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Genotype prevalence and age distribution of human papillomavirus from infection to cervical cancer in Japanese women: A systematic review and *meta*-analysis

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ABSTRACT

Background: National HPV vaccination coverage in Japan is less than one percent of the eligible population and cervical cancer incidence and mortality are increasing. This systematic review and *meta*-analysis aimed to provide a comprehensive estimate of HPV genotype prevalence for Japan.
Methods: English and Japanese databases were searched to March 2021 for research reporting HPV genotypes in cytology and histology samples from Japanese women. Summary estimates were calculated by disease stage from cytology only assessment – Normal, ASCUS, LSIL, HSIL and from histological assessment – CIN1, CIN2, CIN3/AIS, ICC (ICC-SCC, and ICC-ADC), and other. A random-effects meta–analysis was used to calculate summary prevalence estimates of any-HPV, high-risk (HR) and low-risk (LR) vaccine types, and vaccine genotypes (bivalent, quadrivalent, or nonavalent). This study was registered with PROSPERO: CRD42018117596.
Results: A total of 57759 women with normal cytology, 1766 ASCUS, 3764 LSIL, 2017 HSIL, 3130 CIN1, 1219 CIN2, 869 CIN3/AIS, and 4306 ICC (which included 1032 ICC-SCC, and 638 ICC-ADC) were tested for HPV. The summary estimate of any-HPV genotype in women with normal cytology was 15·6% (95% CI: 12·3–19·4) and in invasive cervical cancer (ICC) was 85·6% (80·7–89·8). The prevalence of HR-HPV was 86·0% (95% CI: 73·9–94·9) for cytological cases of HSIL, 76·9% (52·1–94·7) for histological cases of CIN3/AIS, and 75·7% (68·0–82·6) for ICC. In women with ICC, the summary prevalence of bivalent vaccine genotypes was 58·5% (95% CI: 52·1–64·9), for quadrivalent genotypes was 58·6% (52·2–64·9) and for nonavalent genotypes was 71·5% (64·9–77·6), and of ICC cases that were HPV positive over 90% of infections are nonavalent vaccine preventable. There was considerable heterogeneity in all HPV summary estimates and for ICC, this heterogeneity was not explained by variability in study design, sample type, HPV assay type, or HPV DNA detection method, although studies published in the 1990s had lower prevalence estimates of any-HPV and HR HPV genotypes.
Interpretations: HPV prevalence is high among Japanese women. The nonavalent vaccine is likely to have the greatest impact on reducing cervical cancer incidence and mortality in Japan.

1. Introduction:

The WHO global strategy to accelerate the elimination of cervical cancer as a public health problem has stated an ambitious goal to achieve cervical cancer incidence of <4/100,000 in all countries within 100 years.[1] It's goals to set all countries on the path to

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elimination are that by 2030, 90% of girls are fully vaccinated with the human papillomavirus (HPV) vaccine by 15 years of age, 70% of women are screened with a high performance HPV test by 35 and again by 45 years of age, and 90% of women identified with cervical disease receive treatment and care. In Japan, urgent action is needed if these goals are to be met by 2030.

First-generation HPV vaccines have both been available since 2007 in Japan and initially, vaccination coverage for eligible adolescent girls in some prefectures was as high as 80%. [2] In light of such success, the HPV vaccine was added to the national routine vaccination register in April 2013. It was recommended under the Preventative Vaccination Law that the vaccine should be made available to all girls between the age of 12 to 16. However, in response to a series of media reported adverse events, the HPV immunisation programme was partially suspended by the Japanese Ministry of Health, Labour and Welfare (MHLW) in June 2013. [3] Since then, the MHLW has suspended proactive recommendation of adolescent HPV immunisation. [4,5] HPV vaccination coverage remains below 1·0%. [2,5,6,22,23] Encouragingly, in late 2020 the nonavalent vaccine was approved for use, but resumption of widescale use of the vaccination is yet to occur.

National level data for HPV-type distribution is a prerequisite to predict and then assess the impact of HPV vaccination policy. In most comprehensive reviews of global HPV prevalence, Japanese studies are under-represented or grouped with Asia or other East Asian countries, limiting their usefulness for guiding vaccination policy in Japan. We undertook a comprehensive systemic review and *meta*-analysis to provide estimates for Japan of HPV genotype prevalence and age distribution of human papillomavirus across the disease trajectory from infection to cervical cancer in Japanese women.

2. Methods:

This review was conducted according to a registered protocol (PROSPERO: CRD42018117596), and published elsewhere. [7] There were no deviations from the original protocol with the exception of including a sensitivity analysis (see below for details). This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Appendix Table A1).

2.1. Search strategy

A systematic search of PubMed, EMBASE, and ICHUSHI for all studies reporting HPV prevalence data in Japan was conducted to March 2021. The search strategy was developed in both English (MP) and Japanese (ES, HS) and included combinations of general terms, expanded, and adapted to each database: 'Japan' and 'human papillomavirus' or 'HPV,' and 'cervical cancer,' and 'genotype,' and'normal cytology,' and 'cervical disease' or 'cervical intraepithelial neoplasia' (Appendix Table A2). Conference papers specific to HPV and cervical cancer were manually searched, Japanese government documents, and published guidelines from the Japan National Diet Library were also manually reviewed.

2.2. Eligibility criteria

The population of interest was Japanese women with no restriction on the age of participants. Studies were eligible if they were randomised control trials, case control studies, cohort studies or cross–sectional studies and reported primary data for Japan. Systematic reviews were not eligible, but their reference lists were searched. Based on previous global HPV genotype prevalence systematic reviews, eligible studies needed to include: at least 20 cases of histology confirmed cervical intraepithelial neoplasia 1 (CIN1), cervical intraepithelial neoplasia 2 (CIN2), cervical intraepithelial neoplasia 3 (CIN3) or invasive cervical cancer (ICC); at least 20 cases of cytology reported low–grade squamous intraepithelial lesion (LSIL) or high–grade squamous intraepithelial lesions (HSIL), atypical squamous cells of undetermined significance (ASCUS), [8-10] or; iii. 100 cases of normal cytology. [11-13] Studies needed to use PCR (polymerase chain reaction) based assays (RNA/DNA), or HC2 (Hybrid Capture 2); and include a detailed description of sampling techniques.

2.3. Selection of studies

Covidence Review Software was used to merge search results and remove duplicate records of the same report. The titles and abstracts of all records were screened by two independent reviewers (MP, CAM - English, HS, and SI - Japanese). [14] Text of all potentially relevant studies was evaluated in detail against the selection criteria by two independent reviewers (MP, CAM – English, HS, and SI - Japanese).

2.4. Primary outcome

The outcome of interest was HPV prevalence measured as HPV test positivity where the numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test with an assay able to detect the respective type.

2.5. Data extraction

Data from studies published in English were extracted by three independent reviewers (MP, CAM, HS). Data from studies published in Japanese were extracted by two independent Japanese reviewers (SO, SI, HS). Variables extracted were author and year of publication; location of study, study year, setting, study design, sample collection method (practitioner, self, or other), sample collection method (cervical swab, cytobrush or surgical), type of cervical specimen (biopsy or exfoliated), and HPV assay (PCR or HC2). If PCR was used, the primer type and typing method (DNA/RNA) was recorded. Primer type was further classified as broad spectrum (MY09/11, GP5+/6+ and SPF10) or narrow spectrum (GP5/6, L1C1/C2 or PU1M/2R). If HC2 was used, the high–risk probe or the low-risk probe was recorded. For cohort and randomised studies, only baseline data were extracted. Additional information was requested from authors of both English and Japanese studies regarding PCR primer, sample collection method, age specific prevalence and HPV genotype-specific prevalence. The PRISMA diagram is summarised in Appendix Fig. 1, and Appendix Table A3 lists all the included studies. Sample size (N), and number of HPV-positive samples (n), were extracted for all studies. Data were extracted by cytological disease stage (Normal, ASCUS, LSIL, HSIL, ICC) and or histological disease stage (CIN1, CIN2, CIN3/AIS, ICC) depending on the study. Cases of ICC were further classified as ICC-ADC (ICC of adenocarcinoma type), and ICC-SCC (ICC of squamous cell carcinoma type), or other. Multiple infections were separated and recorded as their constituent types.

2.6. Statistical analysis

Analysis was performed using a Freeman Tukey double arcsine transformation and Der Simonian-Laird random effects model to compute summary estimates with confidence intervals (CIs). [15] Summary prevalence estimates were calculated for any-HPV genotype, and for the following sub-groups: any high risk (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) genotype, any low risk vaccine genotype (HPV6 or 11), any vaccine genotype (bivalent – HPV16 or

18), quadrivalent – HPV6, 11, 16 or 18, or nonavalent – HPV6, 11, 16, 18, 31, 33, 45, 52 and 58) vaccine or cross-protection genotypes (HPV31, 33, or 45). We also calculated summary estimates of possibly (HPV26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, or 97) or probably carcinogenic genotypes (HPV68) according to the IARC classification of human carcinogens[16] separately for each cytological or histological diagnosis (Appendix Table A4). Summary estimates of individual HPV genotypes were also calculated where possible. All studies contributed data to the estimates of any-HPV. Studies that did not provide genotype specific data and were excluded from sub-group estimates.

Statistical heterogeneity was quantified using Cochrane's Q and I^2 test statistic to determine the extent of variation in summary estimates due to heterogeneity rather than chance. We anticipated high heterogeneity and opted to use the random effects model for analysis. Sources of heterogeneity were assessed in our sub-group and *meta*-regression analysis. A sensitivity analysis was conducted to investigate impact of older studies with expected less-sensitive detection methods published in the 1990s on summary estimates of any-HPV and HR-HPV genotype prevalence for cases of ICC. Age specific prevalence of any-HPV was calculated for 10-year age groups for the interval 10 to >80 years. This analysis was limited to those studies that provided data in these 10-year age groups. Age standardised estimates were calculated using the 2020 standard Japanese female population. [17]

2.7. Quality assessment and publication bias

The Joana Briggs assessment tool for prevalence studies was used to assess the quality of studies (Appendix Table A5) and the results presented in Appendix Table A6. Publication bias was assessed using funnel plots and Egger's test (Appendix Fig. 2).

3. Results:

3.1. Literature search

The literature search resulted in a total of 714 citations, from which 113 (15·8%) full text articles were screened in detail and 87 (12·2%) studies were eligible for inclusion (Appendix Fig. 1). Study sample sizes varied from 20 to 62625 with a total of 504035 women. Overall, there were 57759 women tested for HPV with normal cytology, 1766 with ASCUS, 3764 with LSIL, 2017 with HSIL, 3130 with CIN1, 1219 with CIN2, 960 with CIN3/AIS and 4306 with ICC including 1032 ICC-SCC and 638 ICC-ADC. Most studies used either PCR with an HPV DNA array (28, 32·1%), or L1C1/L1C2 primer (25, 28·7%). The age of women ranged from 14 to 95 years and all studies were published between 1990 and 2019. The majority were cohort (49, 56·3%) or cross–sectional studies (26, 29·8%). Overall, 65·5% (57) of studies used exfoliated samples, and 82·5% (71) samples were practitioner collected. Thirty-seven (37) studies (42·5%) used a cytobrush, followed by 25·3% (22) which used a cervical swab for sample collection. Most studies were from the Kanto (28, 32·2%), or Kansai (18, 20·7%) region.

3.2. HPV prevalence (any-HPV, any-HR or LR vaccine type) in women with normal cytology through to invasive cervical cancer

The total number of studies that provided prevalence data by cytological or histological stage were: Normal cytology(26), [18-44] ASCUS(14), [19,23,27,32,34,35,37,39,42,45-49] LSIL(20), [18,20-24,27,29,32,34,38,39,42,45,47,49-52] HSIL(15),[18,20,21, 23,24,27,29,34,39,46,47,49-52] CIN1(21), [18,19,21,49,53-69] CIN2(17), [18,48,49,53–55,59–63,66,67,69–71,92] CIN3/AIS(17), [18,21,43,52,54,59-61,63,67,69,71-77] and ICC (31), [20,21,26,28,

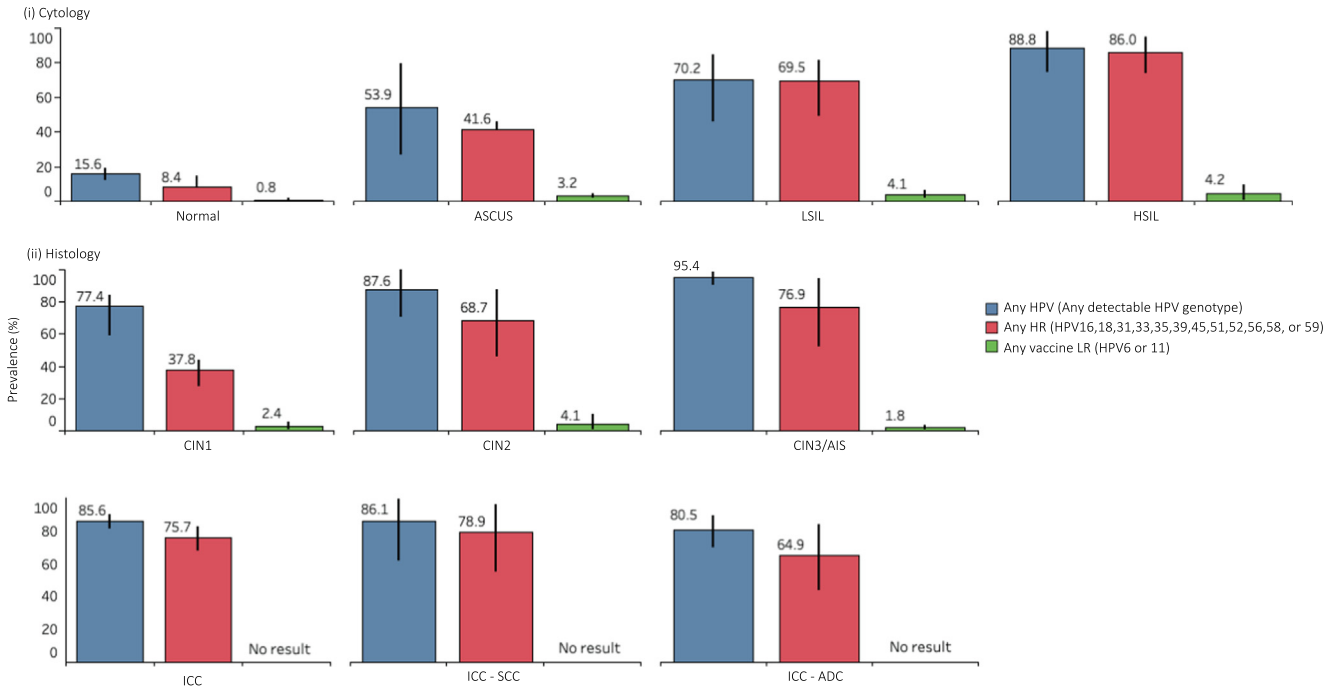

Fig. 1. Any detectable, any high risk, and vaccine low risk HPV genotype prevalence in women with normal cytology through to invasive cervical cancer. Summary estimates of HPV prevalence are measured as HPV test positivity where the numerator was the number who tested HPV positive for any one of the HPV genotypes (i.e. an individual can only count once in the numerator regardless of how many genotypes they test positive for), and the denominator was the number who had an HPV test. Error bars represent 95% confidence intervals for each summary estimate. Any-HPV prevalence represents the detection of any detectable HPV genotype. Any-HR represents the detection of any of the following: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. Any vaccine LR represents the detection of HPV6 or 11. Total number of women tested stratified as follows: 57759 for normal cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 960 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. I-squared not quantifiable with fewer than three estimates. For detailed stage specific information see Appendix Table A7. NB: All studies contributed data to the estimates of any-HPV, but not all studies provided genotype specific data and were excluded from the HR and LR estimates.

