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Assessing 10-Year Safety of a Single Negative HPV Test for Cervical Cancer Screening: Evidence from FOCAL-DECADE Cohort

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ABSTRACT

Background: Long-term safety of a single negative human papillomavirus (HPV) test for cervical cancer screening is unclear. The HPV FOr cerviCAL Cancer Trial (FOCAL) was a randomized trial comparing HPV testing with cytology. The FOCAL-DECADE cohort tracked women who received one HPV test during FOCAL, and were HPV negative, for up to 10 years to identify cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and grade 3 or worse (CIN3+) detected through a provincial screening program.

Methods: FOCAL participants who received one HPV test, were negative, and had at least one post-FOCAL cervix screen were included ($N = 5{,}537$). We constructed cumulative incidence curves of CIN2+/CIN3+ detection, analyzed cumulative risk of detection at intervals post-HPV test, calculated average incidence rates for detection, and compared hazard across ages.

Results: Ten years after one negative HPV test, the probability of CIN2+ detection was lower than 1%, with most lesions detected 7 years or later. Average incidence rates of CIN2+/CIN3+ lesions over follow-up were 0.50 [95% confidence interval (CI), 0.31–0.78] and 0.18 (95% CI, 0.07–0.36) per 1,000 person-years, respectively. Hazards were higher for younger ages (nonsignificant trend).

Conclusions: Among women with a single negative HPV test, long-term risk of CIN2+ detection was low, particularly through 7 years of follow-up; thus, one negative HPV test appears to confer long-term protection from precancerous lesions. Even 10-year risk is sufficiently low to support extended testing intervals in average-risk populations.

Impact: Our findings support the safety of screening policies using HPV testing alone at 5-year or longer intervals.

Introduction

The World Health Organization (WHO) has called for the elimination of cervical cancer by the end of the century (1). To assist countries in realizing this goal, a Draft Global Strategy was developed, which sets global vaccination, screening, and treatment targets (2). In line with this strategy, the Canadian Partnership Against Cancer developed an action plan to eliminate cervical cancer by 2040, by meeting a vaccination target of 90% of students fully vaccinated by age 17 by 2025, a screening target of 90% of eligible individuals screened with high-risk type human papillomavirus (HPV) testing and up-to-date with cervical screening by 2030, and a treatment target of 90% of those testing HPV positive having a clear plan of follow-up by 2030 (3, 4). Implementation of this elimination strategy is occurring during a global shift in recommended cervix screening practices from conventional cytologic screening to an HPV-based approach.

Persistent infection with high-risk HPV types is a necessary cause of cervical cancer (5, 6). Accordingly, many countries have, or are considering, switching from cytology to primary high-risk HPV testing for screening (7–9). HPV testing was more sensitive (10) and had a higher negative predictive value than conventional screening methods in controlled trials over 4 to 5 years of follow-up (11). Multiple randomized controlled trials have found lower rates of high-grade cervical lesions, or cervical intraepithelial neoplasia grade 2 or higher (CIN2+) or grade 3 or higher (CIN3+) during follow-up screens when using primary HPV testing compared with cytology, even when the follow-up interval is lengthened (12–15). There is a potential for increased adverse events due to overtreatment from primary HPV testing approaches, attributable to the test's lower specificity to identify those with precancerous lesions versus those with clinically insignificant infections (16). However, with personalized testing, such as HPV genotyping or cytology triage, these events could be reduced (17–19). Given the high sensitivity of HPV-based testing, lengthening the interval between screening visits, particularly in low-risk populations, could also reduce over-referral to colposcopy.

However, although there is evidence that 3- to 5-year intervals are safe for HPV testing (20, 21), there is a gap in the literature assessing safety of primary HPV testing with longer-term follow-up (16, 19, 20). The few studies that have taken follow-up to 10 years (22, 23) have found some evidence of long-term protection, particularly among low-risk populations. These data are essential to guide future screening recommendations, including appropriate length between HPV-based screens.

