Colposcopy referral rates post-introduction of primary screening with human papillomavirus testing: evidence from a large British Columbia cohort study

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Summary

Background Shifting from cytology to human papillomavirus (HPV)-based cervical cancer screening will initially increase colposcopy referrals. The anticipated impact on health systems has been raised as a concern for implementation. It is unclear if the higher rate of colposcopy referrals is sustained after initial HPV-based screens or reverts to new lower baselines due to earlier detection and treatment of precancer. This study aimed to investigate long-term rates of colposcopy referrals after participation in HPV-based screening.

Methods Participants of HPV for Cervical Cancer Screening trial (HPV FOCAL) received one (HPV1, N = 6204) or two (HPV2, N = 9540) HPV-based screens. After exit, they returned to British Columbia's (BC) cytology screening program. A comparison cohort from the BC screening population (BCS, N = 1,140,745) was identified, mirroring trial inclusion criteria. All participants were followed for 10–14 years through the provincial screening registry. Colposcopy referral rates per 1000 screens were calculated for each group. Trial colposcopy referrals for HPV1 and HPV2 were calculated under two referral scenarios: (1) all HPV positive referred to colposcopy; (2) cytology triage with ASCUS or greater referred to colposcopy. Colposcopy referrals from post-trial screens in HPV1 an HPV2 and all screens in BCS were based on actual recommendations from the screening program. A multivariable flexible survival regression model compared hazard ratios (HR) throughout follow-up.

Findings Scenario 2 referral rates were higher during initial HPV screen(s) vs cytology screen (HPV1: 28 per 1000 screens (95% CI: 24, 33), HPV2: 32 per 1000 screens (95% CI: 29, 36), BCS: 8 per 1000 screens (95% CI: 8.9)). However, post-trial rates in HPV1 and HPV2 were significantly lower than in BCS. Cumulative rates in HPV1 and HPV2 approached the cumulative rate in BCS 11–12 years after HPV-based screening (HPV1: 11 per 1000 screens (95% CI: 10, 12), HPV2: 16 per 1000 screens (95% CI: 15–17), BCS: 11 per 1000 screens (95% CI: 10, 11)). Adjusted models demonstrated reductions in referral rates in HPV1 (HR = 0.6, 95% CI: 0.5, 0.7) and HPV2 (HR = 0.7, 95% CI: 0.6, 0.8) relative to BCS by 54 and 72 months post-final HPV screen respectively.

Interpretation Reduced colposcopy referral rates were observed after initial rounds of HPV-based screening. After initial HPV screening, referral rates to colposcopy after cytology triage were below the current rates seen in a centralized cytology program after approximately four years. Any expected increase in referrals at initiation of HPV-based screening could be countered by staged program implementation.

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Research in context

Evidence before this study

Randomized controlled trials and observational studies have confirmed that HPV-based cervix screening detects cervical precancer better than cytology, however, due to its increase sensitivity, the implementation of an initial round of HPV-based cervix screening increases referrals to colposcopy. Concerns about overwhelming heath systems with colposcopy referrals has been a barrier to implementation across many jurisdictions, however there is no evidence about colposcopy referral rates after the initial round of HPV-based screening, which would be expected to decrease significantly due to improved detection of precancer in the initial round of screening. A non-systematic literature review was conducted through PubMed to examine existing research on rates of colposcopy referrals after introduction of HPV-based cervix screening. At the time of publication, a PubMed search using the key words "colposcopy referrals HPV-based cervix screening" returned 10 results, which primarily reported a sharp increase in colposcopy referrals after an initial round of HPV-based screening in cohorts that were previously screened with cytology. To reduce the increase in referrals, triage strategies, such as increased screening interval length and partial genotyping, were suggested, but no articles investigated colposcopy rates after the initial rounds of HPV-based screening, as these data were not yet available. We further reviewed data from jurisdictions that have implemented HPV-based cervix screening in their organized screening programs, which reported increases in colposcopy referrals upon implementation of the first round. However, no organized screening program has used HPV-based screening for long enough to have data from a second round of screening.

Added value of this study

This study provides quality real-world data suggesting that colposcopy referral rates will decline after subsequent rounds of HPV-based cervix screening. We used data from the HPV FOCAL trial, which compared HPV-based cervix screening to cytology, and actual cervical screening results from the BC Cervix Screening Program Registry, which administers cytology-based cervix screening to eligible populations throughout British Columbia, Canada, to investigate longitudinal colposcopy referral rates after initial rounds of HPV-based screening.

We found that after one or two rounds of HPV-based screening in HPV FOCAL, women who completed the study and were then returned in the provincial organized screening program with cytology based testing had about half the rate of colposcopy referral as those who never had HPV-based screening. Furthermore, 10-year cumulative colposcopy referral rates, including those colposcopy referrals related to HPV-based screening, were similar across the populations who did and did not have HPV-based screening, despite the increase in referrals seen at initial rounds of HPV-based screening.

Implications of all the available evidence

The evidence from this study suggests that (1) the increase in colposcopy referrals rates seen at the introduction of HPV-based screening is not sustained; in fact referrals dropped well below the rates seen in the general population of cytology-based screening after initial rounds of HPV-based screening; and (2) over time, the increase in referrals seen at initial rounds of HPV-based screening will even out due to lower colposcopy referral rates with subsequent screening. This implies that with thoughtful programmatic HPV-based cervix screening implementation, such as introduction of structured birth year screening, the initially higher colposcopy referral rates can be managed so that healthcare systems are not overwhelmed.

The results from this study add to earlier work demonstrating that HPV-based cervix screening outperforms cytology in the detection of cervical precancer. When combined with triage strategies that mitigate the potential for overtreatment, these findings should assuage concerns about the implementation of HPV-based cervix screening.

