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Prevalence and risk factors for cervical HPV infection and abnormalities in young adult women at enrolment in the multinational PATRICIA trial

Edith Roset Bahmanyar[1], Jorma Paavonen[2], Paulo Naud[3], Jorge Salmerón[4], Song-Nan Chow[5], Dan Apter[6], Henry Kitchener[7], Xavier Castellsagué[8], Julio C Teixeira[9], S Rachel Skinner[10], Unnop Jaisamrarn[11], Genara A Limson[12], Suzanne M Garland[13], Anne Szarewski[14], Barbara Romanowski[15], Fred Aoki[16], Tino F Schwarz[17], Willy A J Poppe[18], Newton S De Carvalho[19], Diane M Harper[20], F Xavier Bosch[8], Alice Raillard[21], Dominique Descamps[1], Frank Struyf[1], Matti Lehtinen[22] and Gary Dubin[23] for the HPV PATRICIA Study Group.

[1]GlaxoSmithKline Vaccines, Wavre, Belgium; [2]Department of Obstetrics and Gynaecology, University of Helsinki, Finland; [3]University Federal of Rio Grande do Sul, Hospital de Clínica de Porto Alegre, Porto Alegre, Brazil; [4]Unidad de Investigación Epidemiológica y en Servicios de Salud, Instituto Mexicano del Seguro Social, Morelos, Mexico; [5]Department of Obstetrics and Gynecology, College of Medicine and the Hospital, National Taiwan University, Taipei, Taiwan; [6]Family Federation of Finland, Sexual Health Clinic, Helsinki, Finland; [7]Manchester Academic Health Science Centre, Central Manchester University Hospitals NHS Foundation Trust, St Mary's Hospital, Manchester, UK; [8]Institut Català

d'Oncologia, IDIBELL, CIBER-ESP, RTICC, L'Hospitalet de Llobregat, Catalonia, Spain; [9]University of Campinas, Campinas, Brazil; [10]Vaccine Trials Group, Telethon Institute for Child Health Research, Perth, WA and Sydney University Discipline of Paediatrics and Child Health, Children's Hospital Westmead, Sydney, NSW, Australia; [11]Chulalongkorn University, Department of Obstetrics and Gynaecology, Faculty of Medicine, Bangkok, Thailand; [12]University of the Philippines, College of Medicine, Philippine General Hospital, Makati Medical Center, Makati City, Philippines; [13]Department of Microbiology and Infectious Diseases, The Royal Women's Hospital, Parkville/Department of Microbiology, The Royal Children's Hospital, Parkville/Murdoch Childrens Research Institute, Parkville/Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria, Australia; [14]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK; [15]University of Alberta, Edmonton, Alberta, Canada; [16]University of Manitoba, Winnipeg, MB, Canada; [17]Central Laboratory and Vaccination Centre, Stiftung Juliusspital, Academic Teaching Hospital of the University of Wuerzburg, Wuerzburg, Germany; [18]Department of Gynaecology, University Hospital KU Leuven Gasthuisberg, Leuven, Belgium; [19]Department of Gynecology and Obstetrics, Federal University of Paraná, Infectious Diseases in Gynaecology and Obstetrics Sector, Curitiba, Parana, Brazil; [20]Department of Obstetrics and Gynaecology, Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, USA; [21]4Clinics, Paris, France; [22]University of Tampere, School of Public Health, Tampere, Finland; [23]GlaxoSmithKline Vaccines, King of Prussia, PA, USA.

Corresponding author: Edith Roset Bahmanyar, GlaxoSmithKline Vaccines, Av Fleming 20, 1330 Wavre, Belgium; email: edith.y.roset-bahmanyar@gskbio.com; telephone: +32 10 85 41 42; fax: +32 10 85 33 61

Abstract

Objective: We evaluated baseline data from the PApilloma TRIal against Cancer In young Adults (PATRICIA; NCT00122681) on the association between behavioral risk factors and HPV infection and cervical abnormalities.

Methods: Women completed behavioral questionnaires at baseline. Prevalence of HPV infection and cervical abnormalities (detected by cytological or histological procedures) and association with behavioral risk factors were analyzed by univariate and stepwise multivariable logistic regressions.

Results: 16782 women completed questionnaires. Among 16748 women with data for HPV infection, 4059 (24.2%) were infected with any HPV type. Among 16757 women with data for cytological abnormalities, 1626(9.7%) had a cytological abnormality, of whom 1170 (72.0%) were infected with at least one oncogenic HPV type including HPV-16 (22.7%) and HPV-18 (9.3%). Multivariable analysis (adjusted for age and region, N=14404) showed a significant association between infection with any HPV type and not living with a partner, smoking, age <15 years at first sexual intercourse, higher number of sexual partners during the past 12 months, longer duration of hormonal contraception and history of sexually transmitted infection (STI). For cervical abnormalities, only history of STI (excluding *Chlamydia trachomatis)* remained significant in the multivariable analysis after adjusting for HPV infection.

Conclusions: Women reporting 3+ sexual partners in the past 12 months had the highest risk of HPV infection at baseline. HPV infection was the main risk factor for cervical abnormalities, and history of STIs excluding *Chlamydia trachomatis* increased risk to a lesser extent. Although behavioral factors can influence risk, all sexually active women are susceptible to HPV infection.

Key words: Human papillomavirus, risk factor, prevalence, behavior, questionnaire

Introduction

Human papillomavirus (HPV) is the causal agent in virtually all cervical pre-cancer and cancer [1]. Currently, 13 HPV types are believed to be carcinogenic [2], of which types HPV-16 and HPV-18 cause approximately 70% of cervical cancer [3]. Human papillomavirus is the most common sexually transmitted infection (STI), although most infections and low grade lesions clear spontaneously within 2 years [4–6].

Factors affecting viral persistence and lesion development are not well understood [7]. Many studies have investigated the influence of behavioral factors on acquisition and persistence of infection and development of lesions [8–15], as well as the influence of immunosuppression and other infections such as *Chlamydia trachomatis* and *Herpes simplex* virus [16–18]. Although there is some evidence that these factors have an effect, associations are variable and often weak.

The PApilloma TRIal against Cancer In young Adults (PATRICIA) is a phase III efficacy study of the HPV-16/18 AS04-adjuvanted vaccine in over 18000 young women [19–21]. In addition to their primary objective of demonstrating vaccine efficacy, large trials such as PATRICIA can provide epidemiologic and behavioral information about populations and natural history of disease. We collected baseline data from PATRICIA on the prevalence of HPV infections and cervical abnormalities prior to vaccination and evaluated the association between potential behavioral risk factors and HPV infection and/or cervical abnormalities at baseline.

Methods

The PATRICIA trial has been described previously [19, 20]. The objectives of the present analysis were to (1) describe the prevalence of behavioral risk factors, HPV infection, cytological abnormalities, and cervical intraepithelial neoplasia (CIN); (2) assess the association between behavioral risk factors and presence of HPV infection, cytological abnormalities, and CIN.

Participants and study procedures at baseline

This was a phase III, double-blind, randomized, multinational trial (NCT00122681). Participants were healthy women aged 15–25 years, enrolled irrespective of their HPV DNA status, HPV serostatus or cytology at baseline. Written informed consent and/or assent was obtained from all participants or their parents, and the trial was approved by independent ethics committees and institutional review boards.

