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Short Communication

Inefficiencies of over-screening and under-screening for cervical cancer prevention in the U.S.

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ABSTRACT

There is limited information on the cost-inefficiencies of non-adherence to recommended cervical cancer screening or the potential value for improving non-adherence. We estimated the incremental value of adhering to recommended screening every three years with cytology, using a disease simulation model that integrated real-world screening practice data from New Mexico. The amount that can be spent to improve adherence was estimated by calculating the incremental net monetary benefit (INMB) under scenarios of Current Practice (assuming a population of mixed adherence) and Uniformly Non-Adherent populations with imperfect or perfect adherence to follow-up of screen-positive women. Getting unscreened women screened every three years by cytology was a better value than increasing screening in the under-screened or reducing screening in the over-screened. For example, INMBs were $3998 for screening previously unscreened women versus $136 for eliminating annual screening at a willingness-to-pay threshold of $100,000 per quality-adjusted life-year gained. Strategies to reach unscreened women are potentially high-value investments.

1. Introduction

We previously reported inefficiencies of current cervical cancer screening practice in the State of New Mexico as representative for the United States (Kim et al., 2015). We found that Current Practice resulted in lower costs and fewer health benefits than guidelines-based screening and management. Increasing adherence to screening by cytology every three years and colposcopy/biopsy referral of screen-positive women were found to be high-value improvements.

In that analysis, we classified the effects of both over- and under-screening for cervical cancer prevention as “non-adherent” (Kim et al., 2015). However, characteristics and outcomes of sub-populations who are over- and under-screened differ greatly. Over-screening is more likely to occur in higher rather than lower socioeconomic status women (Cooper et al., 2015) and results in over-diagnosis and over-treatment (Habbema et al., 2017), the latter of which has been linked to adverse pregnancy outcomes such as preterm delivery (Kyrgiou et al., 2016). Conversely, under-screening is attributable to social, economic, and geographic barriers to care, and a significant proportion of the cervical cancers in the U.S. are diagnosed in women who are under- or unscreened (Scarinci et al., 2010). Thus, strategies to address the two non-adherent practices are likely to be different. Our objective was to distinguish costs and health effects of over- versus under-screening to inform priorities for quality improvement in cervical-cancer screening.

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2. Methods

Analyses were conducted as previously described in detail (Kim et al., 2015). We used a validated individual-based disease simulation model of the natural history of HPV and cervical cancer to project the health benefits and costs of screening practices, including follow-up of screen-positive women. Main model-projected outcomes for this analysis included health benefit (gains in quality-adjusted life-years [QALYs]), and lifetime costs (in 2012 U.S. dollars). Costs comprised direct medical and non-medical costs as well as patient time. Consistent with guidelines for U.S. cost-effectiveness analysis, future QALYs and costs were discounted at an annual rate of 3% (Gold et al., 1996).

In order to compare the relative value of shifting women from being unscreened, under-screened or over-screened to guidelines-adherent screening, we calculated the incremental net monetary benefit (INMB), which translates the incremental benefit (additional quality-adjusted life-years [QALYs] gained) into monetary terms for a given willingness-to-pay (WTP) threshold (by multiplying the QALYs gained by the WTP) and then subtracting the incremental cost. Closely related to the incremental cost-effectiveness ratio (ICER) used in traditional cost-effectiveness analysis, INMB allows for health benefits and costs to be expressed in a common unit. A positive INMB at a given WTP threshold is explained as a net savings per woman when the QALY benefit is also considered. We can interpret the INMB estimate as the maximum cost that could be additionally incurred per woman before the ICER associated with the scenario exceeds the WTP threshold.

In this analysis, which does not include any programmatic costs of improving screening, the INMB value provides a measure of how much economic investment can be made towards that intervention to achieve the desired improvement in a cost-effective manner. A negative INMB indicates no further investment should be made at that WTP threshold. We used the INMB estimates to identify whether addressing over- and/or under-screening represent a potential high-value improvement(s). We considered cost-effectiveness thresholds (below which an intervention would be regarded as providing good value for money) of $50,000, $100,000, and $200,000 per QALY gained (Neumann et al., 2014).

