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The population impact of HPV/cytology cervical cotesting at 3-year intervals: reduced cervical cancer risk and decreased yield of precancer per screen

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Abstract

Background—Cervical screening aims to detect and treat precancer to prevent cervical cancer mortality and morbidity, while minimizing overtreatment of benign human papillomavirus (HPV) infections and related minor abnormalities. HPV/cytology cotesting at extended 5-year intervals is now a recommended screening strategy in the US, but the interval extension is controversial. We studied the impact of a decade of an alternative, 3-year cotesting, on rates of precancer and cancer at Kaiser Permanente Northern California. We also considered the effect on screening efficiency, defined as numbers of cotests/colposcopy visits needed to detect a precancer.

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Methods—Two cohorts were defined. The “open cohort” included all women screened at least once during the study period; >1 million cotests were performed. In a fixed “long-term screening cohort”, we considered the cumulative impact of repeated screening at 3-year intervals by restricting to women first cotested in 2003–4 (i.e., no women entering screening later were added to this group).

Results—Detection of CIN3/AIS increased in the open cohort (2004–6, 82.0/100,000 women screened; 2007–9, 140.6/100,000; and 2010–12, 126.0/100,000); cancer diagnoses were unchanged. In the long-term screening cohort, detection of CIN3/AIS increased then decreased to the original level (2004–6, 80.5/100,000; 2007–9, 118.6/100,000; and 2010–2, 84.9/100,000). Cancer diagnoses decreased. Seen in terms of screening efficiency, the number of colposcopies performed todetect a single CIN3/AIS increased in the cohort with repeat screening.

Conclusion—Repeated cotesting at a 3-year interval eventually lowers population rates of precancer and cancer; however, a greater number of colposcopies is required to detect a single precancer.

Keywords

cervical cancer; CIN; biopsy; colposcopy; HPV; cotest; screening

Introduction

Cervical cancer screening recommendations are in flux as knowledge of human papillomavirus (HPV) and new, related technologies advance. Annual cervical cancer screening with Pap smears was recommended in the United States for many decades following its introduction. However, consideration of longer screening intervals gradually increased. In 2012, recommendations specifically advising *against* annual screening using any strategy were issued by the US Preventive Service Task Force (USPTF) [1] and, separately, by more than 20 organizations coordinated by the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP). Cytology alone at 3-year screening intervals or cotesting with HPV and cytology at 5-year intervals were both considered acceptable strategies for women aged 30–65 years [2]. The American College of Obstetricians and Gynecologists (ACOG) updated their guidelines shortly thereafter, and became consistent with these other recommendations, though with a preference for 5-yearly cotests over 3-year Pap smears [3, 4].

These policy changes were based on strong evidence. Randomized controlled trials have consistently demonstrated that HPV testing is more sensitive than cytology for the detection of precancer (defined histologically as CIN3/AIS) and provides better reassurance against precancer and cancer [5–9], important for extending screening intervals without placing women at greater risk. Large-scale observational data have shown even greater reassurance against cancer following cotesting compared with HPV testing alone [10] although the gain is quite small.

Assessment of the benefits and harms of different screening intervals is still subjective. Some experts do not accept the 5-year cotesting interval, and recommend instead repeated cotesting every 3 years to provide a greater reassurance against cervical cancer, while acknowledging the extra costs and procedures required when repeating a sensitive screening combination so frequently [11]. Yet, many clinics continue to screen at intervals even shorter than that. However, the impact of screening at an interval that is shorter than recommended has not been sufficiently explored in a clinical setting. Theoretically, one might expect to see a decrease in screening efficiency and fewer precancers detected (compared to benign newly-appearing HPV infections and related minor cytologic changes) per screen over time.

Kaiser Permanente Northern California (KPNC), part of the Kaiser integrated healthcare system, has served as an important source of real-world evidence regarding 3-year cotesting, since it began cotesting all eligible women age 30–65 years at a 3-year interval starting in 2003 [12, 13]. To obtain realistic clinical practice data, we examined the population-level effect on detection of precancer and cancer after a decade-long experience with repeat 3-year screening intervals at KPNC.

