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Characteristics of 44 Cervical Cancers Diagnosed Following Pap-Negative, High Risk HPV-Positive Screening in Routine Clinical Practice

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Abstract

Objective—To characterize the cervical cancers diagnosed following a Pap-negative, high risk human papillomavirus (HPV)-positive (Pap−/HPV+) screen in routine clinical practice.

Methods—Using data from Kaiser Permanente Northern California, we investigated the cases of cervical cancer diagnosed between January, 2003 through January, 2009 following Pap−/HPV+ screen. Two cervical specimens were routinely collected for cervical cancer screening, one for conventional cytology and the other for high risk HPV testing using Hybrid Capture 2 (Qiagen).

Results—Forty-four women (median age at diagnosis = 44 years) were diagnosed with primary invasive cervical cancer with a recent history of one or more Pap−/HPV+ screens. Twenty-six women had one Pap−/HPV+ screen preceding the diagnosis of cancer, 15 had two, and three had three. There were 16 squamous cancers, one small cell cancer, 24 adenocarcinomas, 2 adenosquamous carcinomas, and one case with separate invasive squamous and adenocarcinoma. FIGO Stage was IA in 11 women, IB in 31 women and IIA in 2 women. Treatment included a pelvic node dissection in 230, 2 (6.7%) of whom had positive nodes.

Conclusions—HPV testing contributes to early cervical cancer diagnosis detection in women with negative Pap tests. Most women in this cohort have early stage, node negative, treatable and potentially curable disease. Adenocarcinoma predominated as might be expected because cytology

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Dr. Cox serves on the scientific advisory board of and has received honorariums from Gen-Probe, Inc. Dr. Cox also serves on the data and safety monitoring board of Merck, Inc. The other authors have no conflicts of interest to report.

misses these cancers and their precursors. The majority of cancers were diagnosed following a single Pap−/HPV+ screen, suggesting that effective triage to colposcopy of women with a Pap−/HPV+ screen would be preferable to retesting in one year as currently recommended.

Keywords

cytology; cervical cancer; human papillomavirus (HPV); HPV testing

Introduction

While it has successfully reduced the burden of cervical cancer by 75% or more in the U.S. [1], a single Papanicolaou (Pap) smear/cervical cytology test is insensitive for the detection of precancer and cancer of the cervix [2]. The reduction in cervical cancer incidence associated with cytologic screening has occurred primarily among squamous cancers. Cervical cytology has not been effective in reducing the incidence of cervical adenocarcinomas [3-5], and increases in the incidence of cervical adenocarcinomas have been reported in some populations despite cytologic screening. This is despite epidemiologic evidence that a long preclinical course precedes invasive adenocarcinoma as is known to occur in squamous cancers [6]. Carcinogenic or high-risk human papillomavirus (HPV) has been detected in at least 85-90% of cervical adenocarcinomas [7,8].

Adoption into clinical practice of the addition of testing for the detection of high-risk HPV DNA (henceforth, referred to as HPV) to cytology for cervical cancer screening (co-testing) in women age 30 was motivated by the recognition that HPV testing provides greater reproducibility [9,10] and greater sensitivity for detection of cervical intraepithelial neoplasia grade 3 (CIN3) and cancer (CIN3+) [2,11-16] than cytology. However the performance of multiple tests requires defining an appropriate clinical response to discordant Pap and HPV results: Pap-positive, HPV-negative and Pap-negative/HPV-positive (Pap−/HPV+) results. In 2004, an interim guidance [17] for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening promulgated, which recommended that women with Pap−/HPV+ results undergo retesting in 6-12 months, and colposcopy for a second Pap−/HPV+. Specific recommendations for the location of biopsies to be obtained at colposcopy in this clinical setting have not been made to date. This is relevant because the insensitivity of cytology for glandular cancers and their precursors suggests that the Pap−/HPV+ women may be at disproportionate risk for these lesions compared to women whose cancers were preceded by other screening results or who were unscreened. Guidance about the conduct of colposcopy in this clinical setting would be welcome, as the diagnosis of glandular lesions such as cervical adenocarcinoma *in situ* at colposcopy is notoriously challenging [18].