We evaluated shifting those who are unscreened (i.e., never screened), under-screened (i.e., cytology every 4 or 5 years), or over-screened (i.e., cytology every 1 or 2 years [biennial]) to cytology screening every 3 years (triennial), each by the proportions of current screening frequencies and follow-up adherence proportions captured by the New Mexico HPV and Pap Registry (NMHPVPR) ("Current Practice") (Kim et al., 2015). The results are presented as INMB per woman and, in the case of Current Practice, represent the weighted average of INMB per woman for shifting each sub-group (unscreened, under-screened, and over-screened) of women to screening adherence according to current guidelines. For screening frequencies in Current Practice, we used the following values (Kim et al., 2015): 14.4% were not screened and 9.3%, 16.2%, 10.6%, 35.2%, and 14.4% were screened every 1 year, 2 years, 3 years, 4 years, and 5 years, respectively. For adherence to diagnostic (colposcopy/biopsy) follow-up of screen-positive women, we used the following values conditioned on a woman's preceding cytology result (Kim et al., 2015): 76.0% for high-grade squamous intraepithelial lesion (HSIL) cytology, 62.3% for atypical squamous cells, cannot rule out HSIL, 50.7% for low-grade squamous intraepithelial lesion cytology, 49.4% for human papillomavirus (HPV)-positive atypical squamous cells of undetermined significance (ASC-US) cytology, and 6.8% for ASC-US cytology (unqualified by HPV testing).

We used triennial cytology in our analysis as it the most widely recommended method of cervical screening, including being recommended in current guidelines (Saslow et al., 2012) and draft recommendations by the U.S. Preventive Task Force (https://www.uspreventiveservicestaskforce.org/Page/Document/draft-evidence-review/cervical-cancer-screening2), and cytology is the most commonly used method for cervical screening in New Mexico (Saslow et al., 2012).

We also assessed the value (INMB per woman) of shifting screening for a particular non-compliant interval ("Uniformly Non-Adherent"), in which all women are assumed to be screen at that interval, to every 3 years. This would represent a scenario in which a specific sub-group of women that was uniformly unscreened, under-screened, or over-screened (vs. the weighted average for the Current Practice as mentioned above) were targeted for an intervention to promote adherence with triennial cytology screening. These values were assessed under both imperfect (using NMHPVPR data) and perfect adherence to follow-up of screen-positive women scenarios.

Table 1
The incremental net monetary benefit (INMB) for improvements in cervical cancer screening at different willingness to pay (WTP) thresholds per quality-adjusted life-year (QALY). Positive INMBs means that the improvement is cost effective at that WTP and value can be interpreted as the amount that can be invested to increased adherence. Negative INMBs, which means that the improvement is not cost effective at that WTP, are highlighted with italicized font. "Current Practice" (top panel) represents the proportions of women who are unscreened (0), under-screened (4-yearly [4y] or 5-yearly [5y] screening), and over-screened (1-yearly [1y] or 2-yearly [2y] screening) based on data from the New Mexico HPV Pap Registry (NMHPVPR). "Uniformly Non-Adherent Scenario" represents a theoretical, whole population that is being screened at each interval, either under imperfect adherence to follow-up of screen-positive women as observed in New Mexico (middle panel) or under perfect adherence (bottom panel). The latter is included as a reference to show the upper bound of potential investment in improving adherence to 3-yearly (3y) screening in a cost-effective manner. The following cost-effectiveness thresholds (below which an intervention would be regarded as for good value for money) were considered: $50,000, $100,000, and $200,000 per QALY gained.

Improvement	INMBs for WTP threshold ($ per QALY)		
	$50,000	$100,000	$200,000
Current Practice			
a. All to 3y	$365	$759	$1546
b. Unscreened (0) to 3y	$229	$576	$1269
c. Under-screened (5y) to 3y	$27	$100	$245
d. Under-screened (4y) to 3y	$24	$115	$297
e. Over-screened (2y) to 3y	$8	*−$45*	*−$152*
f. Over-screened (1y) to 3y	$75	$13	*−$112*
Uniformly Non-Adherent Scenario (with imperfect adherence to follow-up)			
a. Unscreened (0) to 3y	$1591	$3998	$8812
b. Under-screened (5y) to 3y	$191	$693	$1698
c. Under-screened (4y) to 3y	$70	$328	$845
d. Over-screened (2y) to 3y	$52	*−$277*	*−$936*
e. Over-screened (1y) to 3y	$807	$136	*−$1207*
Uniformly Non-Adherent Scenario (with perfect adherence to follow-up)			
a. Unscreened (0) to 3y	$2167	$5286	$11,524
b. Under-screened (5y) to 3y	*−$8*	$351	$1069
c. Under-screened (4y) to 3y	*−$22*	$176	$573
d. Over-screened (2y) to 3y	$271	$100	*−$242*
e. Over-screened (1y) to 3y	$1356	$1035	$392

3. Results

Under Current Practice, most INMBs were greater for shifting the current proportion of unscreened and under-screened women to triennial cytology screening than for shifting over-screened women to triennial screening, irrespective of WTP (Table 1). The exceptions were for switching from annual to triennial screening ($75) vs. 4-year ($24) and 5-year ($27) to triennial screening. That is, at a given WTP threshold, a greater economic investment can be made towards increasing adherence with triennial screening among unscreened or under-screened women (while maintaining cost-effectiveness) than with over-screened women.

