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Original article

Efficacy of a Carrageenan gel Against Transmission of Cervical HPV (CATCH): interim analysis of a randomized, double-blind, placebo-controlled, phase 2B trial

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ABSTRACT

Objectives: To evaluate the efficacy of a carrageenan-based lubricant gel in reducing the risk of genital human papillomavirus (HPV) infections in women.
Methods: We conducted a planned interim analysis of a randomized, double-blind, placebo-controlled, phase 2B trial. Women aged 18 years and older were randomly assigned (1:1) to a carrageenan-based gel or a placebo gel to be self-applied every other day for the first month and before and after each intercourse during follow-up. Assessments were performed at 0.5, 1, 3, 6, 9 and 12 months. The primary outcome was incidence of a new infection by an HPV type that was not present at baseline. Intention-to-treat analyses were performed.
Results: Between January 2013 and June 2017, a total of 280 participants were randomly assigned to the carrageenan ($n = 141$) or the placebo ($n = 139$) arm. All participants were included in safety analyses, but three (1%) were excluded from efficacy analyses (HPV results unavailable for two participants in the carrageenan and one participant in the placebo arm). The median follow-up time was 9.2 months (interquartile range, 1.9–13.2 months). A total of 59 (42%) of 139 participants in the carrageenan arm and 78 (57%) of 138 participants in the placebo arm became infected by at least one new HPV type (hazard ratio = 0.64, 95% confidence interval = 0.45–0.89, p 0.009). A total of 62 (44%) of 141 participants in the carrageenan arm versus 43 (31%) of 139 participants in the placebo arm reported an adverse event (p 0.02), none of which was deemed related to the gels.
Conclusions: Our trial's interim analysis suggests that using a carrageenan-based lubricant gel can reduce the risk of genital HPV infections in women. **S. Magnan, Clin Microbiol Infect 2019;25:210**

Introduction

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in women worldwide, with 528 000 estimated new cases and 265 700 estimated deaths in 2012 [1]. Virtually all cases of cervical cancer are caused by human papillomavirus (HPV) infection [2,3]. HPV is the most common sexually transmitted infection in the world, and most sexually active individuals will be infected by HPV at some point during their lifetime [4]. Although the majority of infections will clear within 2 years without any symptoms [5], others can lead to the development of clinical lesions such as warts or anogenital and oral cancers [6–8].

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Universal vaccination of preteen girls is a highly effective intervention against HPV infection and its clinical consequences [9,10]. However, this intervention has important limitations: it only protects against specific HPV types, it is exclusively prophylactic (i.e. only effective in previously uninfected women) and it is too expensive for developing countries, which bear the heaviest burden of HPV and cervical cancer [11,12]. Aside from vaccination, there is currently no other effective intervention against HPV infection.

Carrageenan, an anionic polymer extracted from red algae, has been identified as a potent HPV infection inhibitor in preclinical studies [13–17]. This molecule is widely used as a thickener in many commercially available cosmetic and food products, including personal lubricants. Previous safety and acceptability trials of lubricants containing carrageenan reported that they were safe and well received [18–21]. These results supported clinical efficacy testing.

We conducted a phase 2B trial to assess the efficacy of a carrageenan-based lubricant gel in reducing genital HPV incidence and prevalence among sexually active women. We also aimed to evaluate safety and acceptability of the gel as well as adherence. We report here the planned interim analysis of the first primary outcome: incidence of a new HPV infection.

Methods

Study design

The Carrageenan gel Against Transmission of Cervical HPV (CATCH) study is a randomized, double-blind, placebo-controlled, phase 2B trial conducted in three outpatient clinics in the greater Montreal area, Canada. The study complied with the Guideline for Good Clinical Practice and regulatory requirements of Natural Health Product Directorate and Health Canada. Ethical approval was obtained from institutional review boards at participating centres (McGill University, Concordia University, Université de Montréal and CLSC Samuel-de-Champlain). This trial is registered with ISRCTN (http://www.isrctn.com/, ISRCTN96104919).