Introduction

The WHO recently announced a global call for the elimination of cervical cancer.[1] While cytology-based cervical cancer screening remains the standard of care across most high-income countries,[2,3] many organised screening programs are transitioning to high-risk human papillomavirus (HPV)-based screening at extended intervals[4–6] to accelerate this goal. HPV-based screening is more sensitive than cytology to detect cervical pre-cancer, otherwise known as cervical intraepithelial neoplasia grade 2 (CIN2) or grade 3 (CIN3).[7–9] However, it is less specific than cytology[7,8,10]; the vast majority of HPV infections will resolve on their own without progressing to pre-cancer or invasive cancer.[11,12] Due to increased sensitivity and reduced specificity of HPV-based screening, a shift from cytology to HPV-based screening will initially raise colposcopy referral rates,[11] potentially putting a strain on the healthcare system by increasing wait times and healthcare costs and increasing psychological stress for those undergoing colposcopy.[7,10,13–15]

The HPV FOr cerviCAL Cancer Screening Trial (HPV FOCAL),[8,16] a randomised controlled trial based in British Columbia (BC), Canada comparing HPV-based screening to liquid-based cytology screening (LBC), found higher colposcopy referral rates in the initial round of HPV-based screening compared to LBC, but this led to earlier and more accurate detection of CIN2 or greater (CIN2+) in the HPV arm.[8] Australia and the Netherlands, who have recently implemented primary HPV-based screening, had over twice the number of colposcopy referrals in the first round of HPV-based screening as they did with the cytology-based approach.[4,17–19] However, it is unclear if increased colposcopy referral rates persist past initial rounds of HPV screening, when both incident and prevalent infections are detected, or if rates will subsequently decrease when HPV-based screening reaches a steady state, due to the earlier detection of pre-cancerous lesions, which once treated, have a low risk of recurrence.

No jurisdiction that has adopted HPV-based screening has implemented it long enough for women and individuals with a cervix[20] to have undergone multiple rounds of HPV-based screening. However, analyses from the HPV FOCAL trial showed that by the second round of HPV-based screening, colposcopy referral rates decreased significantly, although were still higher than that seen in the general screening population.[21] Furthermore, while findings from the New Technologies for Cervical Cancer (NTCC)[22] screening study suggested that, without triage, HPV-based screening could lead to over referral to colposcopy and treatment of regressive lesions, results from the POpulation-Based SCreening study AMsterdam (POBASCAM)[23] trial suggest that, with appropriate triage strategies, the additional lesions detected by referral to colposcopy from HPV-based screening are clinically relevant. In addition, a recent modeling study from Wales suggested that an initial peak in colposcopy referrals will decrease substantially by the second round of screening, to rates less than half of those seen in the cytology program.[24]

As the first dataset evaluating HPV-based screening with comprehensive follow-up through an organized cervix screening program, the HPV FOCAL trial is uniquely positioned to answer questions regarding long-term colposcopy referral rates after the introduction of HPV-based cervix screening. HPV FOCAL participants received one or two rounds of HPV-based screening, depending on their allocated arm. After trial exit (at 24 or 48 months), participants returned to the provincial cervix screening program (where the standard of care is currently cytology testing) and were followed for 10 years through the cervix screening registry to identify any post-trial referrals to colposcopy. Referral rates in the trial and throughout follow-up were compared to those from a cohort of participants from the general screening population (who would have been eligible but did not participate in HPV FOCAL), who received cytology. The aim of this analysis was to compare colposcopy referral rates after participation in HPV-based screening to rates in a cytology-based screening program. Prior work has demonstrated elevated colposcopy referral rates observed after the receipt of HPV-based screening, but it is unclear if the elevated rate will persist over time. We hypothesize that colposcopy referral rates for those who have had initial round(s) of HPV-based screening during the HPV FOCAL trial will decreased over time, below the referral rate seen in the general population undergoing cytology-based screening.

Methods

This analysis used data from the FOCAL-DECADE cohort, a longitudinal study of participants from HPV FOCAL who had trial screening data linked to their post-trial screening data in BC Cancer's Cervix Screening Registry. The primary objective was to compare trial and post-trial colposcopy referral rates among FOCAL-DECADE participants who received HPV-based screening during HPV FOCAL, to a comparison cohort from the Cervix Screening Registry who were trial eligible but did not participate in HPV FOCAL and were screened with cytology.

HPV for cervical cancer trial (HPV FOCAL)

HPV FOCAL[8,10,16] (isrctn.org Identifier: ISRCTN79347302) was a three-arm randomized trial conducted among 25,223 women aged 25–65 in Metro Vancouver and Greater Victoria, BC from 2008 to 2016. The intervention arm (HPV Arm) received HPV testing at baseline and co-testing (HPV and cytology testing) at 48-month exit; the control arm (Cytology Arm) received liquid-based cytology (LBC) at baseline and 24 months and co-testing at 48-month exit; and the Safety Arm received HPV testing at baseline and LBC at 24-month exit. The primary finding from this trial was that the risk of CIN2+ was significantly lower at exit among HPV Arm participants, compared Cytology Arm participants.[8] Data from the trial also showed that colposcopy referral rates were higher in the HPV Arm than Cytology Arm at baseline screen, but similar over the 48-month trial period (one round of screening for HPV Arm; two rounds of screening for Cytology Arm).[21] At exit, both arms had higher rates of referral than seen in the general screening program, likely driven by the co-test received and the trial's conservative protocol recommendations for the management of positive screens.[21] Upon trial exit, participants returned to the provincial screening program for the provincial standard of care at the time: cytology-based screening at 2-year intervals (through May 2016) or 3-year intervals (starting June 2016).

