# **Topic Brief:** Adenocarcinoma of the Lung and HPV

**Date:** 12/26/19
**Nomination Number:** 880

**Purpose:** This document summarizes the information addressing a nomination submitted on 10/13/2019 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** The nominator raises concern that adenocarcinoma of the lung in non-smoking women may be associated with HPV infection in another anatomical site. This person wonders if screening for HPV or HPV vaccination in women could improve lung adenocarcinoma outcomes.

**Program Decision:** The EPC Program will not develop an evidence review based on this nomination. We did not find systematic reviews or primary studies of the effect of HPV testing of the cervix or HPV vaccination on improving lung cancer outcomes.

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## Background

- Human Papilloma Virus (HPV) are a group of about 200 related viruses.[1]
- High-risk serotypes of HPV can cause cancers of the cervix, vagina, vulva, penis, anus and oropharynx.[2] HPV infects the squamous cells that line the inner surfaces of these organs, and usually causes squamous cell cancers.[1]
- The biological mechanism of HPV infection leading to lung cancer has in recent years been an active research field. Some case-control studies of lung tissues have found an association between high-risk strains of HPV and lung cancer.[3]
- A recent systematic review found that HPV infection might increase risk for squamous cell and small cell carcinoma of the lung. [3]
- However HPV DNA is present in a small fraction of lung tumors and it is not clear whether HPV infection causes lung cancer.[3, 4]
- In 2016, there were 218,229 people diagnosed with lung cancer; 105,185 of these were in women.[5] Risk factors for lung cancer include smoking, radon exposure, personal or family history of lung cancer, radiation therapy to the chest, and other substances such as asbestos, arsenic, silica and diesel exhaust.[5, 6]
- Non small cell cancer of the lung includes squamous cell cancer, adenocarcinoma, and large cell carcinoma. Adenocarcinoma is the most common type in smoking and nonsmoking men and women. [7]
- HPV is a known risk factor for oropharyngeal cancer. The HPV vaccine was developed to prevent cervical and other cancers of the reproductive system, and can protect against the HPV types that can cause oropharyngeal cancers.[8]

- The CDC recommends HPV vaccine for adolescents 11-or 12 years old; and through 26 years old for gay, bisexual, and other men who have sex with men, transgender people and immunocompromised people. Ideally people should be vaccinated before HPV exposure.[2]
- Currently the only screening test for HPV is performed through collection of cells with a spatula during a pelvic exam. The USPSTF recommends screening for cervical cancer with HPV testing in combination with cervical cytology every 5 years for women aged 21-65 as an alternative to cervical cytology alone every 3 years for cervical cancer.[9]
- Guidelines recommend HPV testing of tissue in oropharyngeal cancer. This however is not a screening test.[10, 11]
- The nominator postulates that because of the association of HPV with lung cancer in nonsmokers that HPV testing might be effective in improving lung cancer outcomes.

## Scope

Initially we focused on non-smoking women <50 years old with cervical cancer. In addition because of the paucity of literature we broadened the population to all ages regardless of whether or not they had cancer or smoked.

Contextual question: What is the incidence of non-small cell lung cancer in women less than 65 years old?

1. Does screening for HPV infection of the cervix improve lung cancer outcomes?
2. Does HPV vaccination prevent lung cancer?

| | **HPV screening of the cervix** | **HPV vaccine** |
|---|---|---|
| **Population** | Women 21-65 years old | Individuals 11 years old and older |
| **Intervention** | HPV screening of the cervix | HPV vaccination |
| **Comparator** | No HPV screening | No HPV vaccination |
| **Outcome** | Lung cancer outcomes<br>Harms of screening | Lung cancer outcomes<br>Harms of HPV vaccination |

## Assessment Methods

We assessed nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

## Summary of Selection Criteria Assessment

Ongoing studies are exploring the association between HPV and certain types of lung cancer, and whether this association could be causal. We found four systematic reviews on the harms of HPV testing of the cervix and HPV vaccination. We found no systematic reviews or primary studies that reported on the impact of HPV testing of the cervix or HPV vaccination on lung cancer outcomes.

## Related Resources

We identified additional information in the course of our assessment that might be useful.