Participants

Women aged 18 years and older (the initial 40-year upper limit was abolished because of recruitment issues) were recruited through advertisements displayed in colleges, universities and venues frequented by students in Montreal and on social media. Participants were eligible if they (a) had an intact uterus, (b) had vaginal sex with a male partner in the last 3 months, (c) were expecting to have vaginal intercourses in the next 3 months with the same or different male partners and (d) were not currently in a relationship for longer than 6 months. Exclusion criteria were having a history of cervical lesions, cancer or genital warts; being HIV positive; being pregnant or currently breast-feeding; having had a pregnancy, abortion or genital surgery in the last 6 weeks; and having a known allergy or hypersensitivity to any lubricant or component of the study gels. All participants provided written informed consent.

Randomization and masking

Research nurses enrolled participants onto the trial. Participants were randomly assigned (1:1) to either the carrageenan-based or placebo gel as per a computer-generated concealed sequence using a block size of eight. Both gels were clear, odourless and tasteless, were of similar viscosity and were bottled in identical containers. To minimize the risk of unblinding, eight different product codes were used (four for each gel). Randomization and product code assignment was done via an online administration platform. Participants, nurses, laboratory staff and investigators were masked to group allocation.

Intervention

Participants were asked to self-apply the gel every other day for the first month and before each intercourse during the study period. Added in October 2015, they were also asked to apply the gel after each intercourse as per recent research findings suggesting that this might provide better protection [15]. They were instructed by a research nurse who followed a standardized protocol to apply the gel (at least 10 mL) inside their vagina and on their genital area using their fingers or an applicator. The carrageenan-based and placebo gels are manufactured in a US Food and Drug Administration good manufacturing processes–compliant facility (Carra-Shields Lab, St Petersburg, FL, USA).

Outcomes and procedures

The first primary outcome was the incidence of a newly detected infection by an HPV type that was not present at baseline. The second primary outcome was clearance of HPV types observed at baseline. Visits with a research nurse were scheduled at enrolment and 0.5, 1, 3, 6, 9 and 12 months. Sociodemographic, behavioural and sexual history data were collected using computer-assisted self-administered questionnaires. HPV testing was performed on vaginal samples that were self-collected as per a validated protocol [22]. HPV detection and genotyping of 36 genital HPV types was performed with Roche's linear array PCR assay (Roche, Basel, Switzerland). Types were analysed separately but also according to phylogenetic grouping based on tissue tropism and oncogenicity: alphapapillomavirus subgenus 1 (low oncogenic risk: HPVs 6, 11, 40, 42, 44, 54), subgenus 2 (high and intermediate oncogenic risk: HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82) and subgenus 3 (commensal types: HPVs 61, 62, 71, 72, 81, 83, 84, 89) [23–25]. Participants were asked to abstain from oral sex, vaginal intercourse and gel use 48 hours before a visit. Previous investigations have shown that carrageenan does not interfere with HPV detection and genotyping [14].

Secondary outcomes were adherence to the intervention and safety/acceptability of the gels. In addition to self-administered questionnaires completed at each visit, participants were asked to fill in an electronic calendar on their daily sexual activities as well as condom and gel use. They also had the opportunity to report any adverse event at any time using this calendar. Research nurses were automatically notified via e-mail when a participant reported an adverse event, and an appointment with the study physician (PPT) was scheduled if needed. The Female Genital Grading Table for Use in Microbicide Studies [26] was used for the reporting and grading of adverse events.

To validate the vaccination history, we e-mailed all participants and asked for a proof of vaccination when applicable. This validation procedure was subsequently adopted for all women reporting having been vaccinated at the screening interview.