FOCAL-DECADE cohort

Participants from HPV FOCAL consented to have their data linked to provincial health registries. The

FOCAL-DECADE cohort was created by linking participants' trial data to their respective data in the BC Cervix Screening Registry (Fig. 1), which is part of the organized population-based cervix screening program maintained by BC Cancer.[25] FOCAL-DECADE was followed through July 2022 to identify all referrals to colposcopy in the provincial registry after exit from HPV FOCAL. For this analysis, two subgroups were created from FOCAL-DECADE: the first composed of HPV FOCAL Safety Arm participants (receiving one round of HPV testing at entry with conventional cytology at 24 month exit) (HPV1, N = 6204), and the second composed of HPV Arm participants (receiving two rounds of HPV testing at entry and at 48 month exit) (HPV2, N = 9540). Given that participants in the Cytology Arm of HPV FOCAL Study received HPV testing at trial exit, they were not deemed appropriate as the comparison cohort, and hence were not included in this analysis. The first screen for HPV1 and HPV2 in HPV FOCAL was considered their index screen for this analysis. A comparison cohort was created from the BC Cancer's Cervix Screening Program.

Comparison cohort identification from BC Cancer's cervix screening program

BC's Cervix Screening Program is responsible for developing provincial guidelines and managing cervical cancer screening across the province, coordinating recall and reminder systems, and maintaining a registry of the results of all screens and follow-up procedures conducted in the province. Average risk women, aged 25–69, are recommended to receive cytology-based screening at 3-years intervals. In the program, women who receive low-grade squamous abnormal cytology results are referred for follow-up cytology at 6-month intervals for up to one year. Persistent low-grade, initial glandular abnormalities, and high-grade squamous abnormalities are immediately referred for colposcopy. Cytology screening, as well as colposcopy recommendations/results and histopathology results, from across BC are captured in a centralized registry. Registry screening and follow-up records were linked to all FOCAL-DECADE participants.

The screening registry from the organized screening program was used to identify a comparison cohort from BC's general screening population who receive conventional cytology as standard of care. This cohort included all persons who received a cytology based cervix screen within the same timeframe as HPV FOCAL recruitment (2008–2012) (considered their index screen for the purpose of this analysis) and who would have been eligible for, but did not participate in, HPV FOCAL (age 25–65, had a family physician, and did not have CIN2+ detected in the five years prior to index screen) (BCS, N = 1,140,745), and therefore, would not have received HPV testing or LBC.

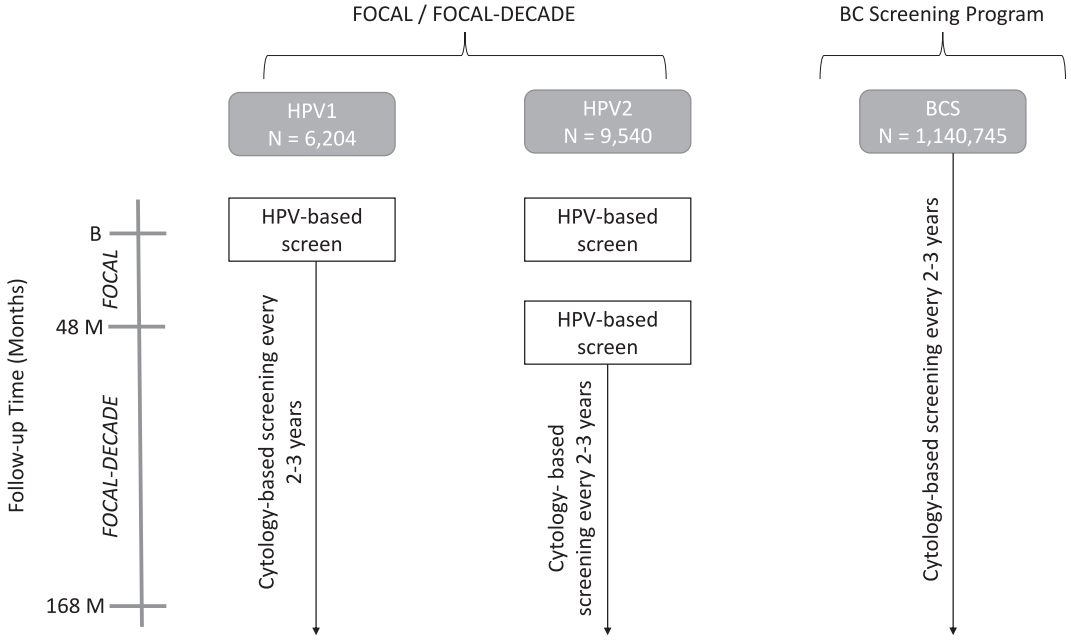

***Fig. 1:* Study activities flow chart**. HPV1 and HPV2 were arms of the HPV FOCAL randomized trial who were then followed through the FOCAL-DECADE cohort by linking FOCAL data to the provincial screening registry. HPV1 received one round of HPV-based screening in HPV FOCAL and HPV2 received two rounds. BCS is a cohort of all screeners in the provincial screening registry who were eligible for HPV FOCAL but did not participate. BCS eligibility criteria included: (1) had a screen during the HPV FOCAL enrollment years (2008–2012; "index screen"), (2) were between the ages of 25–65 at index screen, and (3) did not have a CIN2+ finding in the five years before index screen.

Study design

This analysis used data from three cohorts of participants: HPV1, HPV2, and BCS. For HPV1 and HPV2, colposcopy referrals due to an HPV-based screen were evaluated throughout HPV FOCAL, and follow-up data were extracted from the Cervix Screening Registry for 10 years post-trial exit to evaluate colposcopy referrals due to cytology-based screens. BCS was followed for up to 14 years (4 years during HPV FOCAL and 10 years of follow-up), starting with the date of their index screen, to evaluate colposcopy referrals due to cytology-based screens.

This study investigated rates of colposcopy referrals under three screening scenarios: (1) referrals due to initial rounds of HPV-based screening (HPV1 and HPV2 during HPV FOCAL), (2) referrals due to cytology-based screening after prior initial rounds of HPV-based screening (HPV1 and HPV2 after trial exit); and (3) referrals due to cytology-based screening with no prior HPV-based screening (BCS) (Fig. 1).