Methods

Study Population

This analysis was based on the KP Guidelines Cohort, which includes all women enrolled at KPNC who have undergone cotesting since 2003, as previously described [12, 13]. As of the last data update through 2012, the cohort consists of almost 1.5 million women, 2 million screening visits, and up to 10 years of follow-up per person. Consistent with KPNC screening protocols over the decade, this analysis was restricted to women aged 30 years or older, resulting in a study population of 1,065,273 women.

We defined two different cohorts: The “open cohort” refers to the group of women who were ever enrolled at KPNC and screened for cervical cancer between 2003 and 2012, the most recent year for which complete screening data were available for this analysis. The open cohort represents the total yearly Kaiser experience. The “closed subcohort” includes only the subset of women from the open cohort who were enrolled and received their first cotest in 2003–4 (no addition of women first screened in later years), and they were followed through 2012 as well. This group reveals the impact of repeated screening on a fixed population, and as such will be referred to as the ‘long-term screening cohort’. Approximately 80% of women in this group had two or more cotests over the 10-year follow-up, with only 10% having more than four.

We obtained all cytology and histology records for each of these women starting from their first visit (in 2003 or later) through their last visit or the end of 2012, whichever was earlier. Since we did not have an indicator of whether a woman underwent a colposcopy, we used the presence of a biopsy result as a marker that a colposcopy was performed.

Statistical Analysis

Descriptive statistics of the two cohorts were compared, including numbers of screening visits and screening results. As results were first assessed by year on a population not

individual level, we did not calculate true rates, but rather ratios of the outcome detected (i.e., CIN3/AIS, or cancer) to the number of cotests and colposcopic visits performed. We first calculated the ratios of precancer/cancer diagnosis to the number of cotests performed for all women who received cervical cancer screening from age 30 onward at KPNC from 2003 to 2012 (the open cohort). To estimate the cumulative impact of repeated screening at 3-year intervals, we calculated that same ratios for the long-term screening cohort. We smoothed the trend data by taking the average of 3 years in the early, middle, and late parts of the decade (2004–2006, 2007–2009, and 2010–2012). Statistical significance was determined using trend tests. The number of colposcopies performed (here limited to those resulting in a biopsy) relative to the number of screening tests, and outcomes per colposcopy-biopsy visit were similarly compared. All rates in the tables were age-adjusted using the 2000 US Census population as the reference.

Results

Population characteristics of both cohorts at the time of the enrollment visit are shown in Table 1. Women in the long-term screening cohort, first cotested at KPNC in 2003–4 when cotesting was introduced, were on average two years older than the open cohort and had lower high-risk HPV (HR-HPV) prevalence at baseline using HC2 (Qiagen, Germantown, MD) (5.1% vs 5.9%, p <0.001). They also had a lower prevalence of abnormal (ASC-US or worse) cytology (3.8% vs. 4.6%, p <0.001).

In the open cohort, the ratio of colposcopic biopsy visits to cotests performed nearly doubled from 1373.5 per 100,000 to 2738.4 per 100,000 (Table 2), and the ratio of histologically diagnosed precancer (CIN3/AIS) per cotest increased from the first period to the second (82.0 to 140.6 per 100,000; p=0.001), and then had a small decrease in the third (140.6 to 126.0 per 100,000; p<0.001). The increase in the relative number of biopsies taken combined with the increase in CIN3/AIS detection resulted in a stable number of biopsy visits needed to detect a case of CIN3/AIS (between 16 and 22) in the open cohort over the study period.

