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## Risk of Cervical Cancer Associated with Extending the Interval between Cervical-Cancer Screenings

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### ABSTRACT

#### BACKGROUND

Although contemporary guidelines suggest that the intervals between Papanicolaou tests can be extended to three years among low-risk women with previous negative tests, the excess risk of cervical cancer associated with less frequent than annual screening is uncertain.

#### METHODS

We determined the prevalence of biopsy-proven cervical neoplasia among 938,576 women younger than 65 years of age, stratified according to the number of previous consecutive negative Papanicolaou tests. Using a Markov model that estimates the rate at which dysplasia will progress to cancer, we estimated the risk of cancer within three years after one or more negative Papanicolaou tests, as well as the number of additional Papanicolaou tests and colposcopic examinations that would be required to avert one case of cancer given a particular interval between screenings.

#### RESULTS

Among 31,728 women 30 to 64 years of age who had had three or more consecutive negative tests, the prevalence of biopsy-proven cervical intraepithelial neoplasia of grade 2 was 0.028 percent and the prevalence of grade 3 neoplasia was 0.019 percent; none of the women had invasive cervical cancer. According to our model, the estimated risk of cancer with annual Papanicolaou tests for three years was 2 in 100,000 among women 30 to 44 years of age, 1 in 100,000 among women 45 to 59 years of age, and 1 in 100,000 among women 60 to 64 years of age; these risks would be 5 in 100,000, 2 in 100,000, and 1 in 100,000, respectively, if screening were performed once three years after the last negative test. To avert one additional case of cancer by screening 100,000 women annually for three years rather than once three years after the last negative test, an average of 69,665 additional Papanicolaou tests and 3861 colposcopic examinations would be needed in women 30 to 44 years of age and an average of 209,324 additional Papanicolaou tests and 11,502 colposcopic examinations in women 45 to 59 years of age.

#### CONCLUSIONS

As compared with annual screening for three years, screening performed once three years after the last negative test in women 30 to 64 years of age who have had three or more consecutive negative Papanicolaou tests is associated with an average excess risk of cervical cancer of approximately 3 in 100,000.

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**C**ITING THE LACK OF DIRECT EVIDENCE that annual screening leads to better outcomes than screening performed every three years, the U.S. Preventive Services Task Force recently recommended that screening for cervical cancer be performed “at least every three years” rather than every year.<sup>1</sup> Similarly, guidelines issued by the American Cancer Society suggest lengthening the intervals between screenings to as long as three years among women 30 years of age or older who have had negative results on three or more consecutive cervical cytologic tests.<sup>2</sup> Despite recommendations issued in 1988 that women with previous negative tests undergo screening less frequently than once a year,<sup>3</sup> many clinicians perform screening annually. Resistance to screening less frequently may be due to a perception that there is an unacceptably high excess risk of cervical cancer.

The risk of cancer associated with an interval between screenings of more than 12 months among women in the United States who have had negative results on multiple previous, frequent tests has not been determined, but it is important to quantify this risk. Recently, attention has been paid to the addition of more sensitive tests (such as detection of oncogenic human papillomavirus [HPV] DNA)<sup>4</sup> to cytologic tests; the risk of cancer among women who have undergone conventional cytologic testing represents a base-line level of risk that might be reduced with the use of more sensitive tests. For example, a combined cytologic and HPV DNA test has been recommended by the American Cancer Society as a “reasonable” alternative to cytologic testing alone for women 30 years of age or older, with an explicit recommendation that the test not be performed more often than every three years.<sup>2</sup> It is therefore important to current and future screening strategies that women with previous negative tests and their clinicians accept less frequent screening. Moreover, comparative analyses of various strategies indicate that the frequency of screening is an important variable influencing cost effectiveness.<sup>5</sup> To date, the absence of clinically derived estimates of risk has limited the ability of clinicians, women, and the developers of guidelines<sup>1</sup> to make evidence-based decisions about the frequency of screening and the optimal screening method.