Statistical analysis

In HPV FOCAL, criteria for colposcopy referral due to an HPV-based screen differed at baseline and exit. At baseline, HPV positive participants were triaged with cytology and either referred to colposcopy or 12-month re-screen, while at exit, HPV positive participants were immediately referred to colposcopy, regardless of co-test cytology results.[25] For consistency in this analysis, colposcopy referral rates due to an HPV-based screen were calculated under two constant scenarios: Scenario 1) all HPV positive participants referred to colposcopy without cytology triage (HPV positive participants assumed to be referred to colposcopy based on HPV results alone); Scenario 2) HPV positive participants received cytology triage, and those who also received a result of atypical squamous cells of undetermined significance or greater (ASCUS+) referred to colposcopy (HPV positive participants assumed to be referred to colposcopy if their cytology co-testing results were ASCUS+). We were thus able to compare colposcopy rates under less and more conservative management recommendations. For HPV1 and HPV2 screens that occurred after HPV FOCAL exit and for all BCS screens, colposcopy referrals were calculated based on records from the provincial registry database, in accordance with provincial screening guidelines.

Crude instantaneous (defined as colposcopy referrals occurring in a two-year period) and cumulative (defined as all colposcopy referrals occurring over the entire follow-up period) colposcopy referral rates per 1000 women screened throughout the trial and follow-up period were calculated with 95% confidence intervals (CI) for the three comparison groups (HPV1, HPV2, and BCS). Age and prior screening history was also compared across groups.

The HPV FOCAL population was a well-screened cohort that was older than the screening population in BC.[8] To remove the confounding due to different age distributions and prior screening history and to account for the time-dependent nature of colposcopy risk among comparison groups, we developed an adjusted multivariable model using Royston-Parmar flexible regression model[26] with a single knot (default placement at the median) adjusting for age and number of prior screens. Participants were censored using the last available screen date in the provincial screening program. Median follow-up, reported in Table 1, was calculated as the median of the time difference from index screen to the colposcopy referral or the last available screen date in the provincial screening program. For inference, we plotted the hazard ratios (HR) over time for the average age in the cohort and provide the HRs at specific time points in tables. HRs are provided for both HPV-based screening scenarios, described above. All analysis was performed using R (version 4.2.2).[27]

Ethical approval

Written informed consent was obtained for HPV FOCAL participants; data from the BCS was de-identified and did not require patient consent. Ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board (HPV FOCAL: H06–04032, FOCAL-DECADE: H18–02063).

Role of funding source

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Results

Study arm characteristics

Members of HPV1 and HPV2 were older than BCS at index screen (median ages: 51 (Interquartile range (IQR): 42–58), 50 (IQR: 42–58), 45 (IQR: 35–55) respectively) (Table 1). HPV1 and HPV2 had more screens prior to index screen than BCS (median screens: HPV1: 7, HPV2: 7, BCS: 4). Median follow-up periods were similar across cohorts (HPV1: 59 months (IQR: 0–132), HPV2: 54 months (IQR: 0–126), BCS: 48 months (IQR: 0–123)).

HPV1 (N = 6204) and HPV2 (N = 9504) had 27,341 and 36,982 total screens (HPV based and cytology) throughout follow-up, while BCS (N = 1,140,745), had over five million cytology tests (Table 1). For the two scenarios considered (Scenario 1: all HPV positive participants referred to colposcopy without cytology triage; Scenario 2: HPV positive participants received cytology

Characteristic	HPV1, N = 6204		HPV2, N = 9540		BCS, N = 1,140,745	
	N	%	N	%	N	%
Age at Screen (median, (25th, 75th percentile))	51	(42, 58)	50	(42, 58)	45	(35, 55)
Number of prior screens (median (25th, 75th percentile))	7	(0, 14)	7	(0, 13)	4	(0, 10)
Follow-up time (months) (median, (25th, 75th percentile))	59.3	(0, 132)	54.4	(0, 126)	47.8	(0, 123)
Total screens						
24 months	6261[b]	22.9[a]	9901	26.8	2,129,484	41.9
48 months	6534	23.9	19,119	51.7	3,012,470	59.3
72 months	13,796	50.5	25,309	68.4	3,736,140	73.6
96 months	18,442	67.5	29,639	80.1	4,291,973	84.5
Complete follow-up	27,341	100.0	36,982	100.0	5,076,312	100.0
Total colposcopy referrals (Scenario 1: HPV+)						
24 months	536[b]	81.7[a]	814	59.3	18,975	35.5
48 months	567	86.4	1238	90.2	28,375	53.1
72 months	594	90.5	1285	93.6	36,474	68.2
96 months	625	95.3	1326	96.6	43,862	82.0
Complete follow-up	656	100.0	1373	100.0	53,470	100.0
Total colposcopy referrals (Scenario 2: HPV+/ASCUS+)						
24 months	179[b]	59.9[a]	316	53.7	18,975	35.5
48 months	210	70.2	462	78.4	28,375	53.1
72 months	237	79.3	501	85.1	36,474	68.2
96 months	268	89.6	542	92.0	43,862	82.0
Complete follow-up	299	100.0	589	100.0	53,470	100.0

[a]Cumulative percentages. [b]Cumulative screens.

Table 1: **Distribution of sociodemographic characteristics, screens, and referrals by arm.**

triage, and those who received a result of ASCUS + referred to colposcopy), Scenario 1 yielded 656 and 1373 colposcopy referrals in the HPV1 and HPV2 cohorts respectively, and over 53,000 colposcopy referrals in the BCS cohort over the follow-up period. Scenario 2 led to 299 and 589 referrals in HPV1 and HPV2, respectively. Total screens and colposcopy referrals at 24-month intervals are shown in Table 1.

