Vulvar cancer in high-income countries: increasing burden of disease

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Novelty and impact

This is the first systematic exploration of trends in vulvar cancer incidence across multiple countries using cancer registry data. The study found that the age-standardised incidence rate of vulvar cancer in women <60 years of age has increased significantly in the last 20 years in high-income countries. The findings are consistent with changing sexual behaviours and increasing levels of exposure to HPV in cohorts born around/after 1950.

CONFLICT OF INTEREST

KCa is co-Principal Investigator of an investigator-initiated trial of cytology and primary HPV screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the Victorian Cytology Service. The Victorian Cytology Service has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana. KCa is also a Principal Investigator of Compass in New Zealand (Compass NZ; ACTRN12614000714684), which is conducted and funded by Diagnostic Medlab, now Auckland District Health Board. Diagnostic Medlab received equipment and a funding contribution for the Compass trial from Roche Molecular Systems. Neither KCa nor her institution on her behalf (Cancer Council NSW) receive direct or indirect funding from industry for Compass Australia or NZ, or any other project.

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ABSTRACT

The aim of this study was to assess trends in the age-specific incidence of vulvar cancer in 13 high-income countries satisfying *a priori* conditions regarding the availability of cancer registry data over a 20 year period; these were Canada, USA, 9 European countries, Australia and Japan. Five-yearly incidence and population at risk were obtained from *Cancer Incidence in Five Continents* for the years 1988-1992 (Volume 7) to 2003-2007 (Volume 10). The 5-yearly average percent change (AvPC) over the 20-year period and standardised rate ratios (SRRs) for 2003-2007 vs. 1988-1992 were used to assess changes in the age-standardised incidence rates of vulvar cancer for all ages, and for <60 years and 60+ years. During the study period, the 5-yearly AvPC across the 13 countries increased by 4.6% (p=0.005) in women of all ages, and 11.6% (p=0.02) in those <60 years. No change was observed in women aged 60+ years (5-yearly AvPC=0.1%, p=0.94). The SRR for 2003-2007 vs 1988-1992 was significantly elevated in women <60 years of age (SRR=1.38, 95% CI: 1.30-1.46), but not in women of 60+ years (SRR=1.01, 95% CI: 0.97-1.05). The increase in incidence in women <60 years of age drove a significant increase in the overall SRR in women of all ages (SRR=1.14, 95% CI: 1.11-1.18). The findings are consistent with changing sexual behaviours and increasing levels of exposure to HPV in cohorts born around/after 1950, but younger cohorts offered HPV vaccination are likely to receive some protection against developing vulvar cancer in the future.

INTRODUCTION

Vulvar cancer accounts for 4% of all gynaecological cancers globally, with around 65% of all cases occurring in more developed regions.[1] Human papillomavirus (HPV) is responsible for 22-40% of vulvar cancers worldwide, but geographical variation in the HPV-attributable fraction has been observed.[2, 3] More than 90% of vulvar cancers are squamous cell carcinomas (SCC). The two most frequent morphological variants of SCC are keratinising (>60% of SCCs) and warty/basaloid (~30% of SCCs) types, which are associated with distinct risk factor profiles particularly with regards to age.[4, 5] Keratinising vulvar carcinomas occur more often in older women. These lesions are thought to arise from chronic vulvar dermatoses, especially lichen sclerosus, and are rarely associated with HPV. By contrast, warty/basaloid subtypes are more common in younger women, are very often associated with HPV DNA detection, and share a similar risk factor profile to cervical cancer.[4, 5] SCC of the vulva develops from high-grade vulvar intraepithelial neoplasia (VIN), either HPV-induced usual type (uVIN) or HPV-independent differentiated type (dVIN).[6]

Recent studies in several high-income countries have reported that the incidence rates of vulvar cancer in women of all ages have been stable[7-10] or increasing[11-14]. However, these studies were performed over heterogeneous time periods, mostly focused on one subtype only (i.e. SCC) and often age-specific trends were not well documented. We have previously described trends in incidence and mortality from vulvar cancer in Australia, and found that the increase in the incidence rate in women of all ages in the last few decades was largely driven by an increase in women <60 years of age; we speculated that this may be due to increasing HPV infection in younger women, associated with secular population changes in sexual behaviour over the last several decades.[15]

The aim of the current study was to systematically assess trends in age-specific incidence of vulvar cancer in all countries for which suitable registry data were available, to determine if the significant increase in rates of vulvar cancer incidence that was observed in Australia is also observed in other countries.

MATERIALS AND METHODS

Data sources

Data were obtained from *Cancer Incidence in Five Continents* (CI5), with invasive vulvar cancer cases diagnosed between 1988-1992 (CI5 Volume 7) and 2003-2007 (Volume 10) included in the analysis.[16] Data were available in 5-year aggregate blocks. We included all cases classified as C51 (malignant neoplasm of the vulva) according to the 10th revision of the International Classification of Disease (ICD-10), which includes all histological subtypes.

Countries were included in the analysis if the available registry data satisfied several *a priori* conditions, as follows: i) at least one jurisdictional registry in the country covered the entire catchment area and reported for the whole period from 1988 to 2007; ii) the reported incidence of vulvar cancer for the reference period 1988-1992 was not zero, so any possible change in the incidence of vulvar cancer in the later period could be assessed; and iii) information on the population at risk in each 5-year age group (0-4, 5-9, …, 80-84 and 85+ years) was available. Since vulvar cancer is a rare disease we focused on a pooled estimates to assess trends by combining data across the countries, whilst quantifying statistical uncertainty by providing 95% confidence intervals whether results are presented at a country level or aggregated across countries.

Ethics approval was not required for this study since publicly available aggregate data were used for the analysis.

Analysis of trends in the incidence of vulvar cancer

Pooled analysis (combining all 13 countries and for specific geographical regions) as well as country-specific analyses were performed to describe the trends in the incidence of vulvar cancer in women of all ages, and in women <60 years and 60+ years of age.

Age-specific incidence rates of vulvar cancer were calculated in women 20+ years at diagnosis and the results were stratified by birth cohort to examine trends in the incidence rates with successive birth cohorts. Birth cohort-specific information was analysed for cohorts born every 5 years between 1900 and 1983. Estimates were based on 5-year groupings of age at diagnosis, and 5-yearly diagnosis period. Age-standardised rates (ASRs) for cancer incidence were calculated using the Segi 1960 Standard Population.[17] The 5-yearly average percent change (AvPC) in the age-standardised incidence rate was calculated with regression models using 'Joinpoint' (restricting analyses to a maximum of 1 Joinpoint over the period) to test whether there was a significant change in the ASR over time.[18]

We then calculated the standardised rate ratio (SRR), which is the ratio of the 5-year average aggregated standardised incidence rate at the end of the study period (2003-2007) relative to the rate at the beginning of the study period (1988-1992), as well as the 95% confidence interval (CI)s for the SRRs using Poisson approximation.[19] The SRR for 2003-2007 compared to 1998-2002 was also calculated as a sensitivity analysis in order to confine the period of interest to that in which ICD-10 applied and thus to exclude possible artefactual effects of

change in the disease classification from ICD-9 to ICD-10 on the estimated incidence of vulvar cancer over time.

Prediction of future burden of vulvar cancer

The number of vulvar cancer cases in the year 2025 and the year 2050 in the absence of HPV vaccination was predicted by using the results from this analysis on trends in the age-specific incidence in each country using a conservative approach. That is, when projecting the trends in the age-specific incidence rates, we assumed a linear model for future projections if past trends showed increasing rates, a log-linear model for decreasing rates and the most recent rate for stable rates over time.[20] The predicted future population age-structure in each country was obtained from the United Nations, using the medium variant for fertility, migration and mortality rates.[21]

The number of cases that are potentially preventable by the currently available HPV vaccines was then estimated, considering a range for the HPV-attributable fraction (AF) in vulvar cancer, a range for vaccination coverage rates in each country and alternate vaccine types (quadrivalent and nonavalent vaccines). To inform these estimated ranges, a literature review was performed on the overall and type- and age-specific prevalence of HPV in vulvar cancer worldwide.[2, 3] The target age and observed vaccine dose completion rate of HPV vaccination for the year 2014 in each country were also obtained from the literature (Table C 1).[22] HPV types included in quadrivalent and nonavalent vaccines are HPV 6/11/16/18 and HPV 6/11/16/18/31/33/45/52/58, respectively. Appendix B describes the detailed methods and results for the review of literature on the prevalence of HPV in vulvar cancer and the assumptions used to predict the effect of HPV vaccination on the number of vulvar cancer cases in the future.

RESULTS

Review of cancer registry data

Cancer registration data from 13 countries fulfilled the *a priori* conditions for inclusion in the analysis. These included Canada, USA, Denmark, France, Germany, Iceland, Ireland, Sweden, Switzerland, The Netherlands, UK, Australia and Japan. Table 1 describes the cancer registries included in the analysis and the estimated proportion of the female population covered by the cancer registries for which vulvar cancer data were available, relative to the estimated nationwide female population in 2005 in each country. The female population coverage of the registries ranged from 1% (Germany) to 100% (Denmark, Iceland, Sweden and The Netherlands) with the majority of registries covering >50% of the female population in each country. Because population coverage of the registry included in the analysis for Germany was only 1%, for subsequent trends determinations, alternate analyses were performed with Germany included, and then excluded, in the pooled analysis for European countries. Five-yearly data on the number of vulvar cancer cases and female population at risk are available in Appendix A (Table A 1).

Analysis of trends in the incidence of vulvar cancer

As expected, the incidence of vulvar cancer was higher in older age groups for all birth cohorts examined (Figure 1). Table 2 describes the age-standardised incidence rates in each 5-yearly period and the associated 5-yearly AvPC between 1988-1992 and 2003-2007. During the study period, there was a significant increase in the 5-yearly AvPC in women of all ages (4.6%, p=0.005) and <60 years of age (11.6%, p=0.02) mainly driven by significant increases in the

incidence rate in women <60 years of age in Europe (15.2%, p=0.01); no significant change in the 5-yearly AvPC in women of all ages and <60 years of age in North America and Oceania/Asia. By contrast, no change was observed for 60+ years (0.1%, p=0.94). When looking at each country individually, a significant increase in the 5-yearly AvPC was seen in women of all ages in The Netherlands (8.5%, p=0.04) and the UK (5.4%, p=0.02) driven by significant increases in the incidence rate in women <60 years of age; the 5-yearly AvPC was 15.1% (p=0.02) in Denmark and 15.0% in the UK (P=0.01). Significant increase in the 5-yearly AvPC in women 60+ years of age was not observed in any country examined in the study.