Statistical analysis

On the basis of previous studies involving similar populations [5,27], we assumed a 50% prevalence of HPV infections at baseline as well as a 20% cumulative incidence and a 40% clearance in the placebo group at 12 months. Using the method of Dupont and Plummer [28], we calculated that a total of 465 participants were required to detect a 50% difference in incidence (and 388 to detect a

50% difference in clearance) with 80% power using a two-sided significance level of 0.05 and assuming losses to follow-up of 10%. An interim analysis was planned for the time the study reached about 50% of the target sample size. A Data Safety and Monitoring Committee and a Steering Committee oversaw the study.

Only the first primary outcome (incidence) was analysed in this interim analysis. Analyses were done by intention to treat. We estimated hazard ratios (HR) and 95% confidence intervals (CIs) using univariate Cox models for the first occurrence of a new infection in each participant. We also computed two different models taking into account correlated data and considering all new HPV types acquired by each participant throughout follow-up. The first (model 1) was a Cox model stratified by HPV types and clustered by participants; the second (model 2) was a mixed-effect survival-time model considering an exponential distribution and a random effect for participants.

A priori subgroup analyses considering only the first occurrence of a new infection were performed according to the main baseline characteristics and to cumulative compliance to gel use before intercourse at the time of failure or censoring. A *post hoc* sensitivity analysis was conducted on the data of participants who validated their vaccination status by e-mail. All statistical analyses were performed using Stata 14.2 (StataCorp, College Station, TX, USA).

Results

Between 16 January 2013 and 9 June 2017, a total of 280 women were randomly assigned to the carrageenan (n = 141) or placebo (n = 139) arm (Fig. 1). All participants received the allocated intervention. All participants were included in the safety analysis, but two participants in the carrageenan arm and one in the placebo arm were excluded from the efficacy analysis because their HPV results were not available at the time of interim analysis.

Participants' baseline and follow-up characteristics were similar between arms (Table 1 and Supplementary Fig. S1). The median follow-up time for the whole cohort was 9.2 months (interquartile range, 2.6–13.2 months). More individuals were infected by multiple HPV types (coinfection) in the placebo arm (n = 56, 40.3%) than in the carrageenan arm (n = 42, 29.8%), but this difference did not reach statistical significance (p 0.28). Detailed HPV prevalence data are shown in Supplementary Tables S1 and S2. Overall, 117 (41.8%) participants reported having been vaccinated: 80 (68.4%) with the quadrivalent vaccine, two (1.7%) with a mix of the quadrivalent and the nonavalent vaccines and 35 (29.9%) could not remember the vaccine name. Ninety-nine participants (35.4%) confirmed their vaccination status by e-mail. Of these, 15 changed the answer they gave in the enrolment questionnaire. At the interim analysis closing date, 98 (35.0%) of the 280 participants completed all seven visits: 51 in the carrageenan and 47 in the placebo arm (Supplementary Fig. S1).

Fig. 2 shows the cumulative incidence of newly detected HPV infections for both arms. A total of 137 participants acquired at least one HPV type: 59 (41.8%) in the carrageenan and 78 (56.1%) in the placebo arm. The HR for the first occurrence of a new infection was 0.64 (95% CI = 0.45–0.89, p 0.009) (Fig. 2a). When considering all new HPV types acquired by each participant (not only the first infection), 139 infections occurred in the carrageenan versus 198 in the placebo arm (rate ratio = 0.68, 95% CI = 0.55–0.85, p 0.0007). Fig. 2b shows the cumulative incidence of all new HPV types by arm. When accounting for the correlated data structure and multiplicity of HPV types, the HRs were 0.66 (95% CI = 0.46–0.93, p 0.02) for model 1 and 0.60 (95% CI = 0.39–0.94, p 0.03) for model 2.