49,50,58,59,64,65,67,68,71,72,75,77-92] ICC-SCC(6), [68,71,90, 93-95] and ICC-ADC(9) [68,71,79,81,82,90,93-95]. Not all studies provided genotype specific data and contributed to summary prevalence estimates for any-HPV, any-HR or LR vaccine types [113–120]. The summary prevalence estimates for any-HPV detection stratified by cytology results were: Normal cytology – 15·6% (95% CI: 12·3–19·4), ASCUS – 53·9% (26·9–79·7), LSIL – 70·2% (47·7–88·5), HSIL – 88·8% (74·6–97·9); and stratified by biopsy results were: CIN1 – 77·4% (95% CI: 62·4–89·5), CIN2 – 87·6% (70·7–98·2), CIN3/AIS – 95·4% (90·4–98·9), ICC – 85·6% (80·7–89·8), SCC – 86·1% (61·9–99·6), and ADC – 80.5% (70·0–89·4) (Fig. 1). There was high heterogeneity in all summary estimates (I^2 > 90%) (Appendix Table A7).

The summary prevalence estimates of any-HR HPV genotype increased across the cytological spectrum from 8·4% (95% CI: 3·8–14·6) in normal cytology to 86·0% (73·9–94·9) in HSIL. The prevalence of any-HR HPV genotype by histological stage was lowest for CIN1 [37·8% (95% CI: 29·1–46·9)] and highest for ICC [75·7% (68·0–82·6)]. The summary prevalence of any vaccine LR-HPV genotype by cytology stage was lowest in normal cytology [0·8% (95% CI: 0·2–1·8)], and highest in HSIL [4·2% (0·8–9·8)]. The prevalence of any vaccine LR-HPV genotype by histological stage was lowest in CIN1 [2·4% (95% CI: 0·4–5·7)] and highest in CIN2 [4·1% (0·4–10·5)]. There was considerable heterogeneity in all summary estimates (I^2 > 90%) (Appendix Table A7).

3.3. Vaccine preventable HPV genotype prevalence in women with normal cytology

For women with normal cytology, the summary prevalence of bivalent vaccine genotypes was 2·4% (95% CI: 1·1–4·2), 2·7% (1·2–4·7) for quadrivalent genotypes and 6·8% (3·1–11·8) for nonavalent vaccine genotypes (Fig. 2). The highest prevalence for individual vaccine genotypes was 3.1% (95% CI: 1·5–5·3) for HPV52 (Fig. 3). There was considerable heterogeneity in all summary estimates (I2 > 90%) (Appendix Table A7, Appendix Table A8).

3.4. Vaccine preventable HPV genotype prevalence in women with cytological or histological pre-cancerous abnormalities

In women with cytological or histological abnormalities, the prevalence of vaccine genotypes by cytology stage was highest in HSIL, where the summary prevalence of bivalent vaccine genotypes was 33·3% (95% CI: 26·3–40·6), for quadrivalent genotypes was 38·0% (33·3–42·8) and for the nonavalent vaccine genotypes was 86·3% (71·7–96·4). The prevalence of vaccine genotypes by histology stage was highest in CIN3/AIS where the summary prevalence of bivalent vaccine genotypes was 49·0% (95% CI: 45·2–52·9), for quadrivalent genotypes was 49·6% (45·4–53·7) and for the nonavalent vaccine genotypes was 73·0% (48·0–92·3) (Fig. 2). The distribution of individual vaccine genotypes varied across cytological or histological stages (Fig. 3). There was considerable heterogeneity in all summary estimates (I2 > 90%) (Appendix Table A7, Appendix Table A8).

3.5. Vaccine preventable HPV genotype prevalence in women with invasive cervical cancer

In women with ICC, the summary prevalence of bivalent vaccine genotypes was 58·5% (95% CI: 52·1–64·9), for quadrivalent genotypes was 58·6% (52·2–64·9) and for nonavalent genotypes was 71·5% (64·9–77·6) (Fig. 2). The prevalence of individual

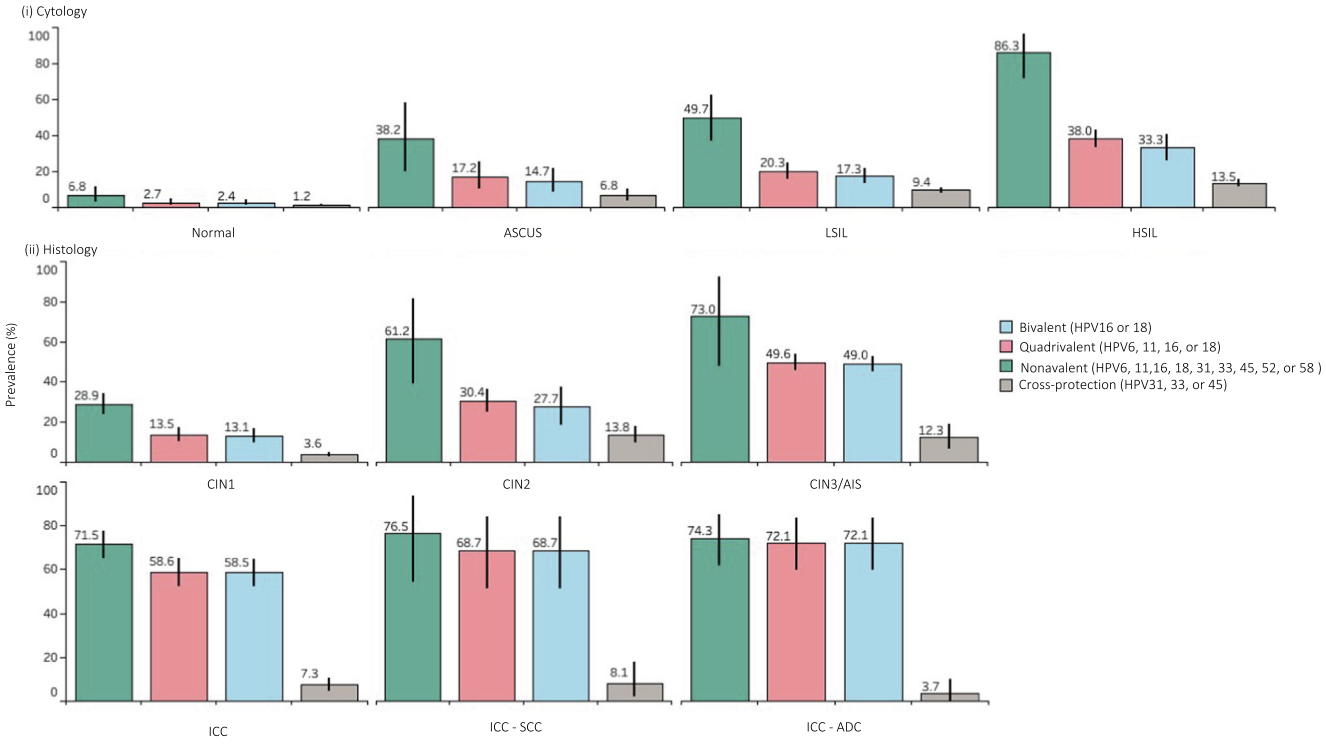

Fig. 2. Vaccine preventable genotype prevalence in women with normal cytology through to invasive cervical cancer. Summary estimates of HPV prevalence are measured as HPV test positivity where numerator was the number who tested HPV positive for any one of the vaccine genotypes (i.e. An individual can only count once in the numerator regardless of how many genotypes they test positive for), and the denominator was the number who had an HPV test able to detect that type. Error bars represent 95% confidence intervals for each summary estimate. Bivalent represents the detection of HPV16, or 18; Quadrivalent represents 6, 11, 16 or 18; Nonavalent represents: HPV6, 11,16, 18, 31, 33, 45, 52, 58, Cross-protection represents: HPV31, 33, or 45. Total number of women tested stratified as follows: 57759 for normal cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 960 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. I–squared not quantifiable with fewer than three estimates. Detailed stage specific information in Appendix Table A7. NB: Only those studies providing vaccine preventable genotype data are included in this Figure.

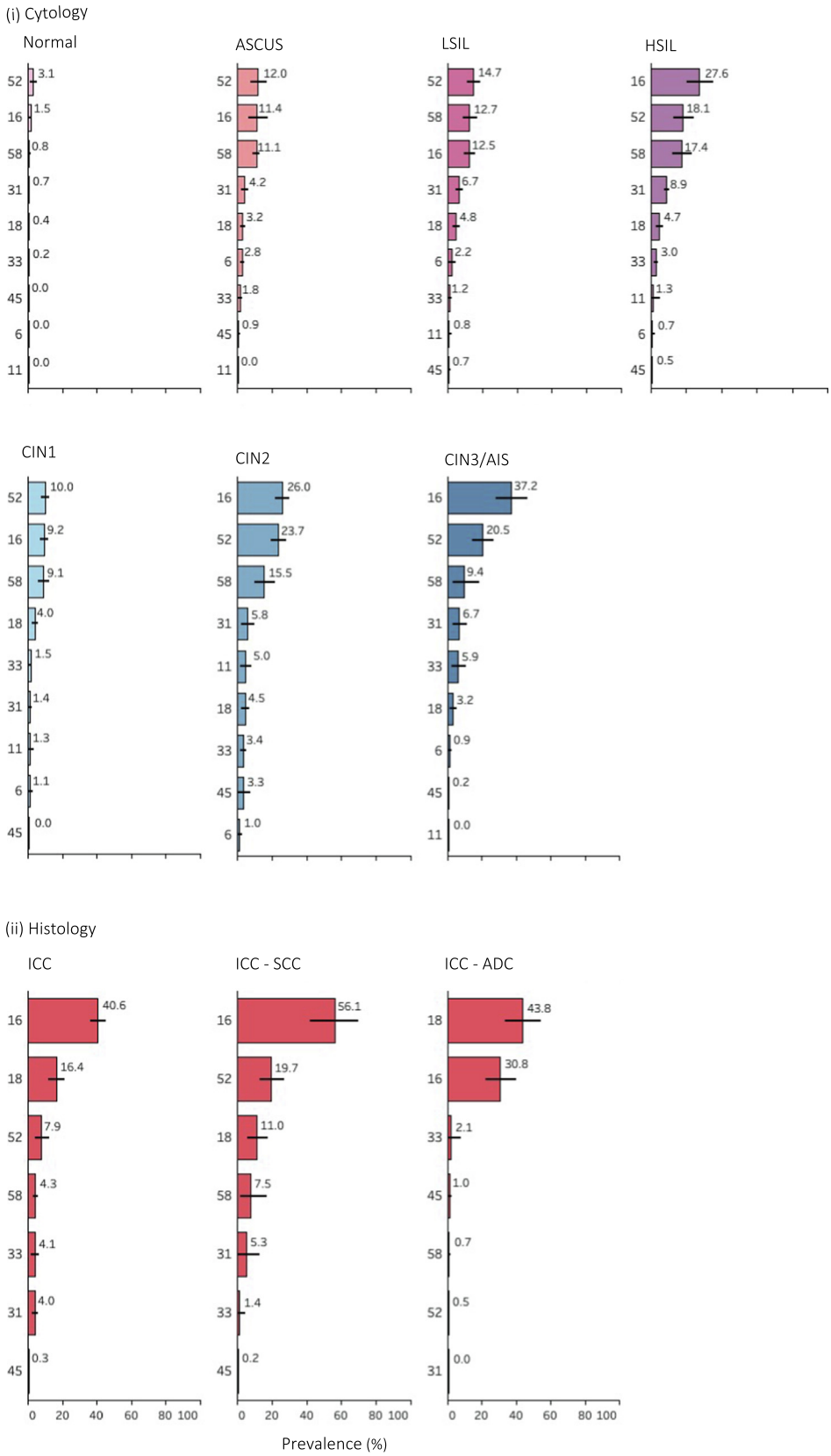

Fig. 3. Individual vaccine preventable genotype prevalence in women with normal cytology through to invasive cervical cancer. Summary estimates of HPV prevalence are measured as HPV test positivity where the numerator was the number who tested HPV positive for each genotype, and the denominator was the number who had an HPV test for that genotype. Error bars represent 95% confidence intervals for each summary estimate. Total number of women tested stratified as follows: 57759 for normal cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 1041 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. HPV 6 or 11 in ICC, ICC-SCC or ICC-ADC was not reported in any studies. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. I–squared not quantifiable with fewer than three estimates. Detailed stage specific information in Appendix Table A8. NB: Prevalence estimates may be different from those in Fig. 2 because not all studies provided genotype specific data estimates for each vaccine type.

vaccine genotypes varied between ICC-SCC and ICC-ADC with HPV 16 being the most prevalent genotype for ICC-SCC and HPV 18 the most common for ICC-ADC (Fig. 3). The prevalence of cross-protective types was 7·3% (95% CI: 5·3–12·0) in ICC, 8·1% (1·8–17·8) in ICC-SCC and 3·7% (0·2–10·0) in ICC-ADC. There was considerable heterogeneity in all summary estimates (I2 > 90%) (Appendix Table A7, Appendix Table A8).

3.6. HPV prevalence estimates in possibly and probably carcinogenic genotypes

In women with normal cytology, the prevalence of possibly or probably carcinogenic genotypes were estimated to be 2·2% (95% CI: 0·5–4·9) and 0·7% (0·2–1·6), respectively (Fig. 4). The prevalence of possibly or probably carcinogenic genotypes were lower in high grade lesions (HSIL, CIN2, or CIN3/AIS) than low grade lesions (LSIL, or CIN1). There was considerable heterogeneity in all summary estimates (I2 > 90%) (Appendix Table A7).