The occurrence of cancers in Pap−/HPV+ women was predicted by the recognition that 99.7% of the invasive cancers reported by Walboomers *et al*. [19] were carcinogenic HPV positive, combined with evidence that the majority of cancers in women participating in screening were preceded by only negative Pap smears in the 3 years preceding their cancer diagnosis. A report from Kaiser Permanente Northern California (KPNC) by Sung *et al* in 2000 [20], noted that 70% of the women who were diagnosed with invasive cancer within 3 years of cytologic screening had had only negative Paps in the 3 years preceding their diagnosis of cancer [20]. This combination of evidence, plus the recognition that annual cytologic screening recognizes mostly transient lesions whose investigation and treatment do not benefit the patient and may prompt potentially injurious treatment [21], led KPNC to adopt co-testing using Hybrid Capture 2 (hc2; Qiagen, Gaithersburg, MD) as the preferred screening modality in women age 30 and older in November of 2002.

Co-testing was introduced into clinical practice at KPNC one facility at a time during 2003 and 2004. By the period from December 1, 2006 through February 26, 2007, 94.6% of KPNC members age 30 and older who participated in screening elected the co-testing option (screening every three years if Pap and HPV were both negative) instead of annual screening with cytology and HPV for atypical squamous cells of undetermined significance (ASC-US) triage only, which was and remains an option for members who prefer it. At the time of implementation of co-testing in late 2002, there were no recommendations about who should undergo colposcopy, so follow-up was recommended in one year with both tests for Pap−/HPV+ women. Following publication of the interim guidance in 2004 [17], colposcopy after two Pap−/HPV+ screens was recommended as an option within KPNC in 2005. This decision was not taken lightly, recognizing that perfect compliance with colposcopy for all women who were Pap−/HPV+ twice at a 12-month interval would double our colposcopy rates per screen in co-tested women age 30 and older in comparison to Pap only screening (data not shown). However, recognition that Pap−/HPV+ women were at risk of CIN3+, negative Paps preceded cancer diagnoses [20], and more precise measurement of the Pap−/HPV+ fraction (published in the first 800,000 co-tests at 3.99%[22]) led to adoption of the 2005 KPNC recommendation . Additional experience prompted strengthening the recommendation for colposcopy as the preferred management after a second Pap−/HPV+ screen in November of 2008. As a consequence, most women in this series awaited at least one additional screening following their first Pap−/HPV+ result prior to proceeding to colposcopy. When diagnosed, their characteristics were sufficiently different from cancers diagnosed by other means to motivate this report.

Methods

As part of our ongoing quality assurance and practice management efforts, the records of all women diagnosed with invasive cervical cancer between January, 2003 and January, 2009, who prior to their cancer diagnosis had had one or more negative Pap smears with a positive HPV DNA test collected within 7 days of the Pap, were identified from the laboratory databases. This activity was approved by Kaiser Institutional Review Board (IRB) and deemed exempt from IRB review by the NCI Office for Human Subjects Research. The Northern California Cancer Registry data was accessed and compared to laboratory records to assure excellent cervical cancer case ascertainment. HPV DNA testing for 13 carcinogenic HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68) was performed using hc2 according to the manufacturer's instructions. Conventional cytology was used. Results for this case series were excluded from this analysis if the HPV testing was performed in duplicate or no result was available, or the Pap result was unsatisfactory or "other" (the 2001 Bethesda System general categorization commonly used for "exfoliated endometrial cells present in a woman >40").

The Kaiser Regional Laboratory, where many of the KPNC Pap slides (~75%) are evaluated, annually meets or exceeds the requirements of the Laboratory Accreditation Program of the College of American Pathology. Approximately 97% of Paps and HPV specimen collected at KPNC are taken by 739 clinicians in Gynecology Departments. Every year since the 2003 to 2009 the reported percentage of unsatisfactory Paps for the central lab has been less 0.5% and has been within the 25th percentile for lowest percentage of all laboratories surveyed by the College of American Pathologists.

While liquid-based cervical cytology is used for in ~90% of U.S. clinics, a recent meta-analysis [23] and two prospective randomized controlled clinical trials indicate that liquid-based cervical cytology is not more sensitive and may be less specific for detection of high-grade cervical intraepithelial neoplasia than the Pap smear [24,25]. Thus, the use of LBC, widely adopted in advance of credible evidence of greater screening accuracy than

conventional Pap smears [26], would not be expected to alter our observations about the addition of HR HPV testing to cytology.