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As global cervix screening practices shift toward primary HPV testing, there is an increasing need for evidence-based research comparing screening strategies. Cervix cancer screening in British Columbia (BC), Canada, is managed through the publicly funded BC Cancer Cervix Screening Program, the first population-based cancer screening program in the world (24). This program reported an age-standardized cervical cancer incidence rate of 7.0/100,000 (higher than the 4/100,000 elimination goal proposed by the WHO) and a precancer detection rate of nearly 7/1,000 women in 2015 (25). The HPV FOr CerviCAL Cancer (FOCAL) Trial (26) was a randomized controlled trial comparing primary HPV testing to liquid-based cytology (LBC). The FOCAL DECADE cohort (FOCAL-DECADE) followed consenting FOCAL participants for up to 10 years after trial baseline by linking FOCAL data to data from the provincial screening program. In this study, we aimed to assess the long-term safety of a single negative primary HPV test for cervix screening by assessing 10-year follow-up CIN2+ and CIN3+ incidence rates.

Materials and Methods

The HPV FOCAL trial (FOCAL)

FOCAL was a three-armed randomized controlled trial conducted through collaborating health clinics in the Metro Vancouver and Greater Victoria areas of BC, Canada. FOCAL recruited women 25 to 65 years old from 2008 to 2012 and followed participants for a maximum of 4 years. The trial results have been previously described (13, 26–28). Briefly, the control arm ($N = 9{,}457$) received LBC at baseline and 2 years and cotesting (HPV testing and LBC) at 4-year trial exit; the intervention arm ($N = 9{,}552$) received HPV testing at baseline and cotesting at 4-year trial exit; and the safety arm ($N = 6{,}214$), which was included because at the time there was a concern about the safety of extended intervals between HPV screens, received HPV testing at baseline and LBC at 2-year trial exit. HPV testing was conducted using the Qiagen digene HC2 HPV DNA assay (29). The primary analysis of the FOCAL trial compared CIN2+ rates in the control arm with rates in the intervention arm at 48 months after baseline testing. The population for the study described here included eligible women from the FOCAL safety arm, who received a single HPV test followed by up to 10 years of cytologic screening through both FOCAL exit testing and the provincial program thereafter.

Cervical screening in British Columbia

The BC Cancer Cervix Screening Program develops the provincial guidelines on screening frequency and coordinates the recall and reminder system for cervical screening for the province of BC. Current guidelines recommend that women ages 25 to 69 be screened every 3 years using conventional cytology. The program has one centralized laboratory where all cytology screening specimens for the entire province are processed and reported, and a centralized registry that includes the cytology and colposcopy (including histopathology and treatment) history for all women who have been screened in the program. Under this program, women who receive low-grade abnormal Pap results (ASC-US—atypical cells of undetermined significance or LSIL—low-grade squamous intraepithelial lesion) are asked to repeat Pap test at 6-month intervals for up to 1 year. Persistent low-grade or an initial high-grade (AGC—atypical glandular cells, ASC-H—atypical squamous cells cannot exclude HSIL, HSIL—high-grade squamous intraepithelial lesion, AIS—adenocarcinoma *in situ*, or invasive carcinoma) results are referred for colposcopy (30). The BC Cancer Cervix Screening program does not currently recommend HPV testing. At the time of this analysis, BC Cancer Cervix Screening program registry data were available through May 2019.

The HPV FOCAL trial safety arm

The safety arm of the FOCAL trial has also been previously described (31). Briefly, women who were HPV positive at baseline receive LBC reflex testing, and if results showed greater than or equal to ASC-US, they were referred to colposcopy. If a cytology finding was atypical glandular cells of undetermined significance (AG-US), standard colposcopy with endocervical curettage (ECC) and endometrial sampling was performed, and any identified lesions were managed according to provincial guidelines. If no lesion was identified and the participant was less than 40 years of age, she was recalled for a repeat colposcopy at 6 months, and if she was 40 or greater, she received excisional treatment. If the cytology finding was ASC-H or LSIL or greater, standard colposcopy was performed, and any identified lesions were managed according to provincial guidelines. If no lesion was identified, ECC was performed and those with less than HSIL were recalled at 6 months and those with HSIL or greater received excisional treatment. If baseline HPV-positive women were LBC negative, they were recommended for HPV and LBC cotesting at 12 months and were recommended for colposcopy if positive by either test, following the same guidelines as described above. Those attending colposcopy but who had no CIN2+ detection at baseline or 12-month follow-up were asked to return for the FOCAL 24-month exit screen with LBC. Any women with CIN2+ detected during the trial ($N = 94$) or who otherwise became ineligible, due to pregnancy, hysterectomy, incomplete or invalid baseline test results, or a move outside of the province ($N = 10$) were removed from the trial and not included in these analyses. After trial exit, women re-entered the provincial screening program.

