The Burden of Genital Warts: A Study of Nearly 70,000 Women from the General Female Population in the 4 Nordic Countries

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(See the article by the Future II Study Group, on pages 1438–46, and the editorial commentary by Hildesheim and Herrero, on pages 1431–2.)

Objective. To asses the burden and correlates of genital warts in women.

Methods. We conducted a population-based cross-sectional study in 69,147 women (18–45 years of age) randomly chosen from the general population in Denmark, Iceland, Norway, and Sweden. Information on clinically diagnosed genital warts and lifestyle habits was collected using a questionnaire.

Results. Overall, 10.6% reported ever having had clinically diagnosed genital warts. In addition, 1.3% reported having experienced genital warts within the past 12 months. The cumulative incidence for different birth cohorts, estimated on the basis of age at first diagnosis of genital warts, increased with each subsequent younger birth cohort ($P < .01$). The lifetime number of sex partners was strongly correlated with a history of genital warts (odds ratio for $\geqslant$15 partners vs. 1 partner, 9.45 [95% confidence interval, 7.89–11.30]). The likelihood of reporting genital warts also increased with a history of sexually transmitted disease, use of hormonal contraceptives, use of condoms, smoking, and higher education.

Conclusions. The data suggest that ~1 in 10 women in the Nordic countries experience genital warts before the age of 45 years, with an increasing occurrence in younger birth cohorts. These data are important for developing and evaluating strategies (e.g., human papillomavirus [HPV] vaccination) to control and prevent HPV infection and disease in the population.

Genital human papillomavirus (HPV) infection is the most common viral sexually transmitted infection (STI). The pathogenetic spectrum of genital HPV infections is broad, ranging from cancer to genital warts. Even though a condition with genital warts is not life-threatening, these lesions can cause clinical symptoms, such as burning, itching, bleeding, and pain. A diagnosis of genital warts can also cause psychosocial stress, resulting in decreased self-esteem, negative self-perception, embarrassment, and anxiety [1, 2]. Although the HPV types associated with genital warts (HPV-6 and HPV-11 account for ~90% of episodes) may not cause cervical cancer, women with a history of genital warts have been shown to have an increased risk of cervical intraepithelial neoplasia (CIN) and cancer [3, 4], which is most likely explained by a higher risk of having other, carcinogenic HPV types.

Genital warts represent not only a health problem for the individual but also an economic burden for society. One study of genital warts among privately insured in-

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dividuals estimated an annual cost of $140 million for US private health plans in relation to the diagnosis and treatment of genital warts [5]. Results from a recent study estimated a cost of £10.1 million for managing incident cases of genital warts only in 2003 in the United Kingdom [6].

Several studies have suggested that HPV infection, including infection with HPV-6 and HPV-11, is a major and most likely increasing problem [7–9]. However, the majority of studies of the prevalence and incidence of genital warts have been conducted in selected populations, such as sexually transmitted disease (STD) clinic attendees, university students, or individuals insured through private health plans [5, 10–12]. Thus, few data have originated from general population studies [13, 14]. As a result, knowledge about the overall and dynamic occurrence of genital warts across different birth cohorts in the female population is limited. Such data are important for developing and evaluating strategies to control and prevent HPV infection and disease (e.g., genital warts) in the population. Given that a prophylactic vaccine against HPV-16, -18, -6, and -11 has recently become publicly available in many countries, establishing and understanding the burden of genital warts at the general population level can inform vaccine policy decisions.

The overall aim of the present study was to assess the occurrence and correlates of genital warts in random samples of the general female population in the 4 Nordic countries.

SUBJECTS, MATERIALS, AND METHODS

Study population. In each of the 4 countries (Denmark, Iceland, Norway, and Sweden), each citizen has a unique personal identification number (PIN), comprising information about sex and date of birth. These PINs are registered in a national, computerized central population registry in each country, together with information on vital status, migration, and current address on the individual level. By use of these computerized population registries, which cover the entire population in the respective country, a random sample of women (18–45 years of age) was drawn from the general female population in each country, using the PIN as the key identifier. Informed consent was obtained from each study participant. The study was approved in each country by the data protection board and the scientific ethics committee.