Crude instantaneous and cumulative colposcopy referral rates

Under Scenario 1, cumulative colposcopy rates remained high in HPV1 and HPV2 (due to high referral rates during initial introduction of HPV testing), while instantaneous colposcopy referral rates decreased after trial exit, dropping below BCS colposcopy rates at the first post-trial screen (Fig. 2). At the first HPV screen, instantaneous referral rates were 85 per 1000 screens for HPV1 (95% CI: 79, 92), 84 per 1000 screens for HPV2 (95% CI: 79, 90), and 8 per 1000 screens for BCS (95% CI: 8, 9) (Table 2). However, by the first screen post-trial exit for HPV1 (time period 1–2) and HPV2 (time period 5–6) instantaneous referral rates were 7 per 1000 screens (95% CI: 2, 26) and 8 per 1000 screens (95% CI: 6, 10), respectively, compared to 10 per 1000 screens (95% CI: 0, 10) for BCS (time period 1–2). By the end of the follow-up period, the cumulative rates remained higher in HPV1 (24 per 1000 screens, 95% CI: 22, 26)) and HPV2 (37 per 1000 screens, 95% CI: 35, 39)) than BCS (11 per 1000 screens, 95% CI: 10, 11)), due to initially high referral rates due to HPV-based screens.

Under Scenario 2, instantaneous colposcopy referral rates due to HPV-based screens were lower in HPV1 and HPV2 compared to Scenario 1 (while still higher than BCS) and cumulative rates decreased faster compared to Scenario 1, ending close to BCS rates (Fig. 2). Instantaneous rates at the first HPV screen were 28 per 1000 screens (95% CI: 24, 33), 32 per 1000 screens (95% CI: 29, 36), and 8 per 1000 screens (95% CI: 8, 9) for HPV1, HPV2, and BCS, respectively, and by the end of follow-up (time period 13–14) the cumulative rates were 11 per 1000 screens (95% CI: 10, 12), 16 per 1000 screens (95% CI: 15, 17), and 11 per 1000 screens (95% CI: 10, 11) in HPV1, HPV2, and BCS, respectively (Table 2).

HRs for colposcopy referrals

The multivariable model adjusted for age at screen and prior screening history demonstrated that for Scenario 1, risk of colposcopy referral was initially higher in HPV1 and HPV2 than BCS, which then decreased over time to lower than the risk in BCS (Fig. 3). Initially the hazard of colposcopy referral was higher in HPV1 and HPV2 than BCS (HPV1 vs BCS at 6 months post–index screen: HR = 10.8, 95% CI: 9.8, 11.8; HPV2 vs BCS at 6

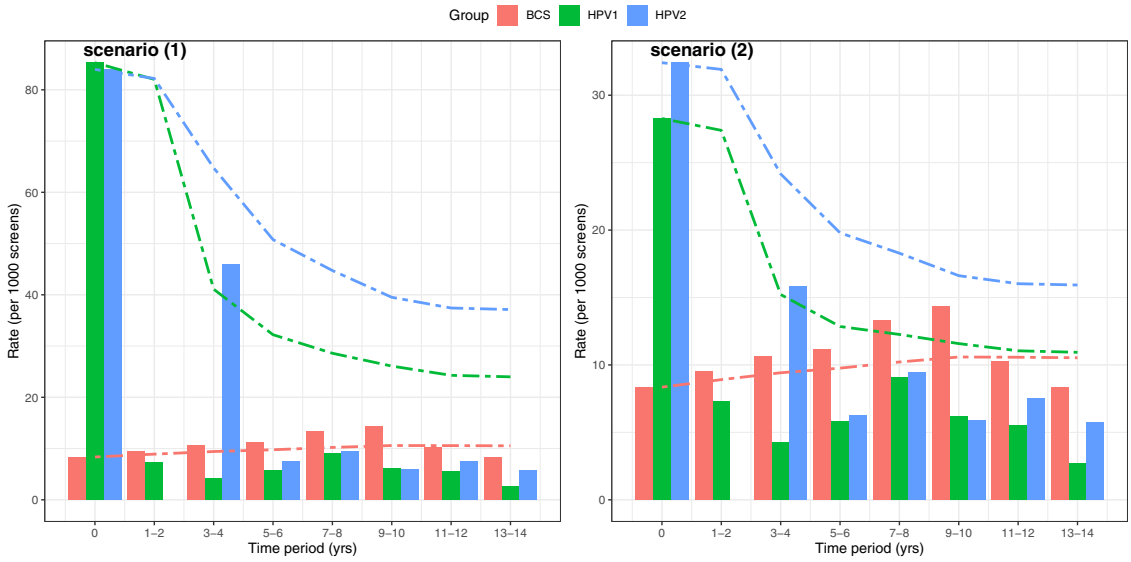

Fig. 2: **Crude instantaneous and cumulative colposcopy referral rates among comparison groups**. Panel A shows colposcopy referral rates under Scenario 1: after HPV-based screens (time periods 0 for HPV1 and 0 and 3–4 for HPV2) all HPV positive participants referred to colposcopy. Panel B shows colposcopy referral rates under Scenario 2: after HPV-based screens (time periods 0 for HPV1 and 0 and 3–4 for HPV2) HPV positive participants are triaged with cytology and those who are ASCUS + are referred to colposcopy. All other time periods (and all time periods for BCS) are based on cytology-related colposcopy referral rates taken from the provincial screening program's registry database. Bars show instantaneous rates at each time period and lines show cumulative rates over the follow-up period.