Records were reviewed by one of the authors (WK) to elicit screening histories, tumor histology and other characteristics such as nodal involvement. Pap smears interpreted as "negative" or "within normal limits (WNL)" or "benign cellular changes" in years prior to the adoption of the current Bethesda terminology were grouped with those with "NIL" results. FIGO staging was garnered from physician and laboratory records according to the definitions in place at the time of cancer diagnosis.

For purposes of comparison, cases were grouped by histology into those containing a glandular component (adenocarcinoma, adenosquamous carcinoma) and those not containing a glandular component (squamous, small cell). Cases were also grouped for analysis by dividing the study period roughly in half, with women diagnosed in 2003-2005 compared to those diagnosed in 2006-2009, representing two time periods with different management recommendations: the 2005 recommendations for colposcopy after two Pap−/HPV+ results were promulgated inside KPNC in November of 2005.

Characteristics of the Pap−/HPV+ cases were tabulated. Fisher's exact test was used to test for statistical significance ($p < 0.05$, two-sided) between time periods of 2003-5 and 2006-9.

For the percentage of positive nodes, we calculated the binomial 95% confidence intervals. We used binomial distribution to test for differences between the observed proportions of cervical cancers of glandular origins and an approximate expected proportion of approximately 20% [3] and between the observed proportions of positive nodes and expected proportion of 15.5%.

Results

During the analysis period January, 2003 through January, 2009, there were 46,674 Pap−/HPV+ results and 44 women were diagnosed with primary invasive cervical cancer following one or more Pap−/HPV+ screens. A summary of the cases is presented in Table 1. Of the 44 cases, 25 (57%), 15 (34%), and 4 (9%) cases had one, two and three Pap−/HPV+ screens, respectively, before cancer diagnosis. A negative or unsatisfactory Pap and HPV positive co-test was the last screening result preceding the cancer diagnosis in 17 (34%) cases.

For perspective, during the same time period, there were 21 cancers (median age = 53 years) that were preceded by a Pap-positive, HPV-negative (Pap+/HPV−) co-test. Seven were adenocarcinoma, 12 were squamous cell carcinoma, one was an unspecified cancer preceded by a carcinoma *in situ* diagnosis, and one was neuroendocrine histology, the latter of which may not be caused by HPV. The Pap interpretations at the most proximal Pap+/HPV− co-test results were 5 atypical squamous cells of undetermined significance, 5 atypical glandular cells or adenocarcinoma *in situ*, 4 cancers, 1 high-grade squamous intraepithelial lesion (HSIL), 4 atypical squamous cells cannot rule out 1 HSIL, 1 low-grade squamous intraepithelial lesion, and 1 negative with endometrial cells (from a post-menopausal woman).

Diagnosis of invasive cancer occurred after a single Pap−/HPV+ co-test with no further screening in 12 of 44 (27%) women. After their first Pap−/HPV+ co-test, 32 (75%) women were rescreened prior to diagnosis: 7 (22%) had a final co-test within 12 months, 8 (25%) between 12 and 18 months, 5 (16%) between 18-24 months, and 12 (38%) for 24 months or longer. Notably, there was a shorter time interval between the first Pap−/HPV+ result and

last co-test in the 2006-9 than 2003-5 ($p = 0.01$), following the adoption of guidelines to send women with a second consecutive Pap−/HPV+ to colposcopy in 2006.

Twenty (45%) were under the age of 40, 15 (34%) were aged 40-49, 6 (14%) were aged 50-59, and 3 (7%) women were aged 60 and above at the time of the first Pap−/HPV+ co-test; the mean and median ages were 42 and 41 years. This distribution did not change appreciably between 2003-2005 and 2006-9. The mean and median ages at the cancer diagnosis were 44 years.

Histology included 16 (36%) pure squamous cancers, one (2%) small cell cancer, 27 (61%) with a glandular component, including 24 adenocarcinomas, two adenosquamous tumors and one “collision tumor” (separate invasive adenocarcinoma and squamous); there was a significantly greater fraction of cervical cancers with glandular component than the expected ($p < 0.001$). FIGO Stage was IA in 11 women, IB in 31 women (6 IB1, 6 IB2, and 19 for whom FIGO sub-staging was not recorded) and IIA in 2 women.