4. Age specific HPV prevalence and age standardised estimates

For women with normal cytology the summary prevalence of any-HPV was highest at 20–29 years of age, peaking at 22·8% (95% CI: 12·8–34·6); before declining gradually to 1·6% (0·0–14·5) in women 80 years and over. For women with ICC, any-HPV prevalence fluctuated across age groups from 93·8% (95% CI: 79·9–100) at 20–29 to 71·1% (46·5–91·1) at 50 to 59 years, to 91·3% (75·5–99·8) at 80 and over (Fig. 5). There was considerable heterogeneity in all summary estimates (I2 > 90%) (Appendix Table A9). The age standardised prevalence for women with normal cytology was 9·6%, and for ICC was 87·0% (Appendix Table A10).

4.1. Subgroup analysis and sources of heterogeneity

Sub-group analysis and *meta*-regression showed that the prevalence of any-HPV genotype in ICC varied by whether it was an exfoliated or biopsy sample. The prevalence of HR-HPV genotypes was lower in studies published in the 1990s, but no other variables contributed to the heterogeneity (Table 1). Our sensitivity analysis found that removing studies published in the 1990s resulted in summary estimates of any-HPV and HR HPV genotype prevalence of 89·5% (95% CI: 85·9–93·2, I^2 = 91·9) and 80·4% (70·5–88·2, I^2 = 96·9%) for ICC and heterogeneity was still marked.

4.2. Quality assessment and publication bias

Quality assessment found that most studies were reported according to quality criteria including appropriate target population, and sampling method (Appendix Table A6). Visual assessment of forest plots, funnel plots and Egger's test indicated limited bias due to study size except for studies reporting LSIL and HSIL that tended to be biased towards smaller study sizes and higher prevalence estimates (Appendix Fig. 2, and Appendix Fig. 3).

5. Discussion:

In this systematic review and *meta*-analysis, we provide the most comprehensive review of HPV prevalence data for Japan to date, finding a prevalence of any-HPV of 15·6% for those with normal cytology and high prevalence of HR-HPV genotypes of 86·0% for cytological cases of HSIL, 76·9% for histological cases of CIN3/AIS, and 75·7% for ICC. There was considerable heterogeneity in all HPV summary estimates and for ICC, this heterogeneity was not explained by variability in study design, sample type, HPV assay type, or HPV DNA detection method, although studies published in the 1990s had lower prevalence estimates of any and HR-HPV genotypes.

Overall, the summary prevalence estimates for any-HPV for ICC was 85.6%. For cancers that could be further histologically classified, the prevalence of any-HPV was 86.1% for SCC and 80.5% for ADC and for any-HR, the summary prevalence estimates were 78.9% for SCC and 64.9% for adenocarcinomas. The lower HR prevalence for adenocarcinomas may be because a subset of cervical ADC occurs independently of HPV infection, and it is possible that

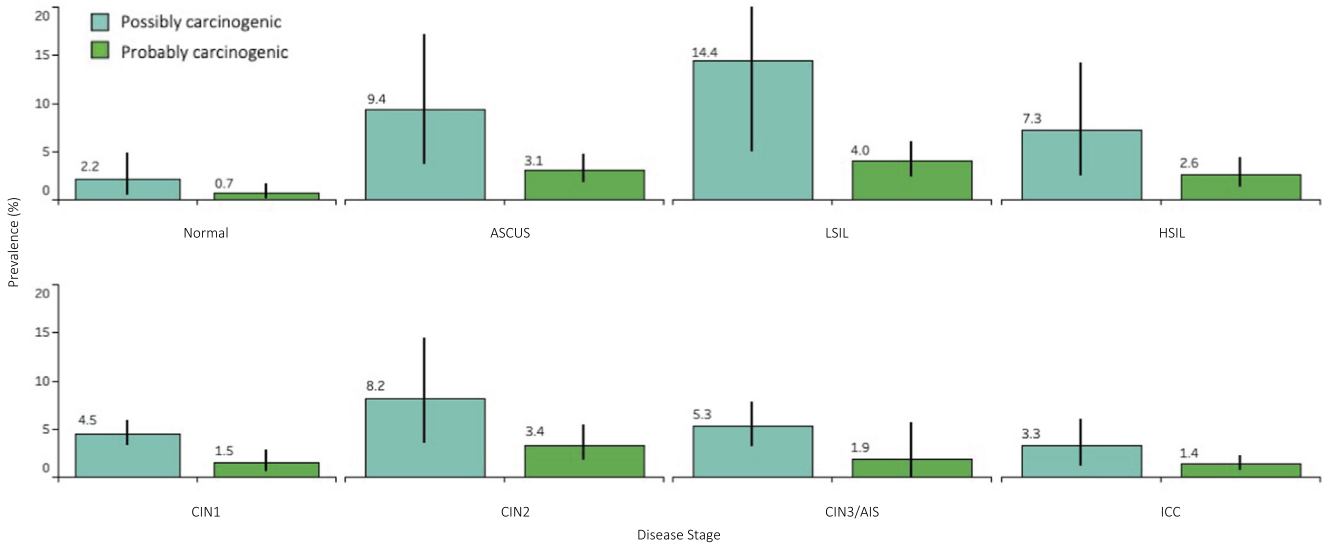

Fig. 4. Possibly and probably carcinogenic HPV genotype prevalence in women with normal cytology through to invasive cervical cancer. HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. Error bars represent 95% confidence intervals for each summary estimate. Possibly carcinogenic prevalence represents detection of any of the following: HPV26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, or 97. Probably carcinogenic prevalence represents detection of HPV68. Total number of women tested stratified as follows: 57759 for normal cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 960 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. I–squared not quantifiable with fewer than three estimates. Detailed stage specific information in Appendix Table A7. NB: Only those studies providing information about possibly or probably carcinogenic genotypes are included in this Figure.

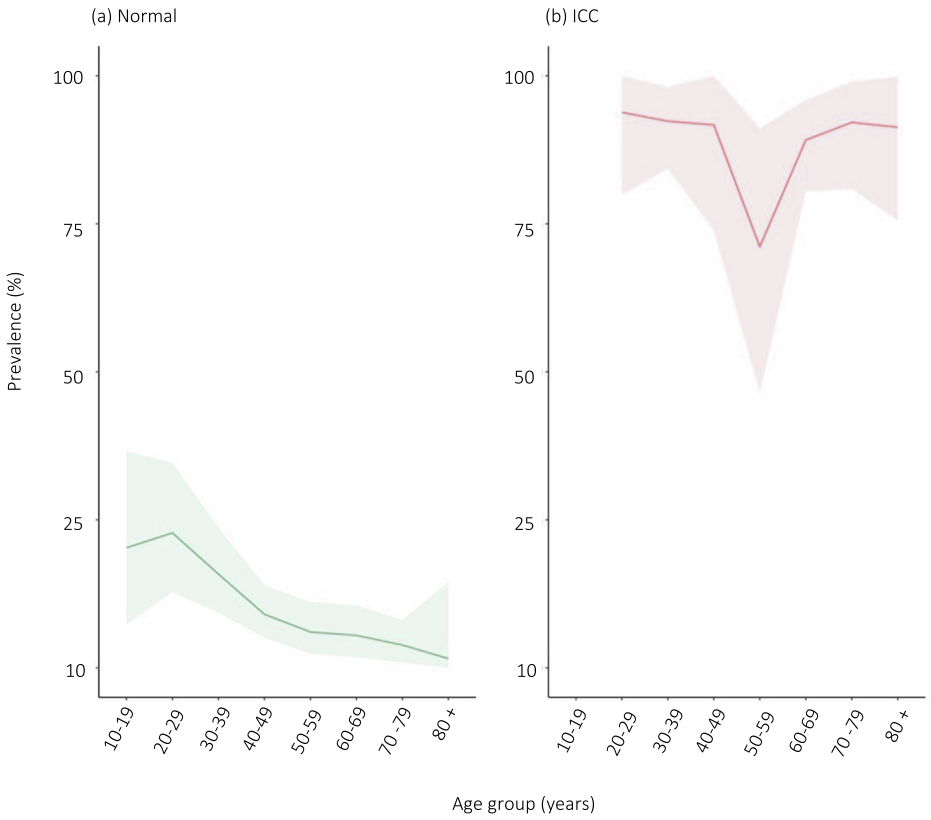

Fig. 5. Age specific any-HPV prevalence women with normal cytology and invasive cervical cancer. HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. Shaded areas represent 95% confidence intervals for each summary estimate. There were 112896 women with normal cytology tested. In this group, 178 women were 10–19, 7218 were 20–29, 32070 were 30–39, 31355 were 40–49, 25370 were 50–59, 10,281 were 60–69, 1049 were 70–79 years old, and 35 women were 80 years old and over. There were 431 women tested with ICC. This included no women tested and aged between 10 and 19 years old. There were 28 women 20–29, 86 were 30–39, 95 were 40–49, 77 were 50–59, 84 were 60–69, 38 were 70–79, and 23 were 80 years old and over. Detailed age specific data in Appendix Table A9.

some of these cases were included in our studies. Further, it is possible that some of the cases of ADC were misclassified and originated in the endometrium which are much less likely to be associated with HPV. [8,81,96] There was marked heterogeneity in these summary estimates and our sub-group analysis found some evidence to suggest that the prevalence of HR-HPV was lower in studies published in the 1990s than in more recent years and while we did not find any difference in prevalence between HPV assay types classified broadly as PCR or HC2, it is possible that the earlier studies used less sensitive assays contributing to lower prevalence estimates across all studies as reported elsewhere. [8] Our sensitivity analysis also showed that the summary prevalence estimates increased when studies published in the 1990s were excluded, but considerable heterogeneity still remained. The impact of increased sensitivity in detection methods over time has been well documented in other large global *meta*-analysis and the results of this study are consistent with their findings. [8,10,12,13] In an additional supplementary analysis, we investigated the summary prevalence estimates for vaccine genotypes among the subset of women whose ICC was HPV positive and found that 94.6% of SCC and 95.2% of ADC cases included were positive for a nonavalent HPV genotype suggesting that most of these infections would be prevented by the nonavalent vaccine (Fig. 6).

Globally, HPV16 and HPV18 have a higher likelihood of persistence and progression to cervical lesions compared with other oncogenic types and generally have the highest prevalence in ICC. [97-99] Together with HPV31, 33, 45, 52 and 58, these seven oncogenic genotypes of the nonvalent vaccine are responsible for approximately 90% of ICC globally. [100,101] However, the distribution of these genotypes varies geographically with a high prevalence of HPV52 and 58 observed in East Asian countries, while HPV31, 33, and 45 are more common in European populations. [13,102] We also observed considerable variation in the distribution in individual vaccine genotypes across the disease spectrum and a higher prevalence for HPV52 and HPV58 in SCC. The 5-additional oncogenic genotypes targeted by the nonavalent vaccine (HPV31, 33, 35, 52, and 58) accounted for more infections in SCC than ADC with HPV16 and HPV52 being the dominant genotypes for SCC and HPV16 and HPV18 dominant for ADC.

We found the age standardised prevalence of any-HPV in women with normal cytology in Japan was 9·6% which is comparable to other regions (10·4% worldwide, 8·1% in Europe and 8·0% in Asia). [13,101] Globally, it has been observed that HPV prevalence peaks in the period immediately following sexual debut and gradually declines with increasing age. In our study we observed the prevalence of any-HPV among women with normal cytology peaked in women at age 20–29 years and then decreased. In contrast, the prevalence of any-HPV was very high across all age groups for ICC. The lower HPV prevalence observed in women aged 50 to 59 may be due to sampling variability as the estimate was based on a sample size of 77 women from 2 studies. However, the confidence intervals for this curve also allow for a consistently high HPV prevalence across all age groups with ICC. Together both curves suggest that women may be infected at an early age and generate immunity thereafter, and that HPV infection is almost always present in ICC.

Table 1
Any-HPV prevalence in invasive cervical cancer cases reported in all included studies in Japan: Subgroup and *meta*-regression analysis.

	Any HPV				Any HR			
	Summary prevalence % (95% CI)	**I^2**	**Mean difference % (95% CI)**	**p-value**	**Summary prevalence % (95% CI)**	**I^2**	**Mean difference % (95% CI)**	**p-value**
Overall	85·6 (80·7–89·8)	92·8	–	–	75·7 (68·0–82·6)	95·6	–	–
Age group (years)								
20 to 29	93·8 (79·9–100)	NA	*Reference*		NA	–	–	–
30 to 39	92·3 (84·3–98·1)	NA	-3·2 (-45·2–38·7)	0·88	NA	–	–	–
40 to 49	91·7 (73·9–100)	50·9	-6·4 (-47·9–35·1)	0·76	NA	–	–	–
50 to 59	71·1 (46·5–91·1)	42·4	-18·9 (-61·5–23·7)	0·38	NA	–	–	–
60 to 69	89·1 (80·5–95·9)	NA	-5·1 (-48·0–36·2)	0·78	NA	–	–	–
70 to 79	92·1 (80·9–98·9)	NA	-0·7 (-48·9–47·4)	0·98	NA	–	–	–
80 +	91·3 (75·5–99·8)	NA	-1·5 (-55·8–52·9)	0·96	NA	–	–	–
Year of publication								
1990–1999	79·2 (59·1–84·9)	90·4	*Reference*		71·8 (60·5–81·8)	83·1	*Reference*	
2000–2005	87·2 (78·9–93·7)	92·8	8·9 (-3·0–20·9)	0·14	74·5 (56·8–88·9)	97·2	2·8 (-14·2–19·8)	0·74
2006–2010	93·9 (80·6–100)	90·0	14·4 (-1·6–30·5	0·08	81·1 (73·2–88·0)	50·0	15·0 (-7·2–37·2)	0·18
2011–2015	91·7 (87·5–95·2)	NA	13·2 (-5·3–31·6)	0·16	99·2 (97·3–100)	NA	33·7 (7·5–60·0)	0·01
2016–2020	91·3 (78·9–93·8)	NA	9·2 (-3·3–21·7)	0·15	96·9 (94·5–99·3)	95·6	32·8 (-19·8–55·5)	0·80
Study design								
Cohort	85·8 (81·1–89·9)	90·1	*Reference*		78·0 (68·8–86.0)	95·6	*Reference*	
Cross-sectional	88·3 (78·9–95·3)	81·3	2.0 (-10·3–10·8)	0·97	73·7 (45·2–94·4)	96·1	-7·3 (28·1–13·5)	0·49
Case-control	100·0 (99·3–100)	NA	12·4 (-0·9–25·8)	0·07	89·2 (85·6–92·4)	NA	12·2 (-14·8–39·2)	0·38
Sample type								
Exfoliated	89·4 (84·4–93·6)	93·4	Reference		72·3 (61·4–82·1)	96·9	*Reference*	
Biopsy	82·9 (75·1–89·7)	88·4	-9·4 (-17·5–1·3)	0·02	79·1 (66·5–89·4)	92·7	3·6 (-11·4–18·6)	0·63
HPV assay type								
HC2	88·6 (81·8–94·1)	0·0	*Reference*		66·6 (45·3–82·8)	NA	*Reference*	
PCR	87·3 (80·1–89·6)	92·9	-1·4 (-20·4–17·5)	0·88	78·1 (70·3–85·2)	96·0	9·1 (-44·5–58·7)	0·79
HPV DNA detection method								
HC2	88·6 (81·8–94·1)	0·0	*Reference*		66·6 (45·3–82·8)	NA	*Reference*	
Narrow spectrum	89·3 (80·1–96·0)	95·6	-0·3 (-20·1–19·5)	0·97	69·2 (55·9–81·1)	96·3	3·7 (-40·7–68·1)	0·99
Broad spectrum	93·1 (88·2–96·8)	72·5	3·3 (-17·5–24·2)	0·76	89·3 (63·6–100)	98·2	19·1 (-38·0–70·3)	0·56
Other	83·7 (72·5–92·5)	92·9	-5·0 (-25·7–15·6)	0·63	78·9 (60·6–92·8)	93·7	13·7 (-40·6–68·2)	0·62
Region								
Kanto	85·1 (77·6–91·4)	91·9	*Reference*		74·4 (63·5–84·1)	94·3	*Reference*	
Kyushu	93·1 (77·0–99·9)	NA	5·4 (-6·3–17·2)	0·31	62·3 (30·6–89·1)	NA	-11·9 (–32·7–8·8)	0·25
Hokkaido	94·4 (88·7–98·4)	NA	7·7 (-14·9–30·3)	0·50	96·3 (91·3–99·4)	NA	19·5 (-10·8–49·8)	0·20
Kansai	81·1 (69·8–90·3)	86·1	-6·2 (-18·5–5·6)	0·31	77·4 (59·9–91·2)	90·4	1·3 (-17·8–20·5)	0·89
Chubu	84·8 (80·9–89·7)	NA	-0·5 (-13·5–12·3)	0·92	72·1 (67·6–76·5)	NA	-0·8 (-26·5–28·3)	0·95

HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. 95% confidence intervals are calculated for each summary prevalence estimate. Any-HPV prevalence represents the detection of any detectable HPV genotype. Any HR represents the detection of any of the following: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59. Primer type was defined as: Broad spectrum (MY09/11, GP5+/6 + and SPF10), or narrow spectrum (GP5/6, L1C1/C2 or PU1M/2R). Mean difference: Regression coefficient multiplied by 100; NA: I-squared not quantifiable with fewer than three estimates. NB: prevalence estimates may be different from those in Fig. 2 because not all studies provided genotype specific data estimates for each vaccine type. N/A: Not available - there were no studies reporting age stratified results for any HR genotype prevalence therefore subgroup analysis for this group could not be performed.

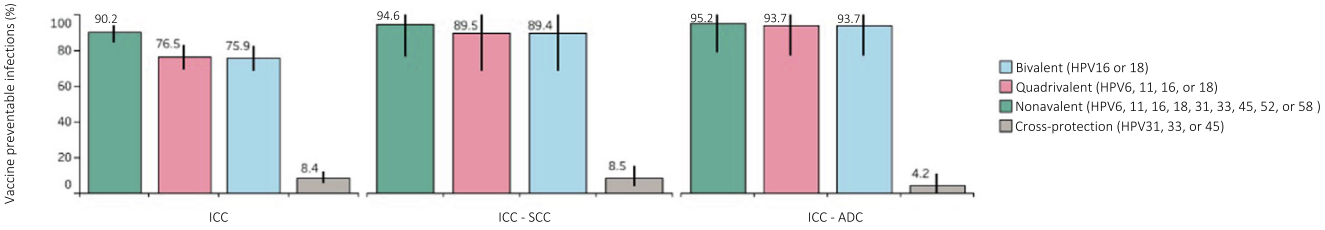

Fig. 6. Vaccine preventable genotype prevalence in women with invasive cervical cancer and positive for any-HPV genotype. HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number of ICC cases that were tested and positive for any detectable HPV. Error bars represent 95% confidence intervals for each summary estimate. Bivalent represents the detection of HPV16, or 18; Quadrivalent represents 6, 11, 16 or 18; and Nonavalent represents: HPV6, 11, 16, 18, 31, 33, 45, 52, or 58; Cross-protection represents: HPV31, 33 or 45. Total number of women tested stratified as follows: 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. I–squared not quantifiable with fewer than three estimates. Detailed stage specific information in Appendix Table A7.

The nonavalent vaccine was approved for use in Japan in late 2020 in line with the WHO Global strategy to accelerate the elimination of cervical cancer. [103] The two-dose schedule is recommended for adolescents between 9 and 14 years of age, however to date, its uptake in Japan has remained low. [63,104,105] The high nonavalent HPV prevalence estimates observed in our *meta*-analysis highlight that further delays in its widespread uptake will delay protection against HR-HPV types. [106] Our results confirm that the nonavalent vaccine in Japan is likely to have substantial impact on reducing cervical cancer incidence. It would be preferable to have a national and unified implementation of a single vaccination type that confers the greatest protection against vaccine genotypes in line with the best available evidence. The underlying cause of hesitancy against HPV vaccination in Japan must be

understood first. Adequate reporting of adverse events, and national guidance to minimise misinformation and confusion is required to ensure successful implementation. Additionally, HPV DNA testing is not currently routinely performed in Japan for population-based screening. [107,108] A pooled analysis of four large RCTs indicated that, compared to conventional cytology, primary HPV DNA testing can prevent more invasive cervical cancer cases. [109] Importantly, adopting primary HPV DNA in place of the conventional cytology test with a high performance test could help directly to evaluate the impact of increasing the coverage of the HPV vaccine.

Our study has several limitations. First, there was considerable heterogeneity in the studies included in the review and our subgroup analysis of ICC did not identify much other than year of publication that contributed to this heterogeneity. However, our review included both English and Japanese language studies ensuring our review was comprehensive in capturing as much available data as possible. Second, the prevalence estimates were mainly derived from convenience samples of women attending clinical settings and do not necessarily represent the general population. However, this is mainly an issue for those studies reporting HPV prevalence among women with normal cytology; it is less an issue for studies reporting cytological and histological abnormalities where all women undergoing investigation for the lesions are usually seen in these settings were included. Thirdly, it is likely that the PCR primer used had an impact on the HPV prevalence reported in each study. Sensitivity varies by whether it is a broad or narrow spectrum assay. [110-112] The availability of these assays also varies over time and it has been previously shown that HPV prevalence increase over times related to improvements in HPV DNA testing protocols rather than due to increases in prevalence of infection. [8] While the primer used and year of study are likely sources of bias in our *meta*-analyses, only year of study was significant in our *meta*-regression of HPV prevalence for ICC cases. Fourthly, not all studies reported genotype specific estimates with some studies only reporting data for any HPV. As a result, studies included in genotype specific estimates represent subsets of all studies included in the any HPV estimates – not all studies are included. Finally, studies included in this analysis were not uniformly drawn from all regions of Japan, limiting its representativeness across the country.

6. Conclusion

To our knowledge this is the most comprehensive assessment of the prevalence of cervical HPV infection in Japanese women across the disease trajectory from normal cytology to cervical cancer. It found that the nonavalent vaccine is likely to have the greatest impact on vaccine genotype infections for women with ICC. With the recent approval of the nonavalent vaccine in Japan, it is hoped that these results will guide and enhance future interventions for the prevention of cervical cancer in Japan.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [Kota Katanoda reports financial support and article publishing charges were provided by Grants–in–Aid for Scientific Research from Japan Society for the Promotion of Science (17H03589), and The Grant of the National Cancer Center, Japan (Gan Kenkyu Kaihatsuhi 31-A-20)].

Appendix

Tables A1–A10.

Table A1
PRISMA Checklist.

Section & topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			1
Title:			
Identification	1a	Identify the report as a protocol of a systematic review·	NA
Update	1b	If the protocol is for an update of a previous systematic review– identify as such·	NA
Registration	2	If registered– provide the name of the registry (such as PROSPERO) and registration number	6
Authors:			
Contact	3a	Provide name– institutional affiliation– e–mail address of all protocol authors; provide physical mailing address of corresponding author·	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review·	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol– identify as such and list changes; otherwise– state plan for documenting important protocol amendments·	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review·	2
Sponsor	5b	Provide name for the review funder and/or sponsor·	2
Role of sponsor or funder	5c	Describe roles of funder(s)– sponsor(s)– and/or institution(s)– if any– in developing the protocol·	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known·	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants– interventions– comparators– and outcomes (PICO)·	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO– study design– setting– time frame) and report characteristics (such as years considered– language– publication status) to be used as criteria for eligibility for the review·	6
Information sources	9	Describe all intended information sources (such as electronic databases– contact with study authors– trial registers or other grey literature sources) with planned dates of coverage·	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database– including planned limits– such that it could be repeated·	75
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review·	6,7

(*continued on next page*)

Table A1 (*continued*)

Section & topic	Item No	Checklist item	Page
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is– screening– eligibility and inclusion in meta–analysis)·	6,7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms– done independently– in duplicate)– any processes for obtaining and confirming data from investigators·	6,7
Data items	12	List and define all variables for which data will be sought (such as PICO items– funding sources)– any pre–planned data assumptions and simplifications·	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought– including prioritization of main and additional outcomes– with rationale·	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies– including whether this will be done at the outcome or study level– or both; state how this information will be used in data synthesis·	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised·	7
	15b	If data are appropriate for quantitative synthesis– describe planned summary measures– methods of handling data and methods of combining data from studies– including any planned exploration of consistency (such as I^2– Kendall's τ)·	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses– meta–regression)·	7
	15d	If quantitative synthesis is not appropriate– describe the type of summary planned·	NA
Meta–bias(es)	16	Specify any planned assessment of meta–bias(es) (such as publication bias across studies– selective reporting within studies)·	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)·	7

Table A2
Database search strategy.

No·	Search Set	Medline/ PubMed	Embase	Ichushi
1	Population	Japan ti– ab	Japan ti– ab	(日本/TH or 日本/AL)
2	Exposure	'Human Papillomavirus' OR 'HPV' OR 'Papillomaviridae' ti–ab	'Human Papillomavirus' OR 'HPV' OR 'Papillomaviridae' ti–ab	((パピローマウイルス科/TH or ヒトパピローマウイルス/AL)) or ((パピローマウイルス科/TH or HPV/AL)) or ((パピローマウイルス科/TH or パピローマウイルス科/AL))
3	Exposure	'Human Papillomavirus' OR 'HPV' OR 'Papillomaviridae'– [MeSH]	'Human Papillomavirus' OR 'HPV' OR 'Papillomaviridae'– [Emtree]	NA
4	Normal	Normal AND Cytology [MeSH]	Normal AND Cytology [Emtree]	(細胞診陰性/AL) or ((細胞診/TH or 細胞診/AL))
5	Abnormal	'Cervical Cancer' OR 'Cervical Disease' OR 'Cervical Intraepithelial Neoplasia' [MeSH]	'Cervical Cancer' OR 'Cervical Disease' [Emtree]	((子宮頸部腫瘍/TH or 子宮頸がん/AL)) or ((子宮頸/TH or 子宮頸部/AL)) or ((子宮頸/TH or 子宮頸部/AL) and (上皮内癌/TH or 上皮内新生物/AL))
6	Detection	Genotype [Mesh]	Genotype [Emtree]	(遺伝子型/TH or 遺伝子型/AL)
7	Complete	#1 OR #2 OR #3 OR #4 OR #5 OR #6	#1 OR #2 OR #3 OR #4 OR #5 OR #6	#1 OR #2 OR #4 OR #5 OR #6
8	Abnormal	#1 AND #2 AND #5 AND #6	#1 AND #2 AND #5 AND #6	#1 AND #2 AND #5 AND #6
9		#1 AND #3 AND #5 AND #6	#1 AND #3 AND #5 AND #6	NA
10	Normal	#1 AND #2 AND #4 AND #6	#1 AND #2 AND #4 AND #6	#1 AND #2 AND #4 AND #6
11		#1 AND #3 AND #4 AND #6	#1 AND #3 AND #4 AND #6	NA

Table A3
Characteristics of included studies.

Author	Year	Age range	Study design	Region	HPV DNA source	Sample collection	Sample collection method	Year first sample collected	Year last sample collected	Primer	Detection method
Abe[35]	2014	20–69	Case Control	Kyushu	Exfoliated	Practitioner	Other	2007	2011	PGMY09/11	DNA
Aiko[48]	2017	20–69	Cohort	Kanto	Fresh Biopsy	Practitioner	Other	2014	2015	HC2	DNA
Aoyama-Kikawa[63]	2018	20–69	Cross Sectional	Hokkaido	Fresh Biopsy	Practitioner	Cytobrush	2013	2014	Cobas 4800	DNA
Asato[26]	2004	18–85	Case Control	Kyushu	Exfoliated	Practitioner	Cervical Swab	1993	2000	L1C1/ L1C2	DNA
Azuma[71]	2014	Not specified	Cohort	Kanto	Exfoliated	Practitioner	Cytobrush	2009	2013	PGMY09/11	DNA
Chen[33]	2013	Not specified	Cohort	Kyushu	Fixed Biopsy	Not Specified	Cytobrush	NA	NA	PGMY09/11	DNA
Fujinaga[85]	1991	Not specified	Cohort	Hokkaido	Fresh Biopsy	Not Specified	Not Specified	NA	NA	PU–1 M/ pU–2R	DNA
Harima[82]	2002	29–90	Cohort	Kansai	Fresh Biopsy	Practitioner	Not Specified	1995	2000	PU–1 M/ pU–2R	DNA
Horikoshi[58]	2005	Not specified	Cross Sectional	Kansai	Exfoliated	Not Specified	Cytobrush	1998	2000	HC2	DNA

Table A3 (*continued*)