Group	Time interval	Scenario 1[a]						Scenario 2[b]					
		Cumulative rate	LCI[c]	UCI[d]	Instantaneous rate	LCI	UCI	Cumulative rate	LCI	UCI	Instantaneous rate	LCI	UCI
HPV1	0	85.29	78.62	92.47	85.29	78.62	92.47	28.27	24.45	32.67	28.27	24.45	32.67
HPV1	1–2	82.03	75.62	88.93	7.33	2.01	26.31	27.40	23.71	31.64	7.33	2.01	26.31
HPV1	3–4	41.10	37.91	44.54	4.27	3.01	6.05	15.22	13.31	17.40	4.27	3.01	6.05
HPV1	5–6	32.21	29.76	34.86	5.81	4.00	8.44	12.85	11.32	14.58	5.81	4.00	8.44
HPV1	7–8	28.59	26.47	30.89	9.08	6.40	12.86	12.26	10.89	13.81	9.08	6.40	12.86
HPV1	9–10	26.09	24.17	28.16	6.18	3.86	9.88	11.58	10.32	13.00	6.18	3.86	9.88
HPV1	11–12	24.29	22.51	26.19	5.50	3.22	9.38	11.05	9.87	12.37	5.50	3.22	9.38
HPV1	13–14	23.99	22.25	25.88	2.70	0.14	15.15	10.94	9.77	12.24	2.70	0.14	15.15
HPV2	0	83.98	78.61	89.68	83.98	78.61	89.68	32.41	29.06	36.13	32.41	29.06	36.13
HPV2	1–2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HPV2	3–4	64.75	61.35	68.33	46.00	41.91	50.47	24.16	22.08	26.44	15.84	13.48	18.60
HPV2	5–6	50.77	48.14	53.55	7.59	5.72	10.08	19.80	18.15	21.59	6.30	4.61	8.60
HPV2	7–8	44.74	42.44	47.15	9.47	6.99	12.82	18.29	16.82	19.88	9.47	6.99	12.82
HPV2	9–10	39.52	37.50	41.63	5.87	4.04	8.53	16.62	15.32	18.03	5.87	4.04	8.53
HPV2	11–12	37.42	35.53	39.42	7.51	4.76	11.84	16.02	14.79	17.36	7.51	4.76	11.84
HPV2	13–14	37.13	35.25	39.10	5.76	1.58	20.77	15.93	14.70	17.25	5.76	1.58	20.77
BCS	0	8.35	8.19	8.52	8.35	8.19	8.52	8.35	8.19	8.52	8.35	8.19	8.52
BCS	1–2	8.91	8.79	9.04	9.55	9.36	9.75	8.91	8.79	9.04	9.55	9.36	9.75
BCS	3–4	9.42	9.31	9.53	10.65	10.43	10.86	9.42	9.31	9.53	10.65	10.43	10.86
BCS	5–6	9.76	9.66	9.86	11.19	10.95	11.44	9.76	9.66	9.86	11.19	10.95	11.44
BCS	7–8	10.22	10.12	10.32	13.29	12.99	13.60	10.22	10.12	10.32	13.29	12.99	13.60
BCS	9–10	10.59	10.50	10.68	14.33	13.97	14.69	10.59	10.50	10.68	14.33	13.97	14.69
BCS	11–12	10.57	10.48	10.66	10.26	9.89	10.64	10.57	10.48	10.66	10.26	9.89	10.64
BCS	13–14	10.53	10.44	10.62	8.32	7.72	8.97	10.53	10.44	10.62	8.32	7.72	8.97

[a]Scenario 1: all HPV + referred to colposcopy. [b]Scenario 2: HPV + triaged with cytology; those with atypical squamous cells of undetermined significance or higher results referred to colposcopy. [c]LCI: lower bound of confidence interval. [d]UCI: upper bound for confidence interval.

Table 2: **Crude instantaneous and cumulative colposcopy referral rates, per 1000 screens.**

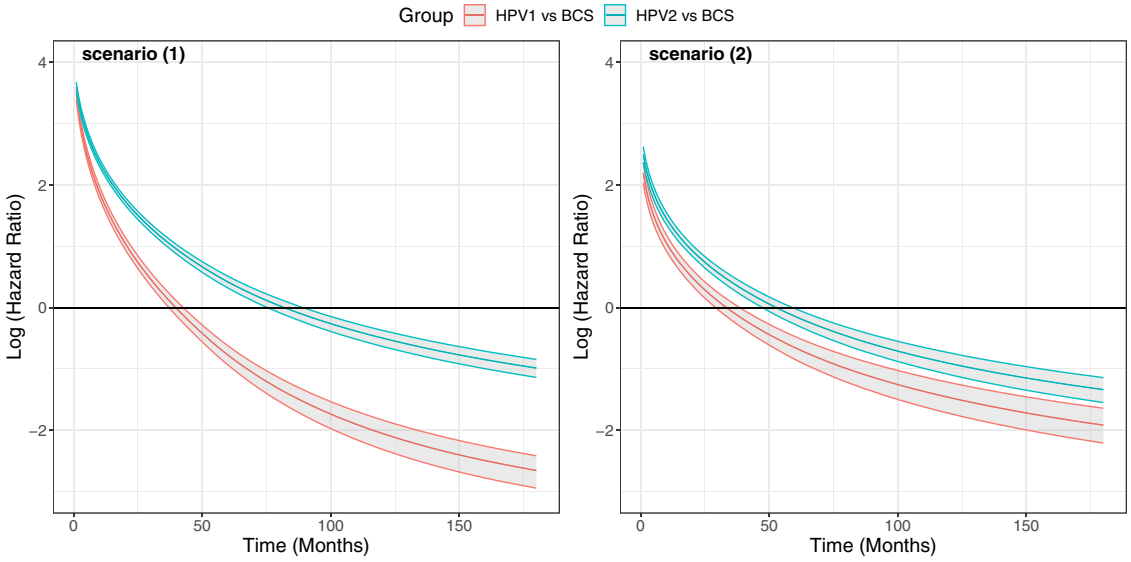

***Fig. 3*: Hazard ratios for HPV1 and HPV2 vs BCS**. Results from the flexible survival regression model on the log scale. Panel 1 shows hazard ratios under Scenario 1: all HPV positive participants referred to colposcopy after HPV-based screens (time periods 0 for HPV1 and 0 and 3–4 for HPV2). Panel 2 shows hazard ratios under Scenario 2: HPV positive participants are triaged with cytology and only those who are ASCUS + are referred to colposcopy after HPV-based screens (time periods 0 for HPV1 and 0 and 3–4 for HPV2).

months post–index screen: HR = 15.7, 95% CI: 14.6, 16.8) (Table 3). By 54 months post–index screen for HPV1 (HR: 0.6, 95% CI: 0.5, 0.7) and 96 months post–index screen for HPV2 (HR: 0.8, 95% CI: 0.7, 0.9) the hazard is lower compared to BCS.

