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Risk of recurrent disease in women with cervical intraepithelial neoplasia grades 2 and 3

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Boston University
RISK OF RECURRENT DISEASE IN WOMEN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA GRADES 2 AND 3

by

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First, I would like to thank my friends and family who have supported, loved, and guided me during my long and winding journey through life and to the PA profession. I would like to thank Dr. Rebecca Perkins for inviting me to work on this topic with her, and for her guidance and patience throughout this project. Thank you also to Dr. Oren Berkowitz for answering my never-ending list of questions. Finally, a huge thank you goes to Patti Paleologos for her endless support, and for graciously volunteering to edit my thesis.
ABSTRACT

Background

Cervical cancer has historically been a major cause of mortality for women worldwide. Over the last 50 years, thanks to advances in screening technologies and the implementation of standardized management algorithms, the incidence of cervical cancer in the United States has been declining.

Literature review

In the most recent set of algorithms, the 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors, the authors conclude that there is high-level evidence to support extended screening intervals for women who are at average-risk for cervical cancer and who have a history of negative screening tests. However, there is large population of women with a history of abnormal screening tests, and their risk of recurrent disease is not well understood. Additionally, the predictive value of the available screening tests for this cohort of women is unknown. The authors of the 2012 Guidelines warn that there is insufficient evidence for optimal management of these women, the current guidelines are based on expert opinion only, and studies providing high-level evidence are lacking.
Proposed project

This thesis proposes a systematic literature review of the existing evidence regarding to what extent women who are treated for cervical abnormalities at baseline are at an increased risk for persistent or recurrent disease in the future. Journal articles will be gathered from three different databases and abstracts will be screened for duplicity and relevancy. After article selection, the quality of evidence presented in each paper will be evaluated using the GRADE system to facilitate a methodical and accurate comparison of the existing evidence. Finally, a scheme for data abstraction from the articles will be outlined.

Conclusions

The results of this systematic literature review will serve multiple purposes, including identifying what research has been done since the latest revision of management guidelines, and aiding in the revision of the algorithms for the population of women who have had abnormal screening test results. It will also identify persistent gaps in the body of knowledge regarding this cohort of patients, and guide the development of additional research studies to fill those gaps.

Significance

Determining the risk of recurrent disease in women with abnormal cervical cancer screening tests will serve to more optimally manage this cohort of women. This will allow providers to effectively monitor patients for the recurrence of cervical disease, while also minimizing the risks associated with overscreening.
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<td>American College of Obstetrics and Gynecology</td>
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<td>ACS</td>
<td>American Cancer Society</td>
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<tr>
<td>AGC</td>
<td>Atypical Glandular Cells</td>
</tr>
<tr>
<td>AIS</td>
<td>Adenocarcinoma in situ</td>
</tr>
<tr>
<td>ASC-H</td>
<td>Atypical Squamous Cells, cannot exclude high-grade squamous intraepithelial lesions</td>
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<td>ASC-US</td>
<td>Atypical Squamous Cells of Undetermined Significance</td>
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<td>ASCCP</td>
<td>American Society of Colposcopy and Cervical Pathology</td>
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<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HPV</td>
<td>Human Papillomavirus</td>
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<td>HSIL</td>
<td>High-grade Squamous Intraepithelial Lesion</td>
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<tr>
<td>LEEP</td>
<td>Loop Electrosurgical Excision Procedure</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low-grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
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<tr>
<td>NILM</td>
<td>Negative for Intraepithelial Lesion or Malignancy</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
</tr>
<tr>
<td>TZ</td>
<td>Transformation Zone</td>
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<td>----</td>
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<tr>
<td>USPSTF</td>
<td>United States Preventative Services Task Force</td>
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<tr>
<td>VLP</td>
<td>Virus-like Particle</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

Background

Once the number one killer of women in the United States, cervical cancer is now much less common thanks to the widespread implementation of screening protocols and advances in technology and treatment.\(^1\) In 2013, there were approximately 12,000 newly diagnosed cervical cancer cases in the U.S. and a little over 4,000 deaths. Fortunately, both incidence and mortality are trending downwards with the institution of screening and treatment algorithms.

One of the results of highly effective cervical cancer screening technologies is an increased rate of detection of precancerous lesions. In addition to the diagnosis of cases of true cervical cancer, 1.4 million women are diagnosed with low-grade cervical abnormalities and 330,000 undergo treatment for high-grade abnormalities each year. It is estimated that 25% of women are diagnosed with an abnormal Papanicolaou (Pap) test at some point in their lifetimes.\(^2\) Until recently, all women were managed with yearly Pap tests regardless of their previous screening results. Now, with advances in technology and insight into the harms inherent to overscreening, providers are lengthening the time between screening tests for certain cohorts of patients. There is strong evidence supporting extended screening intervals for women who have always had negative Pap and negative Human Papillomavirus (HPV) tests because their risk of developing cancer within one year is very low.\(^3\) But for the women who have had an abnormal screening test in the past and were treated, the picture is less clear.
Statement of the Problem

The 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors was endorsed by The American College of Obstetrics and Gynecology (ACOG), American Cancer Society (ACS), United States Preventative Services Task Force (USPSTF), and American Society of Colposcopy and Cervical Pathology (ASCCP) for managing the care of women with abnormal screening results.3 There is high-level evidence demonstrating that women with negative Pap tests, with or without the presence of HPV, can be safely screened every 3-5 years due to the very low risk of developing cervical cancer during that time interval. It has been shown that women who have a history of an abnormal Pap test have an increased risk of developing cervical cancer at some point in the future. However, the length of time that the risk remains elevated and the predictive value of negative Pap and HPV testing is also unclear. Additionally, when the 2012 Updated Consensus Guidelines were generated, there was insufficient high-level evidence supporting optimal management algorithms for women with abnormal Pap tests who were subsequently treated.3 In the years since the guidelines were updated, the scientific community has presumably moved forward to address this gap in the literature. This thesis proposes to design a systematic literature review of the existing research addressing to what extent women who are treated for cervical abnormalities at baseline are at an increased risk for persistent or recurrent disease in the future. This data can then be used to develop optimal long-term surveillance algorithms for women with a history of cervical dysplasia.
Hypothesis

Women who have abnormal screening Pap tests have a sustained, increased risk of persistent and/or recurrent cervical disease, even after treatment.