Figure 2 illustrates the SRRs for the age-standardised incidence rates in 1993-1997, 1998-2002 and 2003-2007, in each case referenced to 1988-1992 (see Table A 2 for the details). Table 3 also summarises the SRRs for 2003-2007 compared to 1988-1992 as well as the SRRs for 2003-2007 compared to 1998-2002 (which was the sensitivity analysis to check for artefact related to ICD coding changes).

During the entire study period (1988-2007), there was a significant 14% increase in the overall incidence of vulvar cancer when pooling data from all 13 countries (SRR=1.14, 95% CI: 1.11-1.18), which was driven by a significant increase in Europe (21%) and Oceania/Asia (18%). When the incidence rates were examined by age, in women <60 years of age the rates increased by 38% overall (SRR=1.38, 95% CI: 1.30-1.46), with the increase ranging from 10% in North America to 69% in Oceania/Asia. By contrast, no significant change was observed in women 60+ years of age overall (SRR=1.01, 95% CI: 0.97-1.05) or in any region (except for Europe when Germany was included, SRR=1.06, 95% CI: 1.01-1.11). When considering each country individually, significant increases in the incidence of vulvar cancer in women of all ages in 2003-2007 compared to 1988-1992 were seen in Denmark (SRR=1.25, 95% CI: 1.07-

1.46), Germany (SRR=2.73, 95% CI: 2.11-3.54), The Netherlands (SRR=1.27, 95% CI: 1.15-1.40), UK (SRR=1.18, 95% CI: 1.10-1.26) and Australia (SRR=1.20, 95% CI: 1.08-1.33), which in each country was also associated with, and driven by, substantial and significant increases in women <60 years of age. The SRRs in 2003-2007 relative to 1988-1992 in women <60 years in these countries were: Denmark (SRR=1.57, 95% CI: 1.19-2.07), Germany (SRR=4.03, 95% CI: 2.48-6.54), The Netherlands (SRR=1.65, 95% CI: 1.37-1.99), UK (SRR=1.49, 95% CI: 1.31-1.68) and Australia (SRR=1.54, 95% CI: 1.27-1.85). The rate in women 60+ years of age remained stable in all countries except for Germany (SRR=2.11, 95% CI: 1.58-2.80) and The Netherlands (SRR=1.11, 95% CI: 1.00-1.24). The results from the sensitivity analysis of the SRRs in 2003-2007 compared to 1998-2002 were broadly consistent with these findings, although the SRRs were lower (as expected, given the shorter time period available for the sensitivity analysis) – see Table 3 for more details.

Prediction of future burden of vulvar cancer

The literature review identified a feasible range of the overall HPV-attributable fraction of vulvar cancer of 22.4-40.0%. Age-specific AFs for any HPV type in invasive vulvar cancers in women <55, 55-64 and 65+ years of age were 48.1-86.7%, 27.3-49.2% and 15.0-27.1%, respectively (see Appendix B). The estimated range of the proportion of vulvar cancers caused by the HPV types included in quadrivalent and nonavalent HPV vaccines were 17-32% and 21-37%, respectively (i.e. type-specific AFs of vaccine HPV types in HPV-attributable vulvar cancer; see Appendix B for further details). Even though significant trends were found overall in women <60 years, there is no guarantee these trends will continue given the trend was not significant for most countries when considering each country individually. To be conservative we used the most recent incidence rates for the forward predictions. The predicted number

of incident vulvar cancer cases in 2025 and 2050 in the absence of HPV vaccination were calculated by applying the observed age-specific incidence rate in 2003-2007 to the predicted population in each year in each country.

In France, Germany, The Netherlands and Japan, population growth was not expected over the next few decades, mainly due to decreases in the projected populations in the younger cohorts; thus the predicted number of vulvar cancer cases in women <60 years of age is predicted to decrease in the future. In other countries, in the absence of HPV vaccination, the number of vulvar cancer cases in 2025 are predicted to increase by 26%, 25% and 26% in women of all ages, <60 years and 60+ years of age, respectively, compared to 2010. In 2050, the corresponding changes are up to 100%, 33% and 129%, respectively. The effect of the quadrivalent HPV vaccine will start to be realised by 2050, and vaccination is expected to decrease the number of vulvar cancer cases overall by 9-17%, driven by a 27-33% decrease in women <60 years of age (assuming the target age for female vaccination and the dose-completion rate observed in 2014 are maintained in the future). An additional 6-11% reduction will occur if 100% HPV vaccination coverage is achieved. Nonavalent HPV vaccine will prevent a further 1-2% of cases compared to the quadrivalent vaccine, again assuming 100% vaccination coverage (Table 4). Key assumptions such as the assumed HPV vaccine uptake in each country and detailed results are found in Appendix C.

DISCUSSION

Brief summary of the main results

We found that, over the 20 year period from 1988-1992 to 2003-2007, when pooling data from 13 high-income countries in North America, Europe, Oceania and Asia, the age-standardised incidence rates of vulvar cancer increased by 14% in women of all ages, and 38% in women <60 years of age, whereas the rate was stable in women 60+ years of age. When considering each geographical area separately, a significant 21% and 18% increase was seen in women of all ages in Europe and Oceania/Asia, respectively; this was driven by increase in incidence in women <60 years of age, 51% in Europe and 69% in Oceania/Asia. In North America, a statistically significant 10% increase in women <60 years of age was not enough to drive a significant increase when averaged across all ages. During the study period, the overall age-standardised incidence rate of vulvar cancer increased by 4.6% every 5 years (on average), largely driven by a significant increase in women <60 years of age in Europe (15.2%) and Oceania/Asia (17.1%). In the absence of HPV vaccination, the overall number of vulvar cancer cases is predicted to increase in the future in areas where population size is expected to grow. However, HPV vaccine with high vaccination coverage is expected to counter effect on the number of vulvar cancer cases in vaccinated cohorts.

Explanation for the findings

The findings of this study are generally consistent with those of previous studies examining trends in the incidence of vulvar cancer in specific countries included in this analysis. This study found no significant increase in vulvar cancer incidence in women of all ages or <60 years in North America and some European countries in the 20-year period. A recent Canadian study reported that the vulvar cancer incidence has significantly increased in women 40+

years of age over the period 1992-2008;[11] consistent with these findings, in a supplementary analysis we conducted with the current data, the SRR in 2003-2007 vs 1993-1997 in Canada was significantly higher in women of all ages but remained stable in women <60 years of age (results not shown). Other studies have found that the reported incidence rate in women of all ages remained stable in the USA in 1999-2005 and in Switzerland in 1974-1994, consistent with our findings.[7, 9]

We observed a significant increase in the age-standardised incidence rates of vulvar cancer in women of all ages, and <60 years of age in Denmark, UK and Australia. In Denmark, a previous study[8] has found that the all-ages incidence rate was stable but the rate in women <60 years doubled over the period from 1978-2007. In the UK, a prior study found a significant 18% increase in the overall incidence over the period from 1990-2009, which is consistent with the current analysis.[14] In Australia, we have previously found that the overall incidence has increased by 13% and this was driven by an 84% increase in women <60 years of age between 1982-2009.[15] We found the incidence rate in women 60+ years of age significantly increased in Germany and The Netherlands. Although we included only one German cancer registry in our analysis, a recent nation-wide study reported that the overall incidence rate more than doubled over the period from 1999-2001, exceeding the rates of the other Eastern European countries, and this significant increase was observed in all age groups.[12] In The Netherlands, a previous study found that the incidence rate in women 60+ years was stable in 1989-2010 but a significant increase was observed from 2004 onwards, which was consistent with our findings.[13] While it is reassuring that our findings are consistent with those reported elsewhere, the novelty of our study is in the detailed analysis of age-specific trends; the increasing incidence of vulvar cancer in women <60 years in many countries appears to have

been “masked” in prior analyses which pooled data across all age groups and thus did not identify the increasing rates in younger women.

HPV 16 is known to be a strong predictor of both *in situ* and invasive vulvar cancer.[23] A Danish study reported that exposure to high-risk HPV types, smoking, and alcohol consumption were significant risk factors for vulvar squamous cell carcinoma.[24] A recent study of a large cohort of UK women 50+ years of age reported that past registration of cervical intraepithelial neoplasia grade 3 (which is a surrogate measure of cervical cancer, and thus HPV exposure), obesity (for vulvar SCC only), and earlier age at menopause are associated with an increased risk of vulvar cancer in post-menopausal women, but that smoking was not associated with an increased risk.[25] Consistent with these findings, we found differing trends in the incidence rates of vulvar cancer in younger *vs* older women, which may be explained by different risk factor profiles across age groups. Vulvar cancers in younger women are more likely to be warty/basaloid types, frequently found adjacent to usual vulvar intraepithelial neoplasia (uVIN), often associated with HPV infection, and have a similar risk factor profile to cervical cancer.[4-6] By contrast, vulvar cancers in older women tend to be keratinizing types that arise from non-HPV-related chronic vulvar dermatoses, such as lichen sclerosis or squamous hyperplasia, and whose precursor lesion is differentiated VIN (dVIN).[4-6] The prevalence of any HPV type in vulvar cancer is around 69% in warty/basaloid types and about 13% in keratinizing types.[2, 3] As a result, women <55 years of age during the period 1980-2011 were found to be more than three times as likely to be HPV DNA positive compared to women 65+ years.[2] It has been well documented that the incidence of *in situ* vulvar cancer has increased in the last few decades, especially in women <50 years of age, and the rate of increase was much faster than the rate seen in invasive vulvar cancer.[8, 9, 26-28] It has also been noted that the incidence

of other HPV-related anogenital cancers, such as anal cancer and HPV-related oropharyngeal cancers, has significantly increased.[29, 30] Therefore, it is plausible to suggest that the marked increase in the incidence of both *in situ* and invasive vulvar cancer in younger women is due to rising HPV infection rates, which is likely to be associated with changes in sexual mores and behaviour that began in the late 1960s.

Although our pooled analysis of data from multiple countries suggests an increasing incidence rate of vulvar cancer in women of all ages, driven by an increase in those <60 years, not all of the individual countries included in this analysis showed a significant increase in vulvar cancer incidence. The literature suggests geographical variation in the prevalence of HPV in vulvar cancer[2, 3]; however it is possible that the reported difference is due to differential case mix in terms of histologic subtype and age group in the various studies, for which detailed information is not available. Different level of risk exposure, to HPV in particular, associated with squamous cell carcinomas - the majority of vulvar cancers - might partly explain the differences between the countries. The heterogeneity in the size of the effect in each country could also be due to slightly different time of changes in sexual behaviour. However, this is an ecological study and neither detailed information on sexual behaviour by birth-cohort nor the different level of risk exposure in each country can be quantified.