Using data on outcomes from a large, national, publicly funded program of cervical-cancer screening, we conducted a study to estimate the excess risk of cancer associated with extended intervals between screenings among women with documentation of

negative results on consecutive conventional Papanicolaou tests. We also estimated the average numbers of additional Papanicolaou tests and colposcopic examinations that would be needed to avert one case of cancer with the use of various screening intervals among women of various ages.

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## METHODS

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### SOURCE OF DATA

We analyzed data from the National Breast and Cervical Cancer Early Detection Program administered by the Centers for Disease Control and Prevention (CDC). This program has provided cervical-cancer screening to low-income, underinsured women throughout the United States since 1991. Methods for the collection and reporting of data have been described previously.<sup>6-8</sup> Briefly, the CDC established minimum data elements to be collected for each woman receiving screening services, including data on demographics, screening results, diagnostic procedures, and histologic outcomes. Local program officials standardize the data categories before submitting information semiannually to the CDC.

Identifying information was removed from the program data. The study was conducted under a data-use agreement approved by the institutional review board of the CDC, and approval was obtained from the Committee on Human Research at the University of California, San Francisco.

We focused on the screening results reported between January 1991 and March 2000. Most tests were conventional, rather than liquid-based, cytologic analyses and were interpreted at laboratories throughout the country. The results were reported according to 1991 Bethesda System categories. We excluded 11,276 tests that were reported to be wholly unsatisfactory, 1446 tests whose results were pending, and 7062 tests reported as unclassified. We excluded 100 women for whom no birth date was given and 57 women with missing screening dates.

### SCREENING AND AGE CATEGORIES

We grouped women into four screening categories: women with only one Papanicolaou test obtained through the CDC program, those with an initial negative Papanicolaou test followed by a second Papanicolaou test, those with two negative Papanicolaou tests followed by a third Papanicolaou test, and those with at least three negative Papanicolaou tests followed by another Papanicolaou test. We defined a

negative Papanicolaou test as a test interpreted as normal or as indicating the presence of infection or reactive changes; we defined consecutive tests as those performed within 36 months of one another. If more than 36 months elapsed between any two tests and additional tests were subsequently performed, the most recent screening history was examined (e.g., if a woman had a single Papanicolaou test performed in 1991, followed by annual tests in 1995, 1996, and 1997, we examined outcomes related only to the latter three tests). We assumed that Papanicolaou tests performed more often than every nine months were for surveillance (e.g., for follow-up after treatment of dysplasia) rather than screening. Therefore, if a test was reported within nine months after another test, we excluded that test and all subsequent tests in order to focus exclusively on tests performed for screening. Screening categories were not mutually exclusive: a woman with four negative Papanicolaou tests, for example, would be counted in each category if she met the criteria described above.

We calculated the age of the woman on the basis of the birth date reported at the time of enrollment in the program and grouped women into four categories according to their age at the time of the most recent test. Since the program currently screens few women who are 65 years of age or older, we did not evaluate outcomes in this age group.

#### HISTOLOGIC CLASSIFICATION

The prevalence of dysplasia and the prevalence of cancer were determined through examination of the histologic findings reported for women in each screening category and each age category. Most histologic dysplasia was identified with the use of colposcopy-guided biopsy in women with abnormal cytologic findings, according to published guidelines.<sup>9</sup> Abnormal histologic findings were classified as biopsy-proven grade 1, grade 2, or grade 3 cervical intraepithelial neoplasia or as cancer (with the cell type not specified). Confidence intervals were calculated by the Wilson-score method with continuity correction.<sup>10</sup>

#### MODEL AND ESTIMATES

We hypothesized that few cases of cancer would be found in women with three or more previous negative tests. Therefore, we used a Markov model of the natural history of cervical cancer to estimate the risk of newly diagnosed cancer that would be predicted to occur on the basis of a given prevalence of dys-

plasia. The components of the model have been described previously.<sup>11,12</sup> Important summary estimates and assumptions are shown in Table 1.