Objectives and specific aims

The objective of this project is to design a systematic literature review that will identify existing research regarding the recurrence of cervical disease in women who have previously had an abnormal screening test result and were subsequently treated.

The Specific Aims of this proposal are to:

1. Perform an exhaustive and systematic review of the literature on risk of recurrent cervical disease after an abnormal Pap smear/biopsy and treatment of the lesion
2. Evaluate the strength of evidence of the existing research
3. Provide an outline for data abstraction of the existing evidence
REVIEW OF THE LITERATURE

Overview

Across the globe, cervical cancer is the fourth most common cancer occurring in women and the second most frequent cause of cancer-related deaths in women. In 2012, over 528,000 new cases of cervical cancer were diagnosed worldwide and 266,000 deaths were reported. Rates of cervical cancer are lower in industrialized nations, with 80% of all cervical cancers occurring in developing nations, the majority being in Africa, Latin America, and the Caribbean.

Historically, cervical cancer was equally prevalent worldwide. However, in the U.S., cervical cancer is now the 14th most common cancer affecting women. In 2013, there were approximately 12,000 newly diagnosed cervical cancer cases in the U.S. and a little over 4,000 deaths. Cervical cancer deaths have decreased by over 70% during the last 50 years, correlating with the widespread implementation of the Pap test as a standard of care in women’s health to facilitate early detection and treatment of precancerous lesions of the cervix.

Dr. George Papanicolaou developed the Pap test technique in the 1920’s and first published a paper on its utility in the 1940’s. By the 1950’s, the use of the Pap test increasingly became a standard of care thanks to preventative medicine campaigns by the American Cancer Society. The establishment of the Pap test as a routine screening tool in the 1970’s revolutionized the field of women’s health care by allowing clinicians to detect cervical precancer in a cost-effective and minimally invasive way. Physicians now use this tool to guide women’s care and treat appropriately in order to prevent the
development of true cervical cancer. The employment of the Pap test as a routine screening tool has been lauded as an exemplary model for successful preventative medicine.\textsuperscript{11}

The uterine cervix is a structure made of firm connective tissue located at the junction of the uterus and the vagina. Its function is to control the passage of materials from inside the uterus to the outside environment and vice versa. Cervical cancer often appears after the tissues of the cervix are exposed to a carcinogen.\textsuperscript{4} Eighty to 90\% of cervical malignancies are squamous cell carcinomas (SCC), and the remaining 10-20\% of cervical cancers are adenocarcinomas. Both types of cancer can be detected by the Pap test, and are considered largely preventable by HPV vaccination and screening.

While multiple risk factors for the development of SCC of the cervix have been identified, persistent infection with certain strains of HPV is considered to be the most important.\textsuperscript{11} Additional risk factors are listed in Table 1. HPV is a DNA virus with over 100 different genotypes, at least 15 of which can cause cervical cancer. Multiple HPV strains have been identified as oncogenic, with types 16 and 18 being the most virulent.\textsuperscript{12} It is estimated that 70\% of cervical cancers and 54\% of high-grade cervical lesions are due to infections with HPV strains 16 or 18.\textsuperscript{11} Clinicians first noted the relationship between cervical cancer and sexual activity over 150 years ago when they noticed that cervical cancer was very prominent in women who worked as prostitutes, but was virtually non-existent in celibate nuns. Epidemiological data also suggested that cervical cancer behaves like a sexually transmitted disease. In the 1970’s scientists proposed a role for HPV in cervical cancer, and in the mid-1980’s HPV types 16 and 18 were
isolated from cervical cancer biopsies and then cloned, illustrating the causal relationship between the virus and cervical cancer.\(^4,13\)

**Table 1.** Risk factors for cervical cancer.\(^4\)

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tr>
<td>Early onset of sexual activity</td>
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<tr>
<td>Multiple or high-risk partners</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>HPV infection, especially strains 16 or 18</td>
</tr>
<tr>
<td>History of sexually transmitted infection</td>
</tr>
<tr>
<td>High parity</td>
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<tr>
<td>Immunosuppression</td>
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<tr>
<td>Low socioeconomic status</td>
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<td>Prolonged use of Oral Contraceptive Pills</td>
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</table>

HPV infection of the cervix is necessary but not sufficient for the development of squamous cell carcinoma of the cervix, with 99% of cervical cancers associated with HPV.\(^4,14\) Furthermore, the majority of HPV infections appear to be transient. (Figure 1) It is estimated that 80% of all sexually active women will be infected with HPV at least once during their lifetime. The average duration of infection is 8 months and 90% of immunocompetent young women who contract HPV will clear the infection without medical intervention within two years. The risk of developing cervical cancer increases when an infection with an oncogenic strain persists, typically longer than 10 years.\(^4\)
Figure 1. Relationship among incidences of cervical HPV infection, precancer, and cancer.\textsuperscript{15}