Another possibility is that the implementation of new terminology (i.e. uVIN and dVIN) and/or adoption of new disease classification coding (i.e. ICD-9 to ICD-10) took place at different time periods in different countries, which might have caused inconsistencies in case-ascertainment or cancer registrations between the geographical regions. ICD-10 separated malignant neoplasm of other and unspecified female genital organs (ICD-9: 184) into three different entities (C51 [Vulva], C52 [Vagina] and C57 [Other and unspecified female genital

organs]). For the period 1983-1987 covered in CI5 Volume 6, IARC presented the results (e.g. incidence and the ASR) according to ICD-9. For the period 1988-1992 (CI5 Volume 7), although ICD-9 code was still used, IARC requested additional information on ICD-O-1/ ICD-O-2 to each registry to present the results equivalent to ICD-10. A total of 92% of the cancer registries reporting to the IARC coded their histological data according to ICD-O-1 or ICD-O-2 and IARC also performed data checking. Regarding vulvar cancer data, when coding for ICD-10, IARC separated the components in ICD-9 code 184 into three different sites equivalent to ICD-10. That is, for the current analysis, the results published in CI5 Volume 7 were equivalent to ICD-10 and registries that did not provide the additional information are not likely to be included in this analysis (e.g. 0 incidence of vulvar cancer in 1988-1992). For the period 1993-1997 onwards, IARC presented the results according to ICD-10. To address this issue, we performed a sensitivity analysis on the SRR for 2003-2007 compared to 1998-2002 in order to exclude the possible effect of change in the disease classification from ICD-9 to ICD-10 on the incidence of vulvar cancer over time. Although the SRRs for 2003-2007 vs 1998-20022 were smaller than those compared with 1988-1992 (as expected given the shorter period), the results from the sensitivity analysis were broadly consistent with those referenced to 1988-1992. We also examined the trend in case numbers and the age-standardised incidence rate in each country from 1983-1987 (CI5 Volume 6) to 2003-2007 (CI5 Volume 10) for each sub-site of the tumours (i.e. vulva, vagina and other and unspecified female genital organs). However we were not able to confirm there was obvious documentation bias in terms of disease classification (results not shown). Studies examining comparability between ICD-9 and ICD-10 in the incidence or death of vulvar cancer were not identified, therefore its impact could not be directly determined.

Previous studies have estimated the number of incident vulvar cancer attributable to HPV infection at a specific year and have not predicted future burden of the disease.[1, 31] De Martel et al. estimated the number of incident vulvar cancer cases diagnosed in 2008 that were attributable to HPV infection in less developed and more developed lesions.[1] Grulich et al. have estimated the number and the proportion of incident vulvar cancer diagnosed in 2005 which were due to infection to any HPV type as well as HPV16/18 in Australia.[31] In a related manner, we provided exploratory estimates of future burden of vulvar cancer at a country level for selected high income countries, as an illustrative example of the future implications of our findings for the vulvar cancer incidence at a country level, whilst taking into account trends in the incidence rates. We estimated the range in the proportion of vulvar cancer cases that would be potentially preventable by HPV vaccination in the year 2025 and the year 2050 after considering the estimated age-specific proportion due to specific HPV types, as well as observed vaccination coverage in each country in 2014, taking into account changes in the predicted population structure. We have chosen the year 2050 to illustrate the effect of HPV vaccination because most vaccinated cohorts in the countries included in the current analysis will be 60+ years of age by year 2050. In the 13 countries included in the current analysis, the overall case number is expected to decrease by 9-17% in 2050 driven by a 27-33% decrease in women <60 years of age at the observed vaccine dose completion rate, with an additional 6-11% reduction if 100% vaccination coverage could be achieved, and a further 1-2% reduction with use of the nonavalent HPV vaccine. While accurate estimates are not possible without involving a detailed modelling of the natural history, dynamic transmission of HPV and herd immunity, we have a calculated conservative estimate of the vaccine effect on the future burden of vulvar cancer. Consistent with our assumption that there would be no

increase in the age-specific incidence rates for 2008 onwards, we also made the simplified assumption that the age-specific proportion of vulvar cancer which is attributable to HPV will remain the same as currently observed (thus that variation in this proportion by age reflects differences in the histological subtypes present in younger vs older women, and their different levels of association with HPV). We also used the more conservative AF of HPV in vulvar cancer of 22.4%. In the current prediction, the wide variation between the countries in the predicted changes in the number of vulvar cancer cases in 2050 is mainly due to the projected future population (e.g., a decreasing number of people in younger age groups over time in France, Germany, The Netherlands and Japan resulted in decrease in the number of predicted vulvar cancer cases in women <60 years of age in these countries) and vaccination coverage in each country (range: 0.6%-86%). Therefore our observations of a recent increasing trend in vulvar cancer among women aged <60 years should eventually be counteracted by the impact of HPV vaccination in cohorts born after around 1990. The impact of HPV vaccination is not observed in our analysis of trends since the period of our data analysis runs until 2007, before or around the time that vaccination programs were being rolled out in adolescents in these countries.

Strengths

This is the first systematic exploration of trends in vulvar cancer incidence across multiple countries using cancer registry data, where registry data for vulvar cancer collection were reliable over 20 years. We analysed incidence rates by age, and considered the range of HPV prevalence in vulvar cancer for all vulvar cancer cases as well as by age groups.

Limitations

Due to data availability, we were not able to describe trends in incidence by histologic subtype or morphologic variant, nor perform age-period-cohort analysis in terms of HPV prevalence and exposure to other risk factors associated with vulvar cancer. As seen in other ecological studies, this study could not demonstrate causality in the increasing incidence of vulvar cancer, however our findings are consistent with previous single-region studies that have suggested that the increasing trend in vulvar cancer incidence is likely due to changing sexual behaviours in women born around or after 1950.

Conclusion

In the 13 high-income countries studied (Canada, USA, Denmark, France, Germany, Iceland, Ireland, Sweden, Switzerland, The Netherlands, UK, Australia and Japan), the age-standardised incidence rate of vulvar cancer in women of all ages has increased significantly between 1988-1992 and 2003-2007, with slight variation by geographical area. This was driven by a significant increase in women <60 years of age, which suggests a secular change in HPV prevalence for women born around or after 1950 associated with changing sexual behaviours and increasing levels of exposure to HPV. The incidence of vulvar cancer is expected to increase in the future due to population growth and an ageing population, but HPV vaccination is likely to counteract the increase to some extent particularly at younger ages, depending on vaccination coverage.

REFERENCES

1. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012 Jun;13(6):607-15.
2. de Sanjose S, Alemany L, Ordi J, Tous S, Alejo M, Bigby SM, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer. 2013 Nov;49(16):3450-61.
3. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009 Apr 1;124(7):1626-36.
4. IARC Monographs on the evaluation of carcinogenic risks to humans. Biological agents. Volume 100 B. A review of human carcinogens. Lyon, France: IARC; 2012.
5. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 2016-02-25.
6. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med. 2005 Nov;50(11):807-10.
7. Watson M, Saraiya M, Wu X. Update of HPV-associated female genital cancers in the United States, 1999-2004. J Womens Health (Larchmt). 2009 Nov;18(11):1731-8.
8. Baandrup L, Varbo A, Munk C, Johansen C, Frisch M, Kjaer SK. In situ and invasive squamous cell carcinoma of the vulva in Denmark 1978-2007-a nationwide population-based study. Gynecol Oncol. 2011 Jul;122(1):45-9.
9. Levi F, Randimbison L, La Vecchia C. Descriptive epidemiology of vulvar and vaginal cancers in Vaud, Switzerland, 1974-1994. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1998 Nov;9(11):1229-32.
10. Somoye GO, Mocroft A, Olaitan A. Analysis of the incidence and mortality of vulval cancer in women in South East England 1960-1999. Archives of gynecology and obstetrics. 2009 Feb;279(2):113-7.
11. Akhtar-Danesh N, Elit L, Lytwyn A. Trends in incidence and survival of women with invasive vulvar cancer in the United States and Canada: A population-based study. Gynecol Oncol. 2014 Aug;134(2):314-8.
12. Buttmann-Schweiger N, Klug SJ, Luyten A, Holleczek B, Heitz F, du Bois A, et al. Incidence patterns and temporal trends of invasive nonmelanotic vulvar tumors in Germany 1999-2011. A population-based cancer registry analysis. PLoS One. 2015;10(5):e0128073.
13. Schuurman MS, van den Einden LC, Massuger LF, Kiemeney LA, van der Aa MA, de Hullu JA. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. Eur J Cancer. 2013 Dec;49(18):3872-80.
14. Lai J, Elleray R, Nordin A, Hirschowitz L, Rous B, Gildea C, et al. Vulval cancer incidence, mortality and survival in England: age-related trends. BJOG. 2014 May;121(6):728-38; discussion 39.
15. Barlow EL, Kang YJ, Hacker NF, Canfell K. Changing Trends in Vulvar Cancer Incidence and Mortality Rates in Australia Since 1982. Int J Gynecol Cancer. 2015 Nov;25(9):1683-9.

16. Ferlay J, Parkin DM, Curado MP. Cancer Incidence in Five Continents, Volumes I to X. Lyon, France: International Agency for Research on Cancer; Available from: http://ci5.iarc.fr/CI5I-X/Default.aspx.
17. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJD, Lozano R, Inoue M. Age Standardization of rates: a new WHO standard. http://www.who.int/healthinfo/paper31.pdf: World Health Organization2001.
18. Joinpoint Regression Program, Version 4.3.1.0. April 2016. Statistical Research and Applications Branch, National Cancer Institute.
19. Boyle P, Parkin DM. Chapter 11. Statistical Methods for Registries. In: Jensen OM, Parkin DM, MacLennan R, editors. Cancer Registration: Principles and Methods. Lyon, France: IARC Press; 1991.
20. AIHW. Cancer mortality projections: technical appendix. Available from: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129555321.
21. World Population Prospects: The 2015 Revision. Population Division, Department of Economic and Social Affairs, United Nations; [30/05/2016]; Available from: http://esa.un.org/unpd/wpp/Download/Standard/Population/.
22. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in theWorld. Summary Report 2015-12-23.
23. Madeleine MM, Daling JR, Carter JJ, Wipf GC, Schwartz SM, McKnight B, et al. Cofactors with human papillomavirus in a population-based study of vulvar cancer. J Natl Cancer Inst. 1997 Oct 15;89(20):1516-23.
24. Madsen BS, Jensen HL, van den Brule AJ, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina--population-based case-control study in Denmark. Int J Cancer. 2008 Jun 15;122(12):2827-34.
25. Coffey K, Gaitskell K, Beral V, Canfell K, Green J, Reeves G, et al. Past cervical intraepithelial neoplasia grade 3, obesity, and earlier menopause are associated with an increased risk of vulval cancer in postmenopausal women. Br J Cancer. 2016 Jun 23.
26. Sturgeon SR, Brinton LA, Devesa SS, Kurman RJ. In situ and invasive vulvar cancer incidence trends (1973 to 1987). Am J Obstet Gynecol. 1992 May;166(5):1482-5.
27. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol. 2006 May;107(5):1018-22.
28. Jones RW, Baranyai J, Stables S. Trends in squamous cell carcinoma of the vulva: the influence of vulvar intraepithelial neoplasia. Obstet Gynecol. 1997 Sep;90(3):448-52.
29. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008 Feb 1;26(4):612-9.
30. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. Sex Health. 2010 Sep;7(3):244-52.
31. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. Sex Health. 2010 9/2010;7(3):244-52.