Overall, 8 cancers had chemoradiation, 33 had surgery (radical hysterectomy), and three had both. Among the 6 Stage IB2, 5 were treated with primary chemoradiation. Among the 25 IB1 and IB unspecified, 20 had primary radical hysterectomy, 2 had primary chemoradiation after positive nodes were diagnosed on pre-operative imaging and laparoscopy, one had a total abdominal hysterectomy for other indications with unrecognized invasive cervical cancer, and 2 had primary chemoradiation for unspecified reasons.

Treatment included a pelvic node dissection in 30; 2 of 30 (6.7%; 95%CI = 0.82%-22.1%) had positive nodes, which was marginally less than expected ($p = 0.1$). Stage distribution and age distributions were similar regardless of the presence or absence of a glandular component, as were the distributions by year of diagnosis, number of Pap−/HPV+ screens preceding diagnosis, and time to diagnosis from first Pap−/HPV+ screen.

Discussion

The strengths of this study are that the size of the experience with co-testing is large enough to permit an evaluation of the rare endpoint of invasive cancer, and that the study cohort was tested in routine clinical practice using a commercially-available test for HR HPV DNA. “Routine clinical practice” in this environment means that providers with different levels of training are providing services, and that no extraordinary follow-up measures are undertaken, as might occur in the clinical trial setting. An additional strength of the study is the assurance of complete case ascertainment provided by independent assessment of the cancer registry and the laboratory database.

The weaknesses of this evaluation are attributable to the gradual introduction of co-testing facility by facility during 2003 and 2004, to the changing clinical practice recommendations during the study period, and to the evolution of data acquisition and collection practices during the study period. At the outset of the study, data concerning screening outcomes and histologic correlations were kept separately by all 6 labs involved in this work. With the implementation of a single computerized system in 2005, it became possible to gather information from all of the 5 smaller labs in addition to the Regional lab that handles approximately 77% of the cytology and all of the HPV testing.

Another limitation is that the cancer tissues and Pap slides were not readily accessible because Kaiser does not store all of these specimens at a single facility, which prevented us from conducting secondary analyses on them such as HPV genotyping and pathology review of the cancer tissue. HPV genotyping would have been particularly useful to know whether there are HPV-genotype specific cancers that are more prone to be missed by cytology. With

regards to pathology review, a retrospective review would have been valuable but limited since it is well known that all tests have error and cytology, with only modest reliability and sensitivity, is no exception. However, the inter-observer agreement for negative cytology is generally better than for any other cytologic categorization [27,28].

Studying time periods in which the denominators are changing and/or unmeasured prevents us from answering many questions that could be addressed in the clinical trial setting, such as the percentage of Pap−/HPV+ screens herald the presence or the subsequent development of cervical cancer. Of the 44 women included in this report, 31 were diagnosed with cancer in 2003-2005 (mean of 10.3/year) and 12 were diagnosed in 2006-2008 (mean of 4/year), with one case from January of 2009. This is perhaps understandable given the change in practice recommendations in November of 2005.

To put these numbers of cervical cancers following a Pap−/HPV+ screen in perspective, we found a total of 506 of cervical cancer cases reported (without chart review and excluding 23 cancers of uncertain origins) during the same time period, of which we expect based on historical experience that approximately 60% occur in women who have not been screened in the preceding 3 years (and most not for the preceding 5+ years) [20]. Therefore, roughly 22% of all cases of cervical cancer among those undergoing routine screening were preceded by at least one Pap−/HPV+ co-test. It is our expectation that this proportion may change further with the implementation of KPNC recommendations, starting in November, 2008, in which women with repeat Pap−/HPV+ are referred to colposcopy.

We emphasis that while a Pap−/HPV+ co-testing result is fairly common, approximately 4% of all screening results [22], it does denotes some risk of cervical cancer. Previous studies have shown that women with Pap−/HPV+ co-testing results are at about a 5% risk of CIN3 or cancer (CIN3+) over a 10 year interval [29]. In a large screening setting, a small fraction of these CIN3 will invade if not identified and treated in a timely fashion.