All women in the safety arm who (i) were baseline HPV negative and (ii) had at least one cytology cervix screen (either LBC at trial exit or conventional through provincial screening) post-baseline HPV testing were included in this analysis ($N = 5{,}537$, 89% of safety arm population). A flow-chart describing selection criteria is shown in **Fig. 1**.

The HPV FOCAL-DECADE cohort (FOCAL-DECADE)

The FOCAL-DECADE cohort was developed to address the emerging health system priorities in cervical cancer prevention by determining optimal strategies for HPV-based screening and triage. The main goal for this study was to determine the long-term efficacy of a single negative test during HPV-based primary screening, using 10-year follow-up data from FOCAL participants enrolled in the safety arm. The FOCAL trial data from eligible women in the safety arm (as described above) were linked to their corresponding data from the BC Cancer Cervix Screening Program, under which all screening after trial exit occurred. Of the 5,537 participants included in these analyses, 5,238 (95%) were linked to data in the screening program. Using this linkage, all CIN2+ lesions that occurred up to a 10-year period after recruitment into the FOCAL trial were identified in the FOCAL-DECADE cohort. Written informed consent was obtained for all participants, and ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board (FOCAL: H06–04032, FOCAL-DECADE: H18–02063).

Variable creation and statistical methods

This article focuses on incidence rates of both CIN2+ and CIN3+ detection (the primary endpoints of FOCAL) during a 10-year follow-up period after one negative HPV test. CIN3+ is a more accurate clinical endpoint, because CIN2+ is more likely to be misclassified or

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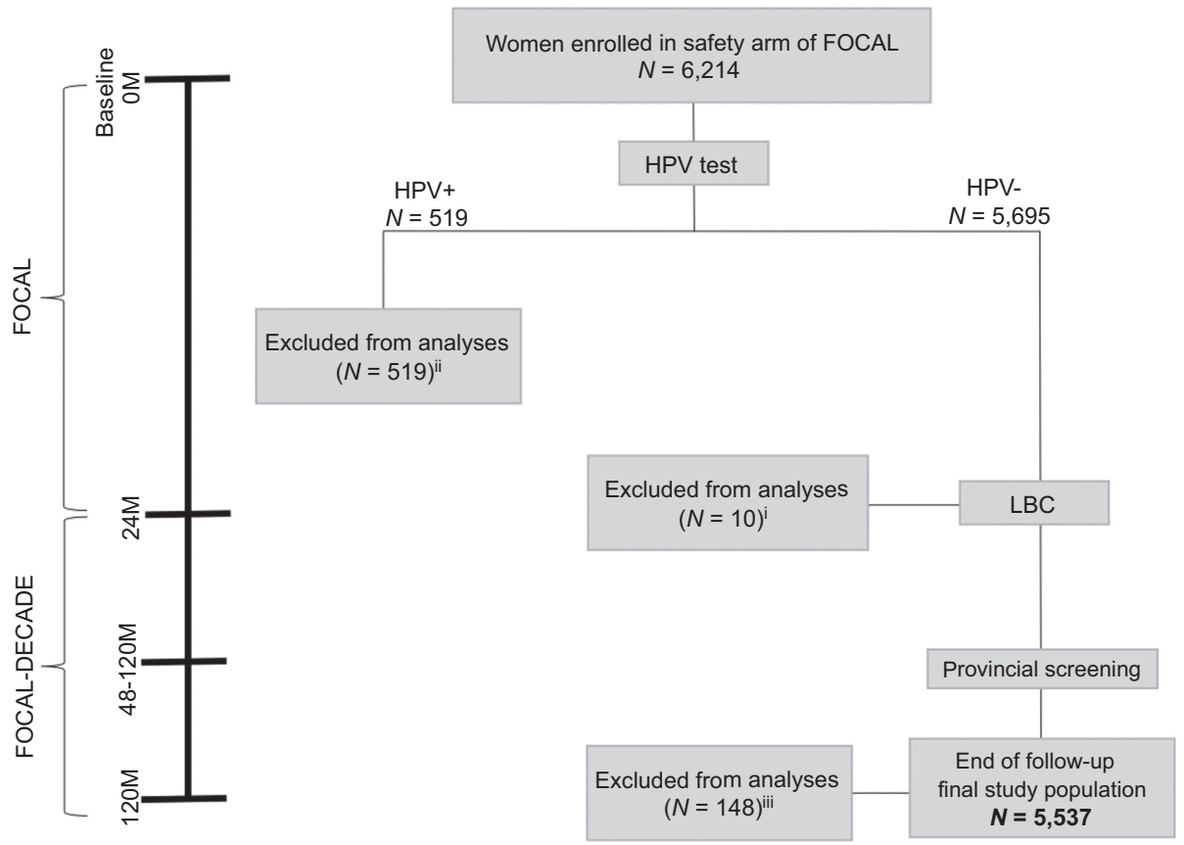