CONTRIBUTORS

YJK, NH, EB and KCa contributed to the conception and design of the study. YJK analysed the data. YJK, MS and KCa interpreted the results. YJK drafted the manuscript. All authors reviewed the manuscript and approved the final manuscript.

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None to declare.

APPENDIX A. INCIDENCE OF VULVAR CANCER

Table A 1. Number of cases diagnosed with vulvar cancer and female population in the cancer registries included in the analysis

	Vulvar cancer cases diagnosed in each period				Female population at risk in the same registry catchment areas			
Country	**1988-1992**	**1993-1997**	**1998-2002**	**2003-2007**	**1988-1992**	**1993-1997**	**1998-2002**	**2003-2007**
Canada	1,088	1,171	1,402	1,572	52,208,108	55,921,380	58,925,418	62,078,324
USA	1,285	1,459	1,684	1,757	54,942,117	63,890,849	67,930,987	70,686,135
Denmark	377	419	429	471	13,047,100	13,263,467	13,497,342	13,689,087
France	272	276	311	341	13,940,799	14,442,466	14,971,554	15,555,804
Germany	95	89	101	255	2,763,518	2,791,846	2,756,706	2,704,391
Iceland	10	14	12	11	635,900	666,700	701,535	740,441
Ireland	26	122	185	217	1,328,945	7,282,001	9,559,339	10,392,200
Sweden	678	774	766	803	21,647,559	22,267,056	22,445,310	22,791,385
Switzerland	124	146	135	169	4,977,581	5,154,482	5,676,964	5,871,505
The Netherlands	795	1,061	1,220	1,416	30,370,100	39,063,226	40,240,535	41,213,162
UK	1,792	2,321	2,277	2,977	56,813,654	65,684,036	68,105,830	82,350,234
Australia	664	826	889	1,057	34,403,062	36,838,902	38,863,311	40,901,898
Japan	132	166	185	251	31,905,412	32,358,634	32,535,342	33,026,825

Note) Data are only included in the current analysis from cancer registries that reported for the entire period 1988-2007 and that also satisfied a priori conditions (see Materials and Methods).

Table A 2. Standardised rate ratios in the age-standardised incidence rates (per 100,000 population) of vulvar cancer, compared to 1988-1992, in selected high income countries

	Standardised rate ratios (95% CIs) relative to 1988-1992								
	All ages			<60 years			60+ years		
Country	**1993-1997**	**1998-2002**	**2003-2007**	**1993-1997**	**1998-2002**	**2003-2007**	**1993-1997**	**1998-2002**	**2003-2007**
(a) Overall (13 countries including Canada, USA, 9 European countries, Australia and Japan)									
Overall	1.04 (1.00-1.07)	1.09 (1.05-1.12)	1.14 (1.11-1.18)	1.08 (1.01-1.15)	1.27 (1.19-1.35)	1.38 (1.3-1.46)	1.01 (0.97-1.05)	0.98 (0.95-1.02)	1.01 (0.97-1.05)
(b) By continent									
North America	0.95 (0.90-1.01)	1.03 (0.98-1.09)	1.03 (0.97-1.09)	0.98 (0.88-1.08)	1.13 (1.04-1.24)	1.10 (1.00-1.21)	0.94 (0.87-1.01)	0.96 (0.89-1.02)	0.98 (0.91-1.05)
Europe	1.06 (1.01-1.11)	1.1 (1.05-1.15)	1.21 (1.16-1.26)	1.09 (0.99-1.20)	1.25 (1.14-1.37)	1.51 (1.39-1.64)	1.04 (0.99-1.10)	1.02 (0.97-1.08)	1.06 (1.01-1.11)
Europe (excl. Germany)	1.06 (1.02-1.12)	1.1 (1.05-1.15)	1.18 (1.13-1.23)	1.1 (1.00-1.21)	1.26 (1.15-1.38)	1.47 (1.35-1.60)	1.05 (1.00-1.10)	1.02 (0.97-1.08)	1.04 (0.98-1.09)
Oceania/Asia	1.13 (1.02-1.25)	1.04 (0.94-1.15)	1.18 (1.07-1.30)	1.31 (1.08-1.59)	1.29 (1.07-1.57)	1.69 (1.42-2.02)	1.05 (0.94-1.18)	0.92 (0.82-1.03)	0.94 (0.84-1.05)
(c) By country									
Canada	0.96 (0.88-1.05)	1.04 (0.96-1.14)	1.04 (0.96-1.13)	1.03 (0.89-1.20)	1.17 (1.02-1.34)	1.12 (0.98-1.28)	0.91 (0.81-1.01)	0.95 (0.85-1.06)	0.98 (0.88-1.09)
USA	0.94 (0.87-1.02)	1.04 (0.96-1.13)	1.02 (0.94-1.10)	0.92 (0.80-1.06)	1.10 (0.97-1.26)	1.08 (0.94-1.22)	0.96 (0.87-1.06)	0.99 (0.90-1.10)	0.98 (0.89-1.08)
Denmark	1.12 (0.95-1.32)	1.11 (0.95-1.30)	1.25 (1.07-1.46)	1.22 (0.91-1.65)	1.31 (0.98-1.75)	1.57 (1.19-2.07)	1.06 (0.88-1.27)	1.00 (0.83-1.19)	1.07 (0.89-1.27)
France	0.98 (0.81-1.19)	1.05 (0.87-1.26)	1.01 (0.83-1.21)	1.22 (0.79-1.89)	1.34 (0.89-2.01)	1.20 (0.79-1.82)	0.90 (0.73-1.10)	0.94 (0.77-1.16)	0.93 (0.76-1.14)
Germany	0.79 (0.57-1.10)	0.92 (0.67-1.27)	2.73 (2.11-3.54)	0.72 (0.35-1.49)	0.72 (0.34-1.52)	4.03 (2.48-6.54)	0.82 (0.58-1.16)	1.02 (0.73-1.43)	2.11 (1.58-2.80)
Iceland	1.05 (0.44-2.54)	0.80 (0.31-2.04)	0.72 (0.28-1.89)	1.02 (0.23-4.58)	0.87 (0.19-3.98)	1.37 (0.37-4.98)	1.08 (0.38-3.06)	0.74 (0.24-2.33)	0.20 (0.04-1.06)
Ireland	0.95 (0.59-1.53)	1.10 (0.71-1.71)	1.21 (0.80-1.85)	3.42 (0.99-11.73)	4.87 (1.81-13.12)	5.62 (2.25-14.06)	0.74 (0.43-1.26)	0.77 (0.46-1.30)	0.83 (0.50-1.37)
Sweden	1.06 (0.94-1.2)	1.1 (0.98-1.25)	1.08 (0.95-1.22)	1.1 (0.86-1.41)	1.33 (1.05-1.68)	1.15 (0.91-1.47)	1.04 (0.91-1.19)	0.98 (0.86-1.13)	1.03 (0.91-1.18)
Switzerland	1.15	0.94	1.14	1.15	0.90	1.34	1.15	0.96	1.03

Country	Standardised rate ratios (95% CIs) relative to 1988-1992								
	All ages			<60 years			60+ years		
	1993-1997	1998-2002	2003-2007	1993-1997	1998-2002	2003-2007	1993-1997	1998-2002	2003-2007
	(0.87-1.52)	(0.71-1.25)	(0.87-1.5)	(0.67-1.99)	(0.52-1.57)	(0.80-2.25)	(0.84-1.56)	(0.70-1.32)	(0.76-1.40)
The Netherlands	1.04 (0.94-1.15)	1.10 (1.00-1.22)	1.27 (1.15-1.40)	1.09 (0.88-1.36)	1.25 (1.01-1.53)	1.65 (1.37-1.99)	1.02 (0.91-1.14)	1.04 (0.93-1.16)	1.11 (1.00-1.24)
UK	1.08 (1.01-1.16)	1.13 (1.06-1.22)	1.18 (1.10-1.26)	1.08 (0.93-1.25)	1.28 (1.11-1.46)	1.49 (1.31-1.68)	1.08 (1.00-1.17)	1.06 (0.98-1.14)	1.01 (0.94-1.09)
Australia	1.17 (1.05-1.31)	1.08 (0.96-1.2)	1.20 (1.08-1.33)	1.31 (1.06-1.61)	1.22 (0.99-1.49)	1.54 (1.27-1.85)	1.1 (0.96-1.25)	1.00 (0.88-1.14)	1.03 (0.91-1.16)
Japan	1.00 (0.78-1.28)	0.92 (0.71-1.18)	1.06 (0.84-1.34)	0.78 (0.42-1.45)	0.94 (0.52-1.69)	1.09 (0.62-1.92)	1.08 (0.83-1.41)	0.91 (0.70-1.18)	1.05 (0.82-1.34)

Note) Data are only included in the current analysis from cancer registries that reported for the entire period 1988-2007 and that also satisfied a priori conditions (see Materials and Methods). Therefore, the standardised rate ratios reported in the above table do not necessarily corresponds to each country's national statistics.

APPENDIX B. PREVALENCE OF HPV IN VULVAR CANCER

The range of the prevalence of any HPV type in vulvar cancer (i.e. AF) was obtained via literature search for all vulvar cancer cases as well as by histology subtype (SCC warty/basaloid, SCC keratinising, SCC mixed and other) and age groups (<54, 55-65 and 65+ years: age groups used in the original studies were mapped accordingly). The ratio of testing HPV DNA positive in younger age groups compared to the oldest age group was calculated where details were not provided. Type-specific HPV prevalence in all vulvar cancer cases was obtained to estimate the proportion of HPV types included in quadrivalent HPV vaccine (i.e. HPV 6/11/16/18) and nonavalent HPV vaccine (i.e. HPV 6/11/16/18/31/33/45/52/58). Detailed data on the HPV type-specific prevalence in vulvar cancer by geographical region, histology and age were not available. The following assumptions were made on the AF of HPV in vulvar cancer due to data limitation: i) there is no geographical variation; and ii) age-specific AF is the same across all histology subgroups and all HPV types.