HPV infection leads to cervical cancer when the virus induces changes in the epithelial cells of the cervix, causing them to become cancerous over time.\textsuperscript{9} Infection occurs when the virus reaches the deepest layer of cervical cells, the basal layer of the epithelium, via microscopic breaks in the epidermis. The presence of the virus in the basal cells leads to morphological changes in those cells as they differentiate and move up through the layers of the epidermis towards the surface. Some changes can be seen on cytopathology, but the type of cellular changes and the extent of involvement of the epidermis are evaluated via tissue biopsy and histological examination. The lesions caused by HPV infection are known as cervical intraepithelial neoplasia, or CIN, and
they are graded on a continuous scale of 1-3, with 3 being the most severe.⁴ (Figure 2) CIN1 is described as having abnormal cellular changes in the lower 1/3 of the epithelial cell layer. As increasingly more of the epithelial layer is involved, the lesion is considered to be a higher grade of abnormality and likelihood that the lesion will progress to cancer increases.

**Figure 2.** Progression from a benign cervical lesion to invasive cervical cancer. ⁹

The identification of these abnormal but not yet cancerous lesions led to the development of evidence-based management guidelines that include multiple algorithms tailored to specific types of abnormalities that may be identified with a Pap test. The 2012 *Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer*
Screening Tests and Cancer Precursors is the most current resource for providers of women’s health care. The goal of the various algorithms is to maximize the chances of identifying precancer and cancer in individual patients, while also minimizing the harms inherent in over-screening, such as over-treatment and emotional distress caused by abnormal test results and anticipation of further interventions.

The general process of screening for cervical cancer is as follows: During a Pap test, the superficial layer of squamous cells of the cervix are collected, fixed and stained on a slide, and examined under a microscope. The key to the success of the Pap test is the fact that any abnormal cells collected from the exterior of the cervix will contain the nuclear abnormalities indicative of neoplastic changes. The presence of neoplastic cells signifies the need for further investigation. The principal cytology results from the Pap test are low-grade or high-grade squamous intraepithelial lesion (LSIL or HSIL). Additional cytology results are listed in Table 2. Atypical Squamous Cells of Undetermined Significance (ASC-US) refers to a Pap result where the cytologist remarks that the cells are not normal appearing, but that they lack sufficient morphologic features to definitively interpret the sample as an intraepithelial lesion. ASC-US is the most commonly encountered abnormal result.

<table>
<thead>
<tr>
<th>Table 2. Possible Pap test cytology results.</th>
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<tr>
<td>Negative for Intraepithelial Lesion or Malignancy (NILM)</td>
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<tr>
<td>Atypical Squamous Cells of Undetermined Significance (ASC-US)</td>
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<tr>
<td>Low-grade Squamous Intraepithelial Lesion (LSIL)</td>
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<tr>
<td>Diagnosis</td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Atypical Squamous Cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H)</td>
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<tr>
<td>High-grade Squamous Intraepithelial Lesion (HSIL)</td>
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<tr>
<td>Atypical Glandular Cells (AGC)</td>
</tr>
<tr>
<td>Cytologic Adenocarcinoma In Situ (AIS)</td>
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<td>Invasive Carcinoma</td>
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Following an abnormal Pap test, the patient may undergo a colposcopy. During this procedure the clinician uses a colposcope, a microscope specially designed for close examination of the cervix, and the application of acetic acid to inspect the cervix for suspicious lesions. Normal cells with typical amounts of intracellular proteins do not react with the acetic acid, and so their appearance remains unchanged with the application of the acid. Cells that are abnormal turn white when acetic acid is applied due to a high nuclear activity and increased amount of protein. The acetic acid denatures the proteins, which results in the abnormal cells appearing white. If a specific lesion is identified using the colposcope, the clinician will perform a punch biopsy of that area of the cervix and send it for histological examination.

Biopsies taken during a colposcopy may result in various outcomes (see Table 3). If a biopsy result shows CIN1, likely no further treatment is needed and the clinician will monitor the patient closely to ensure resolution of the lesion as the patient clears the HPV infection.

If a biopsy result shows CIN2 or 3, treatment is recommended. Most commonly, a Loop Electrosurgical Excision Procedure (LEEP) is performed to remove the lesion while
maintaining the integrity of the cervix. The patient will need to be monitored for residual or recurrent disease, though the frequency and method of surveillance is still under discussion.

If the biopsy shows squamous cell carcinoma \textit{in situ} (non-invasive cancer), treatment usually includes a LEEP or cone excision of the lesion, followed by careful follow up to monitor for local recurrence of the cancer. Adenocarcinoma \textit{in situ}, however, is usually treated by the surgical removal of the cervix and uterus, also known as a complete hysterectomy, due to the potential for multiple noncontiguous lesions in the cervix and the uterus.

Invasive cervical cancer requires imaging to assess the extent of involvement of surrounding tissues and structures. Treatment often combines surgery, chemotherapy, and radiation therapy depending on the characteristics and severity of disease.

\textbf{Table 3.} Possible colposcopy histology results.