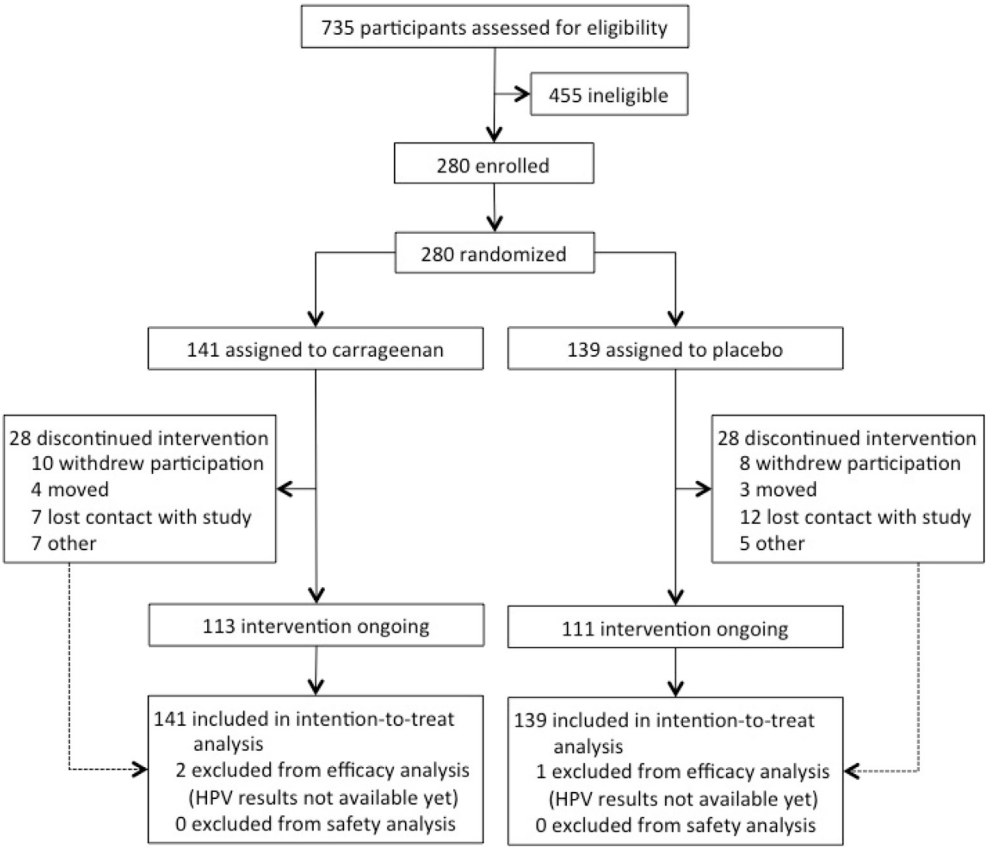

Fig. 1. Trial profile design and participant allocation.