Table B 1 summarises the review of literature on the AF of HPV in vulvar cancer and the assumptions used in the current study to predict the effect of HPV vaccination on the number of vulvar cancer cases in the future. Two large-scale studies - an international collaboration study and a meta-analysis – were identified with different case mix in terms of histology subtypes and age groups. There was a substantial variation in the overall AF of HPV in vulvar cancer ranging from 22.4% to 40.4% across the studies identified. However, the prevalence of any HPV type in each histology subtype or age group was similar in the two studies. The prevalence of HPV was highest in SCC warty/basaloid type (range: 69.4-69.5%) followed by SCC keratinising type (range: 11.5-13.2%). The international collaboration study only reported the age-specific prevalence of HPV by age group, which decreases significantly as women become older (48.1% in <55 years vs 15.0% in 65+ years). We assumed the age-specific AF of HPV in each age group was similar between the two studies since the adjusted ratios of HPV DNA positive in younger age groups compared to the oldest age group was similar between the two studies (3.20-3.63 in <55 years and 1.81-2.19 in 55-64 years, compared to 65+ years). By applying the reported age-specific HPV prevalence in the international collaboration study and the range of the AF of any HPV type reported in the two studies, the AF of any HPV in all invasive vulvar cancer in women <55, 55-64 and 65+ years of age was 48.1-86.7%, 27.3-49.2% and 15.0-27.1%, respectively. The proportion of HPV types included in quadrivalent and nonavalent HPV vaccine was 78.7% and 91.7%, respectively.

Table B 1. Review of literature on the prevalence of HPV in vulvar cancer and the assumptions used to predict the effect of HPV vaccination on the number of vulvar cancer cases in the future

		Prevalence of any HPV type testing HPV DNA positive*			
		de Sanjose et al.[1]: international collaboration study (both HPV DNA and $p16^{INK4a}$ positive)		de Vuyst et al.[2]: meta-analysis (HPV DNA positive)	
Category		**Any HPV type**	**% of cases included in the analysis**	**Any HPV type**	**% of cases included in the analysis**
A) Comparison of the observed data on vulvar cancer testing HPV DNA positive					
Overall	All vulvar cancer cases	22.4%		40.4%	
Histology	SCC warty/basaloid	69.5%	19.1%	69.4%	13.8%
	SCC keratinising	11.5%	72.2%	13.2%	30.8%
	SCC mixed	N/S	5.9%	N/S	0%
	Other	N/S	2.7%	N/S	0%
	Unknown	N/S	0%	48.2%	55%
Age†	≤54 years	48.1%	19.2%	70.9%	9.7%
	55-64 years	27.3%	39.2%	60.2%	6.8%
	≥65 years	15.0%	41.5%	37.4%	15.4%
	Unknown	33.2%	5.3%	34.4%	68%
Adjusted ratio (95% CI)‡	≤54 years	3.20	-	3.63 (2.40 - 5.47)	-
	55-64 years	1.81	-	2.19 (1.41 - 3.40)	-
	≥65 years	1.00	-	1.00	-
B) Assumptions used for HPV vaccination					
AF of any HPV type in all invasive vulvar cancer§	*Overall*	*22.4% (minimum AF)*	-	*40.4% (maximum AF)*	-
	≤54 years	48.1%		86.7%	
	55-64 years	27.3%		49.2%	
	≥65 years	15.0%		27.1%	
AF of 4V HPV types in vulvar cancer testing HPV DNA positive**	*Overall*	*78.7%*	-	*N/S*	-
AF of 9V HPV types in vulvar cancer testing HPV DNA positive††	*Overall*	*91.7%*	-	*N/S*	-

SCC – squamous cell carcinoma; N/S – not specified; AF- attributable fraction.

* As an approximation of population attributable fraction. Geographical variation was not considered due to lack of detailed information.

† Age groups used in the original studies were: i) <56, 56-66 and 67+ years (de Sanjose et al.); and ii) <60, 61-70 and 71+ years (de Vuyst et al.).

‡ Adjusted by: i) geographical region, period of diagnosis and age at diagnosis in quintiles (de Sanjose et al.); and ii) geographical region and PCR primers (de Vuyst et al.)
§ Age-specific AF of any HPV type was based on the ratio of testing HPV DNA positive in each age group compared to the overall HPV DNA positive rate observed in de Sanjose et al. since: i) adjusted age-specific rate of testing HPV DNA positive was not reported in de Vuyst et al.; and ii) age groups used in the de Sanjose et al. were similar to the current analysis; and iii) the adjusted ratios of HPV DNA positive in younger age groups compared to the oldest age group was similar between the two studies.
** AF of HPV types included in quadrivalent HPV vaccine (i.e. HPV 6/11/16/18) in vulvar cancer testing HPV DNA positive. HPV type-specific prevalence by age was not available, therefore we assumed that age-specific AF is the same for all HPV types.
†† AF of HPV types included in nonavalent HPV vaccine (i.e. HPV 6/11/16/18/31/33/45/52/58) in vulvar cancer testing HPV DNA positive. HPV type-specific prevalence by age was not available, therefore we assumed that age-specific AF is the same for all HPV types.

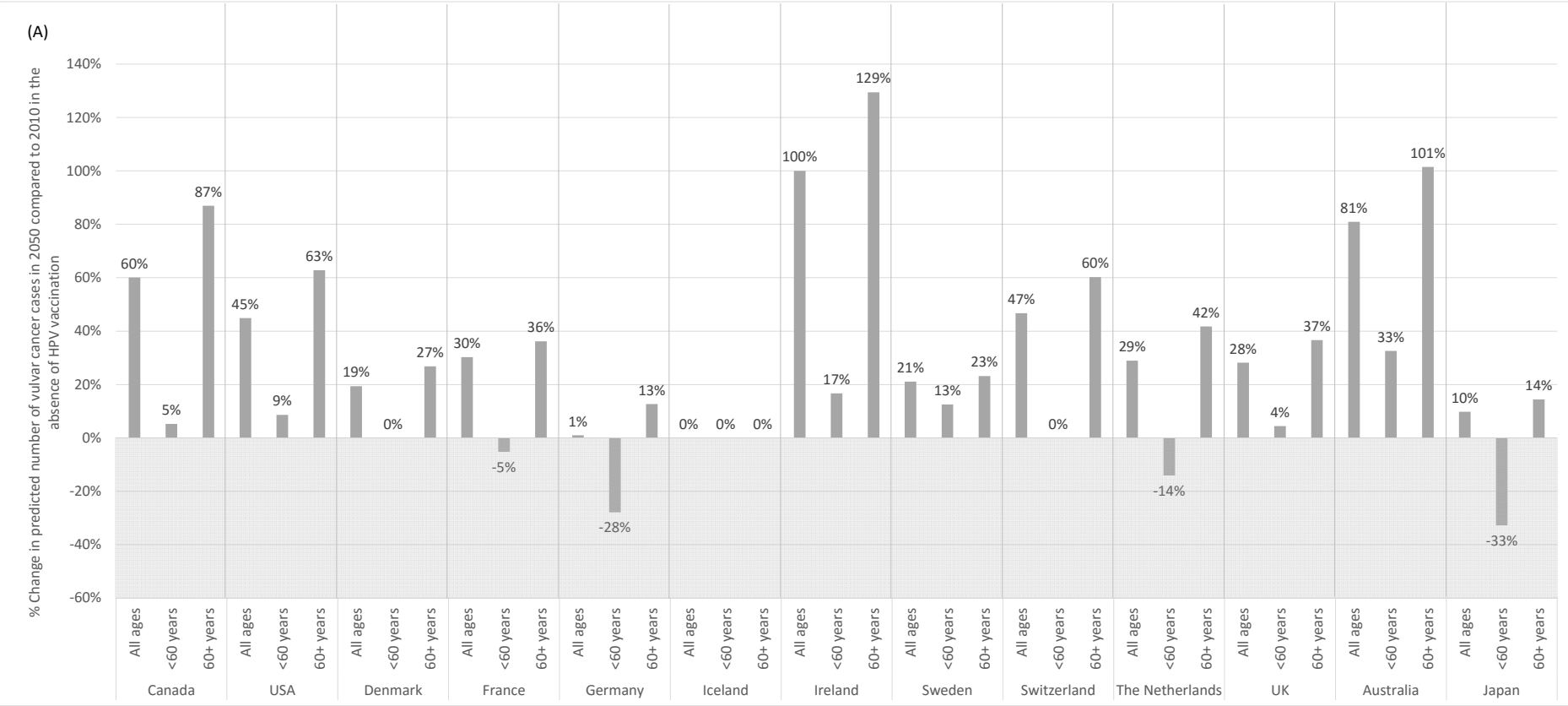
APPENDIX C. FUTURE BURDEN OF VULVAR CANCER

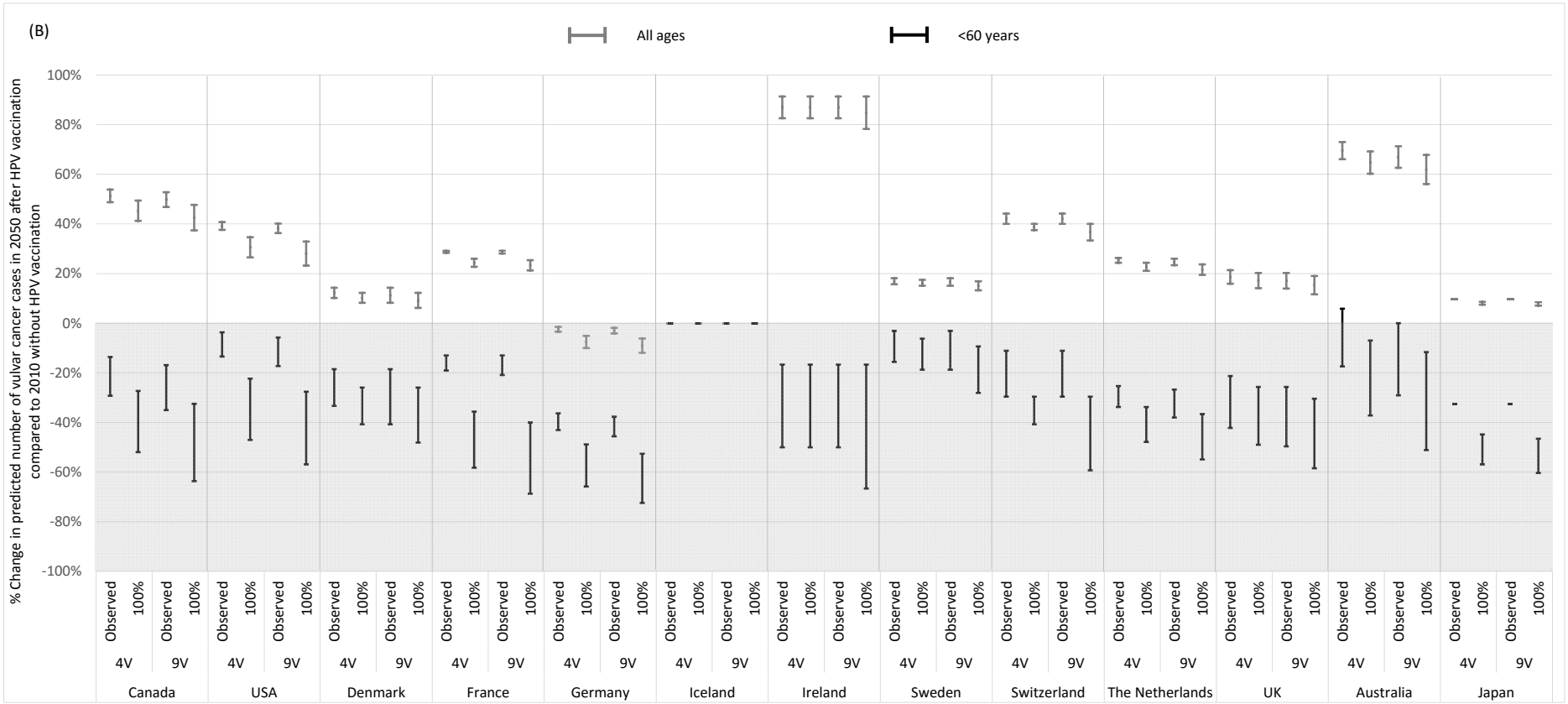
In order to take into account the effect of HPV vaccination, assumptions made were: i) the age-specific proportion of vulvar cancer which is attributable to HPV will remain the same as currently observed; ii) within each 5-year age group, the proportion of women vaccinated is equal for each single year of age and the population is spread equally by single year of age; iii) vaccine duration of protection is lifelong with 100% efficacy; iv) the proportion of females who are fully vaccinated at 9-14 years of age (i.e. target age group) is assumed to be consistent over time and was based on the observed 3-dose uptake rate in 2014; v) vaccination of males and catch-up vaccination for females are not considered; and vi) population estimates were obtained using the medium variant for fertility, migration and mortality rates. Assumed vaccine uptake at target age group based on observed 3-dose uptake in 2014 in each country is described in Table C 1.

