Increased Cervical Cancer Risk Associated With Screening at Longer Intervals

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The 2012 national recommendations for cervical cancer screening will produce a lower level of cervical cancer protection than previously afforded by annual cytology or 3-year cotesting. After a single negative cotest result, the risk of cervical cancer is twice as large at 5 years as it is at 3 years. Modeling published since the 2012 guidelines were drafted indicates that extending the cotesting screening interval from 3 to 5 years at ages 30–64 years will result in an additional 1 woman in 369 compliant with screening receiving a cervical cancer diagnosis during her lifetime, and an additional 1 in 1,639 dying of cervical cancer. The authors believe that a significant number of patients and providers would not choose to accept these additional risks if they understood them, despite the recognition of potential harms associated with more intensive screening.

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In 2012, the American Cancer Society (ACS), the American Society of Colposcopy and Cervical Pathology, and the American Society of Clinical Pathology, cosponsored a conference to develop cervical cancer screening guidelines that were subsequently adopted by the American College of Obstetricians and Gynecologists (the College). The purpose of this article is to provide what is acknowledged to be a minority viewpoint: it is the authors’ opinion that there needs to be additional discussion concerning the level of cervical cancer protection we want to provide to our patients and the level of protection that women would prefer.

Our understanding of screening interventions is changing as our understanding of the balance between risks and harms evolves. This is particularly problematic in the area of screening for cervical cancer prevention, where the time course of the disease prevents randomized prospective trials with cancer endpoints and mortality is sufficiently rare in screened women that most of the differences in benefit between different screening schemes have to do with quality of life (avoidance of the morbidity of cancer treatment compared with the morbidity associated with screening). Test sensitivity and specificity for dysplasia endpoints are therefore less important than the human cost and benefit associated with applying those tests to populations.

For a number of decades, cervical cancer screening guidelines developed by both the ACS and the College made certain that any recommended screening strategy would offer women at least the same level of protection as annual cytology. When the previous screening guidelines were developed in 2002, the available data indicated that liquid-based cytology done at 2-year intervals provided an equivalent level of protection as annual cytology, and therefore both screening approaches were considered acceptable. Moreover, modeling studies indicated that cotesting with both cytology and human papillomavirus (HPV) testing at 3-year intervals provided as much protection as annual...
cytology, a prediction that has been borne out over a decade of experience at Kaiser Permanente Northern California. Therefore, the 2002 recommendations also considered cotesting at 3-year intervals an acceptable screening approach for women aged 30 years or older. Since the 1960s, annual cytologic screening had been recommended in the United States, and the incidence of cervical cancer has dropped dramatically.

We are concerned that the 2012 ACS and College recommendations will produce a lower level of cancer protection than that previously provided by annual cytology. The new recommendations are based on consensus that the best balance between the benefits and harms of screening is achieved by cytology at 3-year intervals. The benefits are measured in terms of cervical intraepithelial neoplasia (CIN) grade 3 immediately detected and the reduction in CIN 3 and cancer (CIN 3+) in the interval before the next screening test, and the harms are measured by the number of colposcopies. Once it was decided that cytology at 3-year intervals provides an acceptable level of cervical cancer protection, this level of protection became the benchmark for other screening recommendations. Because modeling suggests that cotesting at 5-year intervals will provide cancer protection at least as good as cytology at 3-year intervals with fewer colposcopies, this option became “preferred.”

The authors see no reason that the transition to the molecular age of screening should be associated with a decrement in cancer protection. It is our opinion that the decision to consider the level of cancer protection provided by cytology at 3-year intervals as acceptable should be reconsidered, and that we should return to using the level of cancer protection provided by annual cytology as the benchmark. Failing that, if we are going to recommend a screening approach that will result in more cervical cancer cases in screened women than previously, the justification for that recommendation needs to be better defined and communicated to both patients and providers. Otherwise, we cannot expect compliance with the extended screening intervals that have been recommended. What follows is not an argument for any specific screening scheme, and it is not a request to return to annual cytology. Although the level of cancer protection offered by annual cytology is an important benchmark, annual cytology is a profoundly inefficient system that requires recognizing and following a large number of lesions that will resolve on their own and that, as a consequence, have little to do with cancer prevention. Instead, this commentary is a plea for a more informed and complete discussion of what level of cancer risk (not CIN 3+ risk) is preferred by women and their health care providers, as well as the assertion that a greater measure of patient and provider autonomy should be permitted by payers while that discussion takes place.

The first opinion that we want to offer is that rates of cancer, and not CIN 3+, are the most relevant endpoints to patients. As it was during the 2012 guideline-development process, CIN 3+ has been substituted for cancer when statistical power is inadequate using cancer alone, but with the greater experience now available, the discussion should be about cancer risk, which is the paramount concern of patients and providers.

