

# Do Condoms Prevent Genital HPV Infection, External Genital Warts, or Cervical Neoplasia?

## A Meta-Analysis

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**Background:** Although condoms most likely prevent HIV infection, evidence of their effectiveness against other sexually transmitted diseases is mixed.

**Goal:** The goal of the study was to determine whether condom use prevents genital human papillomavirus (HPV) infection and HPV-related conditions.

**Study Design:** We conducted a literature review and meta-analysis of the effect of condom use on the prevention of genital warts, subclinical HPV infection, cervical intraepithelial neoplasia (CIN), and invasive cervical cancer (ICC).

**Results:** Among 27 estimates from 20 studies, there was no consistent evidence that condom use reduces the risk of becoming HPV DNA-positive. However, risk for genital warts, CIN of grade II or III (CIN II or III), and ICC was somewhat reduced.

**Conclusions:** Available data are too inconsistent to provide precise estimates. However, they suggest that while condoms may not prevent HPV infection, they may protect against genital warts, CIN II or III, and ICC.

HUMAN PAPILLOMAVIRUS (HPV) is a common sexually transmitted infection, and it is estimated that over 50% of sexually active men and women aged 15 to 49 years have been infected with one or more genital HPV types at some point in their lives.<sup>1</sup> Of the over 38 different types of this small DNA virus known to infect the genital tract,<sup>2</sup> only two types (HPV 6 and 11) are clearly linked with genital warts, whereas virtually all types have been linked with squamous intraepithelial lesions (SILs) of the uterine cervix. Furthermore, genital HPV types play an etiologic role in the de-

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velopment of virtually all cases of invasive cervical cancer (ICC).<sup>3</sup> Invasive cancers of the vagina, vulva, penis, and anus have also been linked with genital HPV infection, but compared with cervical cancer, these cancers are rare.<sup>4</sup> Papanicolaou (Pap) smear screening has allowed for early detection and treatment of HPV-associated cervical lesions, dramatically decreasing cervical cancer incidence and mortality among women.

As with other infections that cause significant morbidity and mortality, preventing the spread of the infectious agent throughout a susceptible population is generally more cost-effective than approaches involving early detection and treatment. In the absence of a vaccine, abstinence, mutual monogamy, and condoms are options for preventing genital HPV infection. In response to the recent congressional mandate to provide the public with more accurate information on the efficacy of condoms in preventing HPV infection,<sup>5</sup> a comprehensive review of the literature was undertaken and a meta-analysis performed.

The strongest evidence of the role of male condoms in preventing disease transmission is for HIV. A meta-analysis of 25 studies of HIV-serodiscordant heterosexual couples provided a summary efficacy estimate of 87% (95% CI, 60–95%).<sup>6</sup> The evidence is less clear, however, for other STDs. In vitro testing has shown that condoms provide 100% protection as a physical barrier to chlamydia, herpes simplex virus-2 (HSV-2), and HIV,<sup>7</sup> and some reports indicate protection against gonorrhea, chlamydia, and HSV-2.<sup>8–10</sup> However, a study of Baltimore STD clinic attendees revealed that condom use was not associated with any reduction in the incidence of gonorrhea, chlamydia, trichomoniasis, or syphilis.<sup>11</sup> Although no studies have been conducted explicitly to assess the effectiveness of condoms in preventing HPV infections, numerous publications present

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data on the relationship between condom use and HPV-related conditions. The present analysis examines the existing evidence on the effectiveness of condoms against HPV infections and HPV-related conditions (e.g., genital warts, subclinical HPV infection, cervical intraepithelial neoplasia [CIN], and ICC).

### Methods

We examined the peer-reviewed literature on condoms and HPV-related conditions published in the English language since 1980 to identify studies for inclusion in this analysis. The search was limited to the past 20 years of published literature because before the mid-1980s HPV DNA testing was not available, and before the late 1970s classification schemes of HPV-related cervical pathology were not standardized. After initial discussions with experts in the field to identify appropriate studies, we engaged in a MEDLINE search and reviewed reference lists from published articles to identify other publications not already selected. The following search terms were used: human papillomavirus (HPV) and condoms, cervical cancer and condoms, SIL or cervical intraepithelial neoplasia (CIN) and condoms, and warts and condoms, as well as each of these search terms independently. Only studies that examined use of the male condom were included. To date, there have been no studies of the female condom and HPV.

#### *Inclusion Criteria*

Studies were included in this analysis if they met the following criteria: (1) a clear definition of the endpoint (HPV infection; HPV type; warts, SIL, CIN; cancer), (2) an exclusive definition of condom use, and (3) an appropriate comparison group. Nine studies that examined the effect of barrier contraceptive methods lumped together (condom, diaphragm, cervical cap) were excluded, as it was not possible to disentangle the effect of condoms from the other methods. Two studies conducted in populations with high rates of HIV infection were also excluded because the presented data did not allow for assessment of condom use and prevention of HPV-related conditions in the absence of immunosuppression. Compared with individuals who are not infected with HIV, those who are infected tend to have more evidence of HPV-related disease.<sup>4</sup> In case-control studies, we required controls to be selected from the same populations that gave rise to the cases<sup>12</sup>; two studies did not meet this criterion. Four other studies were excluded because of inadequate assessment of either condom use or outcome.