<table>
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<tr>
<td>CIN1</td>
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<tr>
<td>CIN2</td>
</tr>
<tr>
<td>CIN3</td>
</tr>
<tr>
<td>Adenocarcinoma \textit{in situ}</td>
</tr>
<tr>
<td>Invasive Squamous Cell Carcinoma</td>
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Screening for cervical cancer may also include a test to detect the presence of HPV DNA in the cells collected during the Pap test. Current recommendations suggest HPV testing for women over the age of 30. Younger women should not be screened for HPV because they are more likely to test positive, but are also more likely to clear the infection without intervention and without sustaining cellular changes that increase the risk of cervical cancer. Screening women under age 30 will likely lead to an increase in unnecessary procedures and may cause significant distress in patients who in reality have little to worry about.\(^3\)\(^4\)

In addition to regularly conducted Pap tests, the HPV vaccine has the potential to contribute greatly to the reduction in the incidence of cervical cancer in the U.S. The first vaccine was approved by the FDA in 2006 and protected recipients from the most common and oncogenic HPV strains: 6, 11, 16, and 18.\(^6\)\(^6\) In 2015, a nonavalent vaccine became available, which confers immunity to strains 6, 11, 16, 18, 31, 33, 45, 52, and 58.\(^7\)\(^7\) The vaccines use virus-like particles (VLPs) to incite immunity in patients, although the mechanism of action is not clear because the clearance of HPV is thought to be largely a local rather than a systemic process. Nonetheless, the HPV vaccines have been shown to prevent HPV infection and the development of HPV-associated CIN2-3 lesions with 98% efficacy in women who are HPV naïve.\(^4\)

**Existing research**

The current consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors was generated from a systematic review of the
existing literature regarding the risk of developing CIN and/or cancer given various Pap and HPV test results and given variable periods of time, as well as data from a study of 1.4 million women in the Kaiser Permanente Northern California Medical Care Plan. The existing literature demonstrates a strong body of evidence for the management of normal and low-grade abnormal Pap results. However, the authors of the current guidelines point out that high-level evidence is lacking for many aspects of patient management, particularly posttreatment outcomes and optimal long-term follow-up for women with treated high-grade abnormalities; they state, “The path to routine screening for these women is based on consensus expert opinion and should be modified as evidence becomes available.”

Additionally, a large amount of research has been done on the utility of adding HPV testing as part of routine screening algorithms for women in different age groups, and how HPV testing results (positive vs. negative) and type-specific results (16/18 vs. others) impact the risk of developing high-grade abnormalities or cancer. The following papers are examples of the research that was considered when crafting the current consensus guidelines, as well as examples of existing studies addressing the risk of recurrent disease after CIN2/3.

I. The ASCUS-LSIL Triage Study (ALTS) Group, ASCUS Section. This study was undertaken to compare alternate strategies for the initial management of women with an initial diagnosis of ASCUS by Pap test. The outcome of interest was the ability of three different management strategies to detect CIN3 over a two-year study
period. The management strategies included immediate colposcopy, HPV DNA testing and liquid-based cytology triage, or conservative management with repeat cytology. The latter two groups had a threshold of HSIL for referring patients to colposcopy. 3,488 women with ASCUS Pap results participated in the study and were randomly assigned to the three management groups. All groups were followed semi-annually for 2 years and every patient received a colposcopy at the end of the study.

The data analysis of this study examined the sensitivity of each management strategy to detect the presence of CIN3, as well as the percentage of women who were referred to colposcopy in the HPV triage and conservative management groups. The immediate colposcopy group had 53.6% sensitivity in detecting CIN3 over the two-year study period. The HPV triage group detected 72.3% of CIN3 cases and referred 55.6% of women to colposcopy. The conservative group detected 54.6% of CIN3 cases and referred 12.3% of women to colposcopy. The authors then re-estimated the success of the HPV triage and conservative groups in referring women to colposcopy who actually did have CIN3. They found that the HPV triage group correctly identified 92.4% of the women who were diagnosed with CIN3 by colposcopy. The conservative management group would have required multiple repeat cytology visits and a threshold lowered to ASCUS for referral to colposcopy in order to achieve a similar sensitivity for CIN3 diagnosis, and a greater number of women would be referred to colposcopy. The study concluded that managing women with ASCUS Pap results using the HPV triage strategy was at least as sensitive at identifying CIN3 as immediate colposcopy, while only sending half as many women for biopsy. They argue that the HPV triage management strategy is
ideal, given its ability to correctly identify CIN3 while minimizing both the number of unnecessary colposcopies and the number of patient visits.

The strengths of this study include its large study population recruited from four different areas of the U.S., the randomized assignment to management groups, and excellent retention of subjects, with 85% of subjects having an exit visit. This study was integral to the development of the management algorithms for women with ASCUS results on their Pap test.

II. The ASCUS-LSIL Triage Study (ALTS) Group, LSIL Section.\textsuperscript{19}

This study was conducted in parallel with the ALTS ASCUS group, and followed an identical study design with the same three management arms of immediate colposcopy, HPV DNA testing and liquid-based cytology triage, or conservative management with repeat cytology. In this study, the women had an initial Pap result of LSIL. Again, the outcome of interest was the ability of three different management strategies to detect CIN3 over a two-year study period. 1,572 women participated in the study, and were followed biannually for a total of 2 years.

During the study period, the HPV triage management arm was closed due to the fact that over 80% of study participants tested positive for HPV, rendering the triage strategy moot. The immediate colposcopy arm had a sensitivity of 55.9% for cumulative cases of CIN3. The conservative arm had a sensitivity of 48.4% and referred 18.8% of women to colposcopy. The authors concluded that immediate colposcopy is the best management strategy for women with LSIL Pap results. HPV triage is not useful in this
group because the majority of patients appear to be HPV positive. Comparable to the ASCUS group results, the conservative management strategy would be similarly sensitive for detecting CIN3 if the threshold for referring women to colposcopy was lower and repeat Pap tests were performed more frequently, however this would result in very high referral rates and potential over-screening for the majority of patients.

This study added important support for the management algorithm for women with LSIL Pap results, supporting the fact that these women should go for immediate colposcopy. They also demonstrated that HPV triage is not a useful or appropriate test for this group, compared to the ASCUS group in which HPV triage has great utility for directing appropriate management, resulting in sensitive detection of CIN3 while minimizing unnecessary colposcopies.