Using the observed prevalence of dysplasia in combination with the components of the model specific to the regression and progression of dysplasia, we estimated the average risk of cancer in hypothetical cohorts of 100,000 women who were screened once three years after the last negative test rather than annually, with stratification according to age and the number of previous negative tests. We began our analysis with the group of women with one previous test, since the CDC program was not considering extending the intervals between screenings for women with no previous documented negative tests. To avoid underestimating risks, we conservatively assumed that all grade 2 lesions of cervical intraepithelial neoplasia progress to invasive cancer at the same rate as grade 3 lesions progress. We performed sensitivity analyses to determine how the outcomes would change if we assumed that grade 2 cervical intraepithelial neoplasia had a natural history identical to that of grade 1 neoplasia or if the observed prevalence of dysplasia were doubled.

We calculated by subtraction the differences between groups in the absolute risk of cancer and determined the average number of additional Papanicolaou tests and colposcopic examinations that

**Table 1. Summary Estimates Used in the Markov Model.**

Variable	Summary Estimate
Grade 1 cervical intraepithelial neoplasia	
Regression to no dysplasia	
15–34 yr of age	65%/72 mo
≥35 yr of age	40%/72 mo
Progression to grade 2 or 3	
15–34 yr of age	10%/72 mo
≥35 yr of age	35%/72 mo
Grade 2 or 3 cervical intraepithelial neoplasia	
Regression to grade 1 or no dysplasia	35%/72 mo
Progression to stage 1 cervical cancer	40%/120 mo
Sensitivity of cytologic testing*	51%
Specificity of cytologic testing*	97%
Sensitivity and specificity of colposcopy	100% (assumed)
Efficacy of treatment for dysplasia	100% (assumed)

\* A positive test was defined as a test indicating the presence of atypical squamous cells of undetermined significance or a worse condition; the presence of disease was defined by a biopsy result showing a lesion of cervical intraepithelial neoplasia of grade 1 or higher. Estimates were based on previous studies.<sup>13–25</sup>

would be needed to avert one case of cancer in hypothetical cohorts of 100,000 women in each age category who had had three or more negative Papanicolaou tests. The number of Papanicolaou tests required to screen each cohort annually for three years was determined under the assumption that all women adhere to screening and that women found to have atypical squamous cells of undetermined significance would undergo a repeated Papanicolaou test. The number of colposcopic examinations was estimated from the model under the assumption that all women with low-grade squamous intraepithelial lesions or a worse abnormality on cytologic analysis would undergo colposcopy and that women with an initial test interpreted as atypical squamous cells of undetermined significance in whom the repeated test revealed the same or a worse abnormality would undergo colposcopy.

## RESULTS

Our analysis focused on 1,174,727 cervical cytologic tests performed in 938,576 women younger than 65 years of age. The largest percentage of women were 45 to 64 years of age, and about one half were identified in their records as nonwhite (Table 2). In general, the prevalence of biopsy-proven dysplasia of any grade was highest among women younger than 30 years of age and among women with no previous Papanicolaou tests performed through the CDC program (Table 3). The prevalence decreased as the number of previous negative tests increased among women in all age groups. Among women

younger than 30 years of age, we found little difference in the prevalence of dysplasia between women who had had one negative test and those who had had two negative tests. Cancer was rare and was most often diagnosed in women who had not previously undergone a Papanicolaou test through the CDC program. Among the 32,230 women who had had three or more consecutive negative tests, high-grade dysplasia was uncommon in all age groups: 9 women (0.028 percent) had grade 2 cervical intraepithelial neoplasia, 7 women (0.022 percent) had grade 3 cervical intraepithelial neoplasia, and none had cancer. When the analysis was limited to the 31,728 women 30 to 64 years of age who had had three or more consecutive negative tests, the corresponding rates were 0.028 percent and 0.019 percent, respectively.

