cervical cancer in 2010–2014 (Table 1). For cancers in the vulva and vagina, there were 108 and 17 new cases per year, respectively. For anal cancer, 97 women were diagnosed per year, and for OPC 102 women. In men, the annual number of new cases was 61, 41 and 282 for penile cancer, anal cancer and OPC, respectively (Table 1). In total, 700 women and 384 men per year were diagnosed with an HPV-related cancer. This translates into age-standardized incidence rates (World standard population) of 15.4 per 100,000 women and 5.5 per 100,000 men according to a newly published ICO report [32].

3.3. Burden of cancers caused by HPV in men and women

It is widely accepted that persistent HR HPV infection is a necessary condition for development of cervical cancer. Walboomers et al. concluded that all cervical cancers are caused by HPV [17]. A study found an HPV-prevalence of 96% in invasive cervical cancer in Danish women [24]. This included two cases of LR-HPV out of 261 cervical cancers. Although the deficit may be due to technical artefacts, there is probably also a minor group of truly negative cervical cancers. HR HPV is estimated to cause between 32% and 84% of the other HPV-related cancers in men and women (Table 1).

The annual number of cancers in Danish women caused by HR HPV thus became 361, 38 and 13 for cervical, vulvar and vaginal cancer, respectively, 81 for anal cancer, and 55 for OPC (Table 1). The annual number of cancers in Danish men caused by HPV became 20, 34 and 180 for penile cancer, anal cancer and OPC, respectively (Table 1). In total, 548 women and 234 men per year were diagnosed with a cancer caused by HPV (Fig. 1).

3.4. Burden of preventable cancers caused by HPV in men and women

HPV16 is the most common genotype in HPV-caused cancers in both sexes (Table 1). HPV18 is the second or third most common in anal-, vulvar-, vaginal- and cervical cancer, but accounts for a very small part in penile cancer and OPC. In total, 401 cancers in women and 197 cancers in men were caused by HPV 16 and 18, two HPV types covered by the two-/quadrivalent vaccines. Approximately 472 cancers in women and 213 cancers in men are caused by the seven HR HPV covered by the nine-valent vaccine (Table 1).

3.5. Cervical screening in Denmark

In 1962, a pilot-screening program was undertaken in Denmark. In 1967, three regional organized programs began, and opportunistic screening started in 1969. National guidelines first came in 1986 recommending screening of women aged 23–59 years every third year. In 2007 this was changed to screening every third year for women aged 23–49 years and every fifth year for women 50–65 years of age. The present guidelines were issued in 2012, adding an HPV-DNA checkout test for women aged 60–64 [8]. Since the introduction of screening, the incidence of cervical cancer has decreased from 44.4 per 100,000 (Nordic standard population) in 1966 to 14.5 per 100,000 in 2014. Mortality decreased from 16 per 100,000 in 1966 to 3.1 per 100,000 in 2014 (Fig. 2).

Table 1
HPV-related cancers in Denmark, 2010–2014.

HPV related cancer type	Number of new cases per year (2010–2014)	Proportion of cancers caused by HR HPV (%)	HR HPV genotypes (% of prevalence) ^c	HR HPV 16 and 18 prevalence (%)	HR HPV 16, 18 31, 33, 45, 52 and 58 prevalence (%)	Estimated cases caused by		
						All HR HPV	HR HPV 16 and 18	HR HPV 16, 18, 31, 33, 45, 52, and 58
Women								
Cervical	376	96 [20]	16 (66) 18 (7), 31 (3), 33 (6), 45 (4), 52 (2), 58 (1) [2] ^a	74 [20]	90 [20]	361	267	325
Vulvar	108	35 [18]	16 (32.2), 18 (4.4), 31 (0.6), 33 (4.5), 45 (1), 52 (0.7), 58 (0.0) [18]	37	43	38	14	16
Vaginal	17	77 [18]	16 (57.4), 18 (7.1), 31 (0.0), 33 (2.9), 45 (1.5), 52 (1.5), 58 (0.0) [18]	65	71	13	8	9
Anal	97	84 [18] ^b	16 (73.4), 18 (5.2), 31 (1.9), 33 (4.8), 45 (0.5), 52 (0.0), 58 (0.0) [18]	79	86	81	64	70
Oropharyngeal	102	54 [12]	16 (86), 18 (0.9), 31 (0.4) 33 (6.3), 45 (0.2), 52 (-), 58 (0.2) [12]	87	94	55	48	52
Total women	700					548	401	472
Men								
Penile	61	32 [19]	16 (68.7), 18 (1.5), 33 (2.9), 31 (0.8), 45 (2.7), 52 (1.5), 58 (1.3) [19] ^d	70	77	20	14	15
Anal	41	84 [18] ^b	16 (73.4), 18 (5.2), 31 (1.9), 33 (4.8), 45 (0.5), 52 (0.0), 58 (0.0) [18]	79	86	34	27	29
Oropharyngeal	282	64 [12]	16 (86), 18 (0.9), 31 (0.4), 33 (6), 45 (0.3), 52 (-), 58 (0.2) [12]	87	94	180	156	169
Total men	384					234	197	213