III. A Long-term Prospective Study of Type-Specific Human Papillomavirus Infection and Risk of Cervical Neoplasia Among 20,000 Women in the Portland Kaiser Cohort Study.\textsuperscript{20} The outcomes of this study informed the utility of adding HPV testing to screening Pap tests and optimal screening intervals for women over age 30 (30+). The authors aimed to understand the extent to which a negative HPV result reassured against the development of CIN3 or worse histological results over a long period of time. They also calculated the positive predictive value (PPV) of a single positive HPV test for different strains, and the PPV for a positive HPV test (with any strain) compared with the cytologic abnormality.

The results demonstrated that risk of developing CIN3 or worse after a negative HPV result was very low, and the risk remained low over 15+ years, illustrating that a
negative HPV test has an excellent negative predictive value, particularly in women 30+ who have never had a high-grade abnormal screening cytology or histology result. The cumulative probability of developing CIN3 or greater in women over 30 was 0.7% and in women under 30 was 1.8%. From this outcome, the authors propose that screening women over age 30 every 3 years with a Pap and HPV test will likely result in overscreening. For specific types of HPV, only estimates for HPV16 were possible given low numbers of other strains. Comparing HPV16 to other types, and other types to HPV negativity, the log-rank tests yielded significant p-values (p = 0.04 for HPV16 versus other carcinogenic types in women 30+, p < 0.001 for all other comparisons). The hazard ratios (HR) of HPV16 compared to other carcinogenic types and to HPV-negativity in the 30+ age group were 2.7 (95% CI =1.0-7.3) and 6.2 (95% CI = 3.0-12.6), respectively. This data demonstrates an elevated risk of developing CIN3 or worse after diagnosis of HPV16. For women younger than 30, the cumulative probability of developing CIN3 or worse after HPV16 infection was 14.6 (95% CI = 10.0-20.9) and PPV 11.1 (8.1-14.0). For women aged 30+, the cumulative probability of developing CIN3 or worse after HPV16 infection was 8.5 (95% CI = 4.1-17.2) and PPV 13.8 (8.2-19.4). They found that HPV status (positive vs. negative) was a more important determinant of risk of developing CIN2 or greater compared to low-grade abnormal cytology (ASCUS/LSIL or negative). This conclusion supports adding HPV testing to routine Pap tests, and suggests that HPV testing alone may be a viable screening option for low-risk women over age 30.

Major strengths of this study are the very large study population of approximately 20,000 women, and extended length of the study period. One limitation is the inherently
homogenous study population recruited from the Kaiser Permanente participants; narrow geographic distribution of recruitment, majority Caucasian race subjects, and a potential for self-selection bias by individuals voluntarily enrolled in a health maintenance organization. In addition, the population was considered low-risk and well-screened. The authors excluded women who had had a previous result of HSIL or worse cytology and/or CIN2 or worse histology because the aim of the project was to study “the natural history of HPV in the context of routine cervical cytologic screening.” These factors may limit the generalizability of the study results to more diverse and high-risk populations.

IV. Risk of cervical cancer associated with extending the interval between cervical-cancer screenings.21

This study was done to verify the safety of extending the screening interval from one to three years. They determined the prevalence of CIN in a study population of over 900,000 women under the age of 65 and stratified them based on the number of consecutive negative Pap tests they had prior to their diagnosis of CIN. They then used a Markov model (which estimates the rate at which dysplasia will progress to cancer) to estimate the risk of cancer within three years after one or more negative Pap tests. The authors also estimated the number of additional Pap tests and colposcopies that would be required to prevent one case of cancer given a particular interval between screenings.

The results of this study are summarized in the table below.
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 Greater than Three Previous Negative Pap tests.

<table>
<thead>
<tr>
<th></th>
<th>Average Expected No. of Cases of Invasive Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If Grade 2 Progression Like Grade 3</td>
</tr>
<tr>
<td><strong>&lt;30 Years of age</strong></td>
<td></td>
</tr>
<tr>
<td>Screening once 3 yrs. after last negative test</td>
<td>9</td>
</tr>
<tr>
<td>Annual screening</td>
<td>4</td>
</tr>
<tr>
<td><strong>30-44 Years of age</strong></td>
<td></td>
</tr>
<tr>
<td>Screening once 3 yrs. after last negative test</td>
<td>5</td>
</tr>
<tr>
<td>Annual screening</td>
<td>2</td>
</tr>
<tr>
<td><strong>45-59 Years of age</strong></td>
<td></td>
</tr>
<tr>
<td>Screening once 3 yrs. after last negative test</td>
<td>2</td>
</tr>
<tr>
<td>Annual screening</td>
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</tr>
<tr>
<td><strong>60-64 Years of age</strong></td>
<td></td>
</tr>
<tr>
<td>Screening once 3 yrs. after last negative test</td>
<td>1</td>
</tr>
<tr>
<td>Annual screening</td>
<td>1</td>
</tr>
</tbody>
</table>

In order to avert one additional case of cancer by screening 100,000 women annually for three years versus once three years after their last negative Pap test, the following would
be required: for the age group 30-44 years: 69,665 additional Pap tests and 3,861 colposcopies; for the age group 45-59 years: 209,324 additional Pap tests and 11,502 colposcopies.

The authors conclude that for women between the ages of 30 and 44 the risk of developing cancer within three years after three negative Pap tests is sufficiently small (no more than 3 in 100,000) to support screening every three years rather than yearly for women with histories of negative Pap tests. They admit that annual screening would reduce this risk even further, however it would require enormous resources and would raise the risk of harms incurred by overscreening.