Cervical liquid-based cytology samples were gathered and HPV DNA detection and genotyping plus cytopathological examination using the Bethesda system was performed. Cervical samples and biopsy material were tested by PCR for DNA from 14 oncogenic HPV types and 11 non-oncogenic types [22]. Cervical abnormalities evaluated included any cytological abnormalities or histopathologically confirmed CIN. The same case definitions for cytological abnormalities and CIN were used as for the efficacy analyses [19, 20].

The mandatory behavioral questionnaire was a protocol-specified study instrument (Table 1), self-administered (except in Brazil, where it was administered by an investigator) at the second study visit.

Statistical analysis

The analysis of the behavioral questionnaire was performed for the Total Vaccinated Cohort for the Behavioral Questionnaire (TVC-BQ), and included all women who received at least one dose of vaccine and completed the baseline questionnaire (Figure 1).

The number and proportion of women with prevalent HPV infection and cervical abnormalities at baseline were computed with 95% confidence intervals (CI). The association between risk factors and HPV infection or cervical abnormalities was analyzed by frequency distributions, univariate logistic regressions and stepwise multivariable logistic regressions. Risk factors were retained for the multivariable analysis on the basis of their statistical significance in the model ($p<0.05$) and clinical relevance. Potential interactions between risk factors were explored. Odds ratios (OR) for risk factors and associated 95% CI were computed without and with adjustment for age and geographical region. Analyses were stratified by age and region (Table 1). Finland was treated separately from the rest of Europe because the Finnish sites primarily recruited participants through schools and thus had a relatively high proportion of younger participants [23]. The analysis of risk factors associated with cervical abnormalities was also adjusted for prevalent HPV infections.

Women were excluded from the risk factor analysis if they had missing data for HPV infection or if they stated that they had never had sexual intercourse. The lifetime number of sexual partners was not available because the questionnaire asked about the number of sexual partners (1) during the past 12 months and (2) prior to the past 12 months. For analysis of HPV infection, the number of sexual partners during the past 12 months was used in the model, whereas for cervical abnormalities, the number of sexual partners prior to the past 12 months was used because of time needed to develop an abnormality.

The risk factors included in the model are described in Table 1. Several risk factors were not retained in the multivariable analysis due to overlap or correlation with other risk factors. Cigarette smoking history and cigarette smoking (number of packs per day) overlapped and

therefore only the latter was considered. At least one pregnancy and at least one delivery were combined under a separate variable of pregnancy which included no pregnancy, abortion and delivery separately. Duration of exposure was not retained because it was related to age at first sexual intercourse. The use of an intrauterine device (IUD) was strongly correlated with at least one delivery, and therefore was not retained for analysis of HPV infection. However, it was retained for analysis of cervical abnormalities because of its potential impact on the cervix. Condom use was stratified by the number of partners; because number of partners was also considered as an independent risk factor, both risk factors could not be retained in the same stepwise multivariable analysis. In addition, a confusion effect with STI was suspected. Condom use was therefore not retained.

Results

A total of 18644 women were included in the TVC, of whom 1862 were excluded from the TVC-BQ because of no data or obvious discrepancies in the questionnaires following a consistency check by the study statistician. Thus 16782 women were included in the TVC-BQ (Figure 1). Most participants were based in Asia Pacific and Finland; there was a similar number of women in each age stratum (Table 1).The number of women with each behavioral risk factor is shown in Table 1.

Prevalent HPV infections and cervical abnormalities at study entry

Of the 16748 women with data for HPV infection, 4059 (24.2%) were infected with any HPV type at study entry, mainly HPV-16 and HPV-18 (Table 2). The distribution of prevalent HPV infections by region is shown in Table S1. HPV infection was most common in participants aged 16 or 17 years (Figure 2). Of the 16757 women with data for cervical abnormalities, 1627 (9.7%) had any cervical abnormality detected by cytological or histological procedures (Table 2).

Occurrence of cervical abnormalities concomitant with prevalent HPV infection at study entry

Among the 15155 women with normal cytology, 2254 (14.9%) were infected with an oncogenic HPV type (Figure 3). Among the 1626 women who had any cytological abnormality, 1170 (72.0%) were infected with an oncogenic HPV type; a similar pattern was seen with high grade cervical squamous intraepithelial lesion (HSIL) and atypical squamous cells of undetermined significance (ASC-US) (Figure 3).The distribution of individual HPV types is shown in Table S2.

Risk factor analysis – any HPV infection

A total of 14404 women were included in the analyses (Figure 1), of whom 4018 had an HPV infection. Based on the univariate analysis and clinical relevance, the risk factors retained into the multivariable analysis were marital status, number of cigarette packs smoked per day, age at first sexual intercourse, number of sexual partners during the past 12 months, duration of hormonal contraception, pregnancy, and STI history (Table 3).

The multivariable analysis (adjusted for age and region) showed a significant association between infection with any HPV type and not being married or living with a partner, higher number of cigarette packs smoked per day, age <15 years at first sexual intercourse, higher number of sexual partners during the past 12 months, longer duration of hormonal contraceptive use, and history of STI (Table 3). Where risk factors were analyzed for different levels of risk, the OR demonstrated a gradient with the level of exposure. The OR for pregnancies resulting in delivery suggested a protective effect against HPV infection. A relatively high proportion of women were infected with HPV even in the lowest risk group for each risk factor in the analysis (at least 14.5%) (Table 3).

Compared with women who never used condoms and had ≥2 partners (reference category), condom use in the univariate analysis was significantly protective for women who used a condom and had ≥2 partners during the past 12 months; women who never used a condom and had <2 partners also had a significant risk reduction. However, the risk increased among condom users who had <2 partners.

The risk of HPV infection did not significantly change by year of age (OR=1.01 [0.99,1.03]). Women in Latin America and North America were more likely to have an HPV infection than women living in rest of Europe (the reference category) (Table 3).

Risk factor analysis – any cervical abnormality (cytological abnormalities and histopathologically confirmed CIN)

A total of 14404 women were included in the analyses (Figure 1), of whom 1592 had a cervical abnormality. Risk factors were included in the multivariable analysis if they were suspected to have an inherent impact on the cervix and were significant in the univariate analysis: number of cigarette packs smoked per day, age at first sexual intercourse, duration of hormonal contraception, use of IUD, pregnancy, and STI history. Condom use and duration of exposure were not retained in the multivariable analysis for the same reasons as described earlier. A combination of risk factors for cigarette smoking and pregnancy were used as described previously.

The multivariable analysis indicated an increased risk of cervical abnormalities for number of cigarette packs smoked per day (<1 pack/day for ≥6 months/≥1 pack/day for <6 months and ≥1 pack/day for ≥6 months), <15 years at first sexual intercourse, duration of hormonal contraception (1–12 and 13–48 months), and STI history (Table 3). An OR of 0.75 (95% CI: 0.63, 0.89) for pregnancies resulting in delivery indicated a protective effect (Table 3). When the analysis of any cervical abnormality was adjusted for HPV infection, only history of an STI other than *Chlamydia trachomatis* remained significant (Table 3).