Table 1
Baseline and follow-up characteristics of participants

Characteristic	Carrageenan (n = 141)	Placebo (n = 139)
Age (years)		
Mean (SD)	24.6 (5.8)	23.4 (4.7)
Median (IQR)	23.0 (20.4–27.0)	22.2 (19.9–25.2)
Missing, n (%)	0	0
Ethnicity, n (%)		
French Canadian	29 (20.6%)	33 (23.7%)
English Canadian	38 (27.0%)	43 (30.9%)
Black Canadian	11 (7.8%)	9 (6.5%)
Latin American	13 (9.2%)	13 (9.4%)
East Asian	9 (6.4%)	14 (10.1%)
Other	37 (26.2%)	25 (18.0%)
Missing	4 (2.8%)	2 (1.4%)
Marital status, n (%)		
Single	91 (64.5%)	97 (69.8%)
Living with a partner	12 (8.5%)	14 (10.1%)
Married	3 (2.1%)	1 (0.7%)
Divorced/separated/widowed	35 (24.8%)	27 (19.4%)
Missing	0	0
Smoking status, n (%)		
Never	96 (68.1%)	78 (56.1%)
Past	33 (23.4%)	40 (28.8%)
Current	12 (8.5%)	20 (14.4%)
Missing	0	1 (0.7%)
Age at first intercourse (years)		
Mean (SD)	17.5 (3.1)	16.9 (2.5)
Median (IQR)	17 (16–19)	17 (16–18)
Missing, n (%)	3 (2.1%)	3 (2.2%)
No. of lifetime sex partners, n (%)		
1–3	32 (22.7%)	30 (21.6%)
4–6	32 (22.7%)	19 (13.7%)
7–10	26 (18.4%)	32 (23.0%)
11–20	25 (17.7%)	31 (22.3%)
>20	26 (18.4%)	27 (19.4%)
Missing	0	0
No. of sex partners in last month, n (%)		
0	29 (20.6%)	24 (17.3%)
1	87 (61.7%)	85 (61.2%)
≥2	25 (17.7%)	30 (21.6%)
Missing	0	0
HPV DNA status, n (%)		
Negative	72 (51.1%)	58 (41.7%)
Monoinfection	25 (17.7%)	24 (17.3%)
Coinfection	42 (29.8%)	56 (40.3%)
Missing PCR results[a]	2 (1.4%)	1 (0.7%)
Subgenus 1[b]	16 (11.4%)	29 (20.9%)
Subgenus 2[c]	57 (40.4%)	64 (46.0%)
Subgenus 3[d]	29 (20.6%)	45 (32.4%)
Vaccination status, n (%)		
Yes	54 (38.9%)	63 (45.7%)
No	80 (57.6%)	74 (53.6%)
Missing	5 (3.6%)	1 (0.7%)
Validated vaccination status, n (%)		
Yes	15 (10.8%)	16 (11.6%)
No	35 (25.2%)	33 (23.9%)
Missing	89 (64.0%)	89 (64.5%)
Follow-up time (months)		
Mean (SD)	8.5 (6.0)	8.4 (5.8)
Median (IQR)	8.8 (2.6–13.7)	9.8 (2.6–13.0)
No. of visits per woman, n		
Mean (SD)	4.9 (2.0)	5.1 (1.9)
Median (IQR)	5 (3–7)	6 (3–7)

[a] Missing results correspond to vaginal samples that were collected but not yet analysed by laboratory.
[b] Subgenus 1 group includes HPVs 6, 11, 40, 42, 44 and 54.
[c] Subgenus 2 group includes HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82.
[d] Subgenus 3 group includes HPVs 61, 62, 71, 72, 81, 83, 84 and 89.