Our goal was to include at least 14,000 women in each country. A priori, we anticipated an overall response rate of 50%–60%, implying that ~25,000–28,000 women in each country should be invited for the study. The final number of invited women in each country was mostly dependent on what was logistically feasible in the respective country.

From November 2004 to June 2005, a total of 28,000 women were invited to participate in both Denmark and Iceland, whereas 25,001 women and 25,000 women were invited from Norway and Sweden, respectively (1 extra woman was erroneously drawn from Norway). Women who had moved or emigrated, who had died before our contact, or who did not speak the respective Nordic language were ineligible for the study, leaving 27,272 Danish women, 27,548 Icelandic women, 24,424 Norwegian women, and 24,689 Swedish women as potential participants. A total of 1737 Danish women, 422 Icelandic women, 2409 Norwegian women, and 1661 Swedish women explicitly stated that they did not want to participate in the study, whereas no response was obtained from 3336 Danish women, 12,075 Icelandic women, 5411 Norwegian women, and 7315 Swedish women. Thus, we recruited for the study 22,199 Danish women (participation rate, 81.4%), 15,051 Icelandic women (54.6%), 16,604 Norwegian women (68.0%), and 15,713 Swedish women (63.6%), for a total of 69,567 women. We excluded 81 women who had incomplete questionnaires or a discrepancy between their PIN and the year of birth reported, such that the population in this study consisted of 69,486 women (22,173 from Denmark, 15,025 from Iceland, 16,575 from Norway, and 15,713 from Sweden). For this article, we excluded 339 women who did not answer the question about genital warts; consequently, a total of 69,147 women were available for the present analysis.

Data collection. To guarantee confidentiality for the participants, all invited women were appointed a unique study number by the national study centers. An invitation letter and a self-administered structured questionnaire were mailed to each woman in Denmark, Iceland, and Norway. It was also possible to answer the questions by means of a Web-based questionnaire, which could be accessed using the unique study number and a personal access code, which were provided in the invitation letter (in Sweden, this was initially the only option). In all 4 countries, women who did not respond within 3–4 weeks received a reminder, including the questionnaire, by postal mail. For those who still did not respond, either the women were contacted by phone and reminded about the study (Iceland) or a telephone interview was conducted whenever possible (Denmark, Norway, and Sweden). The telephone interview comprised the same questions as those included in the self-administered paper- or Web-based questionnaire.

Via the survey, we obtained information on sociodemographic variables as well as on smoking history, alcohol intake, reproductive history, contraceptive use, and sexual habits. In addition, we collected information on ever having had a clinical diagnosis of genital warts, genital warts during the previous 12 months, age at first diagnosis of genital warts, and previous episodes of other STIs (genital chlamydial infection, gonorrhea, genital herpes, and trichomoniasis).

Statistical analysis. Correlates of self-reported genital warts were examined using univariate and multiple logistic regression, by which odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated. Variables were selected on the basis of the current literature. The multivariate analysis was initially performed separately for each country; however, because the results were very similar (data not shown), we included all 4 countries in 1

Table 1. Mode of response, by country.

Country	Included by means of		
	Paper-based questionnaire	Web-based questionnaire	Telephone interview
Denmark	76	9	15
Iceland	59	38	3
Norway	78	12	10
Sweden	53	36	11

NOTE. Data are percentage of subjects.

analysis, adjusting for country in the final statistical model. We also examined the results restricted to each mode of response (i.e., paper-based questionnaire, Web-based questionnaire, and telephone interview), but, because we found no substantial differences in the overall results according to mode of response, only the combined analysis is presented here.

On the basis of information on age at first diagnosis of genital warts, the cumulative incidence of having had genital warts up to a certain age was estimated by means of the life table (actuarial) method, stratified by country and birth cohort.

RESULTS

Denmark provided the highest proportion of women (32%), followed by Norway (23.9%), Sweden (22.5%), and Iceland (21.6%). Table 1 shows the distribution of mode of response by country, with Iceland and Sweden having the highest proportion of women responding by means of the Web-based questionnaire and Denmark and Norway having the highest proportion responding by mail.