Figure 1.

A diagram of FOCAL and FOCAL-DECADE by baseline HPV result. All women enrolled in the safety arm of the FOCAL randomized control trial were given HPV testing at baseline. All participants who (i) remained eligible for FOCAL during the entire trial ($N = 10$ excluded), (ii) were HPV negative at baseline ($N = 519$ excluded), and (iii) had at least one screen post baseline ($N = 148$ excluded) were included in this analysis ($N = 5,537$). Provincial screening = BC Cancer Cervix Screening Program recommends conventional Pap screening given by individual healthcare providers every 24–36 months (in June 2016, the BC Cancer Cervix Screening program changed the recommended cervix screening interval from 24 months to 36 months for average-risk individuals).

to spontaneously regress (32–35). Because CIN2+ is the threshold for treatment in most jurisdictions, including BC (except in women under 25 years), it is also considered as an endpoint. The study population was analyzed as one group overall as well as stratified by 10-year age groups. HPV-negative FOCAL participants did not receive colposcopy during the trial; therefore, no women included in these analyses had CIN2+ detected prior to trial exit at 24 months. Disease detection rates are reported as rate per 1,000 person-years. Confidence intervals were calculated using the Poisson Exact method.

We plotted the cumulative incidence of CIN2+ detection over time as 1-S(t) actuarial curves using the Kaplan–Meier technique. Time to event was calculated as the difference between the date of CIN2+

Table 1. Average incidence rates of CIN2+ and CIN3+ detection over 10-year follow-up.

		CIN2+			CIN3+		
	Person-years	Cases	IR[a]	95% CI	Cases	IR[a]	95% CI
Overall	39,699.5	20	0.50	(0.31–0.78)	7	0.18	(0.07–0.36)
Age group[b]							
25–34	6,065.0	6	0.99	(0.36–2.15)	2	0.33	(0.04–1.19)
35–44	12,467.8	6	0.48	(0.18–1.05)	1	0.08	(0.00–0.45)
45–54	13,397.7	6	0.45	(0.16–0.97)	2	0.15	(0.02–0.54)
55–65	7,769.0	2	0.26	(0.03–0.93)	2	0.26	(0.03–0.93)
Age group[b]							
25–44	18,532.8	12	0.65	(0.33–1.13)	3	0.16	(0.03–0.47)
45–65	21,166.7	8	0.38	(0.16–0.74)	4	0.19	(0.05–0.48)

[a]Rates per 1,000 person-years.
[b]Age groups consider age at baseline entry into FOCAL trial.