There was no significant association of age as a continuous variable with any cervical abnormality (Table 3). Women in Latin America and North America were more likely, and women in Asia-Pacific less likely, to have a cervical abnormality than women living in the rest of Europe; however, this did not remain significant when adjusted for HPV infection (Table 3).

Discussion

Our analysis showed a significant association between several behavioral risk factors (not married or living with a partner, smoking, young age at first sexual intercourse, higher number of sexual partners, longer duration of hormonal contraceptive use, condom use, and history of STI) and infection with any HPV type. In the analysis of risk factors associated with any cervical abnormality, only STI history was associated with a significantly higher risk after adjustment for HPV infection.

The univariate analysis of condom use and HPV infection produced paradoxical findings. Women who used condoms and had at least two partners during the past 12 months had a lower risk of HPV infection than the reference group (women who never used condoms and had at least two partners during the past 12 months). Women who used condoms and had fewer than two partners during the past 12 months had an increased risk versus the reference group. History of *Chlamydia trachomatis* infection was between two and four times as common in women who used condoms most or all of the time and had fewer than two partners during the past 12 months compared with all other groups (data not shown). A paradoxical increase in HPV infection with condom use has been previously reported, possibly because women may be more likely to use a condom if they believe there is a high risk of STI transmission from a partner [24].

Many studies evaluating the influence of risk factors on HPV infection or cervical abnormalities have produced conflicting results. In common with our findings, several studies have reported a significant association between recent smoking and HPV infection [25–28] and between smoking and HPV persistence [14]. Other studies have shown no association [29–32]. As reported elsewhere [11, 12, 29, 33–36], our study found that smoking increased the risk of cervical abnormalities, although the association disappeared when the analysis was adjusted for HPV infection. One study found that young women who smoke have an impaired antibody response to HPV-16 and HPV-18 compared with non-smokers [37].

We found that longer duration of hormonal contraception use was associated with increased risk of HPV infection. Again, several studies have reported conflicting results for this association [8, 12–14, 38, 39], although a systematic review has shown a consistent association between long-term hormonal contraception use in women infected with oncogenic HPV types and development of cervical cancer or CIN3 lesions [40]. A possible biological mechanism for the impact of hormonal contraception is enhanced hydroxylation of estradiol to 16α-hydroxyestrone in cervical cells infected with some oncogenic HPV types, which in turn induces increased transcription of the E6 and E7 HPV oncogenes [41].

Confounding is a problem in analyses of hormonal contraception use and smoking because both are associated with other risk-taking behaviors [42–44]. However, both factors were independently significant in our multivariable analysis, suggesting a true effect. Our analysis of condom use was confounded by history of STI, as discussed earlier; other studies have produced conflicting results regarding the possible influence of condom use on HPV infection [9, 45]. As in our study, the TOMBOLA study showed that childbirth and previous pregnancy were associated with a lower risk of HPV infection [13].

Women who were not married or living with a partner had a higher risk of HPV infection, as shown previously [46–48]. We also showed an association with increasing number of sexual partners during the past 12 months and HPV infection. An analysis of HPV infection at baseline in studies of the HPV-6/11/16/18 vaccine also showed a correlation between HPV infection and number of lifetime sexual partners [49]. We also found a trend for a stronger association between lower age at sexual debut and HPV infection, although this was not controlled for the lifetime number of sexual partners. It has been suggested that acquisition of HPV infection may be more likely in adolescent women because the structural immaturity of the transformation zone makes the epithelium more susceptible to viral entry and persistence [50, 51].

History of *Chlamydia trachomatis* infection and other STIs was significantly associated with HPV infection, as previously seen for *Chlamydia* infection [52–54]. A possible association with other STIs is less clear [reviewed in 55]. *Chlamydia* infection also increases the risk of persistent HPV infection [56, 57] and invasive cervical cancer [17, 58]. Only history of STIs excluding *Chlamydia* remained significantly associated with cervical abnormalities after adjustment for HPV infection in our study, although it should be noted that the OR was low and only marginally significant, and may be due to chance.

The PATRICIA study population included a diverse group of young women, most of whom were already sexually active [20]. A relatively large proportion had a prevalent HPV infection at study entry, although less than 1% had an active infection with both HPV-16 and HPV-18. Similar levels of infection at baseline were seen in studies of the HPV-6/11/16/18 vaccine [49]. Among the 614 women who were in the lowest category for all risk factors, 10% were infected with HPV (data not shown). This illustrates that, although behavioral factors can influence the risk of HPV infection, 'low risk' sexually active women may still acquire the virus.

The highest prevalence of HPV infection was seen in participants aged 16 and 17 years, in accordance with previous findings that HPV infection often occurs shortly after sexual debut [59]. The high prevalence in this age group may be explained by behavioral factors. A larger proportion of women aged 15–17 years than 18–25 years reported at least three sexual partners in the past 12 months and a smaller proportion reported only one sexual partner, whilst a larger proportion of women aged 18–25 years than 15–17 years reported that they had never smoked or had smoked for ≤6 months (data not shown). Most participants aged 16 and 17 years were recruited from Finland, making it difficult to understand whether the high prevalence in this age group was particular to Finland or applied elsewhere. Few participants aged 15 years were infected with HPV. This suggests that vaccination at 15 years may be a reasonable alternative to vaccination at a younger age if necessary, although this may vary in different geographic regions.

This analysis had several important strengths, including a large sample from a broad population of women with up to six lifetime sexual partners, with high quality data collected as part of a phase III trial. The questionnaire was mainly self-administered, which has been shown to be a reliable way of collecting information about some sexual behaviors [60–62]. However, participants may not have wished to disclose details concerning sexual behavior, and reporting may therefore be biased.

A weakness of the analyses was that there was no opportunity to correct errors and inconsistencies in the responses. Therefore, some entire questionnaires (when major inconsistencies were found) or individual questions (minor inconsistencies) had to be eliminated. A weakness of the questionnaire was the structure of the question about number of partners, i.e., (1) during the past 12 months, or (2) prior to the past 12 months. It was not possible to add the number of partners from the two responses together to estimate the lifetime number of partners, which would have allowed a better comparison of our results with published literature.

In conclusion, a relatively large number of young women in this diverse population was infected with oncogenic HPV types at study entry, although only a small proportion was infected with both HPV-16 and HPV-18. Risk factor analysis showed that behavioral factors can increase the risk of HPV infection, although even those sexually active women who were in low-risk categories were vulnerable. Women with the highest risk of HPV infection were those who had a high (3+) number of sexual partners in the past 12 months. HPV infection was the main risk factor for development of a cervical abnormality. A history of STIs other than *Chlamydia trachomatis* also increased the risk, but to a lesser extent. This study confirms many of the previously identified behavioral risk factors associated with HPV infection, but in a population that is geographically diverse. This study also confirms that, despite behavioral risk factors, all sexually active women are at risk of HPV infection and subsequent development of a cervical abnormality.