Nearly 8% of the women in the overall study population were 20 years of age or younger, with 16%–20% in each of the subsequent 5-year age groups and the age distribution being similar in the 4 countries (mean age, 31.8 years for Denmark, 32.2 years for Iceland, 31.2 years for Norway, and 32.2 years for Sweden). The majority of the women were married or cohabiting (69.6%). The median lifetime number of sex partners was 5 and the median age at first intercourse was 16 years. A little more than 1 in 5 women reported ever having had an STD other than genital warts (data not shown).

A total of 7351 women (10.6%) reported having had at least 1 previous episode of clinically diagnosed genital warts, and 912 women (1.3%) had experienced genital warts during the past 12 months (data not shown). The prevalence of ever having had genital warts ranged from 12.0% (95% CI, 11.5%–12.6%) in Iceland to 9.5% (95% CI, 9.0%–9.9%) in Norway (table 2). The same pattern was reflected in the mean lifetime number of sex partners, for which Icelandic women and Norwegian women had, respectively, the highest (8.8) and the lowest (7.4) mean lifetime number of sex partners. Icelandic women also had the lowest mean age at first diagnosis of genital warts (21.3 years), whereas the Norwegian women had the highest mean age at first diagnosis of genital warts (22.7 years), with Denmark and Sweden in between (21.9 years).

We examined the proportion of women reporting having had genital warts during the past 12 months in relation to age of the women at enrollment in the study, and the same picture emerged in all 4 countries—namely, a decreasing proportion of women with genital warts during the past 12 months with increasing age (figure 1). The proportions for all 4 countries were similar from ages 26 to 45 years, whereas younger Icelandic women were much more likely to report genital warts during the past 12 months (4.7% vs. ~2% in the other 3 countries).

In figure 2*A*, the cross-sectional proportion of women reporting ever having had clinically diagnosed genital warts according to birth cohort is presented for each country. For Iceland, Norway, and Sweden, the prevalence initially increased with increasing birth cohort. However, for older birth cohorts, a lower prevalence of having had genital warts was observed. In contrast, a continuously increasing prevalence with increasingly older birth cohorts was found among Danish women. Icelandic women born after 1973 reported a much higher prevalence of genital warts than in any other country (figure 2*A*). Sexual activity in terms of mean lifetime number of sex partners by birth cohort in the different Nordic countries (figure 2*B*) mirrored the picture observed for the age-specific prevalence of genital warts. We observed a tendency, most pronounced for Iceland, for younger birth cohorts to report more partners than older cohorts, with the exception of women in the youngest birth cohort, who had not yet accumulated that many partners. The pattern differed in Denmark, where the number of partners remained constant for the birth cohorts born in 1974 or before.

Table 3 displays correlates associated with a history of clinically diagnosed genital warts. We found that the most important

Table 2. Selected characteristics with regard to sexual habits and genital warts in the 4 Nordic countries.

Characteristic	Denmark	Iceland	Norway	Sweden
Self-reported history of clinically diagnosed genital warts, % (95% CI)	10.1 (9.7–10.5)	12.0 (11.5–12.6)	9.5 (9.0–9.9)	11.3 (10.8–11.8)
Lifetime no. of sex partners, mean (range)	8.4 (0–500)	8.8 (0–100)	7.4 (0–100)	8.6 (0–450)
Age at first diagnosis of genital warts, mean (range), years	21.9 (6–45)	21.3 (14–43)	22.7 (3–45)	21.9 (14–44)
Genital warts during the last 12 months, % (95% CI)	1.3 (1.2–1.5)	1.9 (1.7–2.1)	1.1 (1.0–1.3)	1.0 (0.9–1.2)

NOTE. CI, confidence interval.