For Scenario 2, the risk of colposcopy in HPV1 and HPV2 decreases more quickly and is below that of BCS by 54 months for HPV1 and by 72 months for HPV2 (HPV1 vs BCS at 54 months post–index screen: HR = 0.6, 95% CI: 0.5, 0.7; HPV2 vs BCS at 72 months post–index screen: HR = 0.7, 95% CI: 0.6, 0.8) (Fig. 3, Table 3).

Group	Time (months)	Scenario 1[a]	Scenario 2[b]
		Hazard ratio	Hazard ratio
HPV1 vs BCS	6	10.76 (9.79, 11.77)	4.04 (3.51, 4.63)
HPV1 vs BCS	24	2.22 (1.99, 2.44)	1.39 (1.20, 1.57)
HPV1 vs BCS	54	0.56 (0.49.0, 0.65)	0.59 (0.49, 0.69)
HPV1 vs BCS	72	0.32 (0.27, 0.38)	0.42 (0.34, 0.51)
HPV1 vs BCS	96	0.19 (0.15, 0.23)	0.30 (0.24, 0.37)
HPV1 vs BCS	120	0.13 (0.09, 0.16)	0.23 (0.18, 0.29)
HPV2 vs BCS	6	15.66 (14.59, 16.76)	5.87 (5.30, 6.52)
HPV2 vs BCS	24	4.70 (4.42, 5.01)	2.17 (1.97, 2.40)
HPV2 vs BCS	54	1.76 (1.60, 1.91)	0.98 (0.87, 1.09)
HPV2 vs BCS	72	1.19 (1.06, 1.31)	0.71 (0.61, 0.81)
HPV2 vs BCS	96	0.81 (0.72, 0.91)	0.52 (0.44, 0.60)
HPV2 vs BCS	120	0.61 (0.54, 0.69)	0.40 (0.34, 0.48)

[a]Scenario 1: all HPV + referred to colposcopy. [b]Scenario 2: HPV + triaged with cytology; those with atypical squamous cells of undetermined significance or higher results referred to colposcopy.

***Table 3*: Hazard ratios for HPV1 and HPV2 vs BCS over time from the multivariable royston-parmar model.**

Discussion

In this study, we observed that colposcopy referrals due to cytology-based screening after one (HPV1) or two (HPV2) prior initial rounds of HPV-based screening with cytology triage (Scenario 2) were significantly lower than referrals due to cytology-based screening where there was no prior HPV-based screening history (BCS). In fact, the cumulative colposcopy referral rates in HPV1 and HPV2 were similar to BCS by the end of follow-up, despite the large increase in referrals seen at initial HPV-based screening rounds. These results held after adjustment for age and prior screening history in multivariable regression models. This suggests that (1) colposcopy referral rates will decrease significantly following the initial increase upon introduction of HPV-based screening and (2) colposcopy referrals will even out over time, leading to cumulative referral rates similar to cytology-based screening programs. To our knowledge, this is the first analysis using real-world data to demonstrate that the initial rounds of HPV testing lead to lower colposcopy referrals over time relative to a counterfactual cohort receiving only cytology testing. This is likely due to HPV-based testing detecting disease and incident and prevalent infections early.

Long-term colposcopy referral rates based on follow-up using cytology-based screens for participants

receiving initial HPV test with immediate referral to colposcopy for HPV positive participants (Scenario 1) were significantly lower compared to colposcopy referral rates due to cytology-based screening with no prior HPV-based screening (BCS). However, cumulative rates remained higher in HPV1 and HPV2 at the end of follow-up, due to the high number of referrals in the HPV-based screening rounds. It has been well established that HPV testing has higher sensitivity but lower specificity than cytology,[8,22] and that a triage test is recommended in primary HPV-based screening approaches to avoid over-referral to colposcopy.[22,28] Our real-world findings confirm this and highlight the importance of effective triage tests in a primary HPV-based screening program.

The elevated colposcopy referral rates seen when HPV-based screening is initially implemented programmatically are likely due to detection of both prevalent and incident HPV infections, given the population's first exposure to HPV testing.[29] The remaining disease detection in consecutive rounds of HPV-based screening will be lower and on par with the HPV prevalence in the respective age cohort and population, leading to a rapid decline in referrals.

A major barrier to the introduction of HPV-based screening has been the concern of significant sustained increases in colposcopy referrals. However, our findings suggest that earlier detection and treatment of pre-cancer will lead to a sharp decrease in referrals after initial HPV-based screening. Our findings are reinforced by the fact that the number of colposcopy referrals in the HPV FOCAL trial was based on a low referral threshold due to pooled HPV testing, leading to more colposcopy referrals than we would observe in a screening program with partial or extended genotyping and cytology triage. Preliminary data from the Netherlands is in line with our findings, showing a downwards trend in the number of colposcopy referrals after first HPV-based screen, suggesting improvements in triage strategies after a positive test could further reduce colposcopy referral rates.[4]

The results from this analysis provide robust initial real-world evidence that colposcopy referral rates likely decrease significantly after initial rounds of HPV-based screening, perhaps below the rates seen in cytology-based programs. Data were obtained from high-quality sources, including clinical data from a randomized trial and an organized, province-wide screening program. The rounds of HPV-based screening in HPV FOCAL followed by the linkage to the comprehensive provincial registry provide some of the longest-term evidence available. To our knowledge, we present the only existing data with 10 years of complete follow-up after the introduction of one or two rounds of HPV-based screening. Additionally, the calculated referral rate for the BCS cohort is similar to what is published in BC Cancer's annual Cervix Program Results report (for 2018, they reported 320,155 smears which led to 4680 colposcopies for a rate of 14.62 colposcopies per 1000 screens),[25] demonstrating the validity of the BCS comparison cohort.