The second point that we want to emphasize is how changing the screening benchmark from annual cytology to cytology at 3-year intervals will affect our patients. The short-term risk of cancer associated with cytology at 1- compared with 3-year intervals always has been measurably different. There is no report that the authors are aware of that suggests that cancer risks do not increase when the interval for cytology is extended from annually to every 3 years. Historically the only disagreement has been about the magnitude of the increased risk. Relative risks of cancer associated with cytology done every 3 years compared with annually range between 1.3 and 4.7, and this increase in risk is not mitigated by limiting 3-year intervals to women with previous negative screening results, nor by requiring three negative cytology results before extending intervals. Before the development of the 2012 guidelines, Katki et al quantified the cancer risk at different time periods after a single negative cytology result in 80 women diagnosed with cervical cancer in the relatively low-risk Kaiser Permanente Northern California population. They found that the risk of cervical cancer after a single negative cytology result doubled between 1 and 3 years, although the 95% confidence intervals (CI) widely overlapped. They now have extended this analysis to 500 previously screened women in Kaiser Permanente Northern California who subsequently developed cancer, 405 of whom did so within 5 years of cotesting; the doubling of risk between 1- and 3-year intervals after a negative cytology result is still present, but the 95% CIs no longer overlap. The absolute risk of cancer in women age 30–64 after a negative cytology result are 0.009% (0.008–0.012%) at 12 months and 0.020% (0.017–0.024%) at 36 months.

A similar effect is observed with extending the cotesting interval from 3 to 5 years. The absolute risks of cancer double from 0.007% (0.006–0.010%) at 3 years after a single negative cotest result to 0.014% (0.011–0.017%) at 5 years. Cancer risk at 3 years after a negative HPV test result alone was very similar but not identical to cancer risk at 3 years after a negative cotest result.
The third point that is important to understanding cervical cancer risk with different screening schemes is the appropriate timeframe. The differences in risk after a single test will no doubt seem small to many readers, but the consequences of cervical cancer screening are not those of a single year or a single test—in the United States they accrue over the many tests in the course of a woman's life. For this reason, modeling is essential to grasp the magnitude of the risks and benefits associated with different screening choices over a woman's lifetime, which the assessment of risk or benefit per test or per annum does not accurately convey. Kulasingam et al11 have published the modeling that they conducted at the behest of the U.S. Preventive Services Task Force to inform the guideline process. The consequences of different screening modalities and intervals predicted by this model are essential to grasp the magnitude of changes in cancer risk and in numbers of procedures because they are reported as events per 1,000 women over a lifetime of screening. This perspective allows what we perceive to be a more realistic and clinically relevant assessment of the potential magnitude over a woman's lifetime of the effects of seemingly small changes in cancer risk. The model indicates that, among women who are compliant with screening recommendations, changing the cotesting interval from 3 years to 5 years results in an additional 1 in 369 (2.71/1,000) being diagnosed with cancer and an additional 1 in 1,639 (0.61/1,000) dying of cervical cancer. If one considers that there are 72 million women between the ages of 30 and 64 years in the United States, a better sense of the magnitude of the increment in cancer protection, which includes additional visits, procedures that may be potentially injurious, and costs to the health care system. Although the number of colposcopies is quantifiable and therefore useful as an outcome for modeling studies, we do not believe it is an accurate measure of the potential “harms” of screening. How many women would prefer treatment of or death from invasive cervical cancer to avoid the minor discomfort and inconvenience of colposcopy? The modeling work done for the U.S. Preventive Services Task Force estimates the effect of different screening intervals on the number of both colposcopies and treatments for CIN 2+. The model predicts that 5-year cotesting would require 575.46 colposcopies per 1,000 women and 3-year cotesting would require 824.74, hence the additional colposcopies required for 3-year cotesting would number 249 (824.74-575.46). That means that every cancer prevented by cotesting at 3-year intervals as opposed to 5-year intervals would require 92 additional colposcopies and treatment of 3.2 additional women for CIN 2+. Every cancer death prevented would require 409 additional colposcopies and treatment of 14.3 additional women. Is it possible that these are risks that some women would consider acceptable, or even desirable, in contrast to the risk of cancer or death from cancer? Should there be greater public awareness of these tradeoffs if informed choices about screening are to be made?