As the number of previous negative tests increased, there was a corresponding decrease in the average number of cases of cancer that the model projected would occur over a three-year period, whether screening was performed annually or once three years after the last negative test (Table 4). Among women with three or more previous negative tests, the average estimated number of cases of cancer per 100,000 women screened annually for three years was highest among women younger than 30 years of age; screening once three years after the last negative test would be anticipated to result in the occurrence of an average of five extra cases of cancer in a hypothetical cohort of 100,000 women in this age group (Table 4). Among women 30 to 44 years of age, three extra cases of cancers would be expected to occur per 100,000 women screened once three years after the last negative test; and among women 45 to 59 years of age, one extra case of cancer per 100,000 women would be expected to occur. We could not demonstrate any difference in the number of cases of cancer that would be anticipated among women 60 to 64 years of age. The average numbers of additional Papanicolaou tests and colposcopic examinations that would be required to avert one case of cancer through annual screening rather than screening performed once three years after the last negative test among women 30 to 44 years of age and women 45 to 59 years of age with at least three previous negative tests are shown in Table 5.

In sensitivity analyses, a doubling of the prevalence of dysplasia was associated with an average of two additional cases of cancer per 100,000 women 30 to 44 years of age, one additional case of cancer

**Table 2. Characteristics of the 938,576 Women Included in the Analysis.**

Characteristic	No. of Women (%)
<b>Age</b>	
<30 yr	127,479 (13.6)
30–44 yr	300,670 (32.0)
45–59 yr	410,910 (43.8)
60–64 yr	99,517 (10.6)
<b>Race or ethnic group</b>	
White	491,745 (52.4)
Hispanic	191,958 (20.5)
Black	134,268 (14.3)
American Indian or Alaskan Native	61,248 (6.5)
Asian or Pacific Islander	33,606 (3.6)
Other or unknown	25,751 (2.7)

**Table 3. Observed Prevalence of Biopsy-Proven Cervical Intraepithelial Neoplasia of Grades 1, 2, and 3 and Invasive Cervical Cancer.**

Variable	No. of Previous Negative Papanicolaou Tests through the CDC Program*							
	0		1		2		≥3	
	no./total no.	% (99% CI)	no./total no.	% (99% CI)	no./total no.	% (99% CI)	no./total no.	% (99% CI)
<b>Grade 1 cervical intraepithelial neoplasia</b>								
<30 Yr of age	9172/127,479	7.19 (7.01–7.38)	177/9759	1.81 (1.49–2.20)	31/1920	1.61 (1.00–2.57)	2/502	0.40 (0.05–2.18)
30–44 Yr of age	3675/300,670	1.22 (1.17–1.28)	245/35,768	0.68 (0.58–0.81)	57/10,842	0.53 (0.37–0.74)	22/5278	0.42 (0.24–0.73)
45–59 Yr of age	1507/410,910	0.37 (0.34–0.39)	248/69,320	0.36 (0.30–0.42)	66/27,126	0.24 (0.18–0.34)	35/18,950	0.18 (0.12–0.29)
60–64 Yr of age	200/99,517	0.20 (0.17–0.24)	43/21,741	0.20 (0.13–0.29)	12/9428	0.13 (0.06–0.27)	11/7500	0.15 (0.06–0.32)
<b>Grade 2 cervical intraepithelial neoplasia</b>								
<30 Yr of age	3676/127,479	2.88 (2.76–3.01)	68/9759	0.70 (0.51–0.96)	14/1920	0.73 (0.35–1.46)	0/502	— (0.00–1.50)
30–44 Yr of age	1541/300,670	0.51 (0.48–0.55)	90/35,768	0.25 (0.19–0.33)	9/10,842	0.08 (0.03–0.20)	3/5278	0.06 (0.01–0.20)
45–59 Yr of age	502/410,910	0.12 (0.11–0.14)	52/69,320	0.08 (0.05–0.11)	20/27,126	0.07 (0.04–0.13)	5/18,950	0.03 (0.01–0.08)
60–64 Yr of age	61/99,517	0.06 (0.04–0.09)	10/21,741	0.05 (0.02–0.10)	5/9428	0.05 (0.02–0.17)	1/7500	0.01 (0.00–0.13)
<b>Grade 3 cervical intraepithelial neoplasia</b>								
<30 Yr of age	2602/127,479	2.04 (1.94–2.15)	45/9759	0.46 (0.31–0.68)	10/1920	0.52 (0.22–1.18)	1/502	0.20 (0.01–1.85)
30–44 Yr of age	2233/300,670	0.74 (0.70–0.78)	72/35,768	0.20 (0.15–0.27)	12/10,842	0.11 (0.05–0.24)	2/5278	0.04 (0.00–0.21)
45–59 Yr of age	1040/410,910	0.25 (0.23–0.27)	73/69,320	0.11 (0.08–0.14)	18/27,126	0.07 (0.04–0.12)	3/18,950	0.02 (0.00–0.07)
60–64 Yr of age	205/99,517	0.21 (0.17–0.25)	18/21,741	0.08 (0.04–0.15)	5/9428	0.05 (0.02–0.17)	1/7500	0.01 (0.00–0.13)
<b>Invasive cervical cancer</b>								
<30 Yr of age	27/127,479	0.02 (0.01–0.04)	0/9759	— (0.00–0.08)	0/1920	— (0.00–0.40)	0/502	— (0.00–1.50)
30–44 Yr of age	166/300,670	0.06 (0.05–0.07)	5/35,768	0.01 (0.00–0.04)	1/10,842	0.01 (0.00–0.09)	0/5278	— (0.00–0.14)
45–59 Yr of age	257/410,910	0.06 (0.05–0.07)	8/69,320	0.01 (0.00–0.03)	1/27,126	0.00 (0.00–0.03)	0/18,950	— (0.00–0.04)
60–64 Yr of age	61/99,517	0.06 (0.04–0.09)	1/21,741	0.00 (0.00–0.04)	0/9428	— (0.00–0.08)	0/7500	— (0.00–0.10)
Total no. of observations	938,576		136,588		49,316		32,230	