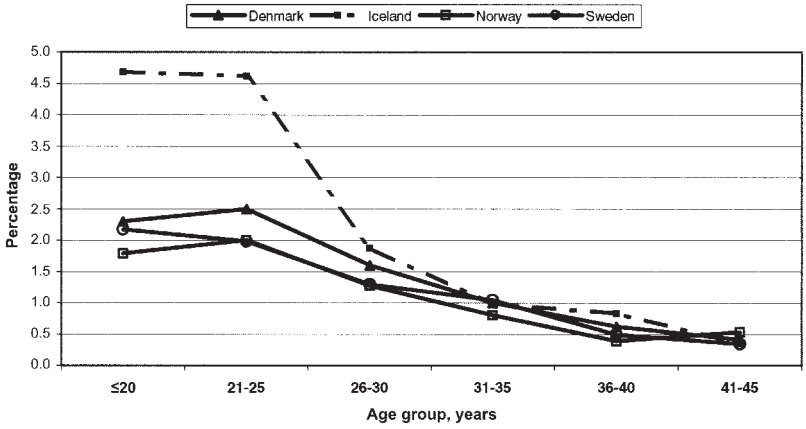

Figure 1. Proportion of self-reported clinically diagnosed genital warts during the past 12 months, by age and country

factor was the lifetime number of sex partners (OR for ⩾15 partners compared with 1 partner, 9.45 [95% CI, 7.89–11.30]). Other important correlates included older age and a history of other STIs. In addition, use of hormonal contraceptives, condom use, ever having had an abortion, more education, and smoking for >59 pack-years increased the probability of reporting genital warts.In contrast, a history of genital warts was not strongly correlated with marital status (data not shown), age at