Because of the instability of estimates derived from studies of small sample size, we also excluded all studies that had fewer than 20 cases and/or controls or less than 20 condom users (2 studies). When more than one publication reported on the same study population, we included only the

one with the clearest presentation of data on the relationship between condom use and the outcome of interest. When several definitions of condom use were evaluated or more than one comparison was reported, we elected to present only one comparison, giving higher priority to the definition of “always use versus never use” and less priority to definitions suggesting occasional use. For many studies, however, condom use was measured as only “yes versus no” or “ever versus never.”

For biologic homogeneity, separate evaluations were performed for the five outcomes of interest: (1) external genital warts, (2) HPV DNA detection in genital samples, (3) cervical warts and SIL, or CIN (grade I or unspecified), (4) CIN II or III, and (5) ICC (squamous cell carcinoma and adenocarcinoma not differentiated). Cervical SIL (Bethesda classification system) and CIN (Richart's classification scheme) define the same set of lesions, although the SIL category includes cellular features of HPV infection (e.g., koilocytosis) alone, as well as classic cellular features of CIN with or without koilocytosis.<sup>4</sup>

Whenever the odds ratio (OR) or relative risk (RR) presented in the publication was calculated from a clear baseline category, we utilized that estimate and corresponding 95% confidence intervals in our analysis. Because most of these studies were not designed to assess the relationship between HPV-related conditions and condom use, in some cases the OR presented in the publication did not reflect always-versus-never use of condoms. For those studies, we recalculated the OR and CI, from data presented in the publication<sup>13</sup> or data obtained from the investigators themselves.<sup>14,15</sup> We also calculated ORs and 95% CIs for studies that presented percentages.<sup>16,17</sup> In all instances, Epi-Info (version 6.04b; Centers for Disease Control and Prevention, Atlanta, GA) was used in the calculation of the 95% CIs.<sup>18</sup> When provided, adjusted ORs (OR<sub>adj</sub>) or adjusted RRs (RR<sub>adj</sub>) were presented.

We conducted a chi-square test of homogeneity<sup>19</sup> for each outcome and concluded that substantial heterogeneity was present in each group. Therefore, we elected not to calculate pooled odds ratios and have presented only the individual estimates.

### Results

A total of 20 studies met all the inclusion criteria (Tables 1 and 2). Five of these studies assessed more than one outcome, providing a total of 27 different estimates on the relationship between HPV-related conditions and condom use. Two studies included data on the relationship between condom use and external genital warts<sup>13,17</sup>; in 6 studies the primary outcome was detection of HPV DNA in cervical samples<sup>14,18–24</sup>; 4 studies examined cervical SIL, cervical warts, or CIN (grade I or unspecified)<sup>16,25–27</sup>; 6 studies used CIN grade II or III as the outcome<sup>25,27–31</sup>; and 5 studies

TABLE 1. Studies Included in Analysis, Stratified by Outcome and Ordered by Date

Date*	Study†	N	Location	Gender	Design
External genital warts					
1992	Hippelainen (17)	432	Finland	Males	Cross-sectional
1996	Wen (13)	1298	Australia	Males	Case-control
1996	Wen (13)	656	Australia	Females	Case-control
Cervical HPV DNA					
1988–1990	Davidson (20)	1126	U.S.	Females	Cross-sectional
1989–1990	Jamison (21)	634	U.S.	Females	Cross-sectional
1992–1993	Kjaer (22)	182	Denmark	Females	Cross-sectional
1992–1995	Young (24)	1477	Canada	Females	Cross-sectional
1994–1997	Ho (14)	608	U.S.	Females	Cohort
1997‡	Kjaer (23)	956	Denmark	Females	Cross-sectional
Cervical warts and SIL or CIN (grade I or unspecified)					
1968–1974	Zondervan§ (25)	1749	England/Scotland	Females	Nested case-control
1981–1985	Kataja (26)	1397	Finland	Females	Case-control
1984‡	Syrjanen (16)	292	Finland	Females	Case-control
2000‡	Adam¶ (27)	430	U.S.	Females	Cross-sectional
CIN II or III					
1968–1974	Zondervan§ (25)	1331	England/Scotland	Females	Nested case-control
1985–1987	Munoz (28)	207	Spain	Females/husbands	Case-control
1985–1988	Munoz (28)	187	Colombia	Females/husbands	Case-control
1989–1991	Becker (29)	538	U.S.	Females	Case-control
1991–1994	Wang (31)	723	Taiwan	Females/husbands	Case-control
1992–1994	Ho (30)	258	U.S.	Females	Cross-sectional
2000‡	Adam¶ (27)	530	U.S.	Females	Cross-sectional
Invasive cervical cancer					
1968–1974	Zondervan§ (25)	354	England/Scotland	Females	Nested case-control
1979–1988	Thomas (15)	522¶	Thailand	Females/husbands	Case-control
1982–1984	Hildesheim (34)	1267	U.S.	Females	Case-control
1984–1987	Slattery (32)	638	U.S.	Females	Case-control
1987–1988	Kjaer (33)	131	Denmark	Females/husbands	Case-control

\*Date study was conducted.

†First author (reference number).

‡Publication date (study date not indicated).

§Single study with three different outcomes: invasive cervical cancer (n = 33), carcinoma in situ (n = 121), and dysplasia (n = 159), by ICD-8 definitions. Ten controls per case from cohort of 17,032 (women with no cervical abnormalities), with the exception of 1 case of invasive cervical cancer for which only 1 control was available.

¶Single study with two different outcomes; compared women with no lesions and no HPV DNA (n = 269) with women with CIN I (n = 161) and women with CIN II/III (n = 261). All diagnoses biopsy-confirmed.