\* CI denotes confidence interval.

per 100,000 women 45 to 59 years of age, and one additional case of cancer per 100,000 women 60 to 64 years of age. In analyses in which grade 2 cervical intraepithelial neoplasia was assumed to have a natural history like that of grade 1 cervical intraepithelial neoplasia, the differences in the risk of cancer were smaller (Table 4) and the number of procedures that would be required to avert one case was greater (data not shown).

#### DISCUSSION

Women 30 to 64 years of age with three or more previous negative Papanicolaou tests who are screened

once three years after the last negative test rather than annually have an excess risk of cancer of no more than 3 in 100,000. Continued annual screening, with the use of more sensitive techniques, in women who have been undergoing regular screening can reduce this risk, but such ongoing screening requires substantial resources and many colposcopic procedures. The fact that the difference in the risk of cancer is small highlights the importance of attention to the costs and the harms associated with overscreening. For comparison, this risk is similar in magnitude to the annual risk of breast cancer among men 45 to 64 years of age (1 to 4 in 100,000).<sup>26</sup>

Our data were derived from a large population in

**Table 4. Projected Outcomes after Cervical-Cancer Screening in Hypothetical Cohorts of 100,000 Women Screened Annually for Three Years and Hypothetical Cohorts of 100,000 Women Screened Once Three Years after the Last Negative Test.**

Variable	Average Expected No. of Papanicolaou Tests*	Average Expected No. of Colposcopic Examinations	Average Expected No. of Cases of Invasive Cervical Cancer†	
			If Grade 2 Progression Like Grade 3	If Grade 2 Progression Like Grade 1
<b>1 Previous negative Papanicolaou test</b>				
<b>&lt;30 Yr of age</b>				
Screening once 3 yr after last negative test	106,457	7,088	52	21
Annual screening	319,640	19,761	23	9
<b>30–44 Yr of age</b>				
Screening once 3 yr after last negative test	102,324	6,020	29	18
Annual screening	311,345	17,825	19	14
<b>45–59 Yr of age</b>				
Screening once 3 yr after last negative test	102,616	5,809	16	13
Annual screening	311,938	17,422	13	12
<b>60–64 Yr of age</b>				
Screening once 3 yr after last negative test	103,397	5,775	9	7
Annual screening	313,519	17,357	7	6
<b>2 Previous negative Papanicolaou tests</b>				
<b>&lt;30 Yr of age</b>				
Screening once 3 yr after last negative test	106,444	7,059	56	24
Annual screening	319,624	19,691	25	11
<b>30–44 Yr of age</b>				
Screening once 3 yr after last negative test	102,313	5,864	17	14
Annual screening	311,326	17,524	14	12
<b>45–59 Yr of age</b>				
Screening once 3 yr after last negative test	102,611	5,751	9	6
Annual screening	311,934	17,308	6	5
<b>60–64 Yr of age</b>				
Screening once 3 yr after last negative test	103,394	5,739	5	2
Annual screening	313,517	17,287	2	1
<b>≥3 Previous negative Papanicolaou tests</b>				
<b>&lt;30 Yr of age</b>				
Screening once 3 yr after last negative test	106,361	6,242	9	9‡
Annual screening	319,469	18,062	4	4
<b>30–44 Yr of age</b>				
Screening once 3 yr after last negative test	102,290	5,785	5	2
Annual screening	311,286	17,368	2	1
<b>45–59 Yr of age</b>				
Screening once 3 yr after last negative test	102,608	5,691	2	1
Annual screening	311,932	17,193	1	0
<b>60–64 Yr of age</b>				
Screening once 3 yr after last negative test	103,395	5,715	1	1
Annual screening	313,520	17,242	1	0