Table C 1. Assumed vaccine uptake at 9-14 years of age in each country

Country	Target age (years)	Assumed vaccine uptake rate (based on 3-dose uptake in 2014[3])
Canada	9-14	60.0%
USA	11-12	39.7%
Denmark	12	82.0%
France	11-14	25.0%
Germany	9-14	40.0%
Iceland	12	88.0%
Ireland	12-13	84.9%
Sweden	10-12	80.0%
Switzerland	11-14	51.0%
The Netherlands	12	61.0%
UK	12-13	86.0%
Australia	12-13	73.1%
Japan	13	0.6%

Figure C 1. Changes in predicted number of vulvar cancer cases in selected high income countries. (A) Vulvar cancer cases in 2050 compared to 2010 in the absence of HPV vaccination; and (B) Vulvar cancer cases in 2050 under various HPV vaccination scenarios compared to 2010 without HPV vaccination





4V - quadrivalent HPV vaccine; 9V - nonavalent HPV vaccine; observed – 3-dose completion rate observed in 2014; 100% - 100% vaccination coverage.
Capped vertical lines represent the range in % change in the predicted number of vulvar cancer cases based on different attributable fraction of any HPV type in all vulvar cancer cases (22.4%-40.4%).
Note) The above graphs illustrate nation-wide prediction in each country included in the analysis, and not limited to the catchment area of the selected cancer registries of which data on the observed incidence of vulvar cancer were used.

Table C 2. Predicted cases of vulvar cancer in 2010 and changes in the predicted number of vulvar cancer cases in 2025 and 2050 (compared to 2010) under different HPV vaccination scenarios

	2010 (Predicted no. of cases)		2025 (range of % changes in the predicted no. vulvar cancer cases)								2050 (range of % changes in the predicted no. vulvar cancer cases)							
	All ages	<60 years	All ages				<60 years				All ages				<60 years			
			Quadrivalent vaccine		Nonavalent vaccine		Quadrivalent vaccine		Nonavalent vaccine		Quadrivalent vaccine		Nonavalent vaccine		Quadrivalent vaccine		Nonavalent vaccine	
Country	No. cases	No. cases	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage	Observed rate	100% coverage
Canada	468	154	16%, 17%	16%, 16%	16%, 16%	16%, 16%	-2%, -1%	-3%, -2%	-2%, -2%	-4%, -2%	49%, 54%	41%, 49%	47%, 53%	48%, 37%	-29%, -14%	-52%, -27%	-35%, -17%	-32%, -64%
USA	4130	1367	12%, 12%	12%, 12%	12%, 12%	12%, 12%	-4%, -4%	-6%, -5%	-5%, -4%	-6%, -5%	38%, 41%	26%, 35%	36%, 40%	33%, 23%	-13%, -4%	-47%, -22%	-17%, -6%	-28%, -57%
Denmark	98	27	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	10%, 14%	8%, 12%	8%, 14%	12%, 6%	-19%, -4%	-41%, -26%	-41%, -19%	-26%, -48%
France	809	115	-1%, -1%	-1%, -1%	-1%, -1%	-1%, -1%	-3%, -3%	-8%, -5%	-3%, -3%	-9%, -6%	28%, 29%	23%, 26%	28%, 29%	25%, 21%	-19%, -13%	-58%, -36%	-21%, -13%	-40%, -69%
Germany	3854	1112	-4%, -4%	-5%, -4%	-4%, -4%	-4%, -5%	-9%, -8%	-10%, -9%	-9%, -9%	-10%, -9%	-3%, -1%	-10%, -5%	-4%, -2%	-6%, -12%	-43%, -36%	-66%, -49%	-46%, -38%	-53%, -72%
Iceland	2	1	-50%, -50%	-50%, -50%	-50%, -50%	-50%, -50%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%	0%, 0%
Ireland	46	12	26%, 26%	26%, 26%	26%, 26%	26%, 26%	25%, 25%	25%, 25%	25%, 25%	25%, 25%	83%, 91%	83%, 91%	83%, 91%	91%, 78%	-50%, -17%	-50%, -17%	-50%, -17%	-17%, -67%
Sweden	166	32	-4%, -4%	-4%, -4%	-4%, -4%	-4%, -4%	6%, 6%	6%, 6%	6%, 6%	6%, 6%	16%, 18%	15%, 17%	15%, 18%	17%, 13%	-16%, -3%	-19%, -6%	-19%, -3%	-9%, -28%
Switzerland	120	27	5%, 5%	4%, 5%	5%, 5%	4%, 4%	15%, 15%	11%, 15%	15%, 15%	11%, 11%	40%, 44%	38%, 40%	40%, 44%	40%, 33%	-30%, -11%	-41%, -30%	-30%, -11%	-30%, -59%
The Netherlands	308	71	8%, 8%	8%, 8%	8%, 8%	8%, 8%	-7%, -7%	-7%, -7%	-7%, -7%	-7%, -7%	24%, 26%	21%, 24%	23%, 26%	24%, 19%	-34%, -25%	-48%, -34%	-38%, -27%	-37%, -55%
UK	1126	296	1%, 1%	1%, 1%	1%, 1%	1%, 1%	4%, 5%	4%, 5%	4%, 5%	4%, 5%	16%, 21%	14%, 20%	14%, 20%	19%, 12%	-42%, -21%	-49%, -26%	-50%, -26%	-30%, -58%
Australia	289	86	18%, 18%	17%, 18%	17%, 18%	18%, 17%	14%, 15%	13%, 14%	13%, 14%	13%, 14%	66%, 73%	60%, 69%	63%, 71%	68%, 56%	-17%, 6%	-37%, -7%	-29%, 0%	-12%, -51%
Japan	593	58	-1%, -1%	-1%, -1%	-1%, -1%	-1%, -1%	-3%, -3%	-3%, -3%	-3%, -3%	-3%, -3%	10%, 10%	7%, 9%	10%, 10%	8%, 7%	-33%, -33%	-57%, -45%	-33%, -33%	-47%, -60%

* Negative signs indicate decrease in the predicted number of vulvar cancer cases

Note) The table above describes nation-wide prediction in each country included in the analysis, and not limited to the catchment area of the selected cancer registries of which data on the observed incidence of vulvar cancer were used.

REFERENCES

1. de Sanjose S, Alemany L, Ordi J, Tous S, Alejo M, Bigby SM, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer. 2013 Nov;49(16):3450-61.
2. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009 4/1/2009;124(7):1626-36.
3. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in theWorld. Summary Report 2015-12-23.

Figure 1. Pooled analysis of the age-specific incidence rates of vulvar cancer by birth cohort in women born from 1900 to 1983

Figure 2. Standardised rate ratios of the age-standardised incidence rates of vulvar cancer in each 5 year time period relative to the rates in 1988-1992

ASR – age-standardised rate. Capped vertical lines represent the 95% CIs of standardised rate ratios. Note that the upper bound of 95% CI is truncated at 6 on the graphs.

Table 1. Cancer registries included in the analysis

Country*	Cancer registries included in the analysis	Registry coverage	Female population coverage†
Canada	The Alberta Cancer Registry, the British Columbia Cancer Registry, the Manitoba Cancer Registry, the New Brunswick Provincial Cancer Registry, the Newfoundland and Labrador Provincial Tumour Registry, the Northwest Territories Cancer Registry, the Nova Scotia Cancer Registry, the Ontario Cancer Registry, the Prince Edward Island Cancer Registry, the Saskatchewan Cancer Registry	Each registry covers the entire province	76%
USA	Participant registries in the Surveillance, Epidemiology, and End Results (SEER) Program: five states (Connecticut, Iowa, New Mexico, Utah, and Hawaii) and four metropolitan areas (the San Francisco Bay area, California; Detroit, Michigan; Atlanta, Georgia; and Seattle, Washington).	Representative of the country	9%
Denmark	The Danish Cancer Registry	National cancer registry	100%
France	The Bas-Rhin Cancer Registry, Calvados, the Doubs Cancer Registry, the Haut-Rhin Cancer Registry, the Hérault Cancer Registry, the Isère Cancer Registry, the Somme Cancer Registry, the Tarn Cancer Registry		10%
Germany	The Saarland Cancer Registry	Covers the entire state	1%
Iceland	The Icelandic Cancer Registry	National cancer registry	100%
Ireland	The National Cancer Registry	National cancer registry	99%
Sweden	The Swedish Cancer Registry	National cancer registry	100%
Switzerland	The Geneva Cancer Registry, the Neuchâtel Cancer Registry, the St. Gallen-Appenzell Cancer Registry, the Valais Cancer Registry, the Vaud Cancer Registry, the Zurich Canton Cancer Registry	Each registry covers the entire canton	31%
The Netherlands	The Netherlands Cancer Registry	National cancer registry	100%
UK	The Eastern Cancer Registry and Information Centre (ECRIC), The North Western Regional Cancer Registry, the Oxford Cancer Intelligence Unit, the South West office of the National Cancer Registration Service, the South West office of the National Cancer Registration Service, the West Midlands Cancer Intelligence Unit (WMCIU), the Scottish Cancer Registry	Each registry covers the entire region	54%
Australia	The Australian Capital Territory Cancer Registry, the New South Wales Central Cancer Registry, the South Australian Cancer Registry, The Tasmanian Cancer Registry, the Victorian Cancer Registry, the Western Australian Cancer Registry	Each registry covers the entire state	81%
Japan	The Miyagi Prefectural Cancer Registry, the Nagasaki Prefectural Cancer Registry, the Osaka Cancer Registry	Each registry covers the entire Prefecture	10%

* Countries were included in the analysis if they satisfy a priori conditions: i) at least one registry should cover the entire catchment area and report for the whole period between 1988-1992 and 2003-2007; ii) reported incidence of vulvar cancer for the period 1988-1992 is not zero; and iii) population at risk at each 5-year age group (0-4, 5-9, …, 80-84 and 85+ years) is available.