Acknowledgments

Conflicts of interest

Dominique Descamps, Gary Dubin, Edith Roset Bahmanyar and Frank Struyf are employees of the GlaxoSmithKline group of companies. Dominique Descamps, Gary Dubin, Edith Roset Bahmanyar and Frank Struyf own stock in the GlaxoSmithKline group of companies, Gary Dubin holds patents in the GlaxoSmithKline group of companies and Pfizer, and Suzanne M Garland previously held stock in CSL Ltd. Alice Raillard's employer, 4Clinics, has received consulting fees from GlaxoSmithKline Biologicals SA. All investigators at study clinical sites were funded through their institutions to do the study protocol. Henry Kitchener, Fred Y Aoki, Willy A J Poppe, F Xavier Bosch, Newton S De Carvalho, Suzanne M Garland, Diane M Harper, S Rachel Skinner, Jorge Salmerón, Tino F Schwarz and Anne Szarewski have received funding through their institutions to do HPV vaccine studies for GlaxoSmithKline Biologicals SA, CSL Ltd or Merck Sharp & Dohme, Sanofi Pasteur MSD. Fred Y Aoki, F Xavier Bosch, Newton S De Carvalho, Suzanne M Garland, Diane M Harper, Paulo Naud, Barbara Romanowski, Tino F Schwarz, Anne Szarewski and Julio C Teixeira have received honoraria from speaker's bureau or continuing medical education; Fred Y Aoki, F Xavier Bosch, Newton S De Carvalho, Suzanne M Garland, Paulo Naud, Barbara Romanowski, Tino F Schwarz, S Rachel Skinner, Anne Szarewski and Julio C Teixeira have received payment for consultant or advisory board membership; Fred Y Aoki and Anne Szarewski have received travel reimbursements. Xavier Castellsagué, Dan Apter, Unnop Jaisamrarn, Matti Lehtinen, Song-Nan Chow, Jorma Paavonen, and Genara Limson declare that they have no conflicts of interest.

Author contributions

FS, DD and GD contributed to the design and concept of PATRICIA study; ERB and AR designed the methodology and performed the analysis of these specific data collected during

the clinical trial. JP, PN, JS, SNC, DA, HK, XC, JCT, SRS, UJ, GL, SMG, AS, BR, FYA, TFS, WAJP, NSDC, DMH, FXB, and ML contributed to data acquisition and study supervision. All authors reviewed and commented upon a draft of the paper and approved it for submission.

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The HPV PATRICIA Study Group

Principal investigators/co-investigators*:*

Australia I Denham, SM Garland, A Mindel, M O'Sullivan, SR Skinner.

Belgium P De Sutter, WAJ Poppe.

Brazil NS De Carvalho, P Naud, JC Teixeira.

Canada FY Aoki, F Diaz-Mitoma, M Dionne, L Ferguson, M Miller, PH Orr, K Papp, B Ramjattan, B Romanowski, R Somani.

Finland D Apter, T Karppa, N Kudjoi, M Lehtinen, L Niemi, J Paavonen, J Palmroth, T Petaja, S Rekonen, U Romppanen, M Siitari-Mattila, L Tuomivaara.

Germany, KH Belling, T Gent, T Grubert, W Harlfinger, WD Höpker, U Kohoutek, K Peters, S Schoenian, K Schulze, TF Schwarz.

Italy CA Liverani.

Mexico J Salmerón.

Philippines C Crisostomo, MR Del Rosario-Raymundo, JEG Raymundo, MJ Germar, G Limson, C Remollino, G Villanueva, S Villanueva, JD Zamora.

Spain J Bajo, J Bayas, FX Bosch, M Campins, X Castellsagué, M Castro, C Centeno, L Rodríguez, A Torné, JA Vidart.

Taiwan SN Chow, M-H Yu.

Thailand S Angsuwathana, U Jaisamrarn, K Wilawan.

UK E Eldin Abdelhakim, M Cruickshank, H Kitchener, D Lewis, J Robinson, A Szarewski.

USA R Ackerman, N Bennett, M Caldwell, C Chambers, A Chatterjee, P Fine, DM Harper, J Hedrick, M Hiraoka, W Huh, T Klein, W Koltun, P Lee, S Luber, M Martens, J Michelson, C Peterson, J Rosen, W Rosenfeld, L Seidman, R Sperling, M Stager, TJ Stapleton, C Thoming, L Twiggs, A Waldbaum, CM Wheeler, E Zbella.

Endpoint committee: N Kiviat, KP Klugman, P Nieminen.

Independent Data Monitoring Committee: C Bergeron, E Eisenstein, R Karron, R Marks, T Nolan, SK Tay.

Laboratory contribution:

A Molijn, W Quint, L Struijk, M Van de Sandt, L-J Van Doorn (DDL Diagnostic Laboratory, Rijswijk, The Netherlands).

E Alt, B Iskaros, A Limaye, X Liu-Jarin, R D Luff, M McNeeley, C Provenzano, B Winkler (Quest Diagnostics Clinical Trials, Teterboro, NJ, USA).

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Other contributors

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Table and figure legends

Table 1. Frequency distribution at study entry of age group, region and risk factors considered in the behavioral questionnaire (TVC-BQ)

[a]Rest of Europe: Belgium, Germany, Italy, Spain, UK; Asia Pacific: Australia, Philippines, Taiwan, Thailand; Latin America: Brazil, Mexico; North America: Canada, USA.

[b]Includes both current and past smoking.

[c]The interviewer informed participants that, for the purpose of the questionnaire, sexual intercourse refers to penetrative, genital-to-genital, or oral-to-genital sexual contact.

[d]For analysis of HPV infection, the number of sexual partners during the past 12 months was considered; for analysis of cervical abnormalities, the number of sexual partners prior to the past 12 months was considered.

[e]The duration of sexual exposure was computed as: date of behavioral questionnaire minus date of first sexual intercourse. The date of the behavioral questionnaire is the date of completion of the questionnaire. The date of first sexual intercourse was computed as: date of birth plus age at first sexual intercourse.

[f]Women with both an abortion and a delivery were counted as a delivery.

Table 2. Prevalence of HPV infections or cervical abnormalities at study entry

N=number of women with available data.

For HPV infections, n=number of women with the specified HPV type (irrespective of the results for other HPV types, except for any multiple infection which excludes single infections).

For cervical abnormalities, n=number of women with the specified abnormality.

%=100*n/N

95% CI=exact 95% two-sided confidence interval for percentage.

[a]Oncogenic or non-oncogenic: oncogenic HPV types were considered as HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; non-oncogenic HPV types as HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70, 74.

[b]Cytological abnormalities included: atypical squamous cells of undetermined significance (ASC-US), high-grade squamous cell intraepithelial lesion (HSIL), atypical squamous cells in which high-grade squamous intraepithelial lesions could not be excluded (ASC-H), low-grade squamous cell intraepithelial lesion (LSIL), and atypical glandular cells of undetermined significance (AGC).

Table 3. Risk factors associated with HPV infection (any type) and any cervical abnormality (cytological abnormality or histopathologically confirmed CIN) at study entry (logistic regression analyses)

For HPV infection, N=14404 (4018 with HPV infection and 10386 without infection) for all univariate and multivariable analyses except the univariate analysis of condom use where N=14284 (3997 with HPV infection and 10287 without infection; women who stated that they had previously been sexually active but had had no sexual partner during the past 12 months were excluded).