¶N represents a subset of the larger study reported in the article (n = 1016); N of 522 includes only those subjects (1) who reported monogamy and (2) whose husbands were interviewed and reported visiting a prostitute at least once.

focused on ICC.<sup>15,25,32–34</sup> The majority of studies measuring HPV DNA as the primary outcome were cross-sectional, with the exception of one cohort study. In contrast, all publications on cervical cancer were reports of case-control studies. Studies assessing (1) external genital warts, (2) cervical SIL, cervical warts, or CIN (grade I or unspecified), and (3) CIN II or III represented a mixture of case-control and cross-sectional designs.

The overwhelming majority of these studies were conducted among women, with one study of men only and another of both men and women. Three of the studies on women, however, gathered condom use data directly from their husbands.<sup>15,28,33</sup> Although the age range of all subjects was large, in general, studies of genital warts, HPV DNA detection, or SIL were conducted among men and women in their twenties and early thirties, while studies of ICC were conducted among slightly older women.

Several different condom measures were used in these studies, but all relied on self-report, which can sometimes

result in misclassification. Time intervals were rarely stated, and only four studies specified a defined measurement period for condom use. Two studies compared users for 5 or fewer years with those who had used condoms for greater than 5 years, 1 assessed condom use in the past 4 months, and 1 compared users for 6 or more months with those who had used them for fewer than 6 months. The type of condom used (latex versus nonlatex) was not specified in any of the studies.

#### External Genital Warts

Only two studies assessed the relationship between condom use and external genital warts, and both found protective effects (Figure 1). One analysis examined young male military recruits, while the other evaluated men and women attending an STD clinic. Among military recruits, those who reported always using condoms were 70% less likely to have genital warts or subclinical HPV infection of the penis than male recruits who occasionally or never used them

TABLE 2. Summary Estimates, Condom Measures, and Potential Confounders Examined for Studies Included in the Analysis, Ordered By Magnitude of the Odds Ratio (OR)

Study*	Population Source	Risk Estimate (95% CI)	Condom Measure	Potential Confounders Examined in Analyses
External genital warts Hippelainen <sup>†</sup> (17)	Military recruits (men)	0.3 (0.2–0.5) <sup>‡</sup>	Always vs. never/occasionally	History of STDs, casual sex contacts (tested, but not significant)
Wen (13)	STD clinic			Crude ORs and 95% CIs presented. Data in article allowed for calculation of adjusted ORs but not 95% CIs.
	Men	0.3 (0.2–0.4) <sup>‡</sup>	Always vs. never	Men: OR = 0.4 after adjustment for age group, no. of lifetime partners, smoking
	Women	0.6 (0.4–0.9) <sup>‡</sup>	Always vs. never	Women: OR = 0.4 after adjustment for age group, marital status, occupation
Cervical HPV DNA Kjaer (22)	Female sex workers in Copenhagen, Denmark	0.2 (0.1–0.6)	Current always vs. never (w/private partners, past 4 mo)	Age (continuous), no. of private partners in past 4 mo, ever gonorrhea
Ho (14)	University health center	0.8 (0.4–1.4) <sup>§</sup>	Always vs. never	Age, race, alcohol consumption, no. of sex partners in prior 6 mo, no. of sex partners in prior 7–12 mo, anal sex, frequency of vaginal sex, male partner's no. of lifetime partners, main partner currently in school (in model)
Davidson (20)	Alaska Native medical center + random sample from Alaska Native population	0.9 (0.5–1.5) <sup>§</sup>	Always vs. never (within past 2 y)	Income; lifestyle; use of cigarettes, recreational drugs, oral contraceptives; no. of casual sex partners, regular partners, new regular partners; frequency of oral sex; sex with alcohol or drugs; postcoital bleeding; sex during menstruation; douching (tested & not significant)
Jamison (21)	Adolescent clinics	1.2 (0.7–2.1)	>75% of time vs. <25% (prior 6 mo)	Age, lifetime no. of sex partners, oral contraceptive use (tested & not significant)
Young (24)	Community health center (43% Aboriginal)	1.5 (1.1–2.0)	Most/always vs. never (during past 1 y)	Ethnicity, age, pregnancy, smoking, oral contraceptives, gonorrhea/chlamydial infection, no. of sex partners in past 6 mo (tested & not significant)
Kjaer (23) Oncogenic	General female population in Copenhagen	1.6 (0.8–3.3)	Current vs. never	Aboriginal, smoking, marital status, age, oral contraceptives, age at first sex, lifetime no. of partners, no. of partners in past 1 y, no. of past pregnancies, Pap test results
Nononcogenic	General female population in Copenhagen	3.8 (1.2–11.6)	Current vs. never	Age (significant); lifetime no. of partners, no. of regular partners (≥3 mo), age at first intercourse, years since first intercourse, history of chlamydia, history of any STD, years of diaphragm use, years of oral contraceptive use, no. of live births, smoking (tested)
Cervical warts and SIL or CIN (grade I or unspecified) Zondervan <sup>  </sup> (25)	Family planning clinics	1.0 (0.7–1.4)	Ever vs. never <sup>  </sup>	Age, lifetime no. of partners, no. of live births, history of chlamydia (significant), no. of partners (≥3 mo), age at first intercourse, years since first intercourse, history of any STD, years of diaphragm use, years of oral contraceptive use, smoking (tested)
Adam <sup>**</sup> (27)	Colposcopy clinic	1.1 (0.7–1.8)	Ever vs. never	Husband's social class, smoking, age at first birth, ever use of oral contraceptives, ever use of diaphragm
Syrjanen (16)	Outpatient OB/GYN university hospital	1.4 (0.7–2.9) <sup>‡</sup>	Yes vs. no <sup>  </sup>	Referral for Pap test result, age, race, high-risk HPV, pregnancies, smoking
Kataja <sup>††</sup> (26)	Communal health centers	1.8 (1.4–2.4)	Yes vs. no <sup>  </sup>	—
CIN II or III Ho (30)	Colposcopy clinics	0.3 (0.1–0.8)	Most/always vs. never	Pap smear result, no. of sex partners in past 2 years, age, intrauterine device, regular use of any contraception, hygiene, smoking, warts in partners, frequency of sex per week
CIN III vs. I <sup>††</sup>				Age, education, ethnicity, no. of Pap smears in last 3 years, oncogenic HPV type (significant)
Wang <sup>††</sup> (31)	Cervical cancer screening sites	0.3 (0.1–0.9)	Any use vs. none	Lifetime no. of partners, no. of partners in past 6 mo, age at first coitus, frequency of vaginal sex, douching after sex, current & past oral contraceptive use, no. of pregnancies (tested & not significant)
Adam <sup>**</sup> (27)	Colposcopy clinic	0.6 (0.4–0.9)	Ever vs. never	No. of sex partners, age at first sex, husband's frequency of visiting prostitutes, HPV infection, oral contraceptive use, ≥4 vaginal deliveries, ≥2 induced abortions
Ho (30)	Colposcopy clinic	0.7 (0.3–1.8)	Most/always vs. never	Referral for Pap test result, age, race, high-risk HPV, pregnancies, smoking
CIN II vs. I <sup>††</sup>				Age, education, ethnicity, no. of Pap smears in past 3 y, oncogenic HPV type (significant)
				Lifetime no. of partners, no. of partners in past 6 mo; age at first coitus; frequency of vaginal sex; douching after sex; current & past oral contraceptive use; no. of pregnancies (tested & not significant)