This study is not without limitations. Although HPV FOCAL participants initially received HPV testing, they did not continue to receive HPV-based screening after trial exit. As long-term data does not exist for population HPV-based cervix screening, we instead compared colposcopy referrals from a population cytology-based screening program between those who had and had not received previous HPV-based screening. While results may differ when using multiple rounds of HPV-based screening, our use of cytology-based screening data for follow-up provides real-world evidence of reduced colposcopy load in the long-term, which is mainly due to HPV–based screening detecting disease earlier compared to cytology-based screening. Furthermore, in many current or proposed HPV-based screening programs, cytology is used as a triage test after a positive HPV result.[30–32] In addition, HPV FOCAL used a "pooled genotyping" HPV assay with cytology triage. HPV-based screening programs today have implemented, or are considering implementation, of both partial genotyping and cytology in triage algorithms. As HPV FOCAL did not implement triage with partial genotyping, a strategy that improves the specificity of the test,[33] our estimates may overestimate the number of referrals that would occur in HPV-based screening based on combined partial genotyping and cytology triage. Additionally we report referrals to colposcopy, not attendance at colposcopy. However, the provincial screening program report shows that nearly 90% of those recommended for colposcopic follow-up attend their appointment within 12 months.[25] Finally, we do not compare long-term detection rates (CIN2+/CIN3+) among HPV-based vs cytology-based screening programs, an interesting topic that is out of scope of this study. It will be addressed in a separate manuscript.

While continuing rounds of HPV-based screening may result in marginally higher colposcopy referral rates than seen when HPV1 and HPV2 re-entered cytology-based screening, it is unlikely that rates will surpass what is seen in the general screening population with cytology, which health systems are currently able to manage. The number of positive HPV tests seen in an HPV-based screening program will be directly proportional to the age-specific HPV prevalence in the screening population. Population prevalence of HPV infections peaks around age 20 (at sexual debut) and then decrease thereafter,[34] with a potential second, much smaller, peak around age 50.[35] We can expect that if infections are detected and treated early, rates of detection and subsequent referrals to colposcopy will continue to decrease with increasing age. In fact, we did see a somewhat decreasing trend in referral rates as our HPV1 and HPV2 cohorts aged throughout follow-up.

Furthermore, as coverage of the HPV vaccine increases and higher rates of vaccinated women enter screening programs, prevalence of HPV infection in the population will decrease, further reducing expected referrals.[36,37]

Echoing the findings of a simulation study,[22] findings from this study suggest that the sharp increase in colposcopy referral rates in the initial round(s) of HPV-based cervix screening is followed by a rapid decrease to levels below those currently seen in cytology-based screening programs. This implies that with thoughtful implementation of HPV-based cervix screening, colposcopy referral rates can be managed so that healthcare systems are not overwhelmed. Introduction of HPV-based screening to cohorts by birth year would limit initial increased referral rates to a portion of the eligible population, which would decrease at the following screen to even out over time. This is similar to Norway's introduction of HPV-based screening: starting in 2015, a subset of women were randomized to HPV-based screening instead of conventional cytology, with a gradual continued rollout.[38] Furthermore, the use of HPV assays that partially genotype could improve specificity and further reduce referrals through improved risk stratification. As more vaccinated individuals enter the screening population, referrals will continue to decline. Future research should focus on appropriate triage strategies after positive HPV tests to minimize unnecessary treatment, with the goal of providing evidence to facilitate transitions from cytology-based screening that avoids unnecessarily high demands on health care resources or added patient distress. Particular care should be taken with those who are of childbearing age to avoid the potential for future adverse birth outcomes related to cervix treatment.[39] Additionally, economic analyses would demonstrate comparative costs over time, which would benefit decision-makers considering a transition to HPV-based screening. Appropriate introduction of HPV-based screening for cervical cancer with evidence-based triage strategies will help meet the WHO's goal of global elimination of cervical cancer.

Contributors

AG (formal analysis, writing—original drafting, writing—review & editing), JJA (formal analysis, writing—original drafting, writing—review & editing), LG (formal analysis, writing—review & editing), LWS (conceptualization, funding acquisition, writing—review & editing), DC (data curation, methodology, writing—review & editing), MK (conceptualization, funding acquisition, writing—review & editing), ML (methodology, project administration, writing—review & editing), REM (conceptualization, funding acquisition, writing—review & editing), JM (conceptualization, funding acquisition, writing—review & editing), SP (conceptualization, funding acquisition, writing—review & editing), LP (project administration, writing—review & editing), GS (conceptualization, funding acquisition, writing—review & editing), ELF (conceptualization, funding acquisition, writing—review & editing), DVN (conceptualization, funding acquisition, writing—review & editing), GO (conceptualization, funding acquisition, writing—review & editing).

AG, LG, and JA directly accessed and verified the underlying data. AG, LS, and GO were responsible for the decision to submit the manuscript.

Data sharing statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Declaration of interests

AG received grant funding and travel support from Michael Smith Health Research BC (RT-2021-1595). LG has no disclosures. LS received a one-time consulting fee stipend for participation in a workgroup for BD Canada on cervical cancer elimination in Canada. JA has no disclosures. DC has no disclosures. MK has no disclosures. ML received honoraria for presentations/educational events with Merck in January of 2023. RM has no disclosures. JM received sub-award funding from the National Institutes of Health (R01 CA221918). SP has no disclosures. LP has no disclosures. GS has no disclosures. EF received consulting fees from Merck and BD and has a patent registered at the Office of Innovation and Partnerships at McGill University Montreal, Quebec, Canada (DNA methylation markers for early detection of cervical cancer, October 2018). DV has no disclosures. GO received grant funding from the National Institutes of Health (R01 CA221918) and the Canadian Institute of Health Research (MCT82072).

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