^a Genotype distribution from other Ref. [2] because of missing separate data on all genotypes in [20].

^b Proportion not separate for men and women.

^c Genotype distribution not separate for men and women for anal and OPC.

^d Genotypes taken from single and multiple, Table 3 [19].

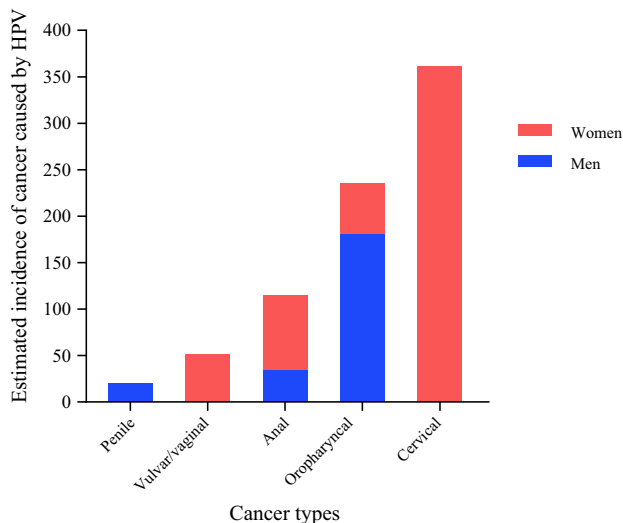


Fig. 1. Cancers cases caused by HPV in Denmark 2010–2014.

In Denmark in 2015, 386,662 cytology samples were performed. Of these 41,003 were abnormal. In total, 24,553 biopsies from the cervical portio and 6119 conisations were performed. In 2010–2014, an annual number of 376 women were diagnosed with cervical cancer, and 99 died from the disease (Fig. 3).

The total burden of HPV-caused cancer in women, including screening prevented cervical cancers resulted in the following estimates based on three earlier described approaches. First, with

6119 conisations per year, we would expect 765–1020 cervical cancer cases to have been prevented by screening; added to the present 376 cases it gives a total of 1141–1396 cases. Second, with a present number of 4399 CIN3 cases per year in Denmark [15], this would give 1377 cervical cancer cases prevented by screening. Added to the 376 present cases this would give 1753 cases. Third, without screening a total of 1846 women (NORDCAN incidence 2006–2010x5) would then have been diagnosed with cervical cancer.

Without screening, every year somewhere between 1100 and 1800 Danish women would have been diagnosed with cervical cancer. When accounting for an HPV prevalence of 96% in cervical cancer [24], and adding the 187 cases of other cancer types caused by HPV in women (Table 1), every year approximately 1300–2000 HPV-caused cancer cases would occur in women in total compared to 234 cases in men.

3.6. HPV-vaccination coverage in Denmark

In Denmark, HPV-vaccination coverage has been quite high until recently. To begin with, coverage for the first dose was around 80% and increased to over 90% for girls born in 1998–2000. The corresponding coverage for full vaccination was close to 80%. However, girls born in 2004, only 45% received the first dose, and – as of today – as few as 17% were fully vaccinated (Fig. 4) [25].