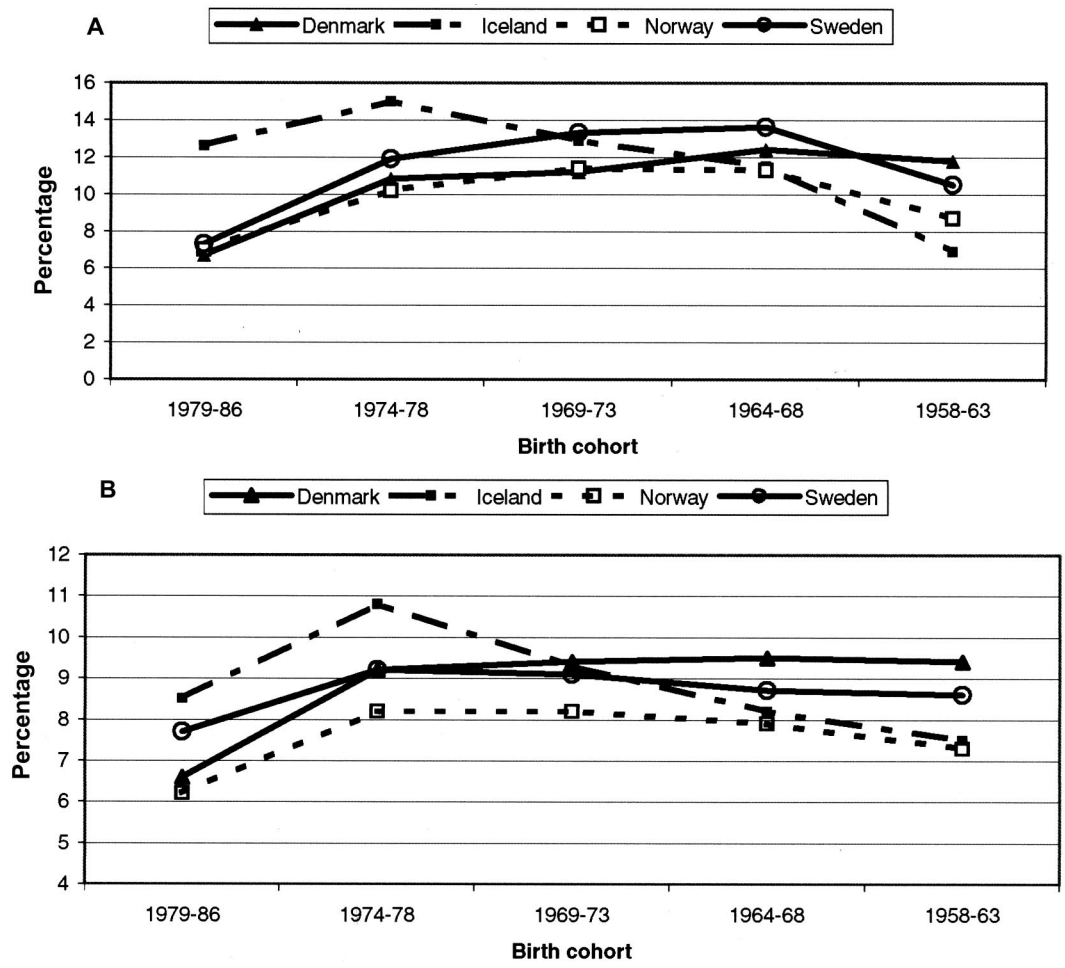

Figure 2. Prevalence of self-reported clinically diagnosed genital warts *(A)* and mean lifetime no. of sex partners *(B)* among 69,147 women 18–45 years of age, by birth cohort and country.

Table 3. Correlates of ever receiving a clinical diagnosis of genital warts among 69,147 women from the 4 Nordic countries.

Category, parameter	No.	% with genital warts	OR[a]	OR[b] (95% CI)
Country				
Denmark	22,106	10.1	1	1
Iceland	14,955	12.0	1.21[c]	1.13 (1.05–1.23)
Norway	16,499	9.5	0.95	0.99 (0.91–1.07)
Sweden	15,587	11.3	1.10[c]	1.13 (1.05–1.22)
Age				
18–20 years	7178	4.3	1	1
21–25 years	13,354	9.1	2.21[c]	1.48 (1.27–1.74)
26–30 years	10,978	12.1	3.03[c]	1.68 (1.43–1.98)
31–35 years	12,321	12.3	3.10[c]	1.83 (1.54–2.16)
36–40 years	13,061	12.4	3.12[c]	1.93 (1.62–2.30)
41–45 years	12,255	10.3	2.55[c]	1.64 (1.37–1.95)
Pregnancy history				
Never pregnant	23,630	8.4	1	1
Pregnant but no births	4937	15.8	1.75[c]	1.16 (1.05–1.28)
1 birth	10,984	12.9	1.23[c]	1.04 (0.95–1.14)
2 births	17,879	11.0	0.98	0.99 (0.90–1.09)
3 births	8280	10.4	0.92	1.02 (0.91–1.14)
⩾4 births	2393	8.4	0.73	0.81 (0.68–0.98)
Hormonal contraceptives				
Never	7319	4.2	1	1
Ever	61,314	11.4	2.75[c]	1.55 (1.36–1.77)
Condom use				
Never	8385	4.3	1	1
Ever	60,157	11.6	2.75[c]	1.44 (1.27–1.63)
Age at first intercourse				
⩾20 years or never	9044	4.5	1	1
17–19 years	23,668	9.4	2.22[c]	0.97 (0.85–1.10)
15–16 years	26,786	12.5	3.17[c]	1.01 (0.88–1.14)
⩽14 years	7452	16.5	4.50[c]	1.06 (0.92–1.22)
Lifetime no. of sex partners				
0	1139	1.1	0.64	0.97 (0.62–1.52)
1	8995	1.9	1	1
2–4	16,642	5.2	2.80[c]	2.60 (2.17–3.11)
5–9	18,231	11.1	6.25[c]	4.98 (4.18–5.93)
10–14	9500	16.6	9.93[c]	6.96 (5.81–8.33)
⩾15	10,441	23.1	14.82[c]	9.45 (7.89–11.30)
STD[d]				
Never	54,033	7.7	1	1
Ever	14,866	21.2	3.12[c]	1.91 (1.80–2.02)
Education				
⩽12 years	27,810	9.2	1	1
13–16 years	27,166	11.4	1.19[c]	1.13 (1.06–1.20)
⩾17 years	13,217	12.2	1.20[c]	1.16 (1.07–1.25)
Smoking (pack-years)				
Never	35,799	8.2	1	1
Less than or equal to median	15,900	12.8	1.59[c]	1.07 (1.00–1.15)
More than median	15,965	14.1	1.82[c]	1.11 (1.03–1.18)
Alcohol (drinks per week)				
Never	8404	7.2	1	1
Less than or equal to median	29,835	10.1	1.44[c]	1.05 (0.95–1.16)
More than median	29,781	12.3	1.91[c]	1.10 (0.99–1.21)