Author	Year	Age range	Study design	Region	HPV DNA source	Sample collection	Sample collection method	Year first sample collected	Year last sample collected	Primer	Detection method
Hosaka[52]	2013	22–84	Cross Sectional	Kansai	Fresh Biopsy	Practitioner	Spatula	2000	2008	PU–1 M/ pU–2R	DNA
Ichimura[74]	2003	19–42	Cohort	Kansai	Exfoliated	Practitioner	Cervical Swab	1999	2001	L1C1/ L1C2	DNA
Imai[31]	2015	18–23+	Cross Sectional	Kyushu	Exfoliated	Self–Collection	Cervical Swab	2011	2012	HC2	DNA
Imajoh[114]	2012	29–74	Cohort	Shikoku	Fixed Biopsy	Not Specified	Not Specified	NA	NA	PGMY09/11	DNA
Inoue[18]	2006	14–94	Cross Sectional	Chubu	Exfoliated	Practitioner	Cytobrush	2003	2004	HC2	DNA
Inoue[54]	2010	30–70	Cohort	Chubu	Fresh Biopsy	Practitioner	Cytobrush	2004	2009	HC2	DNA
Ishi[41]	2000	18–48	Cross Sectional	Kanto	Exfoliated	Practitioner	Cervical Swab	1998	1999	HC2	DNA
Ishi[21]	2004	17–73	Cohort	Kanto	Exfoliated	Practitioner	Cervical Swab	1998	2003	HC2	DNA
Ishikawa[83]	2001	33–87	Cohort	Kanto	Fixed Biopsy	Practitioner	Cytobrush	1980	1997	L1C1/ L1C2	DNA
Iwata[62]	2015	20–50	Cohort	Kanto	Exfoliated	Practitioner	Cervix Brush	2010	2011	Cobas 4800	DNA
Kanao[84]	2005	31–67	Cohort	Kansai	Fresh Biopsy	Practitioner	Surgical	Not specified	Not specifed	PU–1 M/ pU–2R	DNA
Karube[115]	2004	20–81	Cohort	Tohoku	Exfoliated	Practitioner	Cervical Swab	1992	2000	PCR (HPV DNA Array)	DNA
Kashiwabara[78]	1992	Not specified	Cohort	Kanto	Fixed Biopsy	Practitioner	Surgical	1978	1990	L1C1/ L1C2	DNA
Kina[59]	2009	Not specified	Cross Sectional	Kansai	Exfoliated	Not Specified	Cytobrush	1998	2000	HC2	DNA
Konno[45]	1993	20–25	Case Control	Tohoku	Exfoliated	Practitioner	Cytobrush	Not specified	Not specified	Verapaz – Southern Blot	DNA
Konno[42]	2011	20–25	Case Control	Kyushu	Exfoliated	Practitioner	Cytobrush	2006	2006	SPF10 (L1)	DNA
Konno[37]	2014	Not specified	Cross Sectional	Kyushu	Exfoliated	Practitioner	Cytobrush	2010	2014	SPF10 (L1)	DNA
Kubota[40]	1999	18–49	Case Control	Kanto	Exfoliated	Practitioner	Cervical Swab	1997	1998	HC2	DNA
Kurokawa[19]	2018	25–69	Cohort	Chubu	Exfoliated	Practitioner	Other	2015	2016	Cobas 4800	DNA
Kusanagi[81]	2010	26–78	Cohort	Kansai	Fixed Biopsy	Other	Not Specified	2003	2006	PCR (HPV DNA Array)	DNA
Maehama[25]	2000	20–89	Cohort	Kyushu	Exfoliated	Practitioner	Cervical Swab	1994	1997	L1C1/ L1C2	DNA
Maehama[43]	2002	20–89	Cohort	Kyushu	Exfoliated	Practitioner	Cervical Swab	Not specified	Not specified	L1C1/ L1C2	DNA
Maehama[28]	2005	20–89	Cross Sectional	Kyushu	Exfoliated	Practitioner	Cervical Swab	1994	1995	L1C1/ L1C2	DNA
Maki[80]	1991	Not specified	Cohort	Kansai	Fresh Biopsy	Practitioner	Surgical	Not specified	Not specified	L1C1/ L1C2– PCR (HPV DNA Array)	DNA
Matsumoto[60]	2003	Not specified	Cohort	Kanto	Exfoliated	Practitioner	Cervex Brush	2000	2001	HC2– L1C1/ L1C2	DNA
Masumoto[67]	2004	20–89	Cohort	Kanto	Exfoliated	Practitioner	Cytobrush	2000	2001	HC2– L1C1/ L1C2	DNA
Matsumoto[61]	2011	18–54	Cohort	Kanto	Exfoliated – Fresh Biopsy	Practitioner	Surgical	1998	2004	L1C1/ L1C2	DNA
Matsushita[38]	2011	18–45	Cohort	Kansai	Exfoliated	Practitioner	Cytobrush	2007	2007	PGMY09/11	DNA
Minaguchi[95]	2004	31–78	Cross Sectional	Kansai	Fixed Biopsy	Practitioner	Surgical	1989	2003	L1C1/ L1C2	DNA
Morisada[27]	2017	30–64	RCT	Kanto – Chubu	Exfoliated	Practitioner	Other	2013	2015	Cervista™	DNA
Nagai[73]	2000	Not specified	Cohort	Kyushu	Exfoliated	Practitioner	Cervical Swab	1993	1998	L1C1/ L1C2	DNA
Nagai[96]	2001	23–88	Cohort	Kyushu	Exfoliated	Practitioner	Cervical Swab	1993	1997	L1C1/ L1C2	DNA
Nakagawa[68]	1996	31–79	Cohort	Kanto	Fresh Biopsy	Other	Not Specified	1977	1994	L1C1/ L1C2	DNA
Nakagawa[69]	2002	Not specified	Cross Sectional	Kanto	Exfoliated	Practitioner	Cervical Swab	Not specified	Not specified	L1C1/ L1C2	DNA
Nakamura[51]	2015	27–48	Cohort	Kanto	Exfoliated	Practitioner	Not specified	2010	2012	Clinichip™ HPV	DNA
Nakazawa[75]	1992	Not specified	Cross Sectional	Kansai	Exfoliated	Practitioner	Cytobrush	1989	1989	PCR (HPV DNA Array)	DNA
Nawa[116]	1995	23–35	Cohort	Chubu	Fresh	Not	Not	1991	1993	PCR (HPV DNA	DNA

(*continued on next page*)

Table A3 (*continued*)

Author	Year	Age range	Study design	Region	HPV DNA source	Sample collection	Sample collection method	Year first sample collected	Year last sample collected	Primer	Detection method
					Biopsy	Specified	Specified			Array)	
Nishiwaki[47]	2008	19–70	Cohort	Hokkaido	Exfoliated	Practitioner	Cytobrush	Not specified	Not specified	PCR (HPV DNA Array)	DNA
Niwa[117]	2003	Not specified	Case Control	Chubu	Exfoliated	Practitioner	Cervical Swab	1999	2001	L1C1/ L1C2	DNA
Nobeyama[91]	2004	Not specified	Cross Sectional	Kansai	Fresh Biopsy	Practitioner	Surgical	1993	2003	PGMY09/11	DNA
Okadome[70]	2014	20–50	Cross Sectional	Not specified	Fresh Biopsy	Practitioner	Cytobrush	2007	2008	PCR (HPV DNA Array)	DNA
Onuki[64]	2009	15–78	Cohort	Kanto	Exfoliated	Practitioner	Cytobrush	1999	2007	L1C1/ L1C2	DNA
Onuki[65]	2020	16–39	Cohort	Kanto	Exfoliated	Nor specified	Not Specified	2012	2017	PGMY09/11	DNA
Saito[53]	1995	18–72	Cross Sectional	Kansai	Exfoliated	Practitioner	Cervical Swab	1989	1992	PCR (HPV DNA Array)	DNA
Saito[76]	1999	Not specified	Cohort	Kansai	Fixed Biopsy	Practitioner	Surgical	1966	1993	PCR (HPV DNA Array)	DNA
Saito[92]	2000	25–78	Cross Sectional	Kansai	Fixed Biopsy	Practitioner	Surgical	1990	1993	pU–1 M/ pU–2R	DNA
Saito[49]	2001	Not specified	Cross Sectional	Kansai	Exfoliated	Not Specified	Cytobrush	1998	2000	L1C1/ L1C2	DNA
Sasagawa[20]	1997	16–82	Case Control	Chubu	Exfoliated	Practitioner	Cytobrush	1995	1996	pU–1 M/ pU–2R	DNA
Sasagawa[24]	2001	19–75	Cohort	Chubu	Exfoliated	Practitioner	Cytobrush	1995	1999	PCR (HPV DNA Array)	DNA
Sasagawa[32]	2005	15–59	Cross Sectional	Chubu	Exfoliated	Practitioner	Spatula	2000	2003	HC2	DNA
Sasagawa[34]	2016	20–54	Cohort	Chubu	Exfoliated	Practitioner	Cytobrush	2011	2012	HC2– Cobas 4800	DNA
Sasagawa[57]	2018	16–72	Cohort	Chubu	Exfoliated	Practitioner	Other	2014	2015	HC2– Cobas 4800	DNA
Sasaki[118]	2017	14–95	Cohort	Chugoku	Exfoliated	Practitioner	Cytobrush	2005	2011	HC2	DNA
Satoh[49]	2013	19–88	Cohort	Kanto	Exfoliated	Practitioner	Cytobrush	2006	2006	Clinichip™	DNA
Takehara[23]	2011	15–98	Cohort	Chugoku	Exfoliated	Practitioner	Cytobrush	2007	2010	PCR (HPV DNA Array)	DNA
Tanaka[119]	2001	20–80	Cross Sectional	Tohoku	Exfoliated	Practitioner	Cervical Swab	1994	2006	PCR (HPV DNA Array)	DNA
Tenjimbayashi[55]	2017	23–79	Cohort	Kanto	Exfoliated	Practitioner	Cytobrush	2012	2016	PGMY09/11	DNA
Tsuda[86]	2003	Not specified	Cohort	Kansai	Fixed Biopsy	Practitioner	Surgical	Not specified	Not specified	L1C1/L1C2	DNA
Tsuji[44]	2003	Not specified	Cross Sectional	Kansai	Exfoliated	Not Specified	Cytobrush	1998	2003	HC2	DNA
Watari[90]	2011	48·5	Cohort	Hokkaido	Fresh Biopsy	Not Specified	Cytobrush	1999	2004	PCR (HPV DNA Array)	DNA
Yamakawa[79]	1994	Not specified	Cohort	Kanto	Fixed Biopsy	Not Specified	Not Specified	1987	1992	PCR (HPV DNA Array)	DNA
Yamasaki[39]	2011	Not specified	Cohort	Kyushu	Fresh Biopsy	Practitioner	Cytobrush	2007	2009	PGMY09/11	DNA
Yamazaki[29]	2001	Not specified	Cohort	Hokuriku	Exfoliated	Practitioner	Cytobrush	1995	1999	HC2	DNA
Yokota[77]	1990	Not specified	Cross Sectional	Kanto	Exfoliated	Practitioner	Cervical Swab	Not specified	Not specified	FISH	DNA
Yokoyama[66]	2003	20–55	Cross Sectional	Not specified	Exfoliated	Practitioner	Cytobrush	1995	1996	L1C1/ L1C2	DNA
Yoshida[46]	2004	20–80	Cohort	Kanto	Fresh Biopsy	Practitioner	Cytobrush	2002	2003	L1C1/ L1C2	DNA
Yoshida[89]	2009	27–62	Cohort	Kanto	Fixed Biopsy	Practitioner	Surgical	1998	2008	L1C1/ L1C2	DNA
Yoshikawa[72]	1991	Not specified	Cohort	Kanto	Exfoliated	Practitioner	Cervical Swab	Not specified	Not specified	L1C1/ L1C2	DNA
Yoshikawa[56]	1999	<55	Case Control	Kanto	Exfoliated	Practitioner	Cytobrush	1995	1996	L1C1/ L1C2	DNA
Hiromura[120]	2014	30–89	Cohort	Kanto	Exfoliated	Practitioner	Cervical Swab	2010	2013	Qiagen™ Mini Kit	DNA
Sakamoto[87]	2018	20–69	Cohort	Not specified	Exfoliated	Not Specified	Not Specified	1990	2017	Geno Search 31 + 5	DNA
Sakamoto[88]	2017	20–69	Cohort	Chubu	Exfoliated	Not Specified	Not Specified	Not specified	Not specified	Geno Search 31 + 5	DNA
二井 美津穂[50]	2007	NA	Not Specified	Kanto	Exfoliated	Practitioner	Cytobrush	Not specified	Not specified	PGMY09/11	DNA
二井 美津穂[22]	2006	NA	Not Specified	Kanto	Exfoliated	Practitioner	Cytobrush	Not specified	Not specified	Roche™ Linear Array	DNA
坂本[36]	2015	19–80	Cross Sectional	Not specified	Exfoliated	Practitioner	Cytobrush	Not specified	Not specified	Geno Search 31 + 5	DNA

Table A3 (*continued*)

Author	Year	Age range	Study design	Region	HPV DNA source	Sample collection	Sample collection method	Year first sample collected	Year last sample collected	Primer	Detection method
郡司[30]	2011	19–79	Cross Sectional	Chubu	Not Specified	Practitioner	Cervical Swab	2010	Not specifed	Taq Man™	DNA
Kurosu[121]	2013	20–69	Cross Sectional	Kanto	Exfoliated	Practitioner	Cervical Swab	2010	2011	Cobas 4800	DNA

Table A4
HPV genotype group definitions used to calculate summary prevalence estimates.

HPV genotype group name	Definition	Included HPV genotype
Any	One or more detectable HPV genotypes	One or more detectable HPV genotypes
Any HR	One or more high risk HPV genotypes	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59
Any LR	One or more low risk HPV genotypes	HPV6, or 11
Bivalent	One or more bivalent vaccine genotypes	HPV16, or 18
Quadrivalent	One or more quadrivalent vaccine genotypes	HPV6, 11, 16, or 18
Nonavalent	One or more nonavalent vaccine genotypes	HPV6, 11, 16, 18, 31, 33, 45, 52, or 58
Cross protection	One or more cross-protection genotypes	HPV31, 33, or 45
Probably carcinogenic	Probably carcinogenic genotype	HPV68
Possibly carcinogenic	One or more cross-protection genotypes.	HPV26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, or 97

Table A5
Joanna Briggs within study quality assessment tool.

Question	Yes	No	Unclear	NA
Was the sample frame appropriate to address the target population?	□	□	□	□
Were study participants sampled in an appropriate way?	□	□	□	□
Was the sample size adequate?	□	□	□	□
Were the study subjects and the setting described in detail?	□	□	□	□
Was the data analysis conducted with sufficient coverage of the identified sample?	□	□	□	□
Were valid methods used for the identification of the condition?	□	□	□	□
Was the condition measured in a standard– reliable way for all participants?	□	□	□	□
Was there appropriate statistical analysis?	□	□	□	□
Was the response rate adequate– and if not– was the low response rate managed appropriately?	□	□	□	□

Table A6
Detailed quality summary of included studies: By author and year of publication.