The strengths of this study include the very large and diverse study population. Limitations include a lack of information on additional cervical cancer risk factors for the participants and other missing data as a result of the fact that the data used for this study was not originally collected as part of a research protocol, but rather for program administrative and evaluation purposes. Additionally, many assumptions were used in the model employed to calculate risks that certainly impacted the outcomes. For example, the authors assumed that all women would comply with screening, follow up, and treatment recommendations, but this is not always the case in reality, and so the risk of cancer concluded by this study may be underestimated. While this study did not contribute novel information to the body of literature, its conclusions strongly supported the existing guidelines for extended screening intervals for women with negative Pap results.
V. Baseline Cytology, Human Papillomavirus Testing, and Risk for Cervical Neoplasia: A 10-Year Cohort Analysis. 22

The goal of this study was to evaluate the utility of simultaneous Pap and HPV testing for the detection of CIN3 or cancer. Data from 20,000 women with a mean age of 35.9 years were collected over 122 months. During the study period, 171 women were diagnosed with CIN3 or cancer. Of those women, 71.9% (95% CI = 65.2% to 78.7%) had a baseline Pap of ASCUS or worse and/or a positive HPV test. In the first 45 months of the study, 118 women were diagnosed with CIN3 or cancer, 102 of which had baseline abnormal Pap tests and/or a positive HPV test (86.4%, 95% CI = 80.3% to 92.6%). The cumulative incidence of CIN3 or cancer during the first 45 months of the study was 4.54% (95% CI = 3.61% to 5.46%) for women with a Pap test result of ASCUS or worse, positive HPV tests, or both compared with 0.16% (95% CI = 0.08% to 0.24%) for women with negative Pap and HPV tests.

The results of this study confirm the very low risk of developing CIN3 or cancer within 45 months of a negative Pap test and negative HPV test, lending support to the 3 year screening interval for women with a history of negative Pap and HPV tests. The strengths and weaknesses of this research are similar to those identified in the study conducted by Schiffman, et al titled A Long-term Prospective Study of Type-Specific Human Papillomavirus Infection and Risk of Cervical Neoplasia Among 20,000 Women in the Portland Kaiser Cohort Study, mainly due to the fact that the two studies used the same population to recruit research subjects. A major limitation worth emphasizing is the homogeneity of the cohort demographics and well-screened and low-risk nature of the
participants, which likely impacts the generalizability of this study to other heterogeneous or high-risk populations.

VI. *Five-year risk of recurrence following treatment of CIN2, CIN3, or AIS: performance of HPV and Pap contesting in post-treatment management.*

This paper by Katki, *et al* is considered one of the landmark studies looking at the risk of recurrent cervical disease after an abnormal screening test. The authors’ objective was to observe a group of women for recurrence of CIN2 or worse (CIN2+) disease over a 5-year period after treatment for CIN2, CIN3, or AIS. This study looked at a population of over 3,000 women aged 25 and older who had an initial abnormal baseline screen (HPV+/ASC-US, LSIL, AGC, ASC-H, or HSIL+) between 2003 and 2010, followed by colposcopy and biopsy-proven CIN2, CIN3, or AIS, and were then treated with LEEP. The study then observed the women for the 5 years following the baseline screen and treatment to see which women were found to have recurrent disease. The authors stratified the population by the severity of the treated lesion and the original screening result, then calculated the cumulative post-treatment risk of recurrent CIN2+ for each group. The results of the study are shown in Figures 3 and 4.
Figure 3. Cumulative risk of CIN2+ after treatment for CIN2, CIN3, or AIS among women aged 25 and older given antecedent screening test that preceded colposcopy was HPV-positive/ASC-US or LSIL (Left Panel) or HSIL+, ASC-H, AGC (Right Panel).
Figure 4. Cumulative risk of CIN2+ following subsequent negative follow-up tests after treatment for CIN2, CIN3, or AIS, for women age 25 and older. The negative Pap test curves are for all Pap results alone regardless of HPV test results and the HPV negative test curves are for all HPV results alone regardless of Pap test results. A “negative cotest” means testing both HPV-negative and Pap-negative. 23
The results of this study demonstrated that women with a history of abnormal screening test results are at an increased risk of recurrent CIN2+ disease for at least 5 years post-treatment. Results also showed that there is a positive correlation between the risk of recurrent CIN2+ and the severity of the initial screening result. At 5 years after treatment for a CIN2 lesion with an HPV+/ASC-US or LSIL Pap test, the cumulative risk of a recurrent CIN2+ lesion was 5% compared to a 16% cumulative risk of a recurrent CIN2+ lesion after treatment for a CIN3/AIS lesion with an AGC/ASC-H/HSIL+ Pap test (p<0.0001).

This study also looked at how the cumulative risk of recurrent CIN2+ varied given negative Pap and HPV tests after treatment of the original lesion. While the results were not statistically significant, they did illustrate a lower risk of recurrent disease if the patient had a negative Pap and negative HPV test post-treatment compared to a negative Pap test alone or a negative HPV test alone. Results also indicated that two negative post-treatment Pap and HPV tests conferred a slightly lower risk at 5 years post-treatment than a single negative Pap or HPV test.

The major contribution of this paper was the data indicating that women with abnormal screening tests who are then treated remain at a significantly elevated risk for recurrent CIN2+ disease, even 5 years later. Therefore, the authors concluded that these women should not return to the 5-year routine screening schedule recommended for women who are at low or average risk for developing cervical cancer. The authors did observe that multiple negative Pap and HPV cotest results after treatment seem to offer
the most reassurance against recurrent disease, which suggests that post-treatment women should be followed with cotests rather than Pap or HPV tests alone.