† For calculating the population coverage of registry, nationwide female population in each country was estimated via the United Nations (UN) female population estimate in 2005 (using the medium variant for fertility, migration and mortality rates) in each country.

Table 2. The age-standardised incidence rates (per 100,000 women) and the 5-yearly AvPC in the age-standardised incidence rates of vulvar cancer in selected high income countries

	All ages					<60 years					60+ years				
Continent/ Country	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**
(a) Overall (13 countries including Canada, USA, 9 European countries, Australia and Japan)															
Overall	1.23	1.27	1.33	1.40	4.6%§ (3.2%, 6.0%) *P=0.005*	0.50	0.53	0.63	0.68	11.6%§ (4.7%, 18.9%) *P=0.02*	7.12	7.21	7.00	7.20	0.1% (-3.2%, 3.4%) *P=0.94*
(b) By continent															
North America	1.39	1.33	1.44	1.43	1.8% (-5.1%, 9.3%) *P=0.39*	0.67	0.65	0.76	0.74	5.1% (-8.0%, 20.0%) *P=0.25*	7.24	6.77	6.92	7.07	-0.4% (-6.6%, 6.1%) *P=0.79*
Europe	1.32	1.40	1.45	1.59	6.2%§ (2.6%, 9.9%) *P=0.02*	0.50	0.54	0.62	0.75	15.2% (6.8%, 24.2%) *P=0.01*	7.99	8.34	8.18	8.46	1.5% (-2.0%, 5.2%) *P=0.21*
Europe (excl. Germany)‡	1.32	1.40	1.45	1.55	5.3%§ (3.5%, 7.2%) *P=0.01*	0.49	0.54	0.62	0.73	14.7%§ (9.7%, 19.8%) *P=0.01*	7.98	8.36	8.15	8.26	0.7% (-3.2%, 4.8%) *P=0.52*
Oceania/Asia	0.71	0.80	0.73	0.83	3.3% (-11.6%, 20.8%) *P=0.46*	0.25	0.32	0.32	0.42	17.1%§ (-0.1%, 37.3%) *P=0.05*	4.41	4.64	4.07	4.17	-3.0% (-12.6%, 7.6%) *P=0.33*
(c) By country															
Canada	1.35	1.30	1.41	1.40	2.2% (-4.7%, 9.6%) *P=0.3*	0.65	0.67	0.76	0.73	4.8% (-7.6%, 18.8%) *P=0.3*	7.02	6.36	6.67	6.87	-0.1% (-9.2%, 9.9%) *P=1.0*
USA	1.43	1.35	1.49	1.46	1.7% (-6.9%, 11.0%) *P=0.5*	0.69	0.64	0.76	0.74	4.2% (-9.7%, 20.3%) *P=0.3*	7.44	7.13	7.40	7.27	-0.3% (-4.7%, 4.3%) *P=0.8*
Denmark	1.34	1.50	1.49	1.68	6.9% (-0.9%, 15.4%) *P=0.1*	0.56	0.68	0.73	0.87	15.1%§ (6.5%, 24.4%) *P=0.02*	7.67	8.12	7.63	8.18	1.4% (-6.0%, 9.3%) *P=0.5*

	All ages					<60 years					60+ years				
Continent/ Country	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**	**ASR* (1988-1992)**	**ASR* (1993-1997)**	**ASR* (1998-2002)**	**ASR* (2003-2007)**	**5-yearly AvPC† (95% CI) P value**
France	0.91	0.90	0.96	0.92	0.8% (-5.0%, 6.9%) *P=0.6*	0.27	0.33	0.36	0.33	5.8% (-15.2%, 32.0%) *P=0.4*	6.11	5.49	5.76	5.71	-1.5% (-10.1%, 7.9%) *P=0.6*
Germany	1.49	1.18	1.38	4.08	47.7% (-34.0%, 230.8%) *P=0.2*	0.55	0.39	0.39	2.20	75.4% (-39.5%, 408.2%) *P=0.2*	9.17	7.53	9.39	19.33	33.3% (-25.3%, 138.1%) *P=0.2*
Iceland	1.27	1.33	1.02	0.92	-12.2% (-28.0%, 7.2%) *P=0.1*	0.64	0.65	0.56	0.87	11.2% (-23.7%, 61.8%) *P=0.3*	6.36	6.85	4.73	1.28	-37.8% (-77.2%, 69.6%) *P=0.2*
Ireland	1.07	1.02	1.18	1.30	10.6% (-0.5%, 22.8%) *P=0.1*	0.10	0.33	0.47	0.54	30.0% (-13.7%, 95.8%) *P=0.1*	8.96	6.60	6.92	7.45	0.9% (-21.0%, 28.9%) *P=0.9*
Sweden	1.34	1.42	1.48	1.44	2.6% (-3.4%, 8.9%) *P=0.2*	0.53	0.58	0.70	0.61	6.1% (-15.1%, 32.7%) *P=0.4*	7.88	8.18	7.75	8.14	0.5% (-5.2%, 6.5%) *P=0.8*
Switzerland	1.11	1.28	1.05	1.27	2.1% (-18.4%, 27.8%) *P=0.7*	0.44	0.51	0.40	0.60	7.5% (-24.5%, 52.9%) *P=0.5*	6.50	7.45	6.26	6.72	-0.8% (-16.4%, 17.7%) *P=0.9*
The Netherlands	1.31	1.36	1.44	1.66	8.5%§ (0.5%, 17.1%) *P=0.04*	0.43	0.47	0.53	0.70	19.3%§ (3.6%, 37.3%) *P=0.03*	8.46	8.62	8.80	9.42	3.7% (-0.2%, 7.6%) *P=0.1*
UK	1.43	1.54	1.62	1.68	5.4%§ (2.4%, 8.4%) *P=0.02*	0.57	0.61	0.72	0.84	15.0%§ (8.7%, 21.7%) *P=0.01*	8.37	9.08	8.86	8.45	-0.3% (-8.9%, 9.1%) *P=0.9*
Australia	1.16	1.36	1.25	1.40	4.6% (-8.6%, 19.6%) *P=0.3*	0.45	0.59	0.54	0.69	12.6% (-7.9%, 37.7%) *P=0.1*	6.96	7.63	6.99	7.14	-0.3% (-9.7%, 10.2%) *P=0.9*
Japan	0.24	0.24	0.22	0.26	1.4% (-12.2%, 17.1%) *P=0.7*	0.07	0.06	0.07	0.08	5.7% (-21.3%, 42.0%) *P=0.5*	1.63	1.76	1.48	1.70	-0.1% (-16.8%, 20.0%) *P=1.0*

ASR – age standardised rate; SRR – standardised rate ratio; AvPC – average percent change.
* Age-standardised incidence rates were determined using the Segi 1960 Standard Population.
† 5-yearly average percent change in the standardised incidence rates was estimated over the period 1988-1992, 1993-1997, 1998-2002 and 2003-2007. Negative signs indicate decrease in the age-standardised rates over time.
‡ A sensitivity analysis was performed after excluding Germany from the pooled analysis due to substantially higher increase in the age-standardised incidence rate in 2003-2007 compared to other countries.
Note) The data were from selected cancer registries that were accepted for reporting to Volume 7 to Volume 10 of Cancer Incidence in Five Continents and also satisfy a prior conditions for the current analysis. Therefore, the age-standardised incidence rate of each country reported in the above table does not necessarily corresponds to each country's national statistics.
§ Significant at 0.05 level (i.e. $p<0.05$)

Table 3. The standardised rate ratios (SRRs) of the age-standardised incidence rates of vulvar cancer in 2003-2007 compared to 1988-1992 as well as the SRRs in 2003-2007 compared to 1998-2002