TABLE 2. Continued

Study*	Population Source	Risk Estimate (95% CI)	Condom Measure	Potential Confounders Examined in Analyses
Becker <sup>§§</sup> (29)	University maternal/infant care clinics	0.8 (0.5–1.3)	Ever vs. never	Age, age at first sex, lifetime no. of partners, ethnicity, HPV
Munoz <sup>††</sup> (28)	Hospitals, pathology labs, screening clinics (cases: Spain, Colombia)	0.8 (0.6–1.7)	Ever vs. never <sup>¶¶</sup> (husband's response)	Age, diagnostic center, no. of sex partners, age at first sex, HPV, chlamydia, no. of husband's sex partners (Spain)
	Family planning clinics (Spain) [controls]	0.8 (0.5–2.7)	Ever vs. never <sup>¶¶</sup> (husband's response)	Age, diagnostic center, no. of sex partners, age at first sex, HPV, chlamydia, smoking (Colombia)
	Screening clinics (Colombia) [controls]	1.2 (0.8–1.8)	Ever vs. never <sup>¶¶</sup>	Husband's social class, smoking, age at first birth, ever use of oral contraceptives, ever use of diaphragm
Zondervan <sup>¶¶</sup> (25)	Family planning clinics	0.2 (0.1–0.6)	Ever vs. never (husband's response)	Age, ever genital warts (significant - husband's characteristics)
Invasive cervical cancer Kjaer (33)	Monogamous women (1 or 2 lifetime partners)	0.5 (0.2–1.0)	Always/frequently vs. rarely/never (husband w/ prostitutes)	Male partner's no. of partners, visits to prostitutes, age at first sex, circumcision status, number of genital washes per month (not significant)
	Cancer registry (cases)	0.7 (0.5–1.2)	≥6 mo vs. <6 mo <sup>¶¶</sup>	Woman's age, center, husband's no. of partners, husband's no. of STD episodes
	General population (controls)	0.8 (0.3–2.0)	Ever vs. never <sup>¶¶</sup>	Age, years of education, church attendance, cigarette smoking, no. of sex partners of woman
Thomas (15)	Monogamous women whose husbands ever visited prostitutes	1.0 (0.6–1.5)	≥5 y vs. never <sup>¶¶</sup>	Husband's social class, smoking, age at first birth, ever use of oral contraceptives, ever use of diaphragm
Hospitals (cases & controls)	Cancer registry (cases)			Age, education, income, interval since last Pap, lifetime no. of partners, socioeconomic status
Stattery (32)	Cancer registry (cases)			
Zondervan <sup>¶¶</sup> (25)	RDD (controls)			
Hildesheim (34)	Family planning clinics			
	Hospitals (cases)			
	RDD (controls)			

\*First author (reference number).

<sup>†</sup>Outcome is defined as "HPV-suggestive infection" (n = 113), including (1) typical penile pattern of exophytic warts and/or typical flat lesions (44%), (2) aceto-white lesions without genital warts (48.6%), or (3) HPV positivity by PCR only (7.4%).

<sup>‡</sup>OR calculated from data presented in article.

<sup>§</sup>Relative risk. All other risk estimates presented are ORs.

<sup>¶</sup>Single study with three different outcomes: invasive cervical cancer (n = 33), carcinoma in situ (n = 121), and dysplasia (n = 159), by ICD-8 definitions. Ten controls per case from cohort of 17,032 (women with no cervical abnormalities), with the exception of 1 case of invasive cervical cancer for which only 1 control was available.