While the results of this study are impactful, there are several limitations. First, the study was not a randomized controlled trial, but rather an observational study design with women following post-treatment strategies chosen by their healthcare provider, which may have introduced bias in the study results. Second is the use of the members of the Kaiser Permanente Northern California (KPNC) cohort as the study group, which may introduce bias and limit generalizability. The KPNC cohort is a homogenous and low-risk population that may be more health-literate and more compliant with follow up than the general population. Another limitation of this study is that follow up was limited to 5 years. Finally, despite following more than a million women over 8 years, the number of occurrences of abnormal cervical screening test results and of recurrent disease remained very small. The authors admit that because of the small numbers of events, the risk estimates presented in their study, while informative, remain imprecise.
METHODS

Study design

A systematic literature review was performed to identify existing research on the increased risk of persistent or recurrent disease after treatment of high-grade cervical abnormalities. Relevant articles will be graded for quality of evidence and pertinent data will be abstracted.

Inclusion criteria

Journal articles published after 2007 in the English language were selected for the study. Articles that included immunosuppressed women or pregnant women in their study populations were excluded from this review.

Study variables and measures

Data will be manually abstracted from the articles and will include the variables listed in Table 5.

Table 5. Variables for data abstraction.

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year study was published</td>
</tr>
<tr>
<td>First author</td>
</tr>
<tr>
<td>Study population size</td>
</tr>
<tr>
<td>Average age of study participants</td>
</tr>
<tr>
<td>Geographic location of study</td>
</tr>
<tr>
<td>Baseline Pap test result</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Baseline HPV test result and HPV type (if positive)</td>
</tr>
<tr>
<td>Colposcopy result</td>
</tr>
<tr>
<td>LEEP performed (Y/N)</td>
</tr>
<tr>
<td>Risk of CIN 2 at $X$ years (1-10)</td>
</tr>
<tr>
<td>Risk of CIN 3 at $X$ years (1-10)</td>
</tr>
<tr>
<td>Risk of Cancer at $X$ years (1-10)</td>
</tr>
</tbody>
</table>

**Data collection**

PubMed, Web of Science, and Embase databases were searched for peer-reviewed journal articles published from 2007 to present in the English language. The MeSH search terms included “Cervical Intraepithelial Neoplasia,” “Uterine Cervical Dysplasia,” and “Recurrence.” These terms were adapted according to the language required for optimal search results within each database.

**Search results**

The resulting titles and abstracts from the three databases were merged, checked for duplicity, and then reviewed for relevancy. If relevancy was uncertain after reviewing the abstract, a full text review was conducted. The schema for article selection is shown in Figure 5. The final group included 141 articles. A complete list of the articles selected for inclusion in the systematic review can be found in Appendix 1.
Figure 5. Article Selection Schema.

Analysis

Each study included in the systematic review will be evaluated for quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. 24,25 This system is used widely by organizations such as the WHO, American College of Physicians, and the Cochran Collaboration to clearly and consistently rate the quality of evidence presented by individual studies. The goal is to enable readers to more accurately compare data presented by different studies, as well as to clearly interpret the results of a systematic review. The GRADE approach considers
the following when evaluating the quality of a study: “within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of pollution bias.” Each outcome of a study must be individually assessed for quality. Rating begins by considering the methodology used to acquire the evidence (see Table 6). Quality ratings can then be upgraded or downgraded based on the factors listed above.

Table 6. Levels of quality of a body of evidence in the GRADE approach.

<table>
<thead>
<tr>
<th>Underlying methodology</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials; or double-upgraded observational studies</td>
<td>High</td>
</tr>
<tr>
<td>Downgraded randomized trials; or upgraded observational studies</td>
<td>Moderate</td>
</tr>
<tr>
<td>Double-downgraded randomized trials; or observational studies</td>
<td>Low</td>
</tr>
<tr>
<td>Triple-downgraded randomized trials; or downgraded observational studies; or case series/reports</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Timeline and resources

This study is projected to take place over the span of one year, with one research assistant working part time on the project. It will require intermittent consultation with a research librarian, as well as oversight by a content expert to ensure that the appropriate articles are included and the necessary data points are correctly abstracted from the studies.
Institutional Review Board

This study protocol will be submitted to the Boston University Medical Campus IRB seeking Exempt, Non-Human Research status approval. If the IRB does not approve this study as Exempt, a full IRB protocol will be submitted for expedited review.
CONCLUSION

Discussion

This thesis proposes to conduct a systematic literature review of the existing body of evidence regarding the increased risk of recurrent cervical disease after abnormal cervical cancer screening tests and subsequent treatment. The results of the literature review will contribute to the revision of the current cervical cancer screening and management guidelines, as well as serve as a foundation for generating the next iteration of guidelines. Since the publication of the 2012 Guidelines, the scientific community has continued to investigate the incidence of recurrent disease and evaluate the negative predictive value of Pap and HPV tests in women who have had previous cervical abnormalities. However, the quality of this evidence has yet to be evaluated. This systematic literature review will capture and evaluate the quality of these more recent studies.