For cervical abnormalities, N=14404 (1592 with a cervical abnormality and 12812 with no abnormality) for all univariate and multivariable analyses except the univariate analysis of condom use where N=12452 (1431 with a cervical abnormality and 11021 with no abnormality; women who stated that they had previously been sexually active but had had no sexual partner prior to the past 12 months were excluded).

OR=1 indicates reference category.

[a]Number of sexual partners during the past 12 months was used for the analysis of HPV infection, and number prior to the past 12 months for analysis of cervical abnormalities.

n (%): number and percentage of women in specified category with an HPV infection or cervical abnormality at study entry.

NR: Not reported (results are not reported here because they are different for each univariate analysis).

NRMA: Not retained into the multivariable analysis.

NRSS: Not retained by stepwise selection.

Figure 1. Subject disposition

[a]Women who stated that they were previously sexually active but had had no sexual partner during the past 12 months were excluded from the univariate analysis of condom use and HPV infection (N=14284). Women who stated that they were previously sexually active but had had no sexual partner prior to the past 12 months were excluded from the univariate analysis of condom use and cervical abnormalities (N=12452).

[b]There were some demographic differences between the women who were excluded and the TVC-BQ, with a higher proportion of women aged 22-25+ years and women from Asia Pacific being excluded. Of the women excluded, 13.0% were aged 15-17 years, 34.6% were aged 18-21 years and 52.4% were aged 22-25+ years, whilst 53.8% were from Asia Pacific, 21.1% from North America, 12.4% from Latin America, 6.8% from Finland and 5.9% from rest of Europe.

[c]Questionnaires with major discrepancies were excluded from the analysis (N=1530). If only minor discrepancies were identified, the inconsistency was corrected or recorded as a missing value and included in the analysis if the variable was included in the analysis. If the variable was not included in the analysis, it was not corrected.

Figure 2. Prevalence of HPV infection at study entry according to age

Figure 3. Occurrence of cervical abnormalities concomitant with prevalent HPV infection at study entry

Table 1. Frequency distribution at study entry of age group, region and risk factors considered in the behavioural questionnaire (TVC-BQ)

Risk factor	Categories	Frequency distribution at study entry, n (%) N=16782
Age group	15-17 years	5682 (33.9)
	18-21 years	5116 (30.5)
	22-25+ years	5984 (35.7)
Region	Asia Pacific	5351 (31.9)
	North America	2680 (16.0)
	Latin America	2543 (15.2)
	Finland	4681 (27.9)
	Rest of Europe	1527 (9.1)
Marital status	Married/living with partner	4841 (28.8)
	Divorced/widowed	168 (1.0)
	Single	11773 (70.2)
Education (number of years education completed)	<10	3247 (19.3)
	10-14	10261 (61.1)
	≥15	3274 (19.5)
Cigarette smoking history	Never	10406 (62.0)
	Former	2257 (13.4)
	Current	4119 (24.5)
Cigarette smoking (number of packs per day)[a]	Never smoked	10406 (62.0)
	<1 pack/day for <6 months	1385 (8.3)
	<1 pack/d for ≥6 m or ≥1 pack/d for <6 m	4723 (28.1)
	≥1 pack/day for ≥6 months	268 (1.6)
Age at first sexual intercourse[b]	Never had sexual intercourse	2348 (14.0)
	<15 years	2083 (12.4)
	15-18 years	9548 (56.9)
	19-22 years	2584 (15.4)
	23-25 years	219 (1.3)
Number of sexual partners during the past 12 months[b,c]	Never had sexual intercourse	2348 (14.0)
	0	120 (0.7)
	1	10909 (65.0)
	2-3	2904 (17.3)
	≥4	501 (3.0)
Number of sexual partners prior to the past 12 months[b,c]	Never had sexual intercourse	2348 (14.0)
	0	1955 (11.6)
	1	7414 (44.2)
	2-3	3586 (21.4)
	≥4	1479 (8.8)
Duration of sexual exposure[b,d]	Never had sexual intercourse	2348 (14.0)
	<1 year	1090 (6.5)
	1-5 years	10002 (59.6)
	6-10 years	2987 (17.8)
	>10 years	355 (2.1)
Condom use according to number of sexual partners during the past 12 months[b,c]	Never had sexual intercourse	2348 (14.0)
	No partner	120 (0.7)
	Never (≥2 partners)	2353 (14.0)
	Never (<2 partners)	6662 (39.7)
	Rarely/sometimes (≥2 partners)	174 (1.0)
	Rarely/sometimes (<2 partners)	1670 (10.0)
	Most/every time (≥2 partners)	878 (5.2)
	Most/every time (<2 partners)	2577 (15.4)
Condom use according to number of sexual partners prior to the past 12 months[b,c]	Never had sexual intercourse	2348 (14.0)
	No partner	1955 (11.6)
	Never (≥2 partners)	3605 (21.5)
	Never (<2 partners)	4839 (28.8)
	Rarely/sometimes (≥2 partners)	215 (1.3)

	Rarely/sometimes (<2 partners)	1073 (6.4)
	Most/every time (≥2 partners)	1245 (7.4)
	Most/every time (<2 partners)	1502 (9.0)
Duration of hormonal contraception	Never	6679 (39.8)
	1-12 months	4984 (29.7)
	13-48 months	3873 (23.1)
	≥49 months	1246 (7.4)
Use of copper IUD	Yes	863 (5.1)
	No	15919 (94.9)
At least one pregnancy	Yes	4888 (29.1)
	No	11894 (70.9)
At least one delivery	Yes	3291 (19.6)
	No	13491 (80.4)
Pregnancy[e]	No	11894 (70.9)
	Abortion	1597 (9.5)
	Delivery	3291 (19.6)
STI history	No	15843 (94.4)
	Yes - *Chlamydia trachomatis*	345 (2.1)
	Yes - other	594 (3.5)

[a]Rest of Europe: Belgium, Germany, Italy, Spain, UK; Asia Pacific: Australia, Philippines, Taiwan, Thailand; Latin America: Brazil, Mexico; North America: Canada, USA.

[b]Includes both current and past smoking.

[c]The interviewer informed participants that, for the purpose of the questionnaire, sexual intercourse refers to penetrative, genital-to-genital, or oral-to-genital sexual contact.

[d]For analysis of HPV infection, the number of sexual partners during the past 12 months was considered; for analysis of cervical abnormalities, the number of sexual partners prior to the past 12 months was considered.

[e]The duration of sexual exposure was computed as: date of behavioral questionnaire minus date of first sexual intercourse. The date of the behavioral questionnaire is the date of completion of the questionnaire. The date of first sexual intercourse was computed as: date of birth plus age at first sexual intercourse.

[f]Women with both an abortion and a delivery were counted as a delivery.