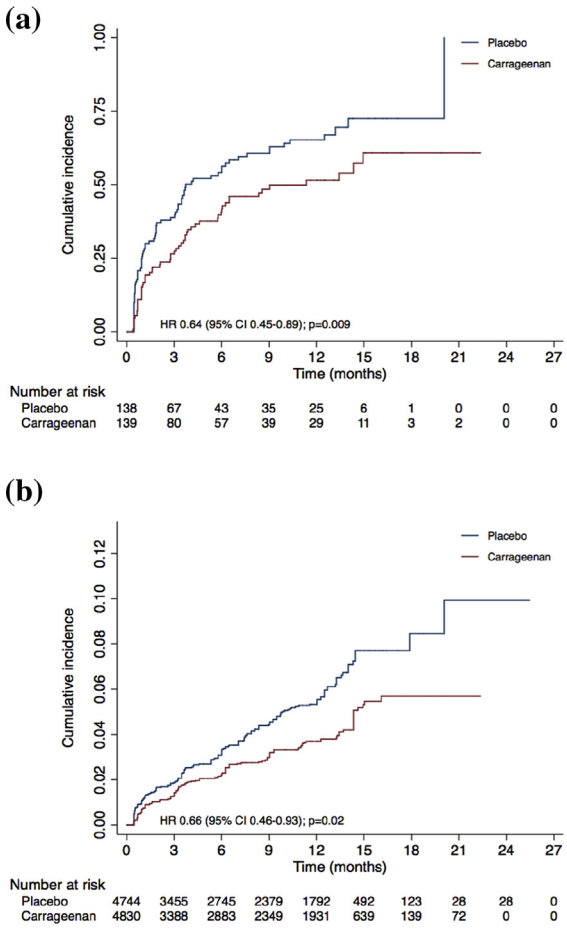

Fig. 2. Cumulative incidence of new HPV infections by arm. Cumulative incidence of (a) first new HPV infection and (b) all new HPV infections. Numbers at risk for (b) correspond to number of HPV types that participants could have potentially acquired at each time point, i.e. 36 HPV types tested multiplied by number of participants at time point minus HPV types positive at baseline for these participants. HPV, human papillomavirus.

The actuarial mean time to a first infection was significantly greater in the carrageenan than in the placebo arm (Table 2). When restricting to the participants who acquired a first episode (arithmetic mean), the differences in time to acquisition were small and nonsignificant. A lower incidence of new HPV infection was consistently observed for all alphapapillomavirus subgenera. The reduction was significant for subgenus 1 (HR = 0.47, 95% CI = 0.24–0.89) and subgenus 2 (HR = 0.64, 95% CI = 0.44–0.94).

The results favouring the intervention were consistent across all subgroups except for self-reported vaccination (Fig. 3). However, there was no indication of heterogeneity of effects when stratifying by validated vaccination status. There was no indication of a dose–response relationship with the estimated cumulative compliance.

Overall, 258 adverse events were reported by 105 (37.5%) of the 280 participants (Supplementary Table S3). More participants reported an adverse event in the carrageenan than in the placebo arm (Table 3). However, none of these adverse events was deemed related to the gels by the study physician, who was blinded to group allocation. No participant withdrew or was withdrawn from the study because of an adverse event.

Discussion

This is the first trial designed to evaluate the efficacy of a carrageenan-based gel in reducing the risk of genital HPV infections in women. In this interim analysis, the use of a carrageenan-based gel was associated with a 36% protective effect compared to the use

Table 2
Incidence of and average time to new HPV infection by study arm[a]

HPV type	Carrageenan				Placebo				Comparison	
	Incident cases	Actuarial mean (95% CI)	Arithmetic mean (95% CI)	Median (95% CI)	Incident cases	Actuarial mean (95% CI)	Arithmetic mean (95% CI)	Median (95% CI)	Hazard ratio (95% CI)	p
Any HPV type	59	11.8[b] (10.0–13.7)	3.5 (2.6–4.5)	11.3 (6.0–)[c]	78	8.3 (6.8–9.9)	3.1 (2.3–4.0)	3.7 (3.2–7.1)	0.64 (0.45–0.89)	0.009
Subgenus 1[d]	14	19.7[b] (18.4–21.0)	5.1 (2.5–7.7)	NR	27	15.3[b] (13.7–16.8)	4.8 (3.0–6.6)	NR	0.47 (0.24–0.89)	0.02
Subgenus 2[e]	47	13.8[b] (12.0–15.7)	4.0 (2.8–5.2)	14.9 (9.3–)[c]	64	10.4 (8.8–12.0)	3.7 (2.6–4.7)	9.0 (5.8–14.0)	0.64 (0.44–0.94)	0.02
Subgenus 3[f]	29	17.0[b] (15.3–18.6)	4.2 (2.7–5.8)	NR	39	13.7[b] (12.1–15.2)	4.8 (3.4–6.2)	NR	0.69 (0.42–1.11)	0.15

CI, confidence interval; HPV, human papillomavirus; NR, not reached.
[a] Actuarial mean, arithmetic mean and median time to incident infection from baseline are in months. Actuarial mean takes into account censoring, while arithmetic mean is restricted to complete observations, i.e. those who had a documented episode of a new type.
[b] Mean is underestimated because largest observed analysis time is censored.
[c] Upper confidence limit could not be determined because survival function never falls below 0.5.
[d] Subgenus 1 group includes HPVs 6, 11, 40, 42, 44 and 54.
[e] Subgenus 2 group includes HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82.
[f] Subgenus 3 group includes HPVs 61, 62, 71, 72, 81, 83, 84 and 89.