<sup>¶¶</sup>Condom use specified as a contraceptive method.

<sup>\*\*</sup>Single study with two different outcomes. Compared women with no lesions and no HPV DNA (n = 269) with women with CIN I (n = 161) and women with CIN II/III (n = 261). All diagnoses biopsy-confirmed.

<sup>††</sup>Biopsy-confirmed SIL. All women included as cases "had a clinically manifest HPV lesion, i.e., flat, inverted, or papillomatous condyloma, with or without concomitant cervical intraepithelial neoplasia."

<sup>¶¶</sup>Biopsy-confirmed CIN.

<sup>§§</sup>"High-grade dysplasia" defined as "moderate dysplasia/severe dysplasia/carcinoma in situ of the cervix," diagnosed on colposcopic examination (biopsy-confirmed). No detail given on number of subjects with moderate dysplasia, severe dysplasia, or carcinoma in situ.

(OR, 0.3; 95% CI, 0.2–0.5).<sup>17</sup> Investigators tested potential confounding factors, but none influenced the association. Among both men and women attending an STD clinic, reported condom use (always versus never) reduced the likelihood of genital warts by approximately 60% (OR<sub>adj</sub>, 0.4). Although 95% CIs were not presented for these estimates, the crude ORs with 95% CIs were similar to the adjusted estimates (men: crude OR of 0.3 and 95% CI of 0.2–0.4; women: crude OR of 0.6 and 95% CI of 0.4–0.9).<sup>13</sup>

#### Cervical HPV DNA

All six studies measuring HPV DNA detection as the outcome were conducted among women, and only one showed a statistically significant protective effect for condom use. Among Danish sex workers who reported always

using condoms with their commercial partners, those who also always used them with their private partners during the past 4 months were 80% less likely to have HPV DNA detected than those who never did (OR<sub>adj</sub>, 0.2; 95% CI, 0.1–0.6).<sup>23</sup>

The odds ratios for the four other cross-sectional studies assessing condom use and HPV DNA detection ranged from 0.8 to 1.6, with the exception of the study reported by Kjaer et al. Among a random sample of women from the general population of Denmark, those who reported current use of condoms were almost four times more likely to have a nononcogenic HPV type detected than women who reported never using condoms (OR<sub>adj</sub>, 3.8; 95% CI, 1.2–11.6).<sup>22</sup> A similar effect, but of lower magnitude, was reported for oncogenic HPV types (OR<sub>adj</sub>, 1.6; 95% CI, 0.8–3.3). Of the four remaining studies, only one showed a statistically sig-