Continent/ Country	All ages		<60 years		60+ years	
	SRR (95% CI) in 2003-2007 relative to 1988-1992	SRR (95% CI) in 2003-2007 relative to 1998-2002*	SRR (95% CI) in 2003-2007 relative to 1988-1992	SRR (95% CI) in 2003-2007 relative to 1998-2002	SRR (95% CI) in 2003-2007 relative to 1988-1992	SRR (95% CI) in 2003-2007 relative to 1998-2002
(a) Overall (13 countries including Canada, USA, 9 European countries, Australia and Japan)						
Overall	1.14 (1.11-1.18)	1.05 (1.02-1.08)	1.38 (1.30-1.46)	1.09 (1.03-1.14)	1.01 (0.97-1.05)	1.03 (0.99-1.07)
(b) By continent						
North America	1.03 (0.97-1.09)	1.00 (0.95-1.05)	1.10 (1.00-1.21)	0.97 (0.90-1.05)	0.98 (0.91-1.05)	1.02 (0.96-1.09)
Europe	1.21 (1.16-1.26)	1.10 (1.06-1.15)	1.51 (1.39-1.64)	1.21 (1.12-1.30)	1.06 (1.01-1.11)	1.03 (0.99-1.08)
Europe (excl. Germany)†	1.18 (1.13-1.23)	1.07 (1.03-1.12)	1.47 (1.35-1.60)	1.17 (1.08-1.26)	1.04 (0.98-1.09)	1.01 (0.97-1.06)
Oceania/Asia	1.18 (1.07-1.30)	1.13 (1.04-1.24)	1.69 (1.42-2.02)	1.31 (1.11-1.54)	0.94 (0.84-1.05)	1.02 (0.92-1.13)
(c) By country						
Canada	1.04 (0.96-1.13)	1.00 (0.93-1.06)	1.12 (0.98-1.28)	0.96 (0.86-1.06)	0.98 (0.88-1.09)	1.03 (0.94-1.12)
USA	1.02 (0.94-1.10)	0.98 (0.91-1.05)	1.08 (0.94-1.22)	0.98 (0.87-1.09)	0.98 (0.89-1.08)	0.98 (0.89-1.08)
Denmark	1.25 (1.07-1.46)	1.13 (0.97-1.31)	1.57 (1.19-2.07)	1.20 (0.93-1.55)	1.07 (0.89-1.27)	1.07 (0.90-1.28)
France	1.01 (0.83-1.21)	0.96 (0.80-1.15)	1.20 (0.79-1.82)	0.90 (0.62-1.30)	0.93 (0.76-1.14)	0.99 (0.81-1.21)
Germany	2.73 (2.11-3.54)	2.95 (2.27-3.85)	4.03 (2.48-6.54)	5.61 (3.26-9.63)	2.11 (1.58-2.80)	2.06 (1.56-2.72)
Iceland	0.72 (0.28-1.89)	0.90 (0.37-2.21)	1.37 (0.37-4.98)	1.57 (0.47-5.23)	0.20 (0.04-1.06)	0.27 (0.06-1.17)
Ireland	1.21 (0.80-1.85)	1.10 (0.89-1.37)	5.62 (2.25-14.06)	1.15 (0.78-1.71)	0.83 (0.50-1.37)	1.08 (0.84-1.39)
Sweden	1.08 (0.95-1.22)	0.97 (0.87-1.10)	1.15 (0.91-1.47)	0.87 (0.70-1.08)	1.03 (0.91-1.18)	1.05 (0.92-1.20)
Switzerland	1.14 (0.87-1.50)	1.21 (0.93-1.58)	1.34 (0.80-2.25)	1.48 (0.89-2.46)	1.03 (0.76-1.40)	1.07 (0.79-1.45)
The Netherlands	1.27 (1.15-1.40)	1.15 (1.06-1.26)	1.65 (1.37-1.99)	1.32 (1.12-1.56)	1.11 (1.00-1.24)	1.07 (0.97-1.18)
UK	1.18 (1.10-1.26)	1.04 (0.98-1.11)	1.49 (1.31-1.68)	1.17 (1.04-1.30)	1.01 (0.94-1.09)	0.95 (0.89-1.02)
Australia	1.20 (1.08-1.33)	1.12 (1.01-1.23)	1.54 (1.27-1.85)	1.26 (1.07-1.49)	1.03 (0.91-1.16)	1.02 (0.91-1.15)
Japan	1.06 (0.84-1.34)	1.16 (0.93-1.44)	1.09 (0.62-1.92)	1.17 (0.69-1.98)	1.05 (0.82-1.34)	1.15 (0.92-1.44)

SRR – standardised rate ratio.

* A sensitivity analysis was performed on the SRR for 2003-2007 compared to 1998-1992 in order to exclude the possible effect of change in the disease classification from ICD-9 to ICD-10 on the incidence of vulvar cancer over time.

† A sensitivity analysis was performed after excluding Germany from the pooled analysis due to substantially higher increase in the age-standardised incidence rate in 2003-2007 compared to other countries.

Note) The data were from selected cancer registries that were accepted for reporting to Volume 7 to Volume 10 of Cancer Incidence in Five Continents and also satisfy a prior conditions for the current analysis. Therefore, the age-standardised incidence rate of each country reported in the above table does not necessarily corresponds to each country's national statistics.

Table 4. Summary of changes in the predicted number of vulvar cancer cases in selected high income countries in 2025 and 2050 under various HPV vaccination scenarios

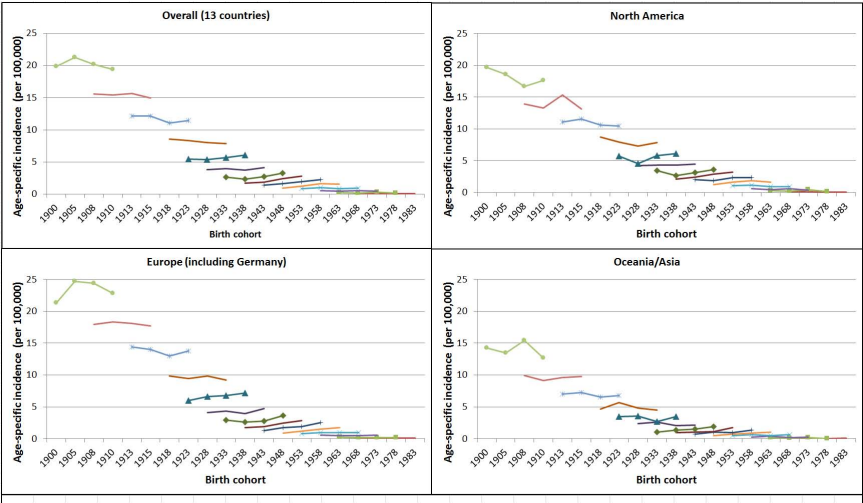
Year	Vaccination scenario*	Range of % change in the predicted no. of vulvar cancer cases in each year under various HPV vaccination scenarios†					
		AF of any HPV (22.4%)			AF of any HPV (40.4%)		
		All ages	<60 years	60+ years	All ages	<60 years	60+ years
2025	No HPV vaccination vs no HPV vaccination in 2010‡	-50%, 26%	-8%, 25%	-100%, 26%	-50%, 26%	-8%, 25%	-100%, 26%
	4V vaccine with observed vaccine dose completion rate vs no HPV vaccination in 2010	-50%, 26%	-8%, 25%	-100%, 26%	-50%, 26%	-9%, 25%	-100%, 26%
	4V vaccine with 100% coverage vs observed vaccine dose completion rate (i.e. additional % change due to 100% coverage of 4V vaccine)	0%, 0%	-2%, 0%	0%, 0%	-1%, 0%	-4%, 0%	0%, 0%
	4V vaccine with 100% coverage vs 9V vaccine with 100% coverage (i.e. additional % change due to 9V vaccine)	0%, 0%	-2%, 0%	0%, 0%	0%, 0%	-1%, 0%	0%, 0%
2050	No HPV vaccination vs no HPV vaccination in 2010‡	0%, 100%	-33%, 33%	0%, 129%	0%, 100%	-33%, 33%	0%, 129%
	4V vaccine with observed vaccine dose completion rate vs no HPV vaccination in 2010	-1%, 91%	-36%, 6%	0%, 129%	-3%, 83%	-50%, 0%	0%, 129%
	4V vaccine with 100% coverage vs observed vaccine dose completion rate (i.e. additional % change due to 100% coverage of 4V vaccine)	-6%, 0%	-23%, 0%	0%, 0%	-11%, 0%	-39%, 0%	0%, 0%
	4V vaccine with 100% coverage vs 9V vaccine with 100% coverage (i.e. additional % change due to 9V vaccine)	-1%, 0%	-4%, 0%	0%, 0%	-2%, 0%	-9%, 0%	0%, 0%

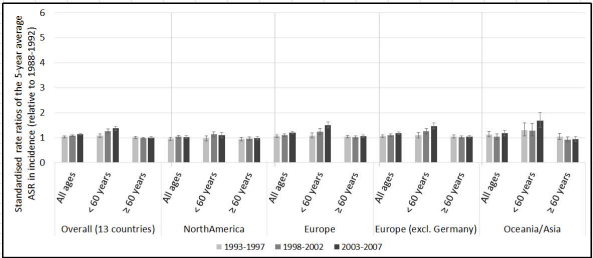
AF – attributable fraction; 4V – quadrivalent; 9V- nonavalent.

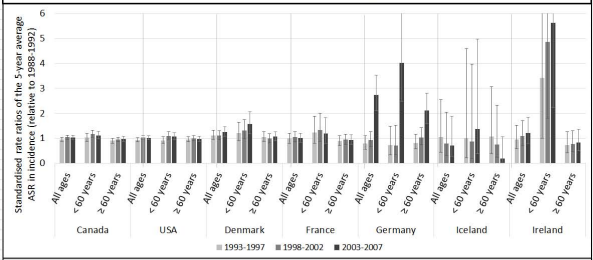
* In order to take into account the effect of HPV vaccination, assumptions made were: i) the age-specific proportion of vulvar cancer which is attributable to HPV will remain the same as currently observed; ii) within each 5-year age group, the proportion of women vaccinated is equal for each single year of age and the population is spread equally by single year of age; iii) vaccine duration of protection is lifelong with 100% efficacy; iv) the proportion of females who are fully vaccinated at 9-14 years of age (i.e. target age group) is assumed to be consistent over time and was based on the observed 3-dose uptake rate in 2014; v) vaccination of males and catch-up vaccination for females are not considered; and vi) population estimates were obtained using the medium variant for fertility, migration and mortality rates. Assumed vaccine uptake at target age group based on observed 3-dose uptake in 2014 in each country is: Canada (60%), USA (39.7%), Denmark (82%), France (25%), Germany (40%), Iceland (88%), Ireland (84.9%), Sweden (80.0%), Switzerland (51.0%), The Netherlands (61.0%), UK (86.0%), Australia (73.1%) and Japan (0.6%).

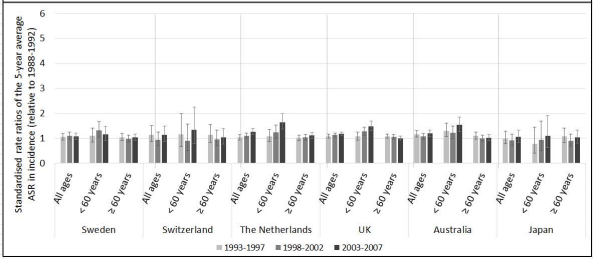
† Negative sign indicates reduction.

‡ In the absence of HPV vaccination, population is expected to shrink in some countries (France, Germany, The Netherlands and Japan), and the predicted number of vulvar cancer cases decreases.


Overall (13 countries)
North America
Europe (including Germany)
Oceania/Asia
Age-specific incidence (per 100,000)
Birth cohort
0
5
10
15
20
25
1900
1905
1908
1910
1913
1915
1918
1923
1928
1933
1938
1943
1948
1953
1958
1963
1968
1973
1978
1983
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
85+


Standardised rate ratios of the 5-year average ASR in incidence (relative to 1988-1992)
0
1
2
3
4
5
6
All ages
< 60 years
≥ 60 years
Overall (13 countries)
NorthAmerica
Europe
Europe (excl. Germany)
Oceania/Asia
1993-1997
1998-2002
2003-2007


Standardised rate ratios of the 5-year average ASR in incidence (relative to 1988-1992)
0
1
2
3
4
5
6
All ages
< 60 years
≥ 60 years
Canada
USA
Denmark
France
Germany
Iceland
Ireland
1993-1997
1998-2002
2003-2007


Standardised rate ratios of the 5-year average ASR in incidence (relative to 1988-1992)
0
1
2
3
4
5
6
All ages
< 60 years
≥ 60 years
Sweden
Switzerland
The Netherlands
UK
Australia
Japan
1993-1997
1998-2002
2003-2007