4. Discussion

Our study showed that although the prevalence of HPV-infection was high in both men and women in Denmark,

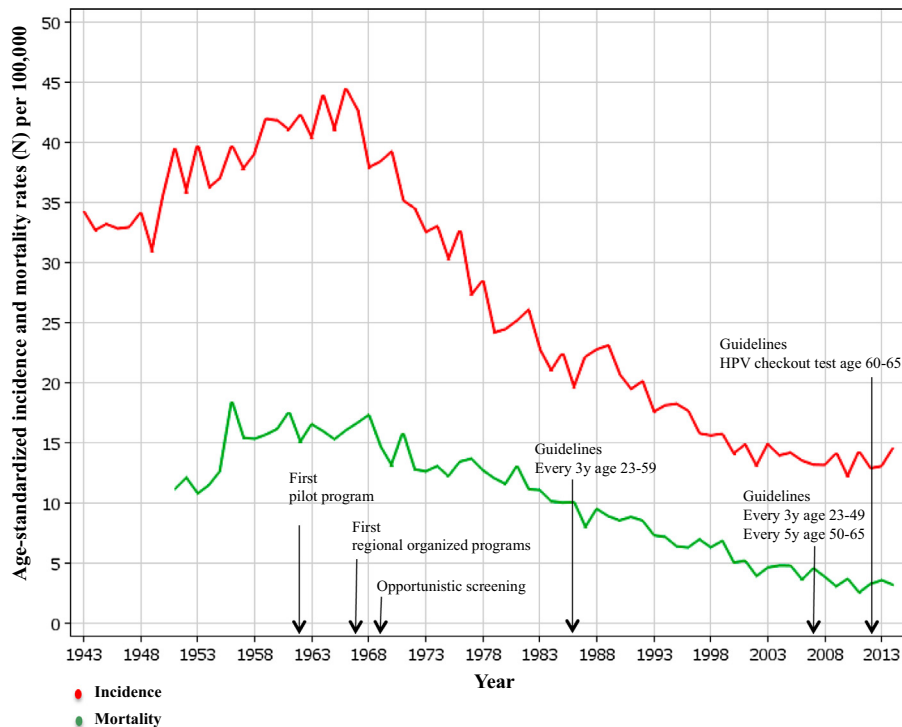


Fig. 2. Age-standardized (Nordic standard population) incidence and mortality rates for cervical cancer with historical marks for the screening program. *Source:* Data retrieved from NORDCAN [18].

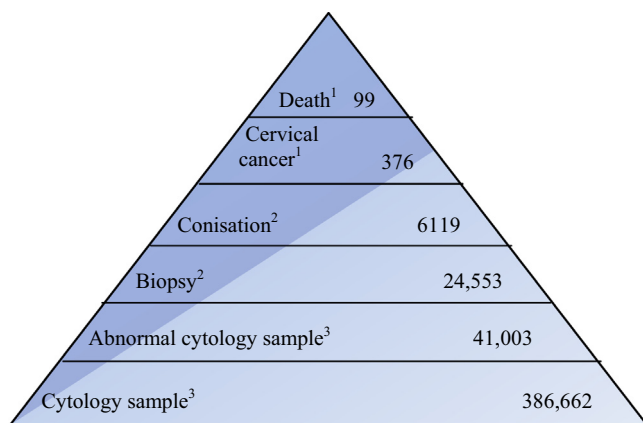


Fig. 3. Activities in the cervical screening program in Denmark. *Source:* ¹NORDCAN, ²NHSR and NPR, ³DKLS annual report 2015.

the burden of cancers caused by HPV-infection was considerably higher in women than in men; 548 cases in women and 234 cases in men, and twice as many cancers in women as in men were preventable with HPV-vaccination. Furthermore, the incidence of cervical cancer has declined significantly since the 1960s due to a well-functioning screening program. We estimated that the actual number of cervical cancers without screening would have been 3–5 times higher than it is today. Including the screening prevented cases, the burden of cancers caused by HPV-infection would be 1300–2000 cases in women as compared to 234 cases in men.

Cervical screening has existed for so long that we tend to take it for granted. But cervical screening is a major burden both for women and for the health care system. In Denmark, with approximately 1.5 million women in screening age [33], every year almost 350,000 women have a screening sample taken; 40,000 have to come back for further examinations; and 25,000 have to visit a

gynecologist to have a cervical biopsy taken. All of these numbers represent women who have to take time off work or other activities to have a test performed and to wait for the answer. Annually, more than 6000 women – equal to 20% of a birth cohort – have a conization performed. Although conization with large loop excision of the transformation zone (LLETZ) is a minor surgical procedure, it can cause bleeding and a risk of infection, and a Danish study found almost a doubling of the risk of preterm birth after LLETZ [34], an observation supported by other studies [35,36].