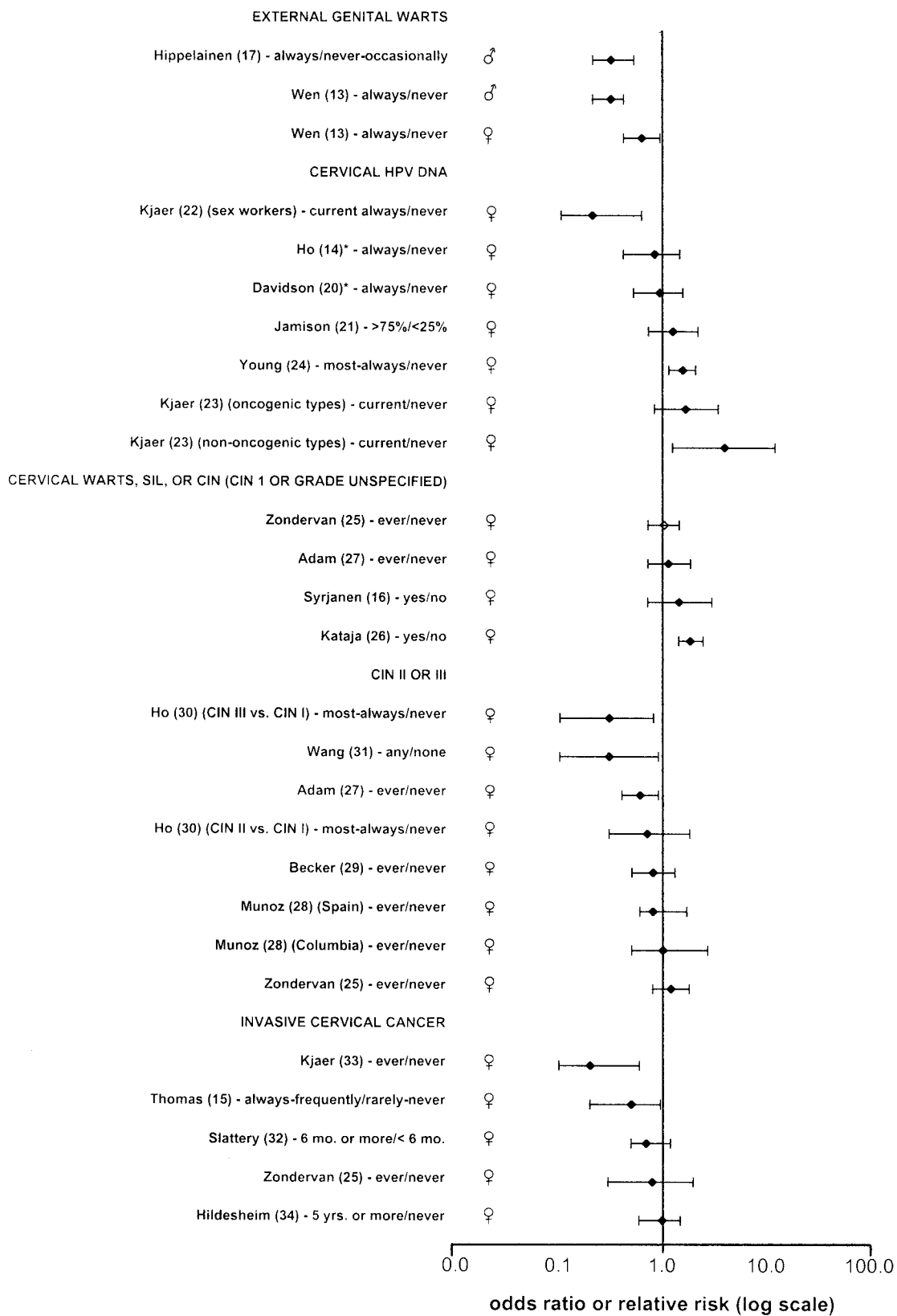


Fig. 1. Effect of condom use on prevention of external genital warts; detection of HPV DNA in cervical samples; cervical SIL, cervical warts, or CIN (grade I or unspecified); and CIN II/III and invasive cervical cancer. Asterisk indicates studies reporting relative risk estimates.

nificant elevated risk for HPV DNA detection among women who reported condom use. Young et al<sup>24</sup> found that women who reported using condoms “most of the time” or “always” were 50% more likely to have HPV DNA detected than those who reported never using condoms (OR<sub>adj</sub>, 1.5; 95% CI, 1.1–2.0). Among female adolescents, Jamison et al<sup>21</sup> found a slight, nonsignificant increase in risk of HPV DNA detection for women who used condoms >75% of the time in comparison with those who used them <25% of the time (OR, 1.2; 95% CI, 0.7–2.1). However, Davidson et al<sup>20</sup> reported virtually no effect among native Alaskan women (RR<sub>adj</sub>, 0.9; 95% CI 0.5–1.5).

In the sole cohort study, Ho et al<sup>14</sup> found that, compared with women who reported never using condoms, those who reported always using them were slightly less likely to become HPV DNA–positive, but the effect was not statistically significant (RR<sub>adj</sub>, 0.8; 95% CI, 0.4–1.4).

#### *Cervical Warts and SIL or CIN (Grade I or Unspecified)*

Four studies examined the effect of condom use among women in whom cervical SIL, cervical warts, CIN I, or CIN of an unspecified grade had been detected. In two of these studies there was no effect of condom use on CIN I (grade I or unspecified) after adjustment for confounding factors.<sup>25,27</sup> Zondervan et al<sup>25</sup> enrolled women attending family planning clinics and found no relationship between ever having used condoms (as a contraceptive method) and dysplasia (OR<sub>adj</sub>, 1.0; 95% CI, 0.7–1.4). Similarly, Adam et al<sup>27</sup> studied women referred to colposcopy clinics with abnormal Pap smears and found no association between ever using condoms and CIN I (OR<sub>adj</sub>, 1.1; 95% CI, 0.7–1.8).

In contrast, two Finnish studies reported increased risk of cervical SIL with condom use as a contraceptive method. Syrjanen et al<sup>16</sup> found a slight, nonsignificant increase in risk for women attending an outpatient OB/GYN unit who reported using condoms compared with those who did not (OR, 1.4; 95% CI, 0.7–2.9). Kataja et al<sup>26</sup> showed an 80% increased risk of SIL among women who reported using condoms (OR, 1.8; 95% CI, 1.4–2.4), but the final estimate was not adjusted for potential confounding factors, and cases were significantly younger than controls.

#### *CIN II or III*

Six studies assessed the relationship between condom use and CIN II or III. All of these studies adjusted for confounding factors, but no two studies adjusted for the same factors. Zondervan et al,<sup>25</sup> Munoz et al,<sup>28</sup> Becker et al,<sup>29</sup> Wang et al,<sup>31</sup> and Adam et al<sup>27</sup> compared women with either CIN II or III with women who had normal cervical cytology. Two of these investigative teams found a significant protective effect, yet three others reported no significant effect of condom use. Wang et al<sup>31</sup> interviewed women and their

husbands and determined that women attending cervical cancer screening sites who reported any use of condoms were 70% less likely to have CIN II or III than women who reported no use of condoms (OR<sub>adj</sub>, 0.3; 95% CI, 0.1–0.8). Adam et al<sup>27</sup> estimated that among women referred to colposcopy clinics for abnormal Pap smears, those who reported ever having used condoms were 40% less likely to have CIN II or III than those who had never used condoms (OR<sub>adj</sub>, 0.6; 95% CI, 0.4–0.9).

Becker et al<sup>29</sup> surveyed women attending university-based women’s and maternal/infant care clinics and found that, compared with women who had never used condoms, those who reported ever using condoms were slightly less likely to have high-grade lesions (OR<sub>adj</sub>, 0.8; 95% CI, 0.5–1.3). Munoz et al<sup>28</sup> conducted parallel studies in Spain and Colombia and interviewed women with and without CIN II or III and their husbands. In Spain a slight protective effect for condom use (ever versus never) was observed, although this was not statistically significant (OR<sub>adj</sub>, 0.8; 95% CI, 0.6–1.7). In Colombia, no relationship between condom use and CIN II or III was found (OR<sub>adj</sub>, 1.0; 95% CI, 0.5–2.7). A slightly elevated, nonsignificant risk of CIN II or III among women who had ever used condoms compared with those who had never used them (OR<sub>adj</sub>, 1.2; 95% CI, 0.8–1.8) was reported by Zondervan et al.<sup>25</sup>

In contrast to the above studies, which compared women with CIN II or III with women with no cervical pathology, Ho et al<sup>30</sup> enrolled only women with histologically confirmed CIN and compared those with CIN II or III with those with CIN I. Compared with women who reported never using condoms, those who reported using condoms most or all of the time were approximately 30% less likely to have CIN II (OR<sub>adj</sub>, 0.7; 95% CI, 0.3–1.8) and nearly 70% less likely to have CIN III (OR<sub>adj</sub>, 0.3; 95% CI, 0.1–0.8). However, the comparison for women with CIN II was not statistically significant.