Author (Year)	1· Appropriate target population	2· Appropriate sampling method	3· Adequate sample size	4· Details description of study subjects	5· Adequate coverage of identified sample	6· Description for methods for identification of condition	7· Standard methodology for identification of condition	8· Description of statistical analysis	9· Adequate response rate
Abe (2014)	1	1	1	1	1	1	1	1	1
Aiko (2017)	1	1	1	1	1	1	1	1	1
Aoyama–Kikawa (2018)	1	1	1	1	1	1	1	1	1
Asato (2004)	1	1	1	1	1	1	1	1	1
Azuma (2014)	1	1	1	1	1	1	1	1	1
Chen (2013)	1	1	1	1	1	1	1	1	1
Fujinaga (1991)	1	1	1	3	1	1	1	1	1
Harima (2002)	1	1	1	1	1	1	1	1	1
Nobeyama (2004)	1	1	1	1	1	1	1	1	1
Hiromura (2014)	1	1	1	1	1	1	1	3	3
Horikoshi (2005)	1	1	1	1	1	1	1	1	1
Hosaka (2013)	1	1	1	1	1	1	1	1	1
Ichimura (2003)	1	1	1	1	1	1	1	1	1
Imai (2015)	1	1	1	1	1	1	1	1	1
Imajoh (2012)	1	1	1	1	1	1	1	1	1
Inoue (2006)	1	1	1	1	1	1	1	1	1
Inoue (2010)	1	1	1	1	1	1	1	1	1
Ishi (2000)	2	1	1	1	1	1	1	1	1
Ishi (2004)	2	3	1	1	1	1	1	1	1
Ishikawa (2001)	1	1	1	1	1	1	1	1	1
Iwata (2015)	1	1	1	1	1	1	1	1	1
Kanao (2004)	1	1	1	1	1	1	1	1	1
Karube (2004)	1	1	1	1	1	1	1	1	1
Kashiwabara (1992)	1	1	1	1	1	1	1	1	1
Kina (2009)	1	1	1	1	1	3	1	1	1
Konno (1993)	1	1	1	1	1	1	1	1	1
Konno (2011)	1	1	1	1	1	1	1	1	1
Konno (2014)	1	1	1	1	1	1	1	1	1
Korosu (2013)	1	1	1	3	1	1	1	3	3
Kubota (1999)	1	1	1	1	1	1	1	1	1
Kurokawa (2018)	1	1	1	1	1	1	1	1	1

Author (Year)	1· Appropriate target population	2· Appropriate sampling method	3· Adequate sample size	4· Details description of study subjects	5· Adequate coverage of identified sample	6· Description for methods for identification of condition	7· Standard methodology for identification of condition	8· Description of statistical analysis	9· Adequate response rate
Kusanagi (2010)	1	1	1	1	1	1	1	1	1
Maehama (2000)	1	1	1	1	1	1	1	1	1
Maehama (2002)	1	1	1	1	1	1	1	1	1
Maehama (2005)	1	1	1	1	1	1	1	1	1
Maki (1991)	1	1	1	1	1	1	1	1	1
Masumoto (2003)	1	1	1	1	1	1	1	1	1
Masumoto (2004)	1	1	1	1	1	1	1	1	1
Matsumoto (2011)	1	1	1	1	1	1	1	1	1
Matsushita (2011)	1	1	1	1	1	1	1	1	1
Minaguchi (2004)	1	1	1	1	1	1	1	1	1
Morisada (2017)	1	1	1	1	1	1	1	1	1
Nagai (2000)	1	1	1	1	1	1	1	1	1
Nagai (2001)	1	1	1	1	1	1	1	1	1
Nakagawa (1996)	1	1	1	1	1	1	1	1	1
Nakagawa (2002)	1	1	1	1	1	1	1	1	1
Nakamura (2015)	1	1	1	1	1	1	1	1	1
Nakazawa (1992)	1	1	1	1	1	1	1	1	1
Nawa (1995)	1	1	1	1	1	1	1	1	1
Nishiwaki (2008)	1	1	1	1	1	1	1	1	1
Niwa (2003)	1	1	3	1	1	1	1	1	1
Okadome (2014)	1	3	1	1	1	1	1	1	1
Onuki (2009)	1	1	1	1	1	1	1	1	1
Saito (1995)	1	1	1	1	1	1	1	1	1
Saito (1999)	1	1	1	1	1	1	1	1	1
Saito (2000)	1	1	1	1	1	1	1	1	1
Saito (2001)	1	1	1	1	1	1	1	1	1
Sakamoto (2017)	1	1	1	3	1	1	1	1	1
Sakamoto (2018)	1	1	1	3	1	1	1	1	1
Sasagawa (1997)	1	1	1	1	1	1	1	1	1
Sasagawa (2001)	1	1	1	1	1	1	1	1	1
Sasagawa (2005)	1	3	1	1	1	1	1	1	1
Sasagawa (2016)	1	1	1	1	1	1	1	1	1
Sasagawa (2018)	1	1	1	1	1	1	1	1	1

(*continued on next page*)

Author (Year)	1· Appropriate target population	2· Appropriate sampling method	3· Adequate sample size	4· Details description of study subjects	5· Adequate coverage of identified sample	6· Description for methods for identification of condition	7· Standard methodology for identification of condition	8· Description of statistical analysis	9· Adequate response rate
Sasaki (2017)	1	1	1	1	1	1	1	1	1
Satoh (2013)	1	1	1	1	1	1	1	1	1
Takehara (2011)	1	1	1	1	1	1	1	1	1
Tanaka (2001)	1	1	1	1	1	1	1	1	1
Tenjimbayashi (2018)	1	1	1	1	1	1	1	1	1
Tsuda (2003)	1	1	1	1	1	1	1	1	1
Tsuji (2003)	1	1	3	1	3	1	1	1	1
Watari (2011)	2	1	1	1	1	1	1	1	1
Yamakawa (1994)	1	1	1	1	1	1	1	1	1
Yamasaki (2011)	1	1	1	1	1	1	1	1	1
Yamazaki (2001)	1	1	1	1	1	1	1	1	1
Yokota (1990)	1	3	1	1	1	1	1	1	1
Yokoyama (2003)	1	1	1	1	1	1	1	1	1
Yoshida (2004)	1	1	1	1	1	1	1	1	1
Yoshida (2009)	1	1	1	1	1	1	1	1	1
Yoshikawa (1991)	1	1	1	1	1	1	1	1	1
Yoshikawa (1999)	1	1	1	1	1	1	1	3	3
二井 (2006)	1	1	1	3	1	3	3	3	3
二井 (2007)	1	1	1	3	1	3	3	3	3
坂本(2015)	1	1	1	3	1	3	3	1	1
竹原 (2012)	1	1	1	3	1	3	3	1	1
郡司(2011)	1	1	1	3	1	3	1	1	1

1 = Yes– 2 = No– 3 = Unclear and additional information requested.

Table A7
HPV genotype prevalence for women with normal cytology through to cervical cancer: All groups.

Disease stage	HPV genotype group	No. of studies	No. of women tested (N)	No. of women HPV positive (n)	Pooled prevalence % (95% CI)	I^2	p–value
Normal	HPV genotype groups						
	Any HPV prevalence	26	57759	6331	15·6 (12·3–19·4)	99·2	<0·01
	Any HR	13	27338	2501	8·4 (3·8–14·6)	99·6	<0·01
	Any LR	7	4031	146	0·8 (0·2–1·8)	94·9	<0·01
	Possibly carcinogenic	7	13506	460	2·2 (0·5–4·9)	98·5	<0·01
	Probably carcinogenic	4	11071	112	0·7 (0·2–1·6)	94·5	<0·01
	Vaccine genotype prevalence						
	Bivalent	12	26560	564	2·4 (1·1–4·2)	98·3	<0·01
	Quadrivalent	13	27338	710	2·7 (1·2–4·7)	98·7	<0·01
	Nonavalent	13	27338	1862	6·8 (3·1–11·8)	99·5	<0·01
	Cross–protection	10	26300	318	1·2 (0·6–1·9)	94·9	<0·01
ASCUS	HPV genotype groups						
	Any HPV prevalence	7	1766	788	53·9 (26·9–79·7)	98·4	<0·01
	Any HR	7	1060	663	41·6 (26·7–57·3)	97·5	<0·01
	Any LR	4	891	32	3·2 (2·1–4·6)	0·00	0·54
	Possibly carcinogenic	4	891	98	9·4 (3·7–17·1)	86·9	<0·01
	Probably carcinogenic	2	635	22	3·1 (1·8–4·7)	NA	NA
	Vaccine genotype prevalence						
	Bivalent	6	995	149	14·7 (8·7–21·9)	82·6	<0·01
	Quadrivalent	6	995	181	17·2 (10·1–25·6)	85·9	<0·01
	Nonavalent	7	1060	517	38·2 (19·9–58·3)	97·0	<0·01
	Cross–protection	6	1022	80	6·8 (3·8–10·6)	66·0	<0·01
LSIL	HPV genotype groups						
	Any HPV prevalence	12	3764	1712	70·2 (47·7–88·5)	99·2	<0·01
	Any HR	12	1937	1477	69·5 (51·4–84·9)	98·9	<0·01
	Any LR	7	1362	65	4·1 (2·1–6·8)	71·9	<0·01
	Possibly carcinogenic	6	1322	239	14·4 (5·0–27·4)	96·8	<0·01
	Probably carcinogenic	4	824	38	4·0 (2·4–6·1)	33·7	<0·01
	Vaccine genotype prevalence						
	Bivalent	12	1937	365	17·3 (13·3–21·7)	81·5	<0·01
	Quadrivalent	12	1937	430	20·3 (15·9–25·1)	82·1	<0·01
	Nonavalent	12	1937	1117	49·7 (36·7–62·7)	96·8	<0·01
	Cross–protection	9	1674	162	9·4 (8·0–10·9)	1·67	0·42
HSIL	HPV genotype groups						
	Any HPV prevalence	9	2017	1485	88·8 (74·6–97·9)	97·7	<0·01
	Any HR	9	1340	1231	86·0 (73·9–94·9)	97·6	<0·01
	Any LR	5	924	33	4·2 (0·8–9·8)	89·0	<0·01
	Possibly carcinogenic	5	1009	90	7·3 (2·5–14·2)	91·2	<0·01
	Probably carcinogenic	2	453	12	2·6 (1·3–4·3)	NA	NA
	Vaccine genotype prevalence						
	Bivalent	9	1340	482	33·3 (26·3–40·6)	85·0	<0·01
	Quadrivalent	9	1340	515	38·0 (33·3–42·8)	61·7	0·01
	Nonavalent	9	1340	1184	86·3 (71·7–96·4)	97·5	<0·01
	Cross–protection	8	1307	181	13·5 (11·6–15·6)	8·71	0·36
CIN1	HPV genotype groups						
	Any HPV prevalence	21	3130	1858	77·4 (62·4–89·5)	98·6	<0·01
	Any HR	14	1904	917	37·8 (29·1–46·9)	93·2	<0·01
	Any LR	2	432	13	2·4 (0·4–5·7)	NA	NA
	Possibly carcinogenic	6	1022	48	4·5 (3·3–5·9)	0·00	0·56
	Probably carcinogenic	6	1350	20	1·5 (0·1–2·9)	56·1	0·04
	Vaccine genotype prevalence						
	Bivalent	13	1865	244	13·1 (9·8–16·6)	74·9	<0·01
	Quadrivalent	13	1865	257	13·5 (10·1–17·3)	76·9	<0·01
	Nonavalent	14	1904	626	28·9 (23·7–34·3)	82·4	<0·01
	Cross–protection	7	1501	60	3·6 (2·5–4·9)	24·6	0·24
CIN2	HPV genotype groups						
	Any HPV prevalence	17	1219	850	87·6 (70·7–98·2)	98·0	<0·01
	Any HR	13	796	557	68·7 (45·6–87·9)	97·7	<0·01
	Any LR	4	420	21	4·1 (0·4–10·5)	84·1	<0·01
	Possibly carcinogenic	6	524	54	8·2 (3·5–14·4)	78·9	<0·01
	Probably carcinogenic	5	433	16	3·4 (1·7–5·4)	0·00	0·41
	Vaccine genotype prevalence						
	Bivalent	12	773	219	27·7 (23·3–29·7)	88·1	<0·01
	Quadrivalent	12	773	240	30·4 (24·7–36·4)	65·8	<0·01

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Table A7 (*continued*)

Disease stage	HPV genotype group	No. of studies	No. of women tested (N)	No. of women HPV positive (n)	Pooled prevalence % (95% CI)	I^2	p–value
	Nonavalent	13	796	516	61·2 (38·9–81·4)	97·5	<0·01
	Cross–protection	6	524	76	13·8 (9·9–18·2)	43·9	0·11
CIN3/AIS	HPV genotype groups						
	Any HPV prevalence	12	960	896	95·4 (90·4–98·9)	86·2	<0·01
	Any HR	9	667	558	76·9 (52·1–94·7)	97·2	<0·01
	Any LR	1	334	6	1·8 (0·6–3·6)	NA	NA
	Possibly carcinogenic	3	408	24	5·3 (3·2–7·9)	0·00	0·54
	Probably carcinogenic	2	379	7	1·9 (0·0–5·7)	NA	NA
	Vaccine genotype prevalence						
	Bivalent	9	667	327	49·0 (45·2–52·9)	0·00	<0·01
	Quadrivalent	9	667	333	49·6 (45·4–53·7)	4·3	<0·01
	Nonavalent	9	667	550	73·0 (48·0–92·3)	97·2	<0·01
	Cross–protection	6	765	104	12·3 (6·8–19·1)	77·7	<0·01
ICC	HPV genotype groups						
	Any HPV prevalence	31	4306	3747	85·6 (80·7–89·8)	92·8	<0·01
	Any HR	26	3716	2531	75·7 (68·0–82·6)	95·6	<0·01
	Any LR						
	Possibly carcinogenic	7	2177	8	3·3 (1·2–6·1)	84·9	<0·01
	Probably carcinogenic	5	2092	6	1·4 (0·7–2·2)	80·8	<0·01
	Vaccine genotype prevalence						
	Bivalent	26	3716	1970	58·5 (52·1–64·9)	92·3	<0·01
	Quadrivalent	26	3716	1973	58·6 (52·2–64·9)	92·3	<0·01
	Nonavalent	26	3716	2419	71·5 (64·9–77·6)	93·4	<0·01
	Cross–protection	19	3346	217	7·3 (5·3–12·0)	86·8	<0·01
	Vaccine genotype prevalence (in HPV positive cases)						
	Bivalent	26	3279	1970	75·9 (68·6–82·7)	93·8	<0·01
	Quadrivalent	26	3278	1973	76·5 (69·1–83·3)	93·9	<0·01
	Nonavalent	26	3278	2419	90·2 (84·5–94·9)	94·1	<0·01
	Cross–protection	19	2988	217	8·4 (5·3–12·0)	86·8	<0·01
ICC-SCC	HPV genotype groups						
	Any HPV prevalence	6	1032	891	86·1 (61·9–99·6)	97·8	<0·01
	Any HR	6	1032	717	78·9 (54·8–95·7)	97·3	<0·01
	Any LR						
	Vaccine genotype prevalence						
	Bivalent	6	1032	603	68·7 (51·2–83·8)	94·3	<0·01
	Quadrivalent	6	1032	604	68·7 (51·3– 83·9)	94·3	<0·01
	Nonavalent	6	1032	683	76·5 (54·1– 93·3)	96·8	<0·01
	Cross–protection	3	853	39	8·1 (1·8– 17·8)	86·4	<0·01
	Vaccine genotype prevalence (in HPV positive cases)						
	Bivalent	6	891	603	89·4 (68·5–100)	96·3	<0·01
	Quadrivalent	6	891	604	89·5 (68·6–100)	96·3	<0·01
	Nonavalent	6	891	683	94·6 (76·5–100)	96·4	<0·01
	Cross–protection	3	805	39	8·5 (1·8–17·8)	85·4	<0·01
ICC-ADC	HPV genotype groups						
	Any HPV prevalence	9	638	533	80·5 (70·0–89·4)	77·47	<0·01
	Any HR	7	638	121	64·9 (43·8–83·6)	87·5	<0·01
	Any LR						
	Vaccine genotype prevalence						
	Bivalent	7	219	121	72·1 (59·5–83·6)	81·0	<0·01
	Quadrivalent	7	219	141	72·1 (59·5–83·6)	81·0	<0·01
	Nonavalent	7	219	146	74·3 (61·6–85·3)	81·6	<0·01
	Cross–protection	2	74	4	3·7 (0·2–10·0)	NA	NA
	Vaccine genotype prevalence (in HPV positive cases)						
	Bivalent	7	170	121	93·7 (76·9–100)	92·1	<0·01
	Quadrivalent	7	170	121	93·7 (76·9–100)	92·1	<0·01
	Nonavalent	7	170	146	95·2 (79·9–100)	91·4	<0·01
	Cross–protection	2	69	4	4·2 (0·3–10·9)	NA	NA