NOTE. Missing values were excluded from the analysis. CI, confidence interval; STD, sexually transmitted disease; OR, odds ratio.

[a] Adjusted for age.
[b] All factors mutually adjusted.
[c] 95% CI excludes 1.0.
[d] Includes genital chlamydial infection, gonorrhea, trichomoniasis, and herpes.

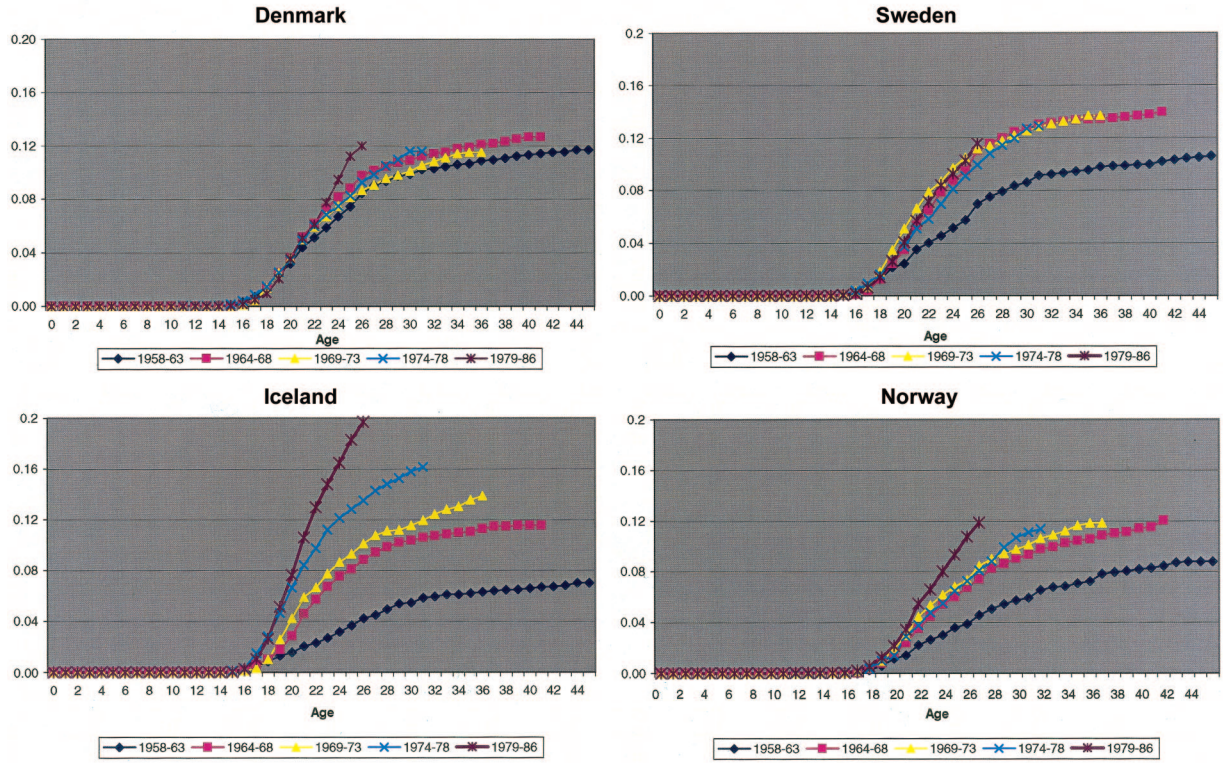

Figure 3. Estimated cumulative incidence of self-reported clinically diagnosed genital warts, by country and birth cohort. The cumulative incidence of having had genital warts up to a certain age was estimated on the basis of information on age at first diagnosis of genital warts.

first sexual intercourse, number of births, and alcohol intake after adjusting for other risk factors. The analysis of correlates associated with the risk of genital warts was also performed separately for each country, but only the analysis for all 4 countries combined is shown, because the results were similar for all countries. In addition, the overall results did not vary according to the way the women responded (data not shown).