Table 2. Prevalence of HPV infections or cervical abnormalities at study entry

	Women with infections or cervical abnormalities		
	n	**%**	**95% CI**
Data available for HPV infections (N=16748)			
No HPV infection	12689	75.8	75.1, 76.4
Any HPV type[a]	4059	24.2	23.6, 24.9
Any oncogenic HPV type	3425	20.5	19.8, 21.1
Any non-oncogenic HPV type	1447	8.6	8.2, 9.1
Any multiple HPV types[a]	1660	9.9	9.5, 10.4
Any oncogenic type excluding HPV-16 and HPV-18	2201	13.1	12.6, 13.7
HPV-16	931	5.6	5.2, 5.9
HPV-18	381	2.3	2.1, 2.5
HPV-16 and HPV-18	88	0.5	0.4, 0.6
HPV-31	393	2.3	2.1, 2.6
HPV-33	169	1.0	0.9, 1.2
HPV-45	143	0.9	0.7, 1.0
HPV-51	702	4.2	3.9, 4.5
Data available for cervical abnormalities (N=16757)			
Normal cytology (no cytological abnormality and no CIN)	15130	90.3	89.8, 90.7
Any cervical abnormality (cytological abnormality or CIN)	1627	9.7	9.3, 10.2
Any cytological abnormality	1626	9.7	9.3, 10.2
ASC-US	773	4.6	4.3, 4.9
ASC-H	19	0.1	0.1, 0.2
LSIL	773	4.6	4.3, 4.9
HSIL	53	0.3	0.2, 0.4
AGC	8	0.0	0.0, 0.1

N=number of women with available data.

For HPV infections, n=number of women with the specified HPV type (irrespective of the results for other HPV types, except for any multiple infection which excludes single infections).

For cervical abnormalities, n=number of women with the specified abnormality.

%=100*n/N

95% CI=exact 95% two-sided confidence interval for percentage.

[a]Oncogenic or non-oncogenic: oncogenic HPV types were considered as HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; non-oncogenic HPV types as HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70, 74.

[b]Cytological abnormalities included: atypical squamous cells of undetermined significance (ASC-US), high-grade squamous cell intraepithelial lesion (HSIL), atypical squamous cells in which high-grade

squamous intraepithelial lesions could not be excluded (ASC-H), low-grade squamous cell intraepithelial lesion (LSIL), and atypical glandular cells of undetermined significance (AGC).

Table 3. Risk factors associated with HPV infection (any type) and any cervical abnormality (cytological abnormality or histopathologically confirmed CIN) at study entry (logistic regression analyses)

		HPV infection			Any cervical abnormality			
Risk factor	**Category**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age, region and HPV infection OR (95% CI)**
Marital status	Married/living with partner	979 (20.3)	1	1	350 (7.3)	1		
	Divorced/widowed	59 (35.1)	1.91 (1.37, 2.65)	1.56 (1.10, 2.21)	21 (12.5)	1.65 (1.02, 2.64)	NRMA	NRMA
	Single	2980 (31.6)	1.60 (1.45, 1.76)	1.36 (1.21, 1.52)	1221 (13.0)	1.42 (1.23, 1.63)		
Education (number of years education completed)	<10	681 (25.3)	1		248 (9.2)	1		
	10-14	2505 (28.7)	1.09 (0.99, 1.21)	NRMA	1038 (11.9)	1.22 (1.05, 1.42)	NRMA	NRMA
	≥15	832 (27.9)	1.15 (1.00, 1.31)		306 (10.3)	1.24 (1.02, 1.52)		
Cigarette smoking (number of packs per day)	Never smoked	2008 (23.7)	1	1	791 (9.4)	1	1	
	<1 pack/day for <6 months	353 (29.0)	1.29 (1.12, 1.48)	1.21 (1.05, 1.39)	137 (11.2)	1.10 (0.91, 1.34)	1.10 (0.90, 1.34)	
	<1 pack/d for ≥6 m or ≥1 pack/d for <6 m	1546 (34.6)	1.67 (1.54, 1.82)	1.36 (1.24, 1.49)	619 (13.9)	1.37 (1.22, 1.54)	1.29 (1.14, 1.45)	NRSS
	≥1 pack/day for ≥6 months	111 (41.9)	2.09 (1.62, 2.70)	1.63 (1.25, 2.13)	45 (17.0)	1.80 (1.29, 2.52)	1.69 (1.20, 2.38)	
Age at first sexual intercourse	23-25	33 (15.1)	1	1	9 (16.0)	1	1	
	19-22	515 (20.0)	1.28 (0.87, 1.89)	1.22 (0.82, 1.80)	203 (4.1)	1.73 (0.87, 3.44)	1.69 (0.85, 3.36)	
	15-18	2673 (28.1)	1.76 (1.20, 2.57)	1.49 (1.00, 2.20)	1047 (7.9)	1.86 (0.94, 3.67)	1.68 (0.85, 3.35)	NRSS
	<15	797 (38.3)	2.75 (1.85, 4.08)	1.88 (1.25, 2.84)	333 (11.0)	2.55 (1.28, 5.10)	2.04 (1.01, 4.14)	
Number of	0	21 (17.5)	1	1	161 (8.2)	1	NRMA	NRMA

		HPV infection			Any cervical abnormality			
Risk factor	**Category**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age, region and HPV infection OR (95% CI)**
sexual partners[a]	1	2442 (22.4)	1.36 (0.84, 2.19)	1.36 (0.84, 2.21)	570 (7.7)	1.23 (1.02, 1.49)		
	2-3	1239 (42.7)	3.50 (2.16, 5.66)	3.09 (1.90, 5.03)	583 (16.3)	2.49 (2.06, 3.02)		
	≥4	316 (63.1)	9.29 (5.57, 15.50)	7.62 (4.55, 12.79)	278 (18.8)	2.97 (2.39, 3.68)		
Duration of sexual exposure	<1 year	157 (14.5)	1		82 (7.6)	1		
	1-5 years	2851 (28.5)	2.56 (2.14, 3.06)		1167 (11.7)	1.85 (1.46, 2.34)		
	6-10 years	907 (30.5)	3.36 (2.73, 4.14)	NRMA	296 (9.9)	2.01 (1.51, 2.68)	NRMA	NRMA
	>10 years	103 (29.2)	3.00 (2.20, 4.08)		47 (13.3)	2.73 (1.80, 4.14)		
Condom use[a]	Never (≥2 partners)	1029 (43.8)	1		621 (17.3)	1		
	Never (<2 partners)	1431 (21.5)	0.34 (0.31, 0.38)		379 (7.8)	0.47 (0.41, 0.54)		
	Rarely/sometimes (<2 partners)	76 (43.7)	1.10 (0.80, 1.51)		34 (15.9)	1.35 (0.92, 1.99)		
	Rarely/sometimes (≥2 partners)	345 (20.8)	0.42 (0.36, 0.49)	NRMA	57 (5.4)	0.45 (0.33, 0.61)	NRMA	NRMA
	Most/every time (<2 partners)	450 (51.3)	1.34 (1.14, 1.57)		206 (16.6)	1.04 (0.88, 1.24)		
	Most/every time (≥2 partners)	666 (25.9)	0.43 (0.38, 0.49)		134 (8.9)	0.56 (0.46, 0.68)		
Duration of hormonal contraception	Never	1026 (22.1)	1	1	400 (8.6)	1	1	
	1-12 months	1422 (30.0)	1.34 (1.22; 1.47)	1.35 (1.22, 1.49)	588 (12.4)	1.33 (1.16, 1.52)	1.27 (1.10, 1.46)	
	13-48 months	1118 (29.6)	1.28 (1.16, 1.42)	1.26 (1.13, 1.40)	457 (12.1)	1.29 (1.11, 1.49)	1.18 (1.01, 1.37)	NRSS
	≥49 months	452 (36.7)	1.80 (1.55, 2.09)	1.59 (1.36, 1.86)	147 (11.9)	1.37 (1.10, 1.70)	1.18 (0.94, 1.47)	