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A further five studies evaluated condom use as a risk factor for ICC. Four of the five studies showed a range of protective effects for condom use, while the fifth showed no effect. None of the studies showed any increased risk.

Two studies revealed a significant protective effect for condom use. Kjaer et al<sup>33</sup> selected women with cervical cancer from the Danish Cancer Registry and compared them with women from the general population. The analysis was restricted to “monogamous women” (women with one or two lifetime sex partners), and data on condom use were collected from the husband. Women whose husbands had ever used condoms were 80% less likely to have cervical cancer than those whose husbands had never used condoms (OR<sub>adj</sub>, 0.2; 95% CI, 0.1–0.6). Thomas et al<sup>15</sup> also gathered data on the husband’s use of condoms and found a signifi-

icantly reduced risk for cervical cancer. Monogamous Thai women whose husbands always or frequently used condoms in their visits to prostitutes were 50% less likely to have cervical cancer than women whose husbands rarely or never used condoms with prostitutes (OR<sub>adj</sub>, 0.5; 95% CI, 0.2–1.0).

Slattery et al<sup>32</sup> studied women from the Utah Cancer registry and compared them with women selected by random-digit dialing who had not been diagnosed with cancer. Women who reported using condoms for 6 or more months were 30% less likely to have cervical cancer than women who had used them for less than 6 months (OR<sub>adj</sub>, 0.7; 95% CI, 0.5–1.2). Among women attending family planning clinics, Zondervan et al<sup>25</sup> found that ever using condoms was associated with a slight decreased risk (20%) of cervical cancer (OR<sub>adj</sub>, 0.8; 95% CI, 0.3–2.0). Hildesheim et al,<sup>34</sup> however, found no effect on risk of cervical cancer when comparing women who had used condoms as a contraceptive method for at least 5 years with those who had never used them (OR<sub>adj</sub>, 1.0; 95% CI, 0.6–1.5).

### Discussion

Condoms are known to be effective in preventing HIV among both men and women,<sup>6,35–37</sup> but data on their protective effect against other STDs are less consistent.<sup>11</sup> The studies included here represent the best available data describing the relationship between condoms and HPV-related conditions. Although the absence of nonpublished studies raises the question of publication bias, exclusive reference to the peer-reviewed literature ensures the highest quality of data. Nevertheless, it was difficult to compare results from these studies because of the variety of different measures of condom use and the numerous different outcomes. All of the studies we evaluated had at least one of two problems: (1) they were not designed to evaluate condom use and therefore did not include precise measures of consistent or correct usage and/or (2) the temporal sequence was not established.

Generally, condom use was asked about in the context of contraception and only of female subjects (rather than of their male partners, who are the actual users). Previous studies have shown that important modifiers of condom efficacy include measures of user experience such as frequency and consistency of use and correct coverage. Individuals who often use condoms report fewer problems with breakage or slippage than infrequent users,<sup>38,39</sup> yet even experienced users report episodes where problems (putting it on inside out, application after penetrative intercourse has begun, breakage, and slippage) resulted in potential transmission risk.<sup>40,41</sup>

Other investigators have determined that the level of reported condom use varies, depending on the type of sur-

vey questions used. “Always use” versus “never use” is a popular epidemiologic measure, because the exclusive categories clearly define opportunity for exposure to HPV. However, a comparative study determined that “always use” rarely covered use for more than a year,<sup>42</sup> which is inadequate for infections such as HPV that can be present for longer intervals before progressing to CIN II or III or ICC. The type of sex partner also determines the frequency of condom use, with condoms being more often used with new and casual partners than with regular partners.<sup>43</sup> However, questions regarding partner type were rarely posed in these studies: only one study included questions about condom use with prostitutes, and another asked commercial sex workers about use with clients and regular partners.

Temporal sequence is an important criterion in making causal inference, yet only one study<sup>14</sup> was designed to look at new acquisition of HPV. For all other studies, it was impossible to determine whether condoms were used before or after acquisition of HPV. Without determining that individuals began using condoms while they were still infection-free, it is impossible to accurately assess the role that condoms play in preventing new infections. However, it is possible (but unknown) that condom use with the same partner after acquisition of a new HPV infection might reduce the total amount of virus transmitted and the number of genital sites infected.

Despite design problems inherent in the studies available for review, some observations may be made. Although only two studies were conducted among men, both suggested good protection against development of external genital warts. The sole study of external genital warts among women also showed protection; however, the level of protection was somewhat lower among these women than among men included in the same study. The limited data on heterosexual men suggest that, compared with young men who do not always use condoms with vaginal intercourse, those who do may be less likely to develop external genital warts. The evidence among women for protection from external genital warts and other HPV-related conditions is less clear because it is based on only one study.

