Modelling risk assessment for cervical cancer in symptomatic Saudi women

*Wedad Al-Madani, MSc, MPH, **Anwar E. Ahmed**, MSc, PhD, **Haitham Arabi**, MD, **Sumaiah Al Khodairy**, MBBS,
Nashmia Al Mutairi, MD, **Abdul Rahman Jazieh**, MD, MPH.*

ABSTRACT

الأهداف : دراسة ما إذا كان يمكن تحسين فائدة فحص سرطان عنق الرحم عن طريق الجمع بين عوامل متعددة بالإضافة إلى اختبار عنق الرحم .

الطريقة : قام الباحثون بدراسة 300 امرأة تعاني من أعراض يشتبه في إصابتهن بسرطان عنق الرحم وخضعن لفحص الخزعة في مدينة الملك عبد العزيز الطبية في الرياض ، المملكة العربية السعودية خلال الفترة من 1 فبراير 2017م و 31 ديسمبر 2017م.

النتائج : حددنا خطر الاصابة بسرطان عنق الرحم في عينة من النساء العربيات المصابات بأعراض. ارتبط ارتفاع خطر الإصابة بسرطان عنق الرحم لدى النساء السعوديات بـ4 عوامل خطر : تاريخ العائلة (نسبة الأرجحية المعدلة [aOR]؛ 4.216، 95% فاصل الثقة=1.433–12.400)، النزيف المهبلي aOR=3.959 ، فاصل الثقة= 1.272–12.318، ارتفاع ضغط الدم aOR=4.554 فاصل الثقة= 1.606 –12.912، واختبار لطاخة عنق الرحم غير طبيعي AOR=13.985، فاصل الثقة= 5.108–38.284. يعطي النموذج فائدة كافية (مساحة أسفل المنحنى= 87.5%، 95% فاصل الثقة=80.9–94.0% مع درجة ملائمة مقبولة

الخاتمة : اختبار مسحة عنق الرحم وحده غير كافي لتقييم المخاطر العالية للإصابة بسرطان عنق الرحم في مركزنا. قدً يتطلب الكشف المبكر عن سرطان عنق الرحم النظر في مجموعة من العوامل بما في ذلك اختبار عنق الرحم. أظهرت هذه الدراسة أن استخدام مزيج من تاريخ العائلة غير الطبيعي، والنزيف المهبلي، وارتفاع ضغط الدم، واختبار لطاخة عنق الرحم قد ساهم في تحسين فعالية فحص سرطان عنق الرحم. يتمتع النموذج المقترح بقدرة تنبؤية كبيرة ويجب التحقق من صحته باستخدام بيانات خارجية.

Objectives: To assess whether the utility of cervical cancer screening could be improved by combining multiple factors in addition to the pap test.

Methods: A retrospective cohort study of 300 symptomatic women who were suspected to have cervical cancer