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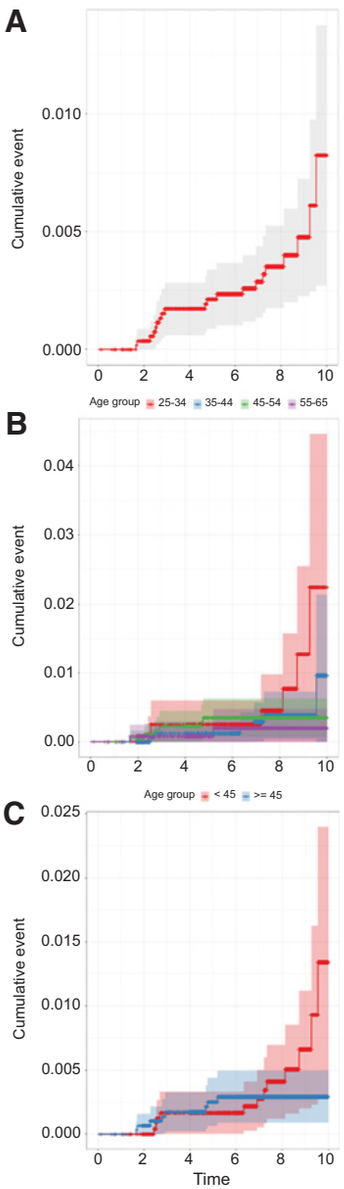

Figure 2.

Cumulative incidence of CIN2+ detection over follow-up. **A,** includes the overall population; **B,** stratifies by 10-year age group; and **C,** by binary age groups. Note that, for clarity, *y*-axes differ for each plot. Women are censored at either CIN2+ detection date or their most recent screening date, with all remaining women censored at 10 years. **Table 2** shows cumulative events and total number at risk at 2-year intervals postbaseline entry into FOCAL.

detection and FOCAL trial entry date. Time to censor was calculated as the difference between date of most recent cytology result and trial entry date for women who had no CIN2+ detection. Due to sparse data after 10 years of follow-up (188 participants had screening data after 10 years with a total of 69.5 person-years contributed and one detection of CIN3+), all women who had screening results from more than 10 years post-FOCAL trial entry were censored at 10 years. Plots were also stratified by age group and included confidence bounds. We calculated the cumulative risks at 3, 5, 8, and 10 years after entry into the trial to determine when risk increased.

A Cox proportional hazard model was run with a categorical variable for each age group to calculate hazard ratios and confidence intervals between each older age group compared with the youngest, and then re-run after replacing the categorical variables with one ordinal variable with a Wald test to test for a trend across the age groups.

All analyses were conducted using R 3.6.3 (R Foundation; ref. 36).

Results

The FOCAL safety arm recruited 6,214 women ages 25 to 65 to receive primary HPV testing at baseline. Of those women, 5,537 (89.1%) were eligible for this study. The omitted 677 participants were excluded for the following reasons: 519 (8.4%) were HPV+ at baseline (94 of whom had CIN2+ lesions detected during the trial), 10 (0.2%) became ineligible during the trial, and 148 (2.4%) had no follow-up screening postbaseline HPV testing. There were no statistical differences in age at screening, smoking status, number of lifetime sexual partners, or marital status between the study population and the population excluded for no follow-up screening.

At FOCAL trial baseline, the median participant age was 46 years (10th percentile = 32, 90th percentile = 59): 841 (15.2%) women age 25–34, 1,685 (30.4%) age 35–44, 1,819 (32.9%) age 45–54, and 1,192 (21.5%) age 55–65. On average, women received two cervix screens post exit from the FOCAL trial (number of screens was similar across age strata). Over the follow-up period, 20 (0.36%) and 7 (0.13%) women had CIN2+ and CIN3+ detected, respectively.

A total of 39,699.5 person-years were contributed by the cohort over follow-up (6,065.0 from participants ages 25–34 at baseline, 12,467.8 from ages 35–44, 13,397.7 from ages 45–54, and 7,769.0 from ages 55–65; **Table 1**). During the 10-year follow-up period, the average incidence rates of CIN2+ and CIN3+ were 0.50 [95% confidence interval (CI), 0.31–0.78] and 0.18 (0.07–0.36) per 1,000 person-years, respectively (**Table 1**). When stratifying by age at baseline, the youngest age group (25–34 years) had the highest rates of CIN2+ and CIN3+ detection: 0.99 (0.36–2.15) and 0.33 (0.4–1.19), respectively, with generally decreasing rates as age increased: 0.48 (0.18–1.05) and 0.08 (0.00–0.45) respectively, for women ages 35–44 at baseline, 0.45 (0.16–0.97) and 0.15 (0.02–0.54), respectively for women ages 45–54, and 0.26 (0.03, 0.93) and 0.26 (0.03, 0.93), respectively, for women ages 55–65.