\* When 100,000 women are screened once, the total number of Papanicolaou tests exceeds 100,000, since a defined proportion of these women will have a test interpreted as showing atypical squamous cells of undetermined significance and will be asked to return in six months for a repeated Papanicolaou test (as a direct result of the initial Papanicolaou test).

† We assumed that grade 2 cervical intraepithelial neoplasia would progress to invasive cancer at the same rate as grade 3 lesions; the last column shows the estimated number of cases of cancer under the assumption that grade 2 lesions would progress to invasive cancer at the same rate as grade 1 lesions.

‡ There is no difference in the estimated number of cases, since, among the women screened through the National Breast and Cervical Cancer Early Detection Program between 1991 and 2000, there were no cases of grade 2 cervical intraepithelial neoplasia found in women younger than 30 years of age who had had three or more negative Papanicolaou tests.

the United States that was racially, ethnically, and geographically diverse. The data set is notable in that the final histologic diagnoses were recorded. Several limitations of our study must be acknowledged. The data set was collected for the purposes of program administration and evaluation, not as part of a research protocol, and we do not have information on other risk factors for cervical cancer in these women. It is possible that the data underestimate or overestimate the prevalence of neoplasia. We did not have verification of the cytologic or histologic outcomes. Previous studies, however, have demonstrated that interpretations of cytologic<sup>27</sup> and histologic<sup>28</sup> findings are routinely downgraded when they are reviewed by an expert panel. Community-based readings, therefore, would be more likely to overestimate rather than to underestimate the severity of abnormal findings. In our population, the prevalence of cervical intraepithelial neoplasia of grade 2 or higher among women who had had no previous Papanicolaou test performed through the CDC program was 1.3 percent overall (range, 0.33 percent among women 60 to 64 years of age to 4.9 percent among women younger than 30 years of age). Although direct comparisons with findings from other populations are complicated by differences in the age ranges, the screening histories, and the methods used for the detection of neoplasia, the prevalence rates found in our study appear to be similar to but somewhat lower than those reported by others (range, 1.6 to 4.3 percent),<sup>29-32</sup> perhaps because of the greater number of women in older age groups in our population or because of underestimation. Sensitivity analyses demonstrated that a doubling of the estimated prevalence of dysplasia had little effect on the number of cases of cancer that would be expected to occur within three years. Our estimates of the risk of cancer after negative results on cytologic testing are also similar to findings in other populations. Swedish investigators reported an annual incidence of squamous-cell cancer of 0.8 per 100,000 women with at least one previous negative test.<sup>33</sup>

Important assumptions used in the model affect the calculated risks. We assumed that all women would adhere to screening, follow-up, and treatment recommendations. The risk of cancer among women without such adherence would be underestimated by our model if important dysplasia were not found and treated. If the sensitivity of colposcopy were lower than we assumed or treatment were less effective than we assumed, the calculated risks