Finally, we estimated age-specific incidences of self-reported clinically diagnosed genital warts by age at first diagnosis and birth cohort. The age-specific incidences were generally higher in Iceland, Denmark, and Sweden than in Norway. In Iceland and Norway especially, the age-specific incidence increased strongly with each subsequent younger birth cohort (figure 3), whereas in Denmark the age-specific incidence did not differ much among the birth cohorts. The biggest difference between birth cohorts was observed in Iceland, for which the age-specific incidence for the birth cohorts 1974–1978 and 1979–1986 exceeded that for all of the other countries.

DISCUSSION

In this population-based study of nearly 70,000 women 18–45 years of age, we found that, overall, 10.6% reported ever having had a clinical diagnosis of genital warts. Thus, 1 in 10 Nordic women experience the medical and psychosocial burden of genital warts, and society bears the economic burden of treatment. Results from recent studies of a quadrivalent HPV-6/11/16/18 vaccine has shown close to 100% protection against genital warts in women [15].

The prevalence of genital warts did not differ much across the 4 Nordic countries, but these prevalences are somewhat higher than those reported in previous prevalence studies that were based on representative random population samples (e.g., from Australia [4.4% among 9134 women 16–59 years of age]) [16]. The overall estimate, however, is a little lower than an estimate reported in a previous Danish study (17% among 11,088 women 20–29 years of age) [13]. Apart from the difference in the ages of participants between the Danish study and the present study, which can explain some of the variation, the Danish study included only women from the greater Copenhagen area, where the lifetime number of sex partners is generally higher than that for the entire country [17]. Our results for genital warts are in line with those regarding another STI, genital herpes simplex virus (HSV) infection, for which a recent review concluded that HSV-2 prevalence is higher in Scandinavia than in other areas of Europe [18]. The results of our study showing that Iceland had the highest prevalence of genital warts, that Sweden and Denmark had the next highest prevalence, and that Norway had the lowest prevalence is consistent with observations for genital chlamydial infection, which displays a similar pattern [18].

In 3 of the countries (Iceland, Norway, and Sweden) included in the present study, we found that the prevalence of genital

warts was higher among the recent birth cohorts, with the pattern being most pronounced in Iceland. This could be due to a truly increased exposure to HPV among younger birth cohorts, or it could reflect differences in health-seeking behavior, implying that a higher proportion of women from younger birth cohorts have their genital warts clinically diagnosed. A similar pattern could also arise if older women were consequently more likely to forget and thus underreport episodes of genital warts. However, in Denmark, an increasing prevalence of genital warts with increasingly older birth cohorts was observed. Interestingly, the pattern of the mean lifetime number of sex partners according to birth cohort in the 4 countries also mirrored the pattern observed for the prevalence of genital warts in a given birth cohort, supporting the view that genital warts is an increasing problem that is due to increasing exposure. There is no reason to believe that significant differences exist in recalling a previous episode of genital warts or lifetime number of sex partners between the 4 Nordic countries. Therefore, these patterns may reflect a paradigm shift in sexual practice in the younger birth cohorts, especially in Iceland but also in Norway and Sweden, with a higher lifetime number of sex partners. In contrast, such a shift may have happened earlier in Denmark (i.e., before the cohorts analyzed in this study), resulting in the observed continuously increasing prevalence of ever having had genital warts with older birth cohorts. Support for this comes from a study that found that age at first intercourse remained unchanged among Danish adolescents from 1986 to 1993 [19] as well as from another recent study that reported no significant changes in the number of partners or in the proportion of sexually experienced persons among adolescent women from 1982 to 2001 [20]. Iceland is usually considered to be very similar to the other Nordic countries, but, in the present study, it differed by having on average the highest lifetime number of sex partners and the youngest age at first intercourse. These findings are in line with a recent study reporting a significantly higher teenage pregnancy rate in Iceland than in the rest of the Nordic countries [21]. In addition, a recent Icelandic study [22] found an increase in the occurrence of high-grade lesions at the first screening visit in women $<$25 years of age after 1980, possibly also indicating a change in exposure to HPV.