For women who were diagnosed with CIN2+, the average time to detection was 5.0 years (6.4 for women ages 25–34 at baseline, 5.9 for ages 35–44, 3.2 for ages 45–54, and 3.4 for ages 55–65). Women who were not diagnosed with CIN2+ over the follow-up had their most recent screen on average 7.2 years after exit from the FOCAL trial (7.2 years for women who entered FOCAL at ages 25–34, 7.4 for women ages 35–44, 7.4 for women ages 45–54, and 6.5 for women ages 55–65). Detection curves show that CIN2+ detection rates were low over the 10-year follow-up period (**Fig. 2**, **Table 2**). When stratified by age groups, older groups had similar detection rates, but women in the youngest group (25–34 for 10-year groups or 25–44 for binary groups) had a higher rate, particularly after 7 years of follow-up.

Table 3 shows the cumulative risk remains extremely low at 3 and 5 years, with the majority of CIN2+/CIN3+ detection occurring after 7 years, particularly among the youngest age group (25–34 years at FOCAL baseline). In the overall population, the risk of CIN2+ was 0.17% at 3 years, 0.21% at 5 years, 0.35% at 8 years, and 0.82% at

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Table 2. Cumulative CIN2+ events and total number at risk at 2-year intervals postbaseline entry into FOCAL.

Years		Overall	Age groups			
			25–34	35–44	45–54	55–65
0	Cum. events	0	0	0	0	0
	No. at risk	5,537	841	1,685	1,819	1,192
2	Cum. events	2	0	0	1	1
	No. at risk	5,474	832	1,669	1,804	1,169
4	Cum. events	9	2	2	4	1
	No. at risk	5,046	766	1,551	1,694	1,035
6	Cum. events	12	2	2	6	2
	No. at risk	4,397	680	1,402	1,520	795
8	Cum. events	16	3	5	6	2
	No. at risk	2,232	335	756	785	356
10	Cum. events	20	6	6	6	2
	No. at risk	189	30	73	61	25

Abbreviations: cum., cumulative; no., number.

10 years. For the youngest age group, risk was the same at 3 and 5 years (0.25%) but increased to 2.24% at 10 years. Among the older groups, the risk stayed fairly stable over time.

The HRs for CIN2+ detection among age groups compared with the youngest group decreased with increasing age but were not statistically significant (HR = 0.47, 95% CI, 0.15–1.47 for 35–44; HR = 0.45, 95% CI, 0.14–1.39 for 45–54; HR = 0.27, 95% CI, 0.05–1.34 for 55–65; **Table 4**). Similar results were found for the hazard of CIN3+; however, due to small counts, the CIs are quite wide. The Wald test for trend was not statistically significant.

Discussion

In this follow-up study of FOCAL-DECADE cohort participants from the safety arm of the FOCAL trial, after up to a maximum of 10 years of follow-up, women who were HPV negative after a single HPV test had very low risk of developing precancerous lesions. In this population, 0.36% and 0.13% of participants were diagnosed with CIN2+ and CIN3+, respectively, over the 10 years of follow-up, similar to what Dijkstra and colleagues found with long-term follow-up after one cotest and lower than what Elfström and colleagues found with long-term follow-up after one HPV test (21, 37). The average 10-year incidence rates of CIN2+ and CIN3+ were 0.53 and 0.18 per 1,000 person-years, respectively, which is much lower than the CIN2+ rate in the general population in British Columbia. The BC Cancer Cervix Screening 2017 Program Results reported an annual precancer (CIN2+) detection rate of nearly 7 per 1,000 person-years (25). Furthermore, the risk of CIN2+ detection remained exceptionally low for many years of follow-up after a negative HPV test, with the majority of detection occurring after the 7-year mark. Compared with Mesher and colleagues' study of precancerous risk of after a negative cytology screen, which found an 8-year cumulative risk of CIN2+ of 1.04% (38), our study found the 8-year cumulative risk of CIN2+ after a negative HPV test to be only 0.35%.

