Striking a balance: Complete evaluation of organised cervical cancer screening programmes is not possible until harms of screening are better quantified

Clare A. Aitken[1], Inge M.C.M de Kok[1]

1. Department of Public Health, Erasmus MC, University Medical Center Rotterdam

Submitted

ABSTRACT

Organised cervical cancer screening programmes need to achieve a careful balance between benefits and harms to maximum effectiveness. Harms of screening can be psychological or physical and can occur at screening, during follow-up or during diagnosis and treatment. We aimed to outline potential harms in each phase of screening, synthesise a list of indicators for quantifying harms and explore why harms are not quantified more regularly. We reviewed three European indicator sets to identify indicators for harms and supplemented this list with additional indicators based on the literature. We identified 16 indicators that cover physical and psychological harms across the whole screening process. Despite multiple organisations identifying indicators measuring harms in their indicator sets, these indicators are not regularly reported. Challenges in quantifying indicators due to difficulties with data collection and lack of organisation should be addressed to facilitate more comprehensive reporting. Quantifying harms will become increasingly important as the underlying population risk for cervical lesions changes. The combination of hrHPV vaccination and hrHPV screening is driving this change in risk, and will necessitate a re-optimisation of organised screening programmes. Complete information about both benefits and harms is required for programme optimisation.

Organised cervical cancer screening programmes are a staple of public health strategies in many countries. While these programmes vary across countries, all programmes have one aim: to reduce incidence of, and mortality from, cervical cancer. Evidence has shown that organised cervical cancer screening is associated with reduced cervical cancer mortality.[1] This is the main benefit of screening for cervical cancer. The ability to correctly identify and treat women at high risk of cervical carcinoma (i.e. those with cervical intraepithelial neoplasia (CIN) grade 2 or higher) is one factor that defines the overall cost-effectiveness of a cervical screening programme. However, in order to be (cost-) effective, organised cancer screening programmes must balance benefits with potential harms of screening across the whole process of screening, which encompasses what occurs within the screening programme (starting with attendance, leading to testing and referral) and what happens in clinician care following referral (colposcopy, diagnosis and treatment).

In this article, we argue why more attention needs to be given to harms in monitoring and evaluation of cervical cancer screening. We outline potential harms in each phase of screening and synthesise a list of indicators for quantifying harms. We explore why harms are not quantified more regularly, the first steps needed in screening programmes before quantification is possible and, finally, explain why current developments in cervical cancer prevention necessitate more attention to harms of cervical cancer screening.

What's the harm? Potential harms across the screening process

In the 'testing and referral' stage of the screening process, harms related to the screening test itself can occur. In one study of screened women, one third of women who receive normal screening results reported finding the screening process somewhat stressful, and around a quarter of women (27%) reported having some physical symptoms (e.g. lower abdominal pain, vaginal bleeding, discharge, urinary problems, or feeling sick) for at least one day after having a smear taken.[2] The use of hrHPV testing as either the primary test or as a triaging method has been found to decrease health-related quality of life; hrHPV-positive women with abnormal cytology reported higher levels of anxiety than women with abnormal cytology who are either hrHPV negative or not tested for HPV,[3] although the increased anxiety levels were short-lived.[4]

If a woman is referred from an organised screening programme to the 'clinical care' stage, harms related to diagnosis and treatment can occur. First and foremost, simply being referred for colposcopy can be distressing for women, with a short-term increase in anxiety found amongst referred women.[5] Referral is necessary to determine if a woman's abnormal screen result is indicative of a clinically relevant lesion (i.e. CIN 2 or worse). CIN 1 lesions are not considered clinically relevant, due to the higher chance of regression. If a screening programme refers too many women to the gynaecologist unnecessarily

(i.e. with CIN 1 or lower), more women are exposed to unnecessary anxiety and worry, as well as physical and psychological impacts and increases risk of overtreatment.

Several large meta-analyses have found an association between excisional treatments for CIN lesions and adverse obstetric outcomes, such as preterm birth, low birth weight, premature rupture of the membranes and perinatal mortality.[6-11] More invasive treatments (i.e. more aggressive techniques or greater depth) are associated with higher risk of adverse obstetric outcomes.[9] Added to this, colposcopy and excisional treatments can cause physical pain and discomfort; two studies found that women who are treated with LLETZ or other conisation techniques were found to experience after-effects such as bleeding, pain and discharge more frequently, more intensely and for a longer duration than women treated with biopsy or colposcopy.[12, 13] Another study in which 75% of women were treated either biopsy or LLETZ found that four out of five women suffers from at least one physical after-effect following colposcopy or colposcopy plus treatment.[14] As the number of after-effects increased within this cohort, so did levels of distress reported in follow-up.[14]. We found that approximately one quarter of CIN 1 lesions detected following referral were treated with excisional treatment,[15] perhaps unnecessarily. For these women, the benefits of having their lesion treated may have been overweighted by the harms that referral and treatment could cause.

Indicators that capture information about harms of cervical cancer screening

Despite evidence that cervical cancer screening can cause harms, most studies are one-off. Monitoring of benefits of screening occurs regularly in many countries, however, physical and psychological impacts of the screening process does not. The lack of reporting is not because harms are not considered relevant performance indicators. There have been efforts by various groups to define a set of indicators for measuring effects of screening within Europe,[16-19] including indicators about harms of screening. We summarised harms indicators from three indicator sets in Table 1, as well as adding indicators to the list that were missing based on our knowledge of the literature. Of the 16 indicators in Table 1, only one was listed in all three of the reviewed indicator sets – interval cancers. Indicators measuring complications of diagnosis and treatment in clinical care were also identified in multiple indicator sets, as were indicators of overtreatment, although the exact definition of overtreatment of low-grade lesions differed between the two indicator sets. No indicator sets define indicators for incidental findings or psychosocial harms of screening, referral or treatment.

Barriers to better quantification of harms

As multiple organisations identify the same indicators as important measures of programme quality, the question remains, why are these indicators not reported more regularly? On a practical level, quantifying harms requires complex data collection and

Table 1: *Overview of health outcomes and quality of life indicators for cervical cancer screening based on review of indicator sets*

Stage of screening	Harms*	Indicator	Aspect of performance measured?
Screening	Harms of the screen test Psychosocial harms	% women with feelings of shame, pain, inconvenience, or nervousness during smear taking amongst all screened women	Patient-centred care
	Harms of the screen test	% women with physical side-effects following screening (lower abdominal pain, vaginal bleeding, discharge, or urinary problems) amongst all screened women	Safety, patient-centred care
Follow-up	False-positives	% participants with Pap 2 or higher result with no clinically relevant histology (i.e. false-positive [women with CIN 1 or lower])**®	Safety
		% women screened with pain, bleeding, or discharge in false-positive women after colposcopy	Safety, patient-centred care
	False-positives Psychosocial harms	% women screened with anxiety or worries following false positives	Patient-centred care
	False-negatives (delayed diagnosis)	Interval cancers (cervical cancer incidence following normal cytology)**○®	Effectiveness
	Psychosocial harms	% HPV-positive women with anxiety or worries amongst all HPV-positive women	Patient-centred care
	Incidental findings	Number of women diagnosed with other conditions discovered as a result of cervical cancer screening	Safety
Referral/ Colposcopy	Psychosocial harms	% women referred with anxiety or worries amongst all referred women	Patient-centred care
	Harms of the diagnostic test	% women referred with pain, bleeding, or discharge after colposcopy®	Safety, patient-centred care
Treatment	Treatment related complications	% complications following diagnosis and treatment of false-positive women**®	Safety
		% complications as a result of diagnosis and treatment of preclinical stages**®	Safety
		% complications as a result of diagnosis and treatment of clinical stages**®	Safety
	Overtreatment	Medicalisation of < CIN 1 or CIN 1** (Proportion [%] of women treated for CIN1)○	Patient-centred care
		Proportion (%) of women hysterectomised on screen-detected intraepithelial lesions○	Patient-centred care
Long-term outcomes	Treatment related complications	Number of women treated for CIN lesions with excisional techniques that go on to experience adverse obstetric outcomes®	Safety

* Based on EU–TOPIA, Deliverable 2.1: Definition of benefits and harms of cancer screening, 2016[19]

** Based on Indicators for the new Dutch cervical cancer screening programme[17]

○ Based on European Guidelines for Quality Assurance in Cervical Cancer Screening[16]

® Based on EU–TOPIA, Deliverable 2.2: Key benchmarks and indicators to quantify equity, benefits and harms of screening, 2016[18]

analysis, supported by appropriate ICT systems. For ten of the indicators, data needs to be collected via questionnaire. This includes indicators relating to psychosocial harms (four indicators) and to physical side-effects of screening, colposcopy or treatment (six indicators). The rest of the indicators in Table 1 require complex linkage between screening programme data and other data sources, such as hospital registries or national pathology archives.

Another barrier to the quantification of these indicators is the governance structure of screening programmes. If governance of the various stages of screening are run by different organisations, thereby dividing financial responsibility, no single organisation has a mandate to quantify the potential harms across the entire screening process. As cohort studies have been identified as the most effective method of monitoring overtreatment in cancer screening,[20] collaboration and joint funding between organisations is necessary to set up and maintain such studies.

Optimising screening requires the most accurate information available

In the Netherlands, like in many European countries, women are able to participate in a very high quality, well-regulated, organised screening programme. There are, however, further opportunities for improvement of the monitoring and evaluation of the programme. Taking the Dutch programme as an example, opportunities include creating a national register for colposcopy and treatments so that trends in follow-up and treatments can be evaluated and linking national datasets to evaluate the impact of treatments on obstetric outcomes. Additionally, women who have participated in the programme could be regularly surveyed by means of a 'patient experience' style questionnaire to quantify their experiences of screening as well as short-term harms, such as anxiety or pain or bleeding post-screening.

The rapid pace of development within cervical cancer prevention make it vital that quantification of harms is improved. Cervical cancer prevention is becoming increasingly sophisticated and the possibility of eliminating cervical cancer is becoming ever more feasible.[21] Combining hrHPV vaccination and hrHPV screening, as well as improvements in treatments, will impact on the careful balance of harms and benefit in cervical cancer screening. While primary hrHPV screening offers greater protection against cervical cancer than cytology-based screening,[22] the number of unnecessary referrals increased after implementation in the Netherlands.[23] Both hrHPV screening and hrHPV vaccination have shown substantial benefits in the reduction of disease burden,[24] however, declining disease prevalence will necessitate changes to organised programmes.[25] Applying current screening protocols to vaccinated women may lead to overscreening of this population. Therefore, research is needed to determine the most optimal screening strategy for screening partly vaccinated cohorts, which can be achieved using microsimulation modelling. The outcomes of these modelling studies are impacted by

the quality of life assumptions used.[26] Therefore, having the most accurate data on both benefits and harms is necessary for ensuring that the most optimal programme can be implemented.

CONCLUSIONS

Organised cervical cancer screening programmes need to maintain a balance between benefits and harms of screening in order to be effective. With hrHPV vaccination and hrHPV-based screening making elimination of cervical cancer possible, screening programme algorithms will need to be adapted to maintain this balance. While the benefits of screening are regularly quantified, the physical and psychosocial harms of cervical cancer screening are less frequently reported. Efforts should be made within organised programmes to enable quantification of harms so that screening programmes can be optimised using the most up-to-date information on both benefits and harms.

DECLARATIONS

Ethics approval and consent to participate: Not applicable
Consent for publication: Not applicable
Availability of data and materials: Not applicable
Competing interests: The authors declare that they have no competing interests
Funding: C.A. Aitken and I.M.C.M de Kok received funding from the Rijksinstituut voor Volksgezondheid en Milieu as part of the Evaluation of the Dutch cervical cancer screening programme, project 'LEBA 2017' with grant number '072/2018 DG AvdZ/em'.
Authors' contributions: CAA reviewed the indicator sets and wrote the manuscript with significant input from IdK. All authors read and approved the final manuscript.
Acknowledgements: We wish to thank Dr Heleen van Agt for assisting with our initial literature search and Dr Jan-Willem Weenink for his helpful feedback on an early version of this article.

REFERENCES

1 Jansen EEL, Zielonke N, Gini A, *et al.* Effect of organised cervical cancer screening on cervical cancer mortality in Europe: a systematic review. European Journal of Cancer 2020;**127**:P207-23.

2 Korfage IJ, van Ballegooijen M, Wauben B, *et al.* Having a Pap smear, quality of life before and after cervical screening: a questionnaire study. BJOG 2012;**119**:936-44.

3 Maissi E, Marteau TM, Hankins M, *et al.* Psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: cross sectional questionnaire study. BMJ 2004;**328**:1293.

4 Maissi E, Marteau TM, Hankins M, *et al.* The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: 6-month follow-up. Br J Cancer 2005;**92**:990-4.

5 Korfage IJ, Essink-Bot ML, Westenberg SM, *et al.* How distressing is referral to colposcopy in cervical cancer screening?: a prospective quality of life study. Gynecol Oncol 2014;**132**:142-8.

6 Arbyn M, Kyrgiou M, Simoens C, *et al.* Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ 2008;**337**:a1284.

7 Danhof NA, Kamphuis EI, Limpens J, *et al.* The risk of preterm birth of treated versus untreated cervical intraepithelial neoplasia (CIN): a systematic review and meta-analysis. European journal of obstetrics, gynecology, and reproductive biology 2015;**188**:24-33.

8 Jin G, LanLan Z, Li C, *et al.* Pregnancy outcome following loop electrosurgical excision procedure (LEEP) a systematic review and meta-analysis. Arch Gynecol Obstet 2014;**289**:85-99.

9 Kyrgiou M, Athanasiou A, Paraskevaidi M, *et al.* Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 2016;**354**:i3633.

10 Kyrgiou M, Koliopoulos G, Martin-Hirsch P, *et al.* Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. The Lancet 2006;**367**:489-98.

11 Kyrgiou M, Mitra A, Arbyn M, *et al.* Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ 2014;**349**:g6192.

12 The Tombola Group. After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial. BJOG 2009;**116**:1506-14.

13 Williams J, Jess C, Johnson N. Bleeding, discharge, pain and dysmenorrhoea after large loop excision of the transformation zone (LLETZ). J Obstet Gynaecol 2004;**24**:167-8.

14 O'Connor M, O'Brien K, Waller J, *et al.* Physical after-effects of colposcopy and related procedures, and their inter-relationship with psychological distress: a longitudinal survey. BJOG 2017;**124**:1402-10.

15 Aitken CA, Siebers AG, Matthijsse S, *et al.* Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy. Acta Obstet Gynecol Scand 2019;**98**:737-46.

16 Arbyn M, Anttila A, Jordan J, *et al.* European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition--summary document. Ann Oncol 2010;**21**:448-58.

17 Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Indicators for the new Dutch cervical cancer screening programme [in Dutch]. Bilthoven, NL: Rijksinstituut voor Volksgezondheid en Milieu 2017.

18 Siljander I, Heinavaara S, Sarkeala T, *et al.* EU-TOPIA Deliverable 2.2: Key benchmarks and indicators to quantify equity, benefits and harms of screening. In: EU-TOPIA, ed. Finland: Finnish Cancer Registry, Helsinki 2016.
19 Siljander I, Lehtinen M, Makkonen P, *et al.* EU-TOPIA Deliverable 2.1: Definition of benefits and harms of cancer screening. In: EU-TOPIA, ed. Finland: Finnish Cancer Registry, Helsinki 2016.
20 Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. BMJ 2015;**350**:g7773.
21 Canfell K. Towards the global elimination of cervical cancer. Papillomavirus research (Amsterdam, Netherlands) 2019;**8**:100170-.
22 Ronco G, Dillner J, Elfström KM, *et al.* Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. The Lancet 2014;**383**:524-32.
23 Erasmus MC, PALGA. Monitor 2017. RIVM 2018, Available from https://www.rivm.nl/documenten/landelijke-evaluatie-van-bevolkingsonderzoek-baarmoederhalskanker-leba-tm-2017, Date accessed 18/09/2020.
24 Palmer T, Wallace L, Pollock KG, *et al.* Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ 2019;**365**:l1161.
25 El-Zein M, Richardson L, Franco EL. Cervical cancer screening of HPV vaccinated populations: Cytology, molecular testing, both or none. Journal of Clinical Virology 2016;**76**:S62-S8.
26 de Kok IMCM, Korfage IJ, van den Hout WB, *et al.* Quality of life assumptions determine which cervical cancer screening strategies are cost-effective. International Journal of Cancer 2018;**142**:2383-93.