While the harm of colposcopy per se is small, a potential “harm” of screening that both clinicians and patients are more likely to consider significant is potential for injury to a child as a result of premature delivery secondary to detection and treatment of a CIN 2 lesion that most likely would have spontaneously regressed if it had not been detected. This brings us to the fifth and last point that we would like to make, which is that the risk of premature rupture of membranes, preterm labor, and low birth weight associated with a single one-pass loop electrosurgical excision procedure (LEEP) may have been overstated.
The conflicting results reported in the literature may be explained as follows: First, the volume of tissue removed appears to be relevant to risk, and practices have undoubtedly varied over time and between locations in this regard. The trend that we observe in clinical practice toward smaller excisions may serve to make risk less than historical reports suggest. Secondly, the issue of potential bias in the design of retrospective observational studies is only recently starting to be addressed. The effect of attempting to control for bias is illustrated in recent publications. Data from 18,441 births from 12 National Health Service hospitals indicate that the observed increase in risk of prematurity associated with LEEP was a consequence of confounding and was not caused by treatment. Women who delivered and subsequently received excisional treatment after delivery had a similar increase in risk of prematurity as those treated with excision before delivery. Even if one takes the reports asserting a causal association between prior LEEP and adverse pregnancy outcome at face value, the reported increases in absolute risk are modest. In the National Health Service, the difference in delivery before 37 weeks was 9.1% with previous excisional treatment compared with 8.3% with colposcopic biopsy alone. A recent systematic review of the literature and meta-analysis that included 19 studies with different control groups found that a history of LEEP had a relative risk of 1.61 (95% CI 1.35–1.92) for delivery before 37 weeks of gestation, corresponding to absolute risks of 8.8% compared with 5.1%. However, when women who had undergone LEEP were compared with women with a history of cervical dysplasia but no excisional procedure, the relative risk of prematurity was not significantly increased at 1.08 (0.88–1.33). Therefore, we believe that, after putting the potential harms into perspective, some women would want to accept the risks associated with a 3-year cotesting interval in return for decreasing their risk of developing cervical cancer.

Most opinions come with caveats and those expressed above are no exception. First, our ability to quantify the cancer risk associated with different screening choices (let alone the risks of those choices) is imperfect and will remain so. There are no randomized controlled trials comparing cancer risk at different screening intervals, nor will there ever be. In a disease where the outcome of interest (invasive cancer) occurs in the United States at an incidence of single digits per 100,000 per year, the necessary trial size would be unmanageable. Additionally, the risks and benefits of screening aggregate over a lifetime. The use of surrogate endpoints is no help: the time course from CIN 3 to cancer is measured in decades, and CIN 3 and cancer rates change in opposite directions as more effective screening modalities are introduced. The pooling of cancer and CIN 3 as CIN 3+ is therefore statistically convenient for evaluating test performance, because one wishes to detect both, but potentially misleading as an outcome measure for population screening. We are only trying to prevent cancer, not CIN 3, and changes in detection rates of the vastly more common CIN 3 can conceal changes in the occurrence of invasive cancer.

Second, it is possible that multiple rounds of cotesting at 5-year intervals will provide cancer protection of a magnitude similar to annual cytology, although this is not predicted by any of the models. There is also reason to believe that risk will fall over time with increasing adoption of the HPV vaccines. These effects may combine (multiple rounds of cotesting and decreased prevalence of HPV 16 and 18) to provide the desired level of protection using 5-year or even longer intervals in the distant future.

For the reasons cited above, the authors recommend the following steps to encourage trust in and compliance with future screening recommendations:

1. Reexamine the benchmark cancer risk on which all of the recommendations are predicated, recognizing that the risks associated with annual cytology and cytology at 3-year intervals are not identical.
2. Permit a range of acceptable screening options, because this would better reflect the imprecision involved in estimating lifetime risks and harms associated with reducing risk as well as the expected diversity of informed patient and provider preferences regarding these competing risks.
3. Give patients and providers the best available estimates for lifetime cancer risk associated with different screening options as opposed to making judgments for them about what level of increased risk they should consider to be “inconsequential.”
4. Avoid the implementation of 3-year intervals for cytology and 5-year screening intervals for cotesting in settings without a formal computerized call and recall system, unless we are ready to countenance screening intervals significantly in excess of the recommendations for patients whose memory of the date of their last screen is imperfect.
5. Understand that current risk data will not be correct forever. Less intensive screening will be required in the vaccinated population now and the general population in the future to meet the desired benchmark level of cancer prevention.
6. Develop and expand data sources that permit examination of cancer risks over time rather than surrogate endpoints.

In conclusion, we believe that the option of screening with: 1) cotesting with cytology and a U.S. Food and Drug Administration–approved HPV test at 3-year intervals or 2) U.S. Food and Drug Administration–approved primary HPV testing at 3-year intervals should be available to all patients and providers who want to maintain a level of cervical cancer protection similar to what was previously available with annual cytology. None of the data that have emerged since the guidelines were published have served to change our opinion that the option of better protection should be an acceptable choice for those who prefer it. Ideally the advent of molecular screening should be used to permit previous levels of cancer protection with fewer visits and procedures rather than heralding an increase in cancer risk.

REFERENCES