Table 3. Cumulative risk of CIN2+ and CIN3+ at intervals over 10-year follow-up.

Lesion		Cumulative risk							
		3 years[a]		5 years[a]		8 years[a]		10 years[a]	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
CIN2+	Overall	0.17	(0.06–0.28)	0.21	(0.09–0.34)	0.35	(0.18–0.53)	0.82	(0.27–1.37)
	10-year age								
	25–34	0.25	(0.00–0.60)	0.25	(0.00–0.60)	0.45	(0.00–0.98)	2.24	(0.00–4.47)
	35–44	0.13	(0.00–0.30)	0.13	(0.00–0.30)	0.39	(0.04–0.73)	0.96	(0.00–2.13)
	45–54	0.23	(0.00–0.45)	0.35	(0.07–0.63)	0.35	(0.07–0.63)	0.35	(0.07–0.63)
	55–65	0.08	(0.00–0.25)	0.08	(0.00–0.25)	0.20	(0.00–0.48)	0.20	(0.00–0.48)
	Binary age								
	25–44	0.17	(0.00–0.33)	0.17	(0.00–0.33)	0.41	(0.12–0.70)	1.34	(0.27–2.40)
	45–65	0.17	(0.02–0.33)	0.25	(0.07–0.44)	0.29	(0.09–0.50)	0.29	(0.09–0.50)
CIN3+	Overall	0.07	(0.00–0.15)	0.07	(0.00–0.15)	0.13	(0.02–0.23)	0.20	(0.02–0.39)
	10-year age								
	25–34	0.00	(0.00–0.00)	0.00	(0.00–0.00)	0.20	(0.00–0.60)	0.71	(0.00–1.78)
	35–44	0.06	(0.00–0.19)	0.06	(0.00–0.19)	0.06	(0.00–0.19)	0.06	(0.00–0.19)
	45–54	0.11	(0.00–0.27)	0.11	(0.00–0.27)	0.11	(0.00–0.27)	0.11	(0.00–0.27)
	55–65	0.08	(0.00–0.25)	0.08	(0.00–0.25)	0.20	(0.00–0.48)	0.20	(0.00–0.48)
	Binary age								
	25–44	0.04	(0.00–0.12)	0.04	(0.00–0.12)	0.11	(0.00–0.26)	0.26	(0.00–0.60)
	45–65	0.10	(0.00–0.22)	0.10	(0.00–0.22)	0.14	(0.00–0.28)	0.14	(0.00–0.28)

[a]Years post baseline HPV testing in FOCAL trial.

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Table 4. HRs for CIN2+ among subpopulations.

	CIN2+			CIN3+		
	HR	95% CI	Wald test[a]	HR	95% CI	Wald test[a]
Age group[b]			$P = 0.097$			$P = 0.997$
25–34	Ref.			Ref.		
35–44	0.47	(0.15–1.47)		0.24	(0.02–2.66)	
45–54	0.45	(0.14–1.39)		0.45	(0.06–3.22)	
55–65	0.27	(0.05–1.34)		0.80	(0.11–5.66)	
Age group[b]						
25–44	Ref.		$P = 0.264$	Ref.		$P = 0.827$
45–65	0.60	(0.25–1.47)		1.18	(0.26–5.28)	

[a]Wald test for trend.
[b]Age groups consider age at baseline entry into FOCAL trial.

The results from this study strengthen conclusions from prior studies (21, 37, 39–41), which suggest that it is safe to extend the length of the interval between cervical cancer screening to 4–5 years when using HPV testing for primary screening, particularly in comparison with the recommended 1–3 years when using cytology screening, which has been found to have a lower long-term safety (42). Among women who are in an HPV-based screening program, extending screening schedules could reduce the cost of the program and the number of women who are overtreated for regressive lesions.