The results of the ARTISTIC (A Randomized Trial of HPV Testing in Primary Cervical Screening) Trial [30] emphasize this point, in which failure to follow up and adequately diagnose disease in Pap−/HPV+ women negated the improved sensitivity for CIN3+ associated with the addition of HR HPV testing to cytology [31]. Without appropriate management and improved strategies such as incorporating biomarkers [32-34] to manage Pap−/HPV+ women, the benefits of including HPV testing in cervical cancer screening may not be fully realized.

Despite the absence of an established triage strategy for Pap−/HPV+ results, these cases were still diagnosed at a younger age and with fewer node positive cases than cervical cancers diagnosed by conventional means, which may provide benefit to patients. The 44 women whose cancers were heralded by Pap−/HPV+ results had median age of 43 years. By comparison, the 584 women in the cancer registry with cervical cancer in 2003 to 2008 who did not have their cancers preceded by this screening result were significantly older, with median age of 49 ($p < 0.01$, Kruskal-Wallis). Only 2/30 (6.7%) of women treated with surgery were node positive, a percentage that is non-significantly ($p = 0.1$) less than the 15.5% based on the pooled series of unradiated Stage I cervical cancer patients [35-38].

One of the challenges in cervical cancer screening has been timely detection of the glandular precursors (e.g., adenocarcinoma *in situ* [AIS]) prior invasion, which happens in the same timeframe as squamous precursors [6]. Finding a high percentage of adenocarcinomas among the Pap−/HPV+ women is consistent with previous findings that cytology preferentially misses adenocarcinoma and its precursors compared with squamous lesions [39]. Pap smears are more effective in reducing the risk of squamous cell carcinoma than adenocarcinoma ([40]. The rise in the incidence of adenocarcinoma juxtaposed with the

decline of squamous cell carcinoma suggests that screening with cytology alone does not effectively detect precursors of invasive adenocarcinoma such as AIS in a timely fashion [3,41]. Recent reports from ongoing randomized trials evaluating HPV testing have found a non-significantly greater proportion of AIS in the HPV study arm compared to the conventional cytology [12,15,16], providing further evidence that HPV testing may help identify women with glandular disease.

Finally, we suggest that HR-HPV-positive/cytology-negative women warrant careful evaluation for adenocarcinoma when referred to colposcopy. This may include endocervical sampling such as endocervical curettage (ECC). However, the diagnostic yield of ECC and therefore its utility is somewhat controversial in other settings [42,43]. In KPNC data and in other clinical databases known to us the ECC collections are often deemed “unsatisfactory” or “scant”. Thus steps need to be taken to improve ECC/endocervical sampling for timely detection and treatment of AIS to prevent invasive cervical adenocarcinoma.

In summary, the addition of HPV testing to cytology appears to identify a cohort of women who have or will soon have invasive cancer despite a negative Pap. When identified, these cancers most frequently have a glandular component, and are diagnosed younger and with less risk of nodal metastases than those identified by other means. Thus, the development of a viable strategy for identifying the subset of women at highest risk of CIN3 at the time of the initial Pap−/HPV+ screen would further improve the efficiency of secondary cervical cancer prevention and potentially benefit those women who already have cancer by detecting it earlier.

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Reference List

[1]. Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine. 2006; 24(Suppl 3):S63–S70. S63-70.

[2]. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer. 2006; 119:1095–101. [PubMed: 16586444]

[3]. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr. Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer. 2004; 100:1035–44. [PubMed: 14983500]

[4]. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. Gynecol Oncol. 2000; 78:97–105. [PubMed: 10926787]

[5]. Reimers LL, Anderson WF, Rosenberg PS, Henson DE, Castle PE. Etiologic heterogeneity for cervical carcinoma by histopathologic type, using comparative age-period-cohort models. Cancer Epidemiol Biomarkers Prev. 2009; 18:792–800. [PubMed: 19258470]

[6]. Plaxe SC, Saltzstein SL. Estimation of the duration of the preclinical phase of cervical adenocarcinoma suggests that there is ample opportunity for screening. Gynecol Oncol. 1999; 75:55–61. [PubMed: 10502426]

[7]. Castellsague X, Diaz M, de Sanjose S, Munoz N, Herrero R, Franceschi S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006; 98:303–15. [PubMed: 16507827]

[8]. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer. 2007; 121:621–32. [PubMed: 17405118]