It is therefore highly desirable to lessen the burden of screening in the control of cervical cancer by primary prevention in terms of vaccination. This is, however, not straightforward due to the differences in progression rates across HR HPV-types. Although Gardasil® prevents 70% of cervical cancer, it prevents only 43% of CIN2+, and 17% of abnormal cytology [37], and Cervarix® prevents 70% of CIN2+ [4]. Gardasil®9 is expected to prevent 70% of CIN2+ (43% as for Gardasil® + 39.6% [6] of the remaining 67%). In Denmark, women with CIN2 in childbearing age are recommended for follow-up with colposcopy and biopsy after 6 months. Women with CIN3 are recommended for immediate conization and for control colposcopy after 6 months [38]. According to the outcome of the randomized controlled trials on HPV-vaccines in women vaccinated as HPV-naïve, the Danish follow-up and treatment burden will thus be reduced by 43% with Gardasil®, 70% with Cervarix® and 70% with Gardasil9® vaccines. With new assays and algorithms, the residual pool of slow progressing lesions can hopefully be controlled with less intensive screening; this is in particular expected if only 10% of cervical cancers remain to be prevented by screening.

Our data presented the current situation in Denmark. However, the pattern of higher burden in women seems to be similar across Northern European. Based on the European ICO report [39] the age-standardized incidence rates (World standard population) for HPV-related cancer in Sweden is 11.1 per 100,000 women and 3.9 per

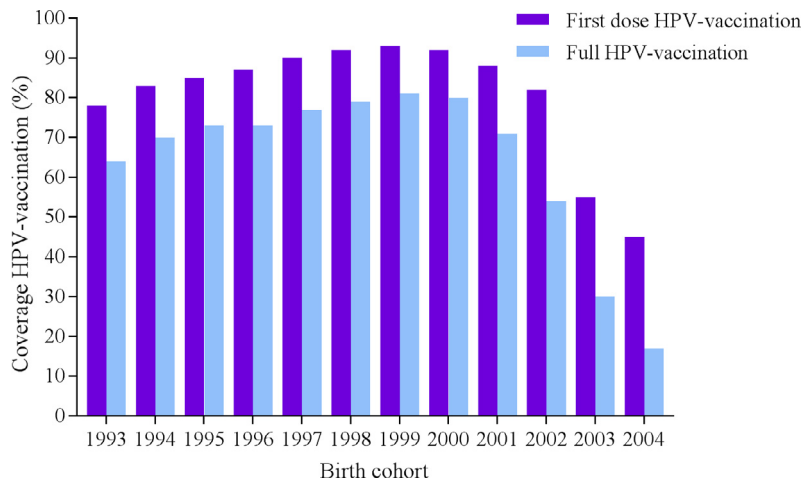


Fig. 4. HPV-vaccination coverage in Denmark. Source: Data retrieved from Statens Serum Institute [25].

100,000 men, in Norway 13.9 per 100,000 women and 3.9 per 100,000 men and in England 11.1 per 100,000 women and 5 per 100,000 men. Recent Danish age-period-cohort modeling of incidence data indicated an increase in the HPV-related cancer burden of men and a decrease in the burden of women [15]. Based on these trends, it was argued that “if the incidence of HPV-associated cervical cancer ... continues to decrease and that of oropharyngeal cancer continues to increase in men” then the cancer burden attributable to HPV “in men will surpass that of women in the near future” [11 p 558]. In eastern Denmark, the age-standardized incidence for OPC increased from 4.0 per 100,000 in 2011 to 4.5 in 2014, and the number of OPC cases was predicted to exceed the number of cervical cancer cases in 2016 [16]. However, when the screening prevented cervical cancer cases are taken into account, the vaccines can prevent 6–8 times more cancers in women than in men.

There is thus from a public health point of view no doubt that the cancer prevention potential of HPV-vaccination is considerably larger for women than for men. So, how are women best protected? Here both vaccination coverage and herd immunity have to be taken into account. A meta-analysis of modeling studies found that with a vaccination coverage of girls of at least 80%, both women and men would be well protected against infection with the vaccine HPV-types [40]. However, if the coverage of vaccination in girls was 60% or below, the relative reduction in HPV-prevalence was considerably improved if both girls and boys were vaccinated. This was in particular true for HPV-16. Another argument for male vaccination is to protect men who have sex with men (MSM), as they are not protected by herd immunity of female vaccination.