There was no consistent evidence of a protective effect of condom use on HPV DNA detection, and in some studies, condom use was associated with a slightly increased risk for these lesions. Only among Danish commercial sex workers was there a strong, statistically significant reduction in risk with report of condom use with private partners. The fact that these sex workers also reported always using condoms with their clients suggests that they were experienced users, and as has been reported following other studies of sex workers,<sup>44</sup> they may have been able to ensure their partners used condoms correctly and consistently.

The studies grouped together under the heading “cervical warts and SIL or CIN (grade I or unspecified)” represent a mixture of conditions that are often indicative of transient

infections. Therefore, this group may be composed of women who have a more recently acquired HPV infection. In the study by Kjaer et al, condom use was associated with a substantially increased risk of detecting nononcogenic HPV types. Common nononcogenic types are HPV 6 and 11, which are the same types associated with external genital warts. Kjaer et al also measured condom use as current versus never use. It may be that women opted to use condoms after noticing genital warts on their male partner. Because the virus was probably present before the warts appeared, condom use then may have begun after transmission had already occurred, thus giving the impression that condom use increased risk for the nononcogenic HPV types associated with genital warts. Alternatively, condoms may do little to protect against initial infection with HPV and subsequent transient conditions, a supposition that may be supported by the slightly increased risk seen for HPV DNA detection.

The individual odds ratios, and thus evidence of a protective role for condoms, varied for studies of CIN II or III. Two studies demonstrated a protective effect of 70% for condom use, four showed only slight protection (20–40%), and two showed either no effect or a slightly increased risk. Ho et al<sup>30</sup> showed a strong protective effect of condoms for CIN III (compared with CIN I). The effect was attenuated for CIN II, perhaps indicating the indistinct nature of CIN II as an intermediate category of cervical intraepithelial neoplasia. Whereas CIN III is a cervical cancer precursor lesion with a high probability of progression to invasion, CIN I appears to be the acute manifestation of cervical HPV infection and has a high likelihood of spontaneous resolution.<sup>45</sup>

Among the available data on condom use and prevention of cervical cancer is a hint that a subset of women was at least partially protected. Notably, the two studies that demonstrated a statistically significant protective effect of condoms against ICC were conducted among monogamous women and collected condom use data from the male sex partners of these women. This rigorous study design accounts for the sexual behavior of both partners and comes closer to approximating a true measure of condom use. Although the three other studies of ICC did not demonstrate statistically significant protective effects of condom use, they used less rigorous condom use definitions, and all but one demonstrated a small reduction in risk associated with condom use.

Some level of protection from HPV-related conditions was observed among 17 of the 27 populations studied; however, in most studies, protection was not substantial. It is unlikely that condoms offer the same level of protection against genital HPV infection as they do for HIV. These data suggest that condoms may prevent progression to lesions (warts, high-grade intraepithelial neoplasia), but per-

haps not actual infection by HPV. We hypothesize this may be due to a reduction in the amount of virus transmitted with condom use, which could decrease the probability of developing a clinical lesion.

The data also indicate that condoms may provide more protection for a susceptible man than for a susceptible woman. All studies that were conducted among men or incorporated data collected from men on condom use showed significant and substantial protective effects. Thus, it may be that susceptible men who use condoms are more likely to be protected from infectious women than the reverse. We hypothesize that, in the process of putting on a condom, an infected man may touch the shaft of the penis, transferring virus onto his fingertips and subsequently depositing it onto the exterior of the condom as he rolls it down the penis. He would then infect his susceptible female partner during intercourse through the same vehicle designed to protect her. Sonnex et al<sup>46</sup> showed that HPV DNA could be detected in fingertip samples from 64% of men with external genital warts. A susceptible man using condoms correctly and consistently might be better protected from an infectious woman because she would be less likely to contaminate the condom.

Complete protection from genital HPV infection may be impossible because infections may occur at epithelial sites not covered by the condom. Also, when condoms are used primarily for contraceptive purposes, the condom may not be put on until after external genital contact has occurred. The least protective estimates for cervical SIL, warts, CIN I, and ICC were from studies that evaluated condom use as a contraceptive method only.<sup>16,25,26,31,33</sup>

Due to the inclusion of inadequate measures of condom use and the lack of information on temporal sequence, it is not possible to use available data to draw definitive conclusions on the efficacy of condoms in the prevention of HPV-related conditions. With the potential for HPV vaccines on the horizon,<sup>47–49</sup> one may ask whether there is a need to collect more conclusive data. Based on what we currently know, the answer is yes. Even if an HPV vaccine becomes available within the next 10 years, the benefits of such a vaccine would not accrue for at least another 10 to 20 years. In addition, as HPV DNA testing becomes more widely used in the management of women with Pap smears showing borderline abnormalities, an increasing percentage of women will be told they have an HPV infection. Both men and women need accurate information on how they can protect themselves and their partners from transmitting or acquiring genital HPV infection.

As suggested in a report from the American College of Obstetricians and Gynecologists,<sup>5</sup> there is a need for studies expressly designed and powered to determine the degree to which condoms prevent acquisition of HPV infection or development of HPV-related sequelae. These studies must incor-

porate accurate measures of condom use (including correct and consistent use), and they must be designed to show a temporal sequence. Unfortunately, the ethical concern associated with randomizing individuals to not using condoms precludes the use of the most rigorous study design: a randomized controlled trial. Given the nature of sexually transmitted diseases, more partner studies similar to those conducted by Kjaer et al<sup>33</sup> and Thomas et al<sup>15</sup> are necessary to accurately measure condom use and sexual behavior among both members of the sexual partnership.

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