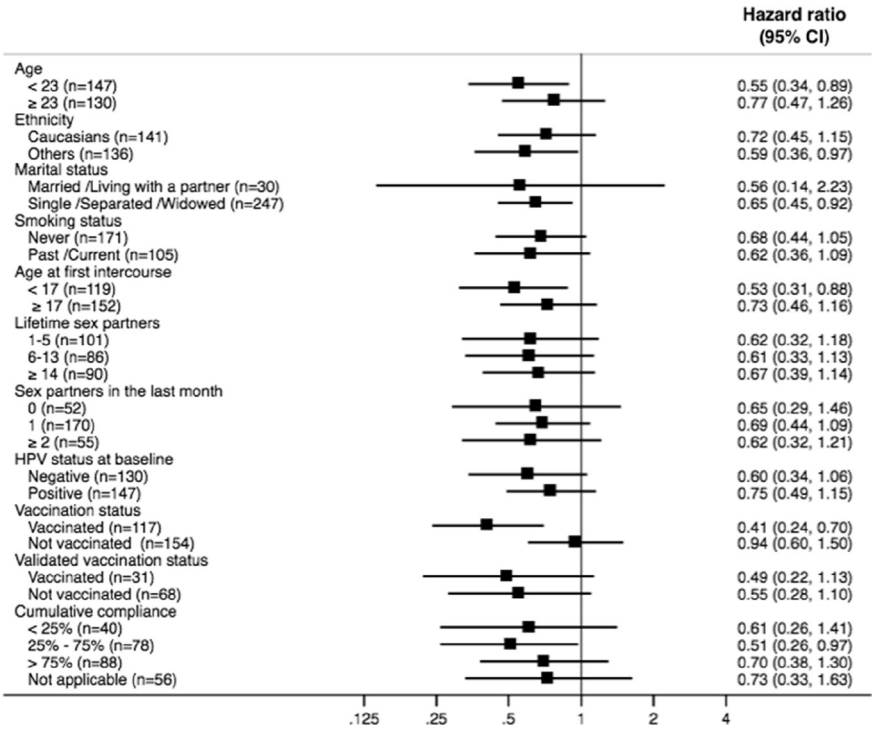

Fig. 3. Subgroup analyses. Cumulative compliance to gel use is calculated from enrolment to time of failure or censoring. 'Not applicable' corresponds to participants who reported no intercourse between enrolment and time of failure or censoring.

Table 3
Adverse events

Adverse event	Carrageenan ($n = 141$)	Placebo ($n = 139$)	p[a]
Any	62 (44.0%)	43 (30.9%)	0.02
Unusually painful or heavy period	0	3 (2.2%)	0.08
Vaginal bleeding in between menstrual periods	3 (2.1%)	4 (2.9%)	0.69
Pain during vaginal sex	8 (5.7%)	2 (1.4%)	0.06
Unusual vaginal discharge	8 (5.7%)	2 (1.4%)	0.06
Itching, burning or pain in genital area	16 (11.3%)	11 (7.9%)	0.33
Genital sore/ulcer	1 (0.7%)	2 (1.4%)	0.55
Needing to urinate more often than usual	1 (0.7%)	3 (2.2%)	0.31
Pain while urinating	4 (2.8%)	1 (0.7%)	0.18
Blood in urine	3 (2.1%)	1 (0.7%)	0.32
Lower abdominal pain	2 (1.4%)	0	0.16
Lower back pain	0	0	—
Other	16 (11.3%)	14 (10.1%)	0.73

[a] By *z* test.

of a placebo gel. The protective effect was observed for both low- and high-risk HPV types, and the gel appeared to be safe.