		HPV infection			Any cervical abnormality			
Risk factor	**Category**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**n (%)**	**Univariate analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age and region OR (95% CI)**	**Multivariable analysis adjusted by age, region and HPV infection OR (95% CI)**
Use of copper IUD	No	3815 (28.2)	1	NRMA	1518 (11.2)	1	1	NRSS
	Yes	203 (23.6)	0.59 (0.50, 0.71)		74 (8.6)	0.72 (0.55, 0.93)	NRSS	
Pregnancy	No pregnancy	2849 (29.9)	1	1	1163 (12.2)	1	1	NRSS
	Abortion	485 (30.5)	1.20 (1.06, 1.36)	1.06 (0.93, 1.21)	181 (11.4)	1.21 (1.01, 1.44)	1.01 (0.84, 1.21)	
	Delivery	684 (20.8)	0.70 (0.63, 0.78)	0.82 (0.72, 0.93)	248 (7.6)	0.82 (0.70, 0.97)	0.75 (0.63, 0.89)	
STI history	No	3533 (26.2)	1	1	1373 (10.2)	1	1	1
	Yes - *Chlamydia trachomatis*	205 (59.4)	3.56 (2.85, 4.45)	2.84 (2.25, 3.58)	86 (24.9)	2.44 (1.89, 3.16)	2.21 (1.70, 2.87)	1.20 (0.90, 1.60)
	Yes - other	280 (47.5)	2.24 (1.89, 2.66)	1.94 (1.63, 2.32)	133 (22.6)	2.34 (1.91, 2.88)	2.21 (1.79, 2.72)	1.57 (1.24, 1.99)
Age (years)	Numerical/continuous variable	4018 (27.9)	NR	1.01 (0.99, 1.03)	1592 (11.1)	NR	0.97 (0.94, 1.00)	0.96 (0.93, 0.99)
Region	Rest of Europe	409 (28.9)	NR	1	159 (11.3)	NR	1	1
	Asia Pacific	892 (18.5)	NR	1.15 (0.98, 1.35)	301 (6.3)	NR	0.76 (0.61, 0.95)	0.79 (0.63, 0.99)
	North America	899 (37.2)	NR	1.48 (1.27, 1.72)	371 (15.3)	NR	1.38 (1.12, 1.70)	1.12 (0.90, 1.40)
	Latin America	879 (36.9)	NR	2.41 (2.06, 2.82)	303 (12.7)	NR	1.45 (1.17, 1.80)	0.96 (0.77, 1.21)
	Finland	939 (27.8)	NR	0.85 (0.72, 1.01)	458 (13.6)	NR	1.10 (0.87, 1.38)	1.13 (0.88, 1.46)

For HPV infection, N=14404 (4018 with HPV infection and 10386 without infection) for all univariate and multivariable analyses except the univariate analysis of condom use where N=14284 (3997 with HPV infection and 10287 without infection; women who stated that they had previously been sexually active but had had no sexual partner during the past 12 months were excluded).

For cervical abnormalities, N=14404 (1592 with a cervical abnormality and 12812 with no abnormality) for all univariate and multivariable analyses except the univariate analysis of condom use where N=12452 (1431 with a cervical abnormality and 11021 with no abnormality; women who stated that they had previously been sexually active but had had no sexual partner prior to the past 12 months were excluded).

OR=1 indicates reference category.

[a]Number of sexual partners during the past 12 months was used for the analysis of HPV infection, and number prior to the past 12 months for analysis of cervical abnormalities.

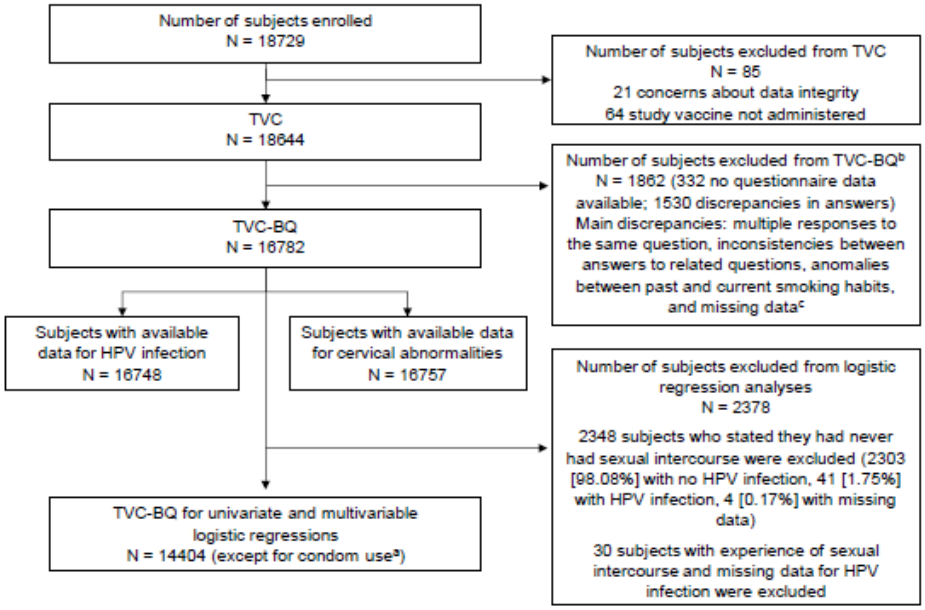
n (%): number and percentage of women in specified category with an HPV infection or cervical abnormality at study entry.

NR: Not reported (results are not reported here because they are different for each univariate analysis).

NRMA: Not retained into the multivariable analysis.

NRSS: Not retained by stepwise selection.

Figure 1. Subject disposition



[a]Women who stated that they were previously sexually active but had had no sexual partner during the past 12 months were excluded from the univariate analysis of condom use and HPV infection (N = 14284). Women who stated that they were previously sexually active but had had no sexual partner prior to the past 12 months were excluded from the univariate analysis of condom use and cervical abnormalities (N=12452).
[b]There were some demographical differences between the women who were excluded and the TVC-BQ, with a higher proportion of women aged 22-25+ years and women from Asia Pacific being excluded. Of the women excluded, 13.0% were aged 15-17 years, 34.6% were aged 18-21 years and 52.4% were aged 22-25+ years, whilst 53.8% were from Asia Pacific, 21.1% from North America, 12.4% from Latin America, 6.8% from Finland and 5.9% from rest of Europe.
[c]Questionnaires with major discrepancies were excluded from the analysis (N=1530). If only minor discrepancies were identified, the inconsistency was corrected or recorded as a missing value and included in the analysis if the variable was included in the analysis. If the variable was not included in the analysis, it was not corrected.