In Denmark, vaccination coverage among girls born 1998–2000 was almost 80%. Vaccination of boys would thus have contributed very limited to the reduction of HPV-prevalence in both girls and boys. However, the HPV-vaccination coverage has dropped dramatically in Denmark in the past couple of years due to public concern about possible side effects. A Swedish modeling study found that gender-neutral HPV-vaccination would offer good protection for both men and women, even in situations of impaired coverage [41]. From a public health point of view this would argue for HPV-vaccination of boys. However, the present situation, with only 17% of a birth cohort of girls being fully vaccinated, could be compensated only by a vaccination program in boys with a high attendance rate. If women were willing to comply with vaccination, extra money might – from a population point of view – be better spent on Gardasil®9 vaccination of girls than on Gardasil®/

Cervarix® vaccination of boys, as Gardasil®9 vaccination would protect both women and men, and reduce the need for screening.

Our study has limitations. The reported prevalence of HR HPV and genotype distribution in different cancers vary between countries and studies probably due to variation in underlying risk, sexual behavior, and method of analysis. Whenever possible we used Danish data and otherwise European data, but data were collected from several studies, and the combined numbers were subject to some degree of uncertainty. The HPV-prevalences we used were largely in accordance with those used in other studies [32,42,43], with some exceptions. For example, the prevalence of HPV16 in vulvar cancer varied from 32.2% in our reference to 68% in another [42], and in the ICO report [32] the HPV prevalence in vaginal cancer was somewhat higher 88.9% compared to our reference 77%. This may lead to an underestimation of preventable cancer cases in women. Likewise the HPV prevalence in penile cancer may have been underestimated in our analysis. In our reference 32% of penile cancers were HPV-positive compared to 51% in another [43]. When calculating cancer cases preventable by vaccination we added the relative contributions across genotypes without accounting for multiple infections. This could result in overestimation. The preventive effect of the nine-valent vaccine on cervical cancer may be underestimated because HPV-52 was not included in the estimate. In our analysis we used an HPV-prevalence of 96% from a Danish study, allowing for a small proportion of invasive cervical cancers to be truly HPV-negative [24]. NORDCAN data on incidence of HPV-related cancer types was used. For Denmark, this database builds on the Danish Cancer Register known to have high accuracy. In this study, we focus only on cancer outcomes. This is a limitation when assessing the potential of HPV-vaccination. However, according to the Danish Health Authorities, a criteria for introducing new vaccines into the child vaccination program is that the illness prevented by the vaccine is serious enough to justify risk of possible side-effects [44]. Protection against benign conditions, such as condyloma, is therefore not included in this study.

In summary, the cancer prevention potential of HPV-vaccination cannot be estimated only from the present number of cancers. For women, we see only the tip of the iceberg because screening today prevents the majority of the cervical cancer cases that would otherwise have occurred. But screening is a serious burden both on women and on the health care system, and HPV-vaccination will decrease the need for screening, especially if 90% of cervical cancers were prevented by vaccination. The potential

impact of HPV-vaccination on the future cancer burden is thus even more beneficial when the hidden iceberg of cervical cancers is taken into account.

5. Conclusion

At present, cancers caused by HPV-infections were twice as common in women as in men in Denmark, and twice as many cancer cases were preventable with HPV-vaccination. Furthermore, there was a hidden burden of HPV-caused cancers in women because the present level of cervical cancer results from 50 years of screening and treatment of precancerous lesions. Indeed, when cervical cancers prevented by screening were included in the estimate, the burden of HPV-caused cancers was 6–8 times higher in women than in men. It is therefore highly desirable to lessen the burden of screening in the control of cervical cancer by primary prevention in terms of vaccination. High vaccination coverage of girls would offer effective protection against HPV-infections in both women and men. Somewhat lower vaccination coverage of girls could be compensated for by vaccination of boys. Unfortunately, Denmark at present has such a low vaccination coverage of girls that compensation from vaccination of boys would be achieved only if the coverage in boys would be high. First of all, the present low vaccination coverage of girls in Denmark has negative consequences for both women and men, and concerted efforts should be taken to increase this coverage.

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Conflict of interest

All authors have completed the disclosure form and declare no financial relationships with any organisation that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work.

Authorship declaration

All authors have contributed to the conception, acquisition and analysis of data, interpretation of results, and writing of the manuscript. All authors have approved the final version of the submitted manuscript.

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