Our results from the analysis of the age-specific incidences of genital warts by birth cohort give additional support to the view of a shift in sexual practices among younger birth cohorts. Because the incidence of a first diagnosis of genital warts at a certain age increased with each subsequent younger birth cohort, the effect could not be explained solely by the younger birth cohorts contracting genital warts earlier.

The results of our study indicating an increasing incidence of genital warts in the younger female population are in line with those from other studies of incident episodes of genital warts [7], with those from studies of rates of new genital wart claims [12], and with some HPV seroprevalences over calendar time [23], but not all [24]. Consistent with other studies [13, 14, 25], we observed that a history of genital warts correlated strongly with indicators of sexual habits, such as lifetime number of sex partners and previous STIs (genital chlamydial infection, gonorrhea, genital herpes, and trichomoniasis), with 82% of all cases occurring in women with 5 or more partners. We also found that reporting previous genital warts correlated with other health-related behaviors and demographic variables, such as the use of hormonal contraceptives, smoking habits, and education, a finding that has also been reported by others [13, 14, 25, 26].

Some potential limitations of the study should be considered. Even though we had a reasonably high overall response rate considering the sensitive nature of many of the questions in the questionnaire, we cannot exclude the existence of bias pertaining to nonparticipation or recall bias. We only had information about age in nonparticipants, and in all 4 countries the age distribution was very similar to that among the participating women (data not shown). In addition, the accuracy of self-reported genital warts has been questioned but is largely unknown [27], and, in the United Kingdom, where STIs are routinely registered, a high consistency has been found between population rates and self-reported behavior [28]. However, in one study, it was found that the concordance between self-reported genital warts and a medical examiner's finding increased if the person had had a previous episode of genital warts. Hence, to obtain the highest possible validity, we restricted our analysis to include only clinically diagnosed genital warts, which may be easier to remember. On the other hand, this may imply that the estimated occurrence is most likely an underestimate of the true prevalence and/or incidence. Finally, in assessing correlates of genital warts, the association between a history of genital warts and some of the behavioral factors cannot automatically be interpreted as being causal or temporal, because of the cross-sectional nature of the study.

Our study has several strengths. First, this is the largest study to date to assess the occurrence of clinically diagnosed genital warts in 4 different countries. Second, in contrast to the majority of studies of genital warts, this investigation was conducted on a nationwide basis, being based on random samples from the general population in the respective countries, thus making the results potentially more generalizable. Third, the fairly high response rates, given the sensitive nature of the subject matter, help reduce potential selection bias.

In conclusion, genital warts frequently occur among women in the Nordic countries. At least 1 in 10 women reported having received a clinical diagnosis of genital warts before the age of 45 years. In addition, the results of this study indicate an increasing incidence of genital warts among younger birth cohorts. Recently, a number of landmark clinical studies have demonstrated that a prophylactic HPV vaccine can prevent HPV infection and disease [29–33]. Given the success of these studies, it is anticipated that an HPV vaccine that prevents infection, CIN, and

genital warts will soon be available in many countries. Although clinical studies are sufficient for vaccine licensure, policymakers will seek additional information to formulate HPV vaccination policy [34]. In particular, policymakers will seek information on the epidemiological trends in HPV infection and diseases in the population, the potential burden of the HPV diseases prevented by vaccination, and projections of the long-term benefits and costs of vaccination. The results for genital warts from this study will fill a gap that is necessary for understanding the changing dynamics of genital warts in the population, for generating estimates of the economic burden of HPV in relation to genital warts, and for developing mathematical models to project the long-term benefits and costs of HPV vaccination.

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