- Gilbert et al. Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis. 2018.[12]
    - While this review did not focus on lung cancer, it focused on oropharyngeal cancer, anal cancer, penile cancer, and cervical cancer.
- The USPSTF has an in-process systematic review on lung cancer screening with low-dose CT. It includes a question on risk prediction, but specifically excludes studies that assess a single variable or biomarker, and those that do not consider smoking and age.[13]

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# Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

### Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years 12/2/19 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/

### Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

### Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last five years 12/20/2014 to 12/18/2019 on parts of the nomination scope not addressed by earlier identified systematic reviews. We reviewed all identified titles and abstracts for inclusion and classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy

HPV[All Fields] AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields]) AND ("lung neoplasms"[MeSH Terms] OR

("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields])

(("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("hpv"[All Fields] AND "vaccine"[All Fields]) OR "hpv vaccine"[All Fields]) AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields])) AND ("2014/12/20"[PDat] : "2019/12/18"[PDat] AND "humans"[MeSH Terms])

https://clinicaltrials.gov/ct2/results?cond=HPV&term=lung+cancer&cntry=&state=&city=&dist=&Search=Search

https://clinicaltrials.gov/ct2/results?cond=HPV+test&term=lung+cancer&cntry=&state=&city=&dist=&Search=Search

# Appendix B. Selection Criteria Assessment

| Selection Criteria | Assessment |
|---|---|
| 1. Appropriateness | |
| 1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.? | Yes |
| 1b. Is the nomination a request for an evidence report? | No |
| 1c. Is the focus on effectiveness or comparative effectiveness? | No |
| 1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic? | Unclear. The causal link between HPV infection of the lung and lung cancer has not been well-established. |
| 2. Importance | |
| 2a. Represents a significant disease burden; large proportion of the population | Yes. Lung cancer among nonsmokers is increasing[14]. A 2007 analysis of three large databases found that 19% of cases of lung cancer are in nonsmoking women, and 9% in nonsmoking men. There is a rising incidence in young women.[15] |
| 2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population | Yes |
| 2c. Incorporates issues around both clinical benefits and potential clinical harms | Yes |
| 2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers | Yes, treatment of lung cancer can be costly. In 2017, the total cost of care associated with lung cancer in the United States was estimated at $13.9 billion[16] |

| Selection Criteria | Assessment |
|---|---|
| 3. Desirability of a New Evidence Review/Absence of Duplication | |
| 3. A recent high-quality systematic review or other evidence review is not available on this topic | There are current systematic reviews that assess the harms of HPV testing and HPV vaccine. No systematic reviews addressed the effect of HPV testing and HPV vaccine on lung cancer outcomes.<br><br>For KQ 1 on HPV screening, we found an in-process systematic review on screening with HPV testing for cervical cancer[17]. This review informed the US Preventive Services Task Force recommendation on cervical cancer screening. It included harms of screening, but did not include lung cancer as an outcome. We found no reviews that included lung cancer as an outcome.<br><br>For KQ 2 on HPV vaccination, we found no SR that assessed the effect of HPV vaccination on lung cancer incidence. We found three systematic reviews on harms of immunization. We identified an evidence review that informed the Advisory Committee on Immunization Practices (ACIP) guidance on HPV vaccination for adults 27-45 years old. [18] This reviewed the evidence on vaccine efficacy and safety but did not include lung cancer as an outcome. We also identified a 2018 Cochrane systematic review on HPV vaccination in girls and women[19]. It looked at harms but did not include lung cancer as an outcome. A third review looked HPV vaccines in males.[20] It included adverse effects and anal, penile and oral cancer, but did not include lung cancer. |
| 4. Impact of a New Evidence Review | |
| 4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)? | Risk prediction for lung cancer continues to evolve. Currently available guidance does not identify HPV infection of the cervix as a risk factor for lung cancer. |
| 4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)? | No. |
| 5. Primary Research | |
| 5. Effectively utilizes existing research and knowledge by considering:<br>- Adequacy (type and volume) of research for conducting a systematic review<br>- Newly available evidence (particularly for updates or new technologies) | We did not find enough studies for a systematic review on this nomination.<br><br>For KQ 1 on HPV screening: we did not identify any studies of HPV screening that included lung cancer as an outcome.<br><br>For KQ 2 on HPV vaccination: We found no studies about the impact of HPV vaccination on incidence of lung cancer.<br><br>ClinicalTrials.gov. none |

*Abbreviations:* AHRQ=Agency for Healthcare Research and Quality