Our results for the incidence of new HPV infections are in accordance with initial observations in preclinical studies [13–17]. Carrageenan was first identified as a potent HPV infection inhibitor in an *in vitro* microbicide study [13]. Carrageenan is a sulphated polysaccharide that is widely used in the food and cosmetic industries for its thickening and stabilizing properties. Its structure is similar to heparan sulphate, an HPV cell-attachment factor, which allows it to bind directly to the HPV virus capsid. It thus prevents HPV infection by precluding the attachment of the virion to cell-surface receptors. In the aforementioned study [13], several commercially available lubricants containing carrageenan exhibited significant inhibition at dilutions up to 10^6-fold. These findings were later confirmed in two animal studies [16,17] and one *ex vivo* study [14]. In our study, carrageenan showed activity against all HPV types tested irrespective of taxonomic grouping, which is

consistent with what has been observed in preclinical studies and with the proposed mechanism of action of carrageenan.

We chose to publish this interim analysis given the observed appreciable effect size of the intervention. Our decision was approved by the Data Safety and Monitoring Committee on the basis of the potential for these interim findings to prompt other investigations in different populations. Although results may fluctuate with more participants enrolled and a longer follow-up time, interim analyses tend to be confirmed by final analyses in most randomized controlled trials [29].

Although considerable, the effect size observed in our study was smaller than what we expected on the basis of preclinical studies. However, preclinical findings often translate into smaller effect sizes in clinical settings, which are much less controlled environments. In a clinical trial, participants' full compliance to the intervention is not guaranteed. Although by design CATCH study participants were at high risk of HPV exposure, we do not know the actual proportion of participants who were exposed to new HPV types during follow-up. Nevertheless, owing to randomization, exposure to HPV can be assumed to be comparable between arms. However, there may have been a difference in the risk of being infected by a new HPV type because there were more coinfections at baseline in the placebo than in the carrageenan arm, although this difference was not statistically significant. If more participants in the placebo arm were in fact not at risk of acquiring a new HPV infection because they were already infected by all the types to which they were exposed during follow-up, this could have biased the estimate towards the null.

Our results are partially in agreement with those of a *post hoc* substudy of a randomized, double-blind, placebo-controlled trial conducted in South Africa that was originally designed to assess the efficacy of a carrageenan-based gel in reducing the risk of HIV infection in women [30]. In this substudy, carrageenan was associated with a 38% protective effect, but only among the most compliant participants. In our study, a higher compliance was not associated with a higher protective effect. However, our exploratory analysis considered only compliance to gel use before intercourse. Other components such as gel use after intercourse and every other day for the first month as well as potential confounders of the relationship between compliance and incidence of HPV infections were not taken into account. A more thorough analysis of compliance will be reported in a subsequent publication.

The number of adverse events reported by participants was surprisingly high. However, none was attributed to the gels, and no participant withdrew from the study because of an adverse event. We believe that the high number of opportunities that participants had to report any noticeable change through the daily electronic calendar (257 days (mean follow-up) $\times$ 280 participants $=$ 71 960 opportunities) could partly explain the high number of events reported. There were also more adverse events in the carrageenan than in the placebo arm, which is in disagreement with previous safety studies that reported no association between carrageenan and any abnormal genital findings and/or change in vaginal flora [18–21]. In these studies, adverse events were mostly mild, not attributed to gel use and comparable between arms.

Considering the theoretical mechanism of action of carrageenan, we have no reason to believe that it would work differently depending on any physical, social or psychologic characteristic. However, our population (mainly composed of students) may not be representative of the general population, and generalization should be done with caution. Personal and/or social acceptability of the gel as well as compliance to its use could potentially limit its benefits.

Although our study is based on interim analysis, the findings to date suggest that the use of a carrageenan-based lubricant gel can reduce the risk of genital HPV infections of both low and high oncogenic risk in women. If confirmed upon final analysis, a carrageenan-based gel could be a useful adjunct to prophylactic HPV vaccines and a more affordable alternative for developing countries.

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Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.04.012.

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