Fig. 2

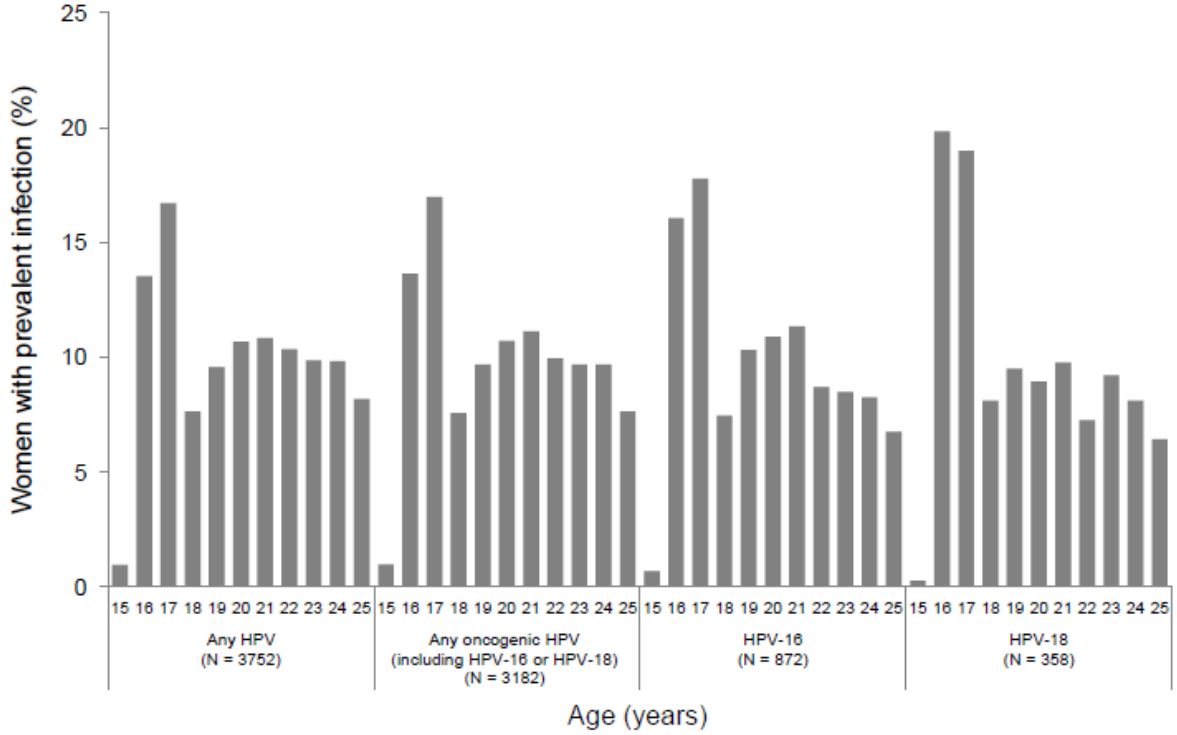
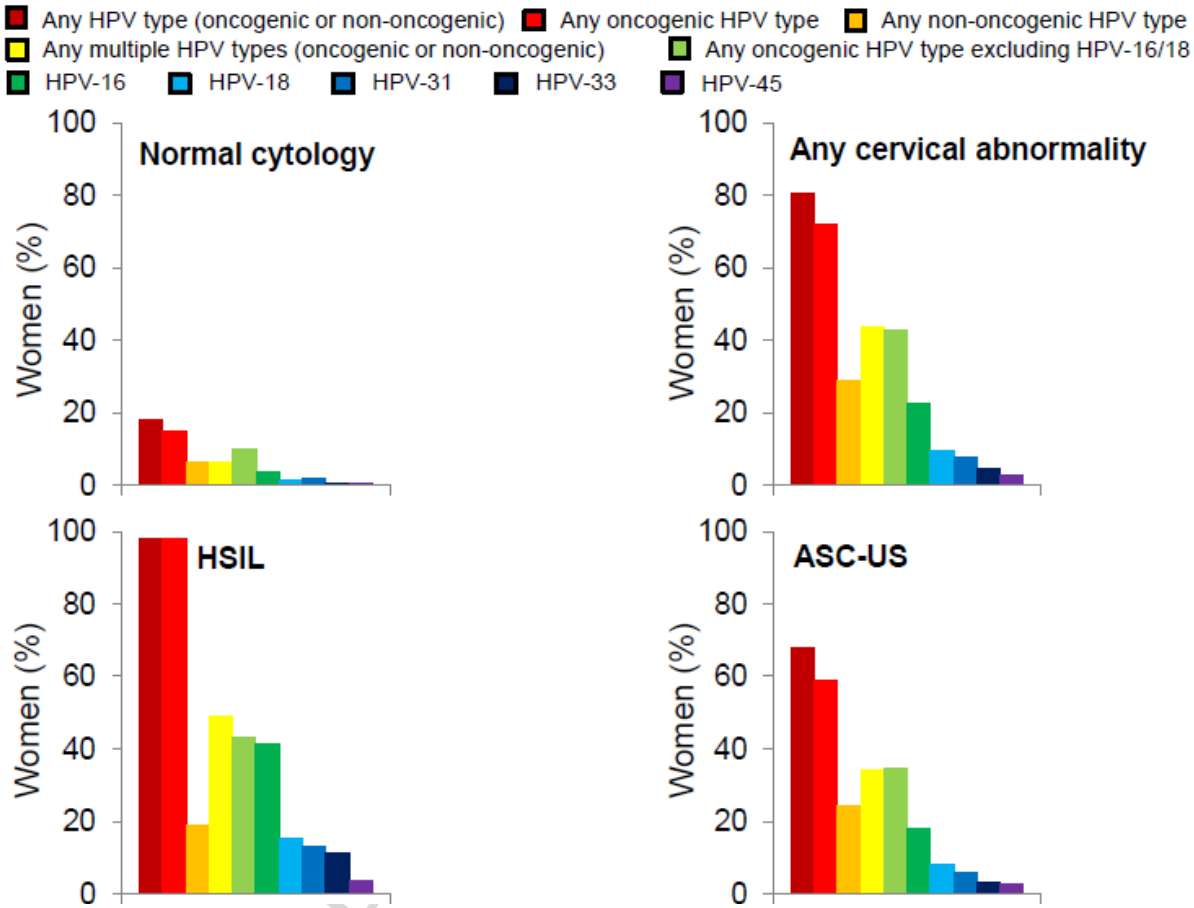


Fig. 3



Research Highlights

- Women with ≥3 sexual partners in the past 12 m had the highest risk of HPV infection.
- HPV infection was the main risk factor for cervical abnormalities.
- History of STIs excluding *C trachomatis* increased this risk to a lesser extent.

Author/s:
Bahmanyar, ER; Paavonen, J; Naud, P; Salmeron, J; Chow, S-N; Apter, D; Kitchener, H; Castellsague, X; Teixeira, JC; Skinner, SR; Jaisamrarn, U; Limson, GA; Garland, SM; Szarewski, A; Romanowski, B; Aoki, F; Schwarz, TF; Poppe, WAJ; De Carvalho, NS; Harper, DM; Bosch, FX; Raillard, A; Descamps, D; Struyf, F; Lehtinen, M; Dubin, G

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