In the long-term screening cohort, the population of women who were enrolled in 2003–4, many of whom continued to be cotested regularly, with a median screening interval of 2.9 years (IQR: 2.1–3.2), the number of biopsy visits relative to cotests increased by 80% (Table 2). Looking at the 3-year averages in the long-term screening cohort, there was a significant increase in the ratio of CIN3/AIS detected per cotest from 80.5 per 100,000 in 2004–2006, to 118.6 per 100,000 in 2007–2009 (p=<0.001), and then the ratio decreased significantly to 84.9 per 100,000 in 2010–2012 relative to 2007–2009 (p<0.001), returning to a level essentially equivalent to that seen in the first time period. Over the course of follow-up, the number of colposcopies with biopsy needed to detect a single CIN3/AIS rose from 19 to 33.

Decreases were seen in the overall amount of invasive cancer detected in the long-term screening cohort (from 20.4 per 100,000 to 9.6 per 100,000), while no change in cancer detection was seen in the open cohort, although small numbers of cases limited the precision of estimates (Table 3). The patterns of detection for the most common cancer subtypes, adenocarcinoma and squamous cell carcinoma, were different. The open cohort showed an

initial increase in detection rates of adenocarcinoma from 2004–6 to 2007–2009 (3.6 per 100,000 to 5.4 per 100,000); however, this was followed by a reduction of almost equal magnitude, resulting in 2010–12 rates similar to those at baseline (4.2 per 100,000). In the long-term screening cohort, no change was seen in the detection of adenocarcinoma over the three time periods (remaining between 4–5/100,000). The open cohort showed a decrease in squamous cell carcinoma detection from the first to the second time period (13.1 per 100,000 to 10.1 per 100,000) but this was followed by an increase in the latest time period to 14.9 per 100,000. The long-term screening cohort showed a much larger decrease in squamous cell carcinoma detection from 13.0 per 100,000 to 4.6 per 100,000 in 2007–09, where it remained in the latest period, resulting in a reduction from the early to late 3-year period of 65%.

Discussion

An ideal cervical screening interval is characterized by detection of a useful number of treatable precancers and extremely few invasive cancers. Too frequent screening will produce many newly appearing HPV infections and low-grade abnormalities but few true precancers at each screening round, increasing the potential for overtreatment. On the other hand, too infrequent screening may allow for the development of an unacceptably large number of invasive cancers. As current guidelines suggest a 3-year cotest interval is too frequent, we expected to see an overall decrease in screening efficiency with time across the system. Instead, we found that the KPNC every 3-year cotesting strategy, judged as an open cohort with continuing influx of women at risk, is yielding an increasing rate of precancers per woman screened, but an unchanged, low rate of adenocarcinomas and invasive squamous cell cancers. This suggests that largely the program is achieving what screening is designed to do ---detecting precancers --- though little corresponding decrease is seen in cancer rates. The cost, however, is still a high referral rate to colposcopy.

The long-term screening cohort represented the accumulated experience of women receiving longitudinal, repeated 3-year cotesting. In this group, the relative detection of precancer to screening tests remained relatively steady, while the ratio of cancer found per screening test was unchanged for adenocarcinoma, but decreased by almost two-thirds for squamous cell carcinoma. It is in this group, with repeated cotests, that a decrease in screening efficiency becomes evident, particularly after the second round of screening where we see an almost doubling in the number of colposcopic biopsies needed for the detection of a single precancerous lesion.

Comparing the open cohort with the long-term screening cohort, there was no decrease in the detection of precancer in the open cohort, but rather a steady increase. The increase in the open cohort is probably due to a combination of women aging into screening eligibility, a change in referring repeatedly HPV-positive women to colposcopy, as well as new enrollees into KPNC. These newly cotested women likely brought along a continued influx of disease that could then be screen-detected. Comparing these cohorts provides two different but equally valid descriptions of the clinical practice outcomes which are occurring simultaneously; the open cohort provides a snapshot of what is occurring at KPNC on a routine basis with in migration of new patients, while the ‘long-term screening cohort’

illustrates a screening program perspective, where women are not just screened once, but repeatedly over a lifetime, both of which are necessary to consider when evaluating the impact of screening.

Over the 10 years, the open cohort and long-term screening cohort yielded a somewhat comparable proportion of cancers per colposcopy performed, but the long-term screening cohort yielded fewer cases of CIN3/AIS per colposcopy than the open cohort. Increased biopsy visits with the detection of fewer precancers among the regularly cotested women in the closed cohort may suggest some loss in screening efficiency.