HPV prevalence measured as HPV test positivity where the numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. Any-HPV prevalence represents the detection of any detectable HPV genotype. Any HR represents the detection of any of the following: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59. Any LR represents the detection of HPV6 or 11. Probably carcinogenic prevalence represents detection of HPV68. Possibly carcinogenic prevalence represents detection of any of the following: HPV26, 53, 66, 67, 67, 70, 73, 82, 30, 34, 69, 85, or 97. Bivalent represents the detection of HPV16, or 18; Quadrivalent represents 6, 11, 16 or 18; and nonavalent represents: HPV6, 11, 16, 18, 31, 33, 45, 52, 58; Cross protection represents: HPV31, 33 or 45. Total number of women tested stratified as follows: 57759 for normal cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 896 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. NA: I–squared not quantifiable with fewer than three estimates.

Table A8
HPV genotype prevalence in women with normal cytology through to cervical cancer: Individual vaccine genotypes.

Disease stage	HPV genotype	No. of studies	No. of women tested (N)	No. of women HPV positive (n)	Pooled prevalence (95% CI)	I^2	p–value
Normal	6	7	14031	112	0·0 (0·0–1·3)	94·4	<0·01
	11	5	10668	34	0·0 (0·0–0·6)	68·2	0·01
	16	13	27338	403	1·5 (0·7–2·7)	97·6	<0·01
	18	12	27184	161	0·4 (0·1–0·9)	94·3	<0·01
	31	10	26300	187	0·7 (0·4–1·2)	93·5	<0·01
	33	9	26047	96	0·2 (0·2–0·4)	66·7	<0·01
	45	6	13917	35	0·0 (0·0–0·3)	89·3	<0·01
	52	10	15208	558	3·1 (1·5–5·3)	97·4	<0·01
	58	11	26414	276	0·8 (0·3–1·6)	96·8	<0·01
ASCUS	6	4	891	29	2·8 (1·8–4·2)	0·00	0·59
	11	4	891	3	0·0 (0·0–0·5)	0·00	0·81
	16	6	995	115	11·4 (6·4–17·6)	79·8	<0·01
	18	5	929	34	3·2 (2·1–4·5)	0·00	0·54
	31	6	1022	48	4·2 (2·4–6·7)	44·6	0·10
	33	4	891	20	1·8 (1·0–3·0)	0·00	0·54
	45	4	891	12	0·9 (0·4–1·9)	0·00	0·61
	52	6	995	146	12·0 (7·8–16·9)	67·8	<0·01
	58	5	957	110	11·1 (9·2–13·3)	0·00	0·46
LSIL	6	7	1362	50	2·2 (0·8–4·7)	75·3	<0·01
	11	7	1362	15	0·8 (0·0–2·7)	74·9	<0·01
	16	12	1937	266	12·5 (9·3–16·3)	78·6	<0·01
	18	10	1763	99	4·8 (3·3–7·0)	62·3	<0·01
	31	9	1674	113	6·7 (5·1–8·8)	44·8	0·07
	33	8	1566	29	1·2 (0·7–2·3)	21·3	0·26
	45	7	1468	20	0·7 (0·2–1·9)	50·9	0·05
	52	10	1790	303	14·7 (11·2–18·8)	77·3	<0·01
	58	8	1576	222	12·7 (9·1–17·1)	79·4	<0·01
HSIL	6	5	951	15	0·7 (0·1–2·6)	60·8	0·03
	11	6	1061	18	1·3 (0·00–5·3)	88·8	<0·01
	16	9	1340	409	27·6 (20·4–35·5)	87·8	<0·01
	18	8	1307	73	4·7 (2·9–7·1)	56·7	0·02
	31	8	1307	122	8·9 (7·5–10·7)	0·00	0·87
	33	8	1307	46	3·0 (2·2–4·3)	0·00	0·46
	45	7	1274	13	0·5 (0·3–1·4)	0·00	0·57
	52	9	1340	293	18·1 (12·7–24·3)	84·0	<0·01
	58	7	1274	243	17·4 (12·6–23·2)	81·9	<0·01
CIN1	6	3	1005	13	1·1 (0·6–2·0)	0·00	0·57
	11	2	891	8	1·3 (0·3–1·5)	NA	NA
	16	13	1865	175	9·2 (6·9–12·0)	64·5	<0·01
	18	10	1596	69	4·0 (2·7–5·8)	46·1	<0·01
	31	8	1994	37	1·4 (0·8–2·1)	0·00	0·77
	33	6	1387	29	1·5 (1·2–2·8)	0·00	0·74
	45	4	1624	7	0·0 (0·0–0·0)	70·4	0·02
	52	12	2178	203	10·0 (6·3–11·7)	68·9	<0·01
	58	9	2113	172	9·1 (6·3–11·6)	73·8	<0·01
CIN2	6	3	329	5	1·0 (0·3–3·2)	0·00	0·95
	11	2	255	16	5·0 (2·3–7·6)	NA	NA
	16	11	682	182	26·0 (21·7–30·5)	36·4	0·11
	18	11	729	37	4·5 (2·5–7·2)	46·5	0·04
	31	6	524	38	5·8 (2·9–10·4)	64·4	0·02
	33	6	524	21	3·4 (2·1–5·6)	0·00	0·50
	45	4	414	17	3·3 (1·0–8·0)	66·8	0·03
	52	7	489	119	23·7 (19·5–28·2)	15·9	0·31
	58	7	547	90	15·5 (10·0–22·3)	71·2	<0·01
CIN3/AIS	6	2	360	6	0·9 (0·1–2·6)	NA	NA
	11	2	360	0	0·0 (0·0–0·1)	NA	NA
	16	13	1041	362	37·2 (28·0–46·7)	87·2	<0·01
	18	12	995	40	3·2 (1·4–5·1)	41·7	0·06
	31	5	745	63	6·7 (3·2–11·6)	71·0	<0·01
	33	5	736	38	5·9 (2·6–10·6)	69·8	0·01
	45	2	379	3	0·2 (0·0–1·7)	NA	NA
	52	5	469	111	20·5 (14·5–27·2)	39·6	0·16
	58	6	765	82	9·4 (2·9–18·7)	89·7	<0·01
ICC	6	–	–	–	–	–	–
	11	–	–	–	–	–	–
	16	26	3716	1467	40·6 (36·2–45·0)	82·3	<0·01
	18	26	3716	525	16·4 (12·1–21·2)	90·8	<0·01
	31	14	2732	97	4·0 (2·3–5·9)	70·6	<0·01
	33	17	3262	107	4·1 (2·0–6·2)	86·8	<0·01
	45	5	2314	13	0·3 (0·1–0·7)	0·00	0·41
	52	14	2571	143	7·9 (4·1–12·6)	91·4	<0·01
	58	15	4306	125	4·3 (2·9–5·9)	65·3	<0·01
ICC - SCC	6	–	–	–	–	–	–
	11	–	–	–	–	–	–

(*continued on next page*)

Table A8 (*continued*)

Disease stage	HPV genotype	No· of studies	No· of women tested (N)	No· of women HPV positive (n)	Pooled prevalence (95% CI)	I^2	p–value
	16	6	2479	525	56·1 (42·1–69·7)	90·4	<0·01
	18	26	2479	86	11·0 (5·6–17·8)	76·8	0·03
	31	3	2674	28	5·3 (0·8–12·9)	83·1	<0·01
	33	3	2674	8	1·4 (0·0–4·6)	65·7	<0·01
	45	2	2734	3	0·2 (0·0–0·7)	NA	NA
	52	3	2674	36	19·7 (0·1–40·6)	97·2	<0·01
	58	3	2674	36	7·5 (1·5–17·1)	86·4	<0·01
ICC -ADC	6	–	–	–	–	–	–
	11	–	–	–	–	–	–
	16	6	2411	177	30·8 (22·4–40·0)	68·9	<0·01
	18	8	2564	179	43·8 (33·5–54·7)	69·5	<0·01
	31	2	3116	3	0·0 (0·0–0·4)	NA	NA
	33	2	4097	2	2·1 (0·0–7·5)	NA	NA
	45	1	3176	4	1.0 (0·4–2·5)	NA	NA
	52	2	3027	4	0·5 (0·0–1·5)	NA	NA
	58	2	3027	5	0·7 (0·0–1·8)	NA	NA

HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. Total number of women tested stratified as follows: 57759 for normal histology confirmed cytology, 1766 for ASCUS, 3764 for LSIL, 2017 for HSIL, 3130 for CIN1, 1219 for CIN2, 1041 for CIN3/AIS, 4306 for ICC, 1032 for ICC-SCC, and 638 for ICC-ADC. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. NA: I–squared not quantifiable with fewer than three estimates. NR: No result.

Table A9
Any-HPV prevalence in women with normal cytology and cervical cancer: By 10-year age group.

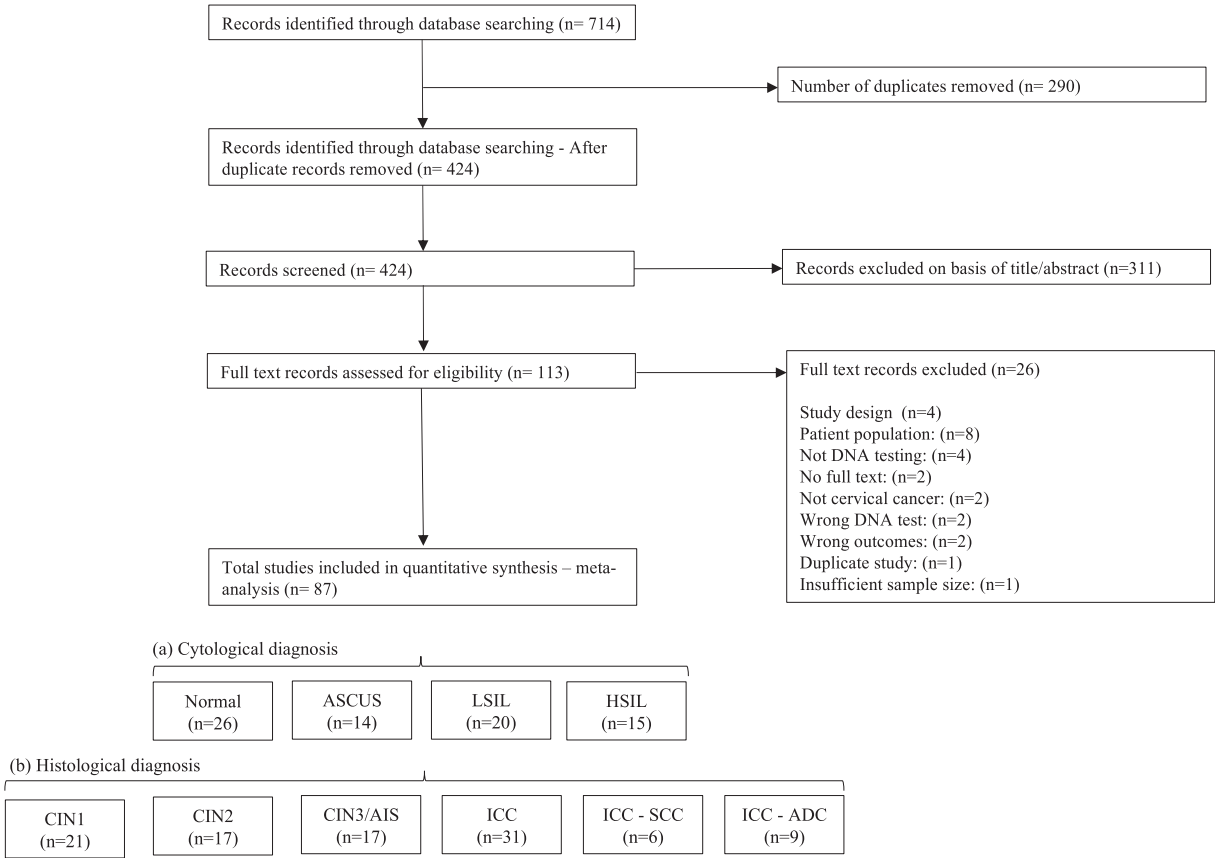
Age group	Number of Studies	Number of women tested (N)	Number of women HPV positive (n)	Pooled prevalence (95% CI)	I^2	p–value
Normal women (N = 112896)						
10 to 19	5	178	45	20·3 (73·6–36·6)	64·7	<0·01
20 to 29	11	7218	900	22·8 (12·8–34·6)	98·9	<0·01
30 to 39	13	32070	1346	15·8 (9·3–23·7)	99·5	<0·01
40 to 49	13	31355	1053	9·1 (5·1–13·9)	99·2	<0·01
50 to 59	12	25370	756	6·1 (2·4–11·1)	99·3	<0·01
60 to 69	12	10281	535	5·5 (1·8–10·5)	98·3	<0·01
70 to 79	9	1049	96	3·9 (0·9–8·1)	63·9	<0·01
80 and over	3	35	3	1·6 (0·0–14·5)	NA	NA
Invasive cervical cancer (N = 431)						
10 to 19	0	–	–	–	–	–
20 to 29	2	28	26	93·8 (79·9–100)	NA	NA
30 to 39	3	86	77	92·3 (84·3–98·1)	NA	NA
40 to 49	2	95	82	91·7 (73·9–100)	50·9	<0·01
50 to 59	2	77	57	71·1 (46·5–91·1)	42·4	<0·01
60 to 69	2	84	73	89·1 (80·5–95·9)	NA	NA
70 to 79	1	38	35	92·1 (80·9–98·9)	NA	NA
80 and over	1	23	21	91·3 (75·5–99·8)	NA	NA

HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. There were 112896 women with normal cytology tested. In this group, 178 women were 10–19, 7218 were 20–29, 32,070 were 30–39, 31355 were 40–49, 25370 were 50–59, 10281 were 60–691049 were 70–79 years old, and 35 women were 80 years old and over. There were 431 women tested with ICC. This included no women tested and aged between 10 and 19 years old. There were 28 women 20–29, 86 were 30–39, 95 were 40–49, 77 were 50–59, 84 were 60–69, 38 were 70–79, and 23 were 80 years old and over. A high level of heterogeneity (I^2 > 90%) was observed in most summary estimates. NA: I–squared not quantifiable with fewer than three estimates.