Relative to Current Practice, Uniformly Non-Adherent Scenarios, in which an entire sub-group of previously unscreened women shifted to triennial screening, had higher INMB values at all WTP thresholds. INMB values were greater still with perfect adherence to diagnostic and

treatment follow-up of screen-positive women, indicating that the value of potential investment in screening previously unscreened women is greater when completion of the screening episode is assured. This was not the case for under-screened women.

With imperfect adherence to follow-up of screen-positive women, potential investments to shift women with some screening (i.e., the under-screened) to triennial screening can be greater to compensate for loss-to-follow-up, compared to perfect adherence; at the $50,000 WTP threshold, shifting women from 4- or 5-year screening to triennial screening had a negative INMB, indicating that further investment in improving adherence to triennial screening would not be of value unless the WTP threshold increased.

While the value of potential investments to promote triennial screening by cytology in unscreened or under-screened women increased as the WTP threshold increased, the opposite was true for reducing over-screening. At the $200,000 WTP threshold with the Uniformly Non-Adherent Scenario (imperfect adherence), INMB values tended to be negative, indicating that further investment to correct over-screening would not be cost-effective i.e., at that WTP, it is more cost effective to permit over-screening rather than correcting it. With perfect adherence, greater investments could be made to correct over-screening, but it was not efficient to shift from biennial to triennial screening at the $200,000 WTP threshold. Even though perfect adherence is unrealistic, it provides an "upper bound" on the value of potential investments to improve screening while maintaining a favorable cost-effectiveness profile.

4. Discussion

In this analysis, we assessed the monetary value of addressing screening inefficiencies due to some women being unscreened, under-screened (4- and 5-year cytology), and over-screened (1- and 2-year cytology), compared to current guidelines-based 3-year cytology. We considered how adherence to follow-up of screen-positive women and WTP modify our results. Under any scenario, the best value was to get unscreened women screened. Notably, even under the least favorable conditions for screening, the lowest WTP of $50,000 and imperfect adherence follow-up of screen-positive women (which reduces the cost-effectiveness of screening since some women with abnormal cytology will not get the care they need), more than $1500 per woman could be spent to get previously unscreened women screened by cytology every 3 years. Based on these data, community-based strategies, even labor-intensive strategies such as going door-to-door, might still be cost-effective. Future research should address this question.

Whether correcting under-screening vs. over-screening is the next best value depending greatly on the scenario. Under the real-world scenario of imperfect adherence with follow-up of screen-positive women, reducing frequency of those over-screened was a better value at WTP of $50,000 than increasing screening frequency of those under-screened. At higher WTP values, increasing the screening frequency, especially from 5 years to 3 years, for the under-screened was a better value than reducing the screening frequency in the over-screened. This is because a higher WTP will be more permissive towards strategies with higher cost-effectiveness ratios (higher ICER) (typically, more aggressive strategies such as 1- or 2-year screening) and therefore the value to invest in correcting them (INMB) is lower.

In conclusion, we have the most to gain from targeting unscreened women for screening rather than getting under-screened women screened sooner or curbing over-screening for adherence with recommended triennial cytology screening, irrespective of WTP. Given the known barriers to screening for under-served populations, alternative screening strategies should be considered to reach the unscreened. One strategy to consider, although not directly evaluated in this analysis because it is not recommended yet, is using self-collection and human papillomavirus testing, which is potentially a highly effective a screening method to reach populations that are reticent to undergo cervical screening (Arbyn et al., 2014; Arrossi et al., 2015; Castle et al., 2011).

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Competing interests

The authors disclose no competing interests.

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Contributor statement

PEC, CMW, and JJK designed of the analysis. NGC, SS, EAB, and JJK conducted the analysis. PEC and JJK drafted the manuscript. All authors contributed to the critical review, revisions, and final draft of the manuscript.

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