[9]. Castle PE, Wheeler CM, Solomon D, Schiffman M, Peyton CL. Interlaboratory reliability of Hybrid Capture 2. Am J Clin Pathol. 2004; 122:238–45. [PubMed: 15323141]

[10]. Carozzi FM, Del Mistro A, Confortini M, Sani C, Puliti D, Trevisan R, et al. Reproducibility of HPV DNA Testing by Hybrid Capture 2 in a Screening Setting. Am J Clin Pathol. 2005; 124:716–21. [PubMed: 16203283]

[11]. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses. Vaccine. 2006; 24(Suppl 3):S78–S89. S78-89.

[12]. Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet. 2007; 370:1764–72. [PubMed: 17919718]

[13]. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. 2007; 357:1579–88. [PubMed: 17942871]

[14]. Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007; 357:1589–97. [PubMed: 17942872]

[15]. Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. BMJ. 2010; 340:c1804. c1804. doi: 10.1136/bmj.c1804. [PubMed: 20423964]

[16]. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Palma PD, Del MA, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010

[17]. Wright TC Jr. Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol. 2004; 103:304–9. [PubMed: 14754700]

[18]. Ferris, DG.; Cox, JT.; O'Connor, DM.; Wright, CV.; Foerster, J. Modern Colposcopy. Kendall Hunt Publishing Company; Dubuque, Iowa: 2004. p. 329-49.

[19]. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189:12–9. [PubMed: 10451482]

[20]. Sung HY, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. Cancer. 2000; 88:2283–9. [PubMed: 10820350]

[21]. Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ. 2008; 337:a1284. a1284. doi: 10.1136/bmj.a1284. [PubMed: 18801868]

[22]. Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Five-year experience of human papillomavirus DNA and papanicolaou test cotesting. Obstet Gynecol. 2009; 113:595–600. [PubMed: 19300322]

[23]. Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol. 2008; 111:167–77. [PubMed: 18165406]

[24]. Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. JAMA. 2009; 302:1757–64. [PubMed: 19861667]

[25]. Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla PP, Naldoni C, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ. 2007; 335:28. [PubMed: 17517761]

[26]. Sawaya GF. Evidence-based medicine versus liquid-based cytology. Obstet Gynecol. 2008; 111:2–3. [PubMed: 18165385]

[27]. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA. 2001; 285:1500–5. [PubMed: 11255427]

[28]. Sherman ME, Dasgupta A, Schiffman M, Nayar R, Solomon D. The Bethesda Interobserver Reproducibility Study (BIRST): a web-based assessment of the Bethesda 2001 System for classifying cervical cytology. Cancer. 2007; 111:15–25. [PubMed: 17186503]

[29]. Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst. 2003; 95:46–52. [PubMed: 12509400]

[30]. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol. 2009; 10:672–82. [PubMed: 19540162]

[31]. Sasieni P, Castle PE, Cuzick J. Further analysis of the ARTISTIC trial. Lancet Oncol. 2009; 10:841–2. [PubMed: 19717086]

[32]. Carozzi F, Confortini M, Palma PD, Del MA, Gillio-Tos A, De ML, et al. Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. 2008

[33]. Szarewski A, Ambroisine L, Cadman L, Austin J, Ho L, Terry G, et al. Comparison of predictors for high-grade cervical intraepithelial neoplasia in women with abnormal smears. Cancer Epidemiol Biomarkers Prev. 2008; 17:3033–42. [PubMed: 18957520]

[34]. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005; 20:97, 1072–9.

[35]. Tanaka Y, Sawada S, Murata T. Relationship between lymph node metastases and prognosis in patients irradiated postoperatively for carcinoma of the uterine cervix. Acta Radiol Oncol. 1984; 23:455–9. [PubMed: 6099039]

[36]. MORTON DG, Lagasse LD, Moore RD, Jacobs M, AMROMIN GD. Pelvic lymphnodectomy following radiation in cervical carcinoma. Am J Obstet Gynecol. 1964; 88:932–43. 932-43. [PubMed: 14141464]

[37]. Graham, JB.; Sotto, LSJ.; Paoloucek, FP. Carcinoma of the Cervix. WB Saunders; Philadelphia: 1962. p. 190