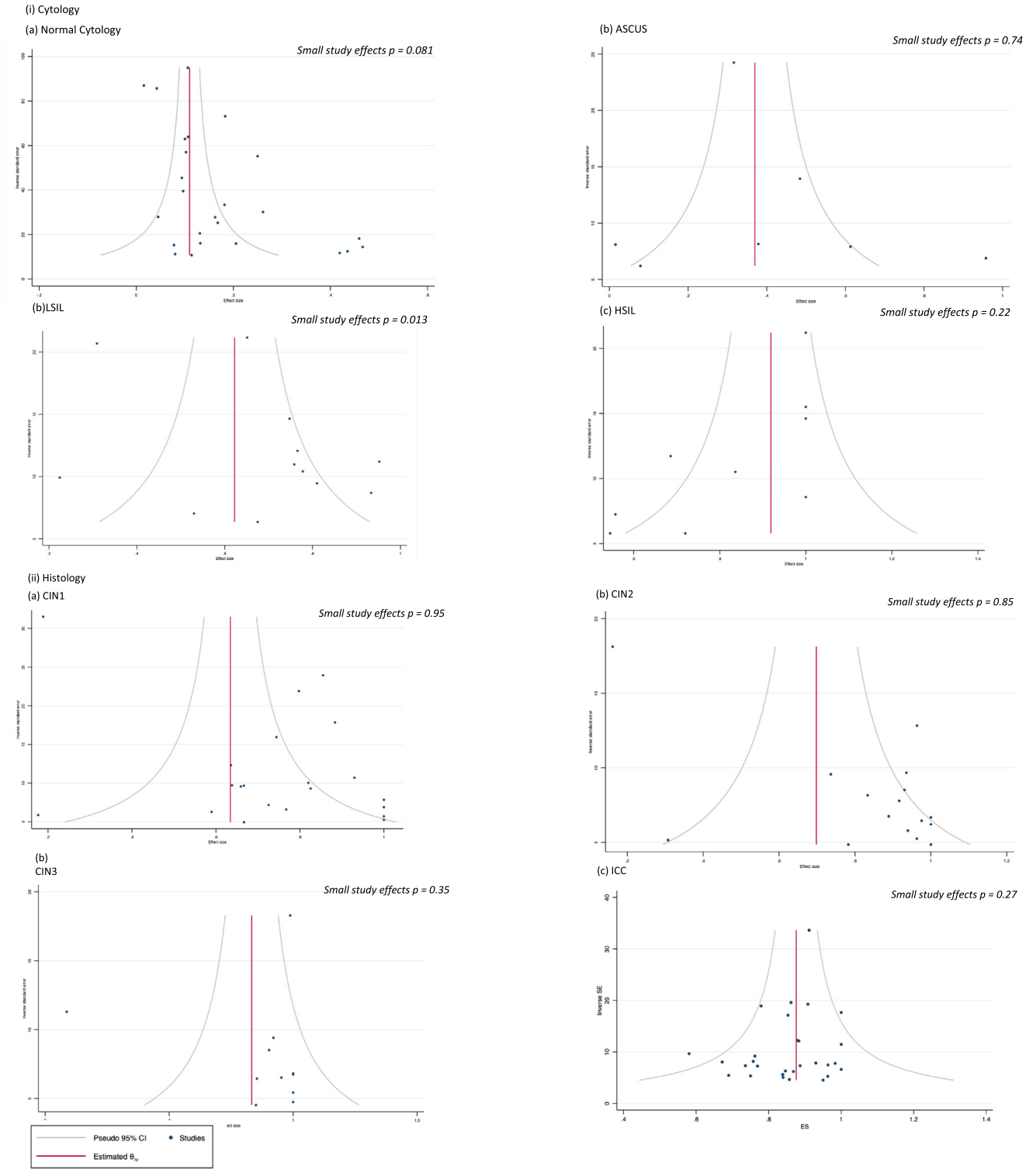
Table A10
Age standardised any-HPV prevalence in women with normal cytology and invasive cervical cancer in Japan.

Age group (years)	Age specific prevalence of infection (%)	National age standardised prevalence (%)
Normal cytology		
10 to 19	20·3 (73·6–36·6)	9·6
20 to 29	22·8 (12·8–34·6)	
30 to 39	15·8 (9·3–23·7)	
40 to 49	9·1 (5·1–13·9)	
50 to 59	6·1 (2·4–11·1)	
60 to 69	5·5 (1·8–10·5)	
70 to 79	3·9 (0·9–8·1)	
80 and over	1·6 (0·0–14·5)	
ICC		
10 to 19	No data	
20 to 29	93·8 (79·9–100)	87·0
30 to 39	92·3 (84·3–98·1)	
40 to 49	91·7 (73·9–100)	
50 to 59	71·1 (46·5–91·1)	
60 to 69	89·1 (80·5–95·9)	
70 to 79	92·1 (80·9–98·9)	
80 and over	91·3 (75·5–99·8)	

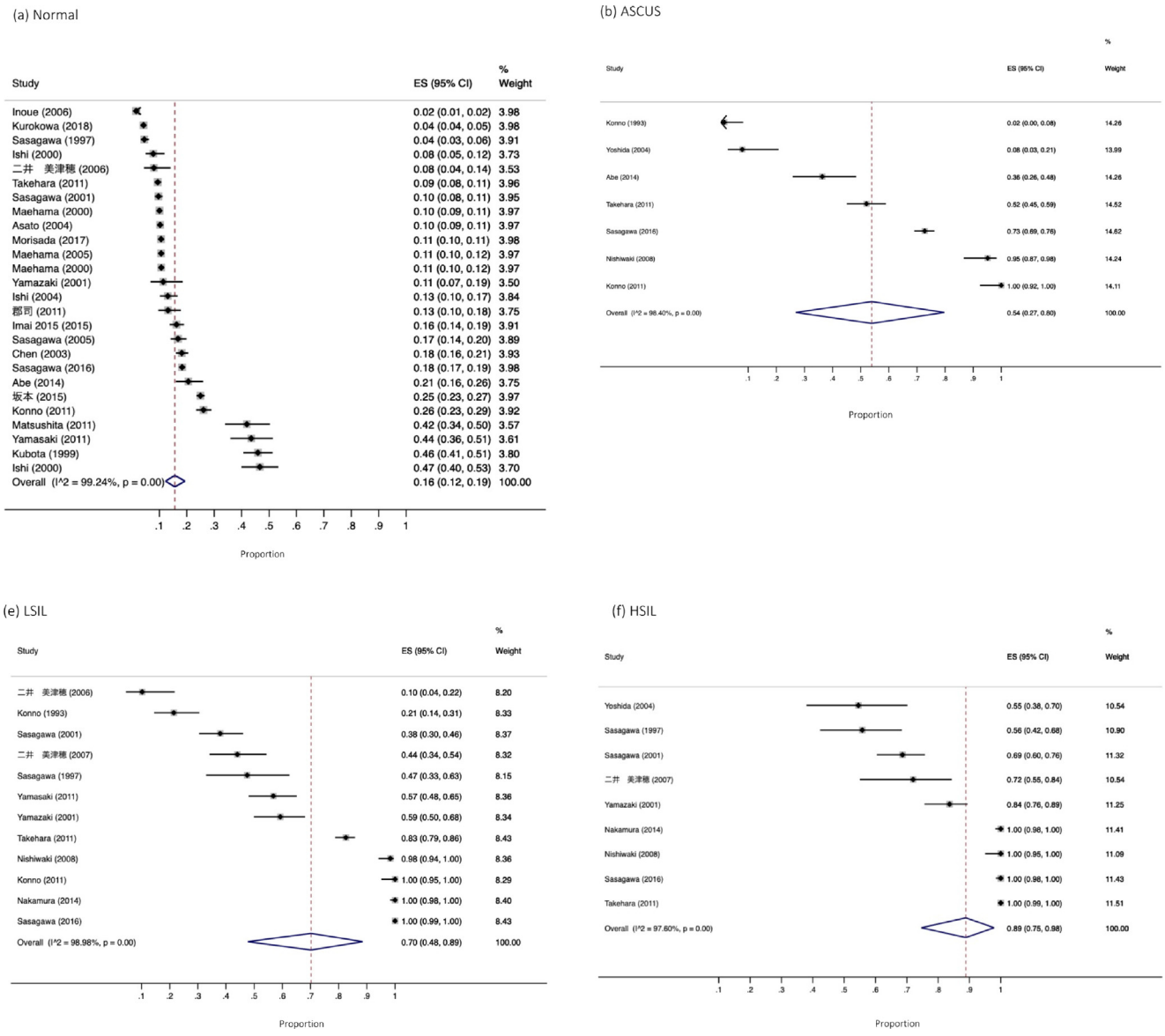
HPV prevalence measured as HPV test positivity where numerator was the number who tested HPV positive, and the denominator was the number who had an HPV test. The 95% confidence intervals were calculated for each summary estimate. HPV prevalence is the detection of any detectable HPV genotype. National age standardise prevalence: Standardised using Japan 2020 standard population.[17] There were 112896 women with normal cytology tested. In this group, 178 women were 10–19, 7218 were 20–29, 32070 were 30–39, 31,355 were 40–49, 25,370 were 50–59, 10281 were 60–69, 1049 were 70–79 years old, and 35 women were 80 years old and over. There were 431 women tested with ICC. This included no women tested and aged between 10 and 19 years old. There were 28 women 20–29, 86 were 30–39, 95 were 40–49, 77 were 50–59, 84 were 60–69, 38 were 70–79, and 23 were 80 years old and over. Detailed age specific data in Appendix Table A9.



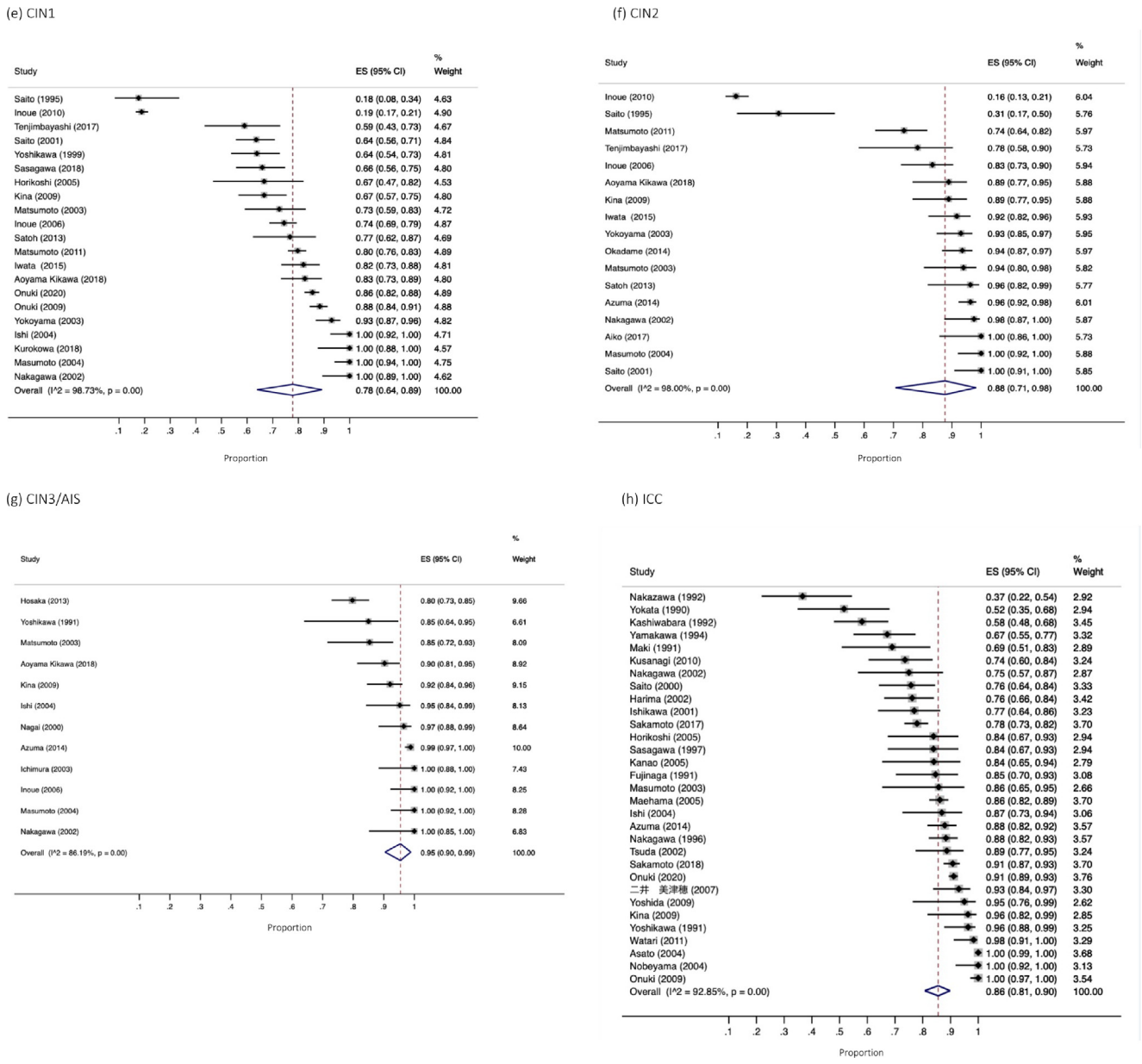
Appendix Fig. A1. PRISMA Diagram.



Appendix Fig. A2. Any-HPV prevalence in women with normal cytology through to cervical cancer: Funnel plots.



Appendix Fig. A3. Any-HPV prevalence in women with normal cytology through to cervical cancer: Forest plots.



Appendix Fig. A3 (*continued*)

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