Determining the risk of recurrent disease in women with abnormal cervical cancer screening tests will serve to more optimally screen and manage this cohort of women with previously treated abnormalities. Having high-level, evidence-based guidelines allows clinicians to accurately weigh the costs and benefits of screening and treatment for their patients based on individual health factors, such as a history of an abnormal screening result. The development of screening tests for the detection of early disease is a cornerstone of preventative medicine and affords many benefits to patients. However, the tests are not without risk. Screening tests need to be frequent enough to identify disease while it is still in its early stages and effective treatment is possible. On the other hand, screening should not be conducted so frequently that it leads to harm. In addition to the
risks inherent to interventions, many patients experience significant emotional distress
during the process of being diagnosed and treated for abnormal cervical findings. Sharp, 
et al suggest that much of the distress is anxiety and anticipation of procedures and side 
effects, as well as worries about being diagnosed with cancer.27 Lerner, et al also point 
out that along with emotional distress, the time required to manage abnormal screening 
results has a negative effect on patients. Multiple clinic visits and procedures are often 
required, potentially leading to decreased productivity in the work place, increased 
absences from work or school, and strained relationships.28 These potential consequences 
illustrate the importance of optimizing screening algorithms. The ideal screening 
intervals must be based on evidence demonstrating 3 things: 1) the level of increased risk, 
2) how long the increased risk persists, and 3) what assurance negative Pap and HPV 
tests afford these patients. Without this information, guidelines can only be based on 
expert opinion, and this cohort of women remains at risk for substandard management. 

In addition to updating the current management guidelines, this systematic review 
will also illustrate what gaps still exist in the current body of literature regarding 
recurrent cervical disease. If this thesis demonstrates that high-level evidence is still 
lacking, it will provide direction for clinicians and researchers to design and implement 
new studies in order to fill those gaps. 

This systematic literature review has several limitations. While every effort was 
made to include all of the appropriate studies on the topic of recurrent cervical disease, 
time and practicality necessitated selecting relatively narrow search terms and a finite 
number of databases to generate a list of possible articles that could feasibly be evaluated
by a single researcher. It is very possible that additional research on the topic was omitted from this literature review. In addition, the results of the systematic review will necessarily be limited by the quality of the evidence presented by the existing studies. If there is a paucity of high-level evidence, it will be difficult to draw definitive conclusions regarding the recurrence of cervical disease. Additionally, making meaningful revisions to the existing screening and management guidelines will be difficult without high-level evidence to support the amendments.

**Summary**

Worldwide, cervical cancer is the fourth most common cancer occurring in women and the second most frequent cause of cancer-related deaths in women.\(^4,5\) In the U.S., thanks to the implementation of the Pap test as a standard of care in women’s health, cervical cancer is now the 14\(^{th}\) most common cancer affecting women, and deaths from cervical cancer have decreased by over 70% during the last 50 years.\(^6,8\) Along with the development of the Pap test, the discovery of HPV, its association with cervical cancer, and the discovery of the HPV vaccine have armed clinicians with effective tools to facilitate the early detection and treatment of precancerous lesions of the cervix.\(^8\)

The **2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors** is the most current resource for providers of women’s health care.\(^3\) The purpose of the guidelines is to tailor screening and management algorithms to particular cervical abnormalities with the goal of maximizing chances of identifying precancer and cancer, while also minimizing the
harms inherent in over-screening. The existing literature demonstrates a strong body of evidence for the management of normal and low-grade abnormal Pap results. However, at the time of publication of the 2012 Guidelines, high-level evidence was lacking for women with treated high-grade abnormalities with regards to posttreatment outcomes and long-term follow-up intervals. Current management of this cohort is based largely on expert opinion. This thesis proposes a systematic literature review to identify what further evidence has been published in the years since the 2012 Guidelines were released, to assess the quality of that evidence, and to use the evidence to further tailor the existing protocols for more optimal management of women with high-grade cervical abnormalities.

Updating screening and management guidelines for cervical cancer will improve outcomes, both for individual patients as well as for the greater healthcare system. Identifying and treating cervical precancer improves morbidity and mortality, as well as decreases the financial burden of treating advanced disease and end-of-life care. Conversely, over-screening negatively impacts patients by inducing emotional distress, anxiety, and loss of productivity. In addition, over-screening is financially burdensome to the healthcare system by requiring additional appointments, tests, and procedures that may in reality be unnecessary. Everyone stands to benefit from optimizing cervical cancer screening and management guidelines.
Clinical and/or public health significance

The aim of this systematic literature review is to identify and evaluate existing evidence regarding the recurrence of cervical disease in women with previously abnormal screening tests who were then treated. The results of the systematic review will then be used to inform the revision of the management guidelines and identify areas for further research. Improving screening and management algorithms for cervical cancer will improve outcomes for women worldwide. The costs associated with treating cervical cancer will be decreased if the disease is caught in the early stages, avoiding costly surgical procedures, chemotherapy, and radiation. Conversely, over-screening has the potential to cause significant financial burden for the healthcare system in the form of unnecessary tests, the aforementioned procedures, as well as provider time and compensation. Optimizing screening guidelines to achieve the proper balance of preventative care without over treating will save women undue anxiety and stress as well as relieve the potential financial burden brought about by the inappropriate management of women with recurrent cervical disease and/or abnormal screening results.
APPENDIX

Articles to be Included in Systematic Literature Review


83. Munro A, Codde J, Spilsbury K, et al. Risk of persistent or recurrent neoplasia in conservatively treated women with cervical adenocarcinoma in situ with negative


140. Zhu M, He Y, Baak JP, et al. Factors that influence persistence or recurrence of high-grade squamous intraepithelial lesion with positive margins after the loop

### LIST OF JOURNAL ABBREVIATIONS

<table>
<thead>
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<th>Abbreviation</th>
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<td>Archives of Pathology &amp; Laboratory Medicine</td>
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<td>BMJ.</td>
<td>British Medical Journal</td>
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<td>Cancer Cytopathology</td>
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<td>Cancer Epidemiology, Biomarkers &amp; Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology</td>
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<td>Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases</td>
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REFERENCES