**Table 5. Average Estimated Number of Additional Tests That Would Be Required to Avert One Case of Invasive Cervical Cancer through Annual Screening Rather Than Screening Performed Once Three Years after the Last Negative Test in Hypothetical Cohorts of 100,000 Women with Three or More Previous Negative Papanicolaou Tests.**

Age	Average No. of Additional Papanicolaou Tests per Case of Invasive Cervical Cancer Averted	Average No. of Additional Colposcopic Examinations per Case of Invasive Cervical Cancer Averted
<30 Yr	42,621	2,364
30-44 Yr	69,665	3,861
45-59 Yr	209,324	11,502
60-64 Yr*	—	—

\* There were no differences in the expected rates of invasive cervical cancer according to screening strategy in this age group.

of cancer would be higher. We also assumed that the sensitivity and specificity of conventional cytologic testing<sup>34</sup> are applicable to the settings in which the tests offered through the CDC program were performed. The accuracy of tests may vary considerably according to the setting and depending on the methods used for collection, processing, and interpretation. Since the CDC program screens women in many different clinical settings and cervical tests are read at laboratories throughout the United States,<sup>8</sup> our findings are representative of outcomes throughout the country. Most tests were based on conventional cytologic analysis; if liquid-based cytologic testing has greater sensitivity than conventional cytologic testing, as some have suggested,<sup>34-36</sup> the prevalence of dysplasia and the risk of cancer among women who have had three or more negative results on liquid-based tests will be lower than those reported here.

Because of the low prevalence of dysplasia among women 60 to 64 years of age who had had three or more negative tests, annual screening yielded the same number of expected cases of cancer as screening once three years after the last negative test. For this relatively small group of women (7500 women), however, the estimates of the prevalence of dysplasia may be imprecise. Nonetheless, sensitivity analyses in which the prevalence of dysplasia was doubled indicated that only one additional case of cancer would be expected. Among women younger than 30 years of age, we found inconsistent relations between the prevalence of dysplasia and the number of previous negative tests. The American Cancer Society suggests that the intervals between screenings be increased after negative tests only among wom-

en 30 years of age or older. Given that widespread screening appears to have had minimal effect on the incidence of cervical cancer among younger women<sup>37,38</sup> and that the long-term effects of the treatments used for cervical dysplasia are unclear, additional data are required in order to evaluate the implications of more frequent screening of women in this age group.

The observed prevalence of neoplasia among women who were screened after having negative cytologic tests may be influenced by selection bias. Women who are more likely to return for screening may be either women with lower risk who are concerned about their health or women with higher risk who have a history of cervical abnormalities. We do not know whether the women in our study had other risk factors for cervical neoplasia or how such risk factors may have affected our results. Lower socioeconomic status is a risk factor for cervical neoplasia, and since participants in the CDC program are underinsured and of low income, our study is likely to reflect outcomes among women at higher-than-average risk who return for screening after multiple negative tests.

In part because of the current findings, the CDC program changed its screening policy, increasing the interval between screenings to three years after three consecutive negative tests and thereby focusing resources on screening in women who have rarely or never undergone screening. These women account for more than half of all cases of cervical

cancer that occur in the United States each year.<sup>39</sup> The policy is similar to recommendations by the American Cancer Society and the U.S. Preventive Services Task Force.<sup>1</sup>

Our findings provide reassurance to women and their health care providers that extending the intervals between screenings to three years after three or more consecutive negative Papanicolaou tests is a safe option. Women who undergo screening less often, however, should be made aware of other effective preventive interventions that may involve more frequent clinical visits. Since more than 80 percent of the women in the United States have undergone screening within the past three years<sup>40</sup> and most of the tests have been negative,<sup>7</sup> our results are applicable to many women. The low prevalence of dysplasia and cancer in this and other populations indicates the need for caution in adopting more sensitive but less specific tests (such as HPV DNA tests) for use in women with several previous negative tests,<sup>41,42</sup> given the increased costs,<sup>5</sup> the increased number of interventions,<sup>43</sup> and the reduction in the quality of life associated with false positive results.<sup>44,45</sup> The incremental assurance conferred by an additional negative screening test needs to be evaluated in the context of the observed low level of risk.

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