We began this analysis with a prior hypothesis that cotesting at repeat 3-year intervals would lead to some degree of inefficiency and “over-management”. The results proved more complicated than we expected. Changes over time in screening program policies, in particular who is referred to colposcopy, might have influenced the ratios and introduced bias in the time trends. Moreover, this analysis was conducted on a population level, not the individual level. Given the importance of the issues and the ambiguous secular trends, we will conduct a women-level longitudinal analysis of cumulative incidence rates to assess better the cumulative effect of long-term cotesting at 3-year intervals. As many clinics have yet to attain a 3-year screening interval, data demonstrating the impact of this interval may prove important to encouraging the shift to a 3-year model, likely a necessary step on the way toward the recommended 5-year interval.

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Table 1

Population Characteristics

	Open Cohort*	Closed Cohort
Number of women	1,065,273	210,557
Median Age at First Visit (IQR)	44 (35–53)	46 (37–55)
Median Number of Visits (IQR)	2 (1–3)	3 (2–4)
Enrollment hc2 Positivity (%)	5.9%	5.1%
Enrollment Cytology		
Normal	1,008,658 (95.4)	202,511 (96.2)
Abnormal	48358 (4.6)	8066 (3.8)
Enrollment Cotest Results#		
Normal Cytology/HPV Negative	971954 (92.0)	194727 (92.5)
Abnormal Cytology/HPV Negative	22976 (2.2)	5176 (2.5)
Normal Cytology/HPV Positive	36704 (3.5)	7784 (3.7)
Abnormal Cytology/HPV Positive	25382 (2.4)	2870 (1.4)
Enrollment Histology		
Normal	11740 (41.1)	3117 (59.9)
Atypical squamous	1274 (4.5)	295 (5.7)
Atypical glandular	28 (0.1)	21 (0.4)
CIN1	10539 (36.9)	1073 (20.6)
CIN2	2581(9.0)	298 (7.6)
CIN3/AIS	2074 (8.3)	259 (5.0)
Cervical cancer, histology unknown	37 (0.1)	6 (0.1)
Adenocarcinoma	72 (0.3)	11 (0.2)
Squamous Cell Carcinoma	204 (0.7)	25 (0.5)
Adenosquamous Carcinoma	9 (0.0)	2 (0.0)

*Open cohort includes all women cotested at KPNC between 2003 and 2012

Closed cohort (long-term screening cohort) includes only women who were cotested at KPNC in 2003/2004; lack of influx of new patients permitted examination of repeated cotests

#Abnormal cytology includes ASCUS and higher

Table 2

Rate* of biopsies and precancer detection over 3 year periods and ratio of detection

Years	Open Cohort			Closed Cohort^		
	Rate of Biopsy	Rate of Precancer#	Biopsy: Precancer	Rate of Biopsy	Rate of Precancer	Biopsy: Precancer
2004–2006	1373.5	82.0	16.8	1535.5	80.5	19.1
2007–2009	2230.8	140.6	15.9	2347.5	118.6	19.8
2010–2012	2738.4	126.0	21.7	2793.9	84.9	32.9

*Rate is per 100,000 women screened and has been age-adjusted to the 2000 US census population

^Closed cohort = long-term screening cohort

#Precancer= CIN3 and AIS

Table 3

Rate* of adenocarcinoma and squamous cell carcinoma by year

Years	Open Cohort			Closed Cohort^		
	Adeno	SCC	All Cancers**	Adeno	SCC	All Cancers**
2004–2006	3.6	13.1	19.8	4.1	13.0	20.4
2007–2009	5.4	10.1	18.4	4.7	4.6	13.0
2010–2012	4.2	14.9	20.1	4.8	4.5	9.6

* rate is per 100,000 women screened

** includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and cervical cancer with unknown histology

^ Closed cohort = long-term screening cohort