Although many studies that compared short-term outcomes of cytology versus HPV testing have found that HPV testing identifies more precancerous lesions than cytology (13, 14, 43, 44), there is a lack of long-term data on the safety of one negative HPV test. This study, which investigated the rates of precancerous lesions among women who underwent primary HPV testing without cotesting and were HPV negative, is the first of its kind in North America to have up to 10 years of follow-up. Our findings confirm that women who have one negative HPV test have low risk of developing precancerous cervical lesions over an extended time period, similar to what has been seen in cotesting and short-term follow-up studies (21, 45). However, this study has several limitations. Women who participated in the FOCAL trial were selected from a well-screened population. High-risk women (i.e., those who had previously had CIN2+ lesions detected) could have been excluded from the study population, as FOCAL excluded women who had CIN2+ detection in the 5 years prior to trial entry. Women with inadequate screening histories may not receive the same safety from one negative HPV test (22). Furthermore, potentially missed cases when women did not comply with recommendations for follow-up colposcopy after abnormal screening cannot be accounted for. However, in the FOCAL trial, there was over a 95% rate of colposcopy compliance (13), and throughout the FOCAL-DECADE follow-up, only 5 of 43 (12%) women included in this study's population who were referred for colposcopy do not have histopathology results recorded in the database for the recommended diagnostic test. Furthermore, the BC Cancer Cervix Screening Program reported that in 2018, nearly 90% of women recommended to have colposcopy for either persistent low-grade (89%) or high-grade (88%) cytology results received the follow-up procedure within 12 months of their abnormal Pap test (30).

There is some concern over the potential increase in adverse outcomes that would accompany a transition from cytology to HPV testing. HPV testing has a lower positive predictive value than cytology, meaning that the test is less predictive of precancerous lesions when positive than an abnormal cytology result because it will detect both incident and prevalent infections, regardless of whether or not they are associated with CIN2+. This could lead to an increase of potentially unnecessary colposcopies and treatment. However, reduced frequency of HPV testing lengthens the interval in which transient HPV infections can self-resolve and could help to mitigate needless diagnostic testing and treatment. The results from this study show that women who have one negative HPV test, particularly at older ages, are at extremely low risk for developing CIN2+ lesions over the following decade.

The WHO has called for the elimination of cervical cancer as a public health problem. Each country must now decide the appropriate context-specific plan to achieve the goals set by the Draft Elimination Strategy, along with country-specific goals. HPV testing could offer an effective and cost-saving method for cancer screening worldwide. Some countries, such as Australia and the Netherlands, have already transitioned their screening programs to HPV testing at 5-year intervals (46, 47). Furthermore, with the rising prevalence of HPV vaccination, there is a need to consider less aggressive screening intervals to reduce over treatment (46).

Among women who test negative for HPV, the long-term future risk of cervical cancer is low. Future research is needed to identify the best interval length for HPV testing, as well as if and how this interval length should differ by subpopulations (i.e., age, race, screening history).

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Role of the Funder

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Data Availability

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

Authors' Contributions

A. Gottschlich: Formal analysis, investigation, methodology, writing-original draft, writing-review and editing. **D. van Niekerk:** Conceptualization, resources, supervision, funding acquisition, writing-review and editing. **L.W. Smith:** Conceptualization, supervision, investigation, project administration, writing-review and editing. **L. Gondara:** Data curation, methodology, writing-review and editing. **J. Melnikow:** Conceptualization, supervision, funding acquisition, writing-review and editing. **D.A. Cook:** Conceptualization, resources, investigation, writing-review and editing. **M. Lee:** Conceptualization, resources, funding acquisition, writing-review and editing. **G. Stuart:** Conceptualization, funding acquisition, writing-review and editing. **R.E. Martin:** Conceptualization, supervision, methodology, writing-review and editing. **S. Peacock:** Conceptualization, funding acquisition, writing-review and editing. **E.L. Franco:** Conceptualization, supervision, funding acquisition, methodology, writing-review and editing. **A. Coldman:** Conceptualization, funding acquisition, writing-review and editing. **M. Krajden:** Conceptualization, funding acquisition, writing-review and editing. **G. Ogilvie:** Conceptualization, supervision, funding acquisition, methodology, writing-review and editing.

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Assessing 10-Year Safety of a Single Negative HPV Test for Cervical Cancer Screening: Evidence from FOCAL-DECADE Cohort

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