[38]. Christensen A, LANGE P, NIELSEN E. Surgery and radiotherapy for invasive cancer of the cervix. Surgical treatment. Acta Obstet Gynecol Scand. 1964; 43(Suppl2):59–87. [PubMed: 14154707]

[39]. Pak SC, Martens M, Bekkers R, Crandon AJ, Land R, Nicklin JL, et al. Pap smear screening history of women with squamous cell carcinoma and adenocarcinoma of the cervix. Aust N Z J Obstet Gynaecol. 2007; 47:504–7. [PubMed: 17991118]

[40]. Sasieni P, Castanon A, Cuzick J. Screening and adenocarcinoma of the cervix. Int J Cancer. 2009; 125:525–9. [PubMed: 19449379]

[41]. Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev. 2005; 14:2191–9. [PubMed: 16172231]

[42]. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004; 191:430–4. [PubMed: 15343217]

[43]. Solomon D, Stoler M, Jeronimo J, Khan M, Castle P, Schiffman M. Diagnostic utility of endocervical curettage in women undergoing colposcopy for equivocal or low-grade cytologic abnormalities. Obstet Gynecol. 2007; 110:288–95. [PubMed: 17666602]

Table 1

Description of the 44 cases of cervical cancer following an index Pap−/HPV+ cotesting result in women 30 and older

	All		2003-5		2005-9		
	N	col%	N	col%	N	col%	p
Age at 1st Pap−/HPV+ result							
<40	20	45%	13	42%	7	54%	0.9
40-49	15	34%	11	35%	4	31%	
50-59	6	14%	5	16%	1	8%	
60+	3	7%	2	6%	1	8%	
Age at Cancer Diagnosis							
<40	19	43%	12	39%	7	54%	0.8
40-49	16	36%	12	39%	4	31%	
50-59	6	14%	5	16%	1	8%	
60+	3	7%	2	6%	1	8%	
Number of Pap−/HPV+ before Diagnosis							
1	25	57%	16	52%	9	69%	0.7
2	15	34%	12	39%	3	23%	
3	4	9%	3	10%	1	8%	
Number of Screens after 1st Pap−/HPV+							
0	12	27%	7	23%	5	38%	0.1
1	17	39%	10	32%	7	54%	
2	12	27%	11	35%	1	8%	
3	3	7%	3	10%	0	0%	
Time between 1st Pap−/HPV+ and Last Co-test †							
≤12 months	7	22%	2	9%	5	56%	**0.01**
12-18 months	8	25%	5	22%	3	33%	
18-24 months	5	16%	5	22%	0	0%	
≥24 months	12	38%	11	48%	1	11%	
Final Co-testing Results before Diagnosis							
Pap+/HPV+*	27	61%	21	68%	6	46%	0.3
Pap−/HPV+ (includes unsatisfactory Paps)	17	39%	10	32%	7	54%	

	All		2003-5		2005-9		
	N	col%	N	col%	N	col%	p
Pap+/HPV−	0	0%	0	0%	0	0%	
Pap−/HPV−	0	0%	0	0%	0	0%	
Cancer Histology							
adenocarcinoma	24	55%	16	52%	8	62%	0.6
adenocarcinoma & squamous	1	2%	0	0%	1	8%	
adenosquamous	2	5%	2	6%	0	0%	
small cell	1	2%	1	3%	0	0%	
squamous	16	36%	12	39%	4	31%	
Figo Stage							
IA	11	25%	10	32%	1	8%	0.2
IB	31	70%	20	65%	11	85%	
IIA	2	5%	1	3%	1	8%	
Pelvic Node Dissection							
No	14	32%	7	23%	7	54%	0.2
Yes and Negative	28	64%	20	65%	8	62%	
Yes and Positive	2	5%	2	6%	0	0%	
Treatment							
Chemoradiation	8	18%	3	10%	5	38%	0.07
Surgery	33	75%	26	84%	7	54%	
Surgery& Chemoradiation	3	7%	2	6%	1	8%	

[†] Restricted to those who had at least one additional cotest

[*] Includes cytologic interpretations of squamous cell cancer (n = 2), high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma *in situ* (n = 8), atypical glandular cells (AGC) (n = 6), atypical squamous cells (ASC) or ASC, cannot rule out HSIL (ASC-H) (n = 8), ASC-H/AGC (n = 1), and LSIL (n = 2).