Appendix 5 (as supplied by the authors): Summary of evidence for the effect of screening with cytology on incidence of invasive cervical cancer

Quality Assessment							Summary of findings: Cervical cancer		Summary of findings: Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Screening, no. (%)	Control, no. (%)	Relative (95% CI)	Absolute per million (range)	GRADE quality of evidence	Importance
Incidence of invasive cervical cancer												
1[1]	Randomized trial	No serious risk of bias*	No serious inconsistency†	Serious‡	No serious imprecision§	None¶	*n* = 32,058 152 (0.47%)**	*n* = 31,488 118 (0.37%)**	HR 1.34 (0.99 to 1.81)	1,271 more (from 38 fewer to 3,040 more)	Moderate	Critical
1[2]	Observational study	No serious risk of bias††	No serious inconsistency†	No serious indirectness	No serious imprecision§	None¶	63/103,491 (0.06%)‡‡	20/12,531 (0.16%)§§	RR 0.38 (0.23 to 0.63)	987 fewer (from 590 fewer to 1,228 fewer)	Low	Critical
Exposure to cytologic screening												
13[3-14]¶¶	Observational studies***	No serious risk of bias†††	No serious inconsistency‡‡‡	Serious§§§	No serious imprecision	Reporting bias¶¶¶	4,781 cases 17,916 controls		OR 0.35 (0.30 to 0.41)		Very low	Critical

Note: CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative risk.

* Random sequence generation unclear and allocation concealment not described; however, study limitations were not downgraded for these risks/uncertainties.

† Inconsistency not applicable for single study.

‡ Directness downgraded owing to concerns regarding population (rural women living in a low-income country) and intervention characteristics (1-time opportunistic screening; short duration [3 mo] of training received by technicians responsible for processing and reading the samples).

§ The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes); however, considering the specific outcome, the evidence is not downgraded.

¶ Insufficient number of studies to assess publication bias.

** Rates were adjusted for age by study authors.

†† Newcastle-Ottawa Scale for cohort studies was completed; 8 out of a possible 9 stars were awarded.

‡‡ 63 cases of cervical cancer diagnosed in women who had been screened in the 0.5 to 5.5 year interval; 37 of these cases were screen-detected cancers, 26 cases were symptomatic cancers.

§§ 20 cases of cervical cancer diagnosed in women who had been screening in the 0.5 to 5.5 year interval; 6 of these cases were screen-detected cancers, 14 cases were symptomatic cancers.

¶¶ There are 12 included case-control studies[3-14]. The number of studies appears as thirteen because 2 different data sets from 1 study[13] were used as separate entries in the meta-analysis.

*** Case-control.

††† Newcastle-Ottawa Scale completed to assess the quality of each of the studies. None of the studies satisfied all of the rating criteria. Despite some uncertainties (e.g., lack of information on non-response rates in some studies) and limitations (e.g., one-third of the studies used hospital controls rather than community controls) the evidence was not downgraded.

‡‡‡ Heterogeneity statistics were significant: $\chi^2 = 50.98$, 12 degrees of freedom ($p < 0.001$); $I^2 = 76\%$. Sensitivity analyses were conducted but heterogeneity could not be explained by differences in study design, populations, interventions, or length of exposure. All studies favour screening; only two of the studies marginally intersect the line of no difference.

§§§ Directness was downgraded due to concerns over the inclusion of both organized and opportunistic screening approaches, the diversity of study locations (both developed and developing

Appendix to: Canadian Task Force on Preventive Health Care. Recommendations on screening for cervical cancer. *CMAJ* 2013. DOI:10.1503/cmaj121505.

countries, e.g. Canada, US, Finland, Sweden, Japan, Italy, South Africa, Columbia, Costa Rica, Panama, Mexico), and the related potential for important differences in participants and screening procedures.

¶¶¶ Publication bias was strongly suspected owing to asymmetry in the funnel plot and recognition that the risks of publication bias may be substantial for observational studies, particularly small studies that use data from electronic medical records or disease registries.

References

1. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *New England Journal of Medicine*. 2009;360:1385.

2. Herbert A, Stein K, Bryant TN, et al. Relation between the incidence of invasive cervical cancer and the screening interval: Is a five year interval too long? *Journal of Medical Screening*. 1996;3:140.

3. Andrae B, Kemetli L, Sparén P, et al. Screening-preventable cervical cancer risks: Evidence from a nationwide audit in Sweden. *Journal of the National Cancer Institute*. 2008;100:622.

4. Aristizabal N, Cuello C, Correa P, et al. The impact of vaginal cytology on cervical cancer risks in Cali, Colombia. *International Journal of Cancer*. 1984;34:5.

5. Berrino F, Gatta G, d'Alto M, et al. Efficacy of screening in preventing invasive cervical cancer: A case-control study in Milan, Italy. *IARC Scientific Publication Series*. 1986;76:111.

6. Clarke EA, Anderson TW. Does screening by "pap" smears help prevent cervical cancer? *The Lancet*. 1979;2(8132):1.

7. Decker K, Demers A, Chateau D, et al. Papanicolaou test utilization and frequency of screening opportunities among women diagnosed with cervical cancer. *Open Medicine*. 2009;3:e140.

8. Hernandez-Avila M, Lazcano-Ponce EC, de Ruiz PA, et al. Evaluation of the cervical cancer screening programme in Mexico: A population-based case-control study. *International Journal of Epidemiology*. 1998;27:370.

9. Herrero R, Brinton LA, Reeves WC, et al. Screening for cervical cancer in Latin America: A case-control study. *International Journal of Epidemiology*. 1992;21:1050.

10. Hoffman M, Cooper D, Carrara H, et al. Limited pap screening associated with reduced risk of cervical cancer in South Africa. *International Journal of Epidemiology*. 2003;32:573.

11. Jiménez PM, Thomas DB. Has the use of pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico? *International Journal of Cancer*. 1999;82:804.

12. Makino H, Sato S, Yajima A, et al. Evaluation of the effectiveness of cervical cancer screening: A case-control study in Miyagi, Japan. *Tohoku Journal of Experimental Medicine*. 1995;175:171.

13. Nieminen P, Kallio M, Anttila A, et al. Organised vs. spontaneous pap-smear screening for cervical cancer: A case-control study. *International Journal of Cancer*. 1999;83(1):55.

14. Talbott EO, Norman SA, Kuller LH, et al. Refining preventive strategies for invasive cervical cancer: A population-based case-control study. *Journal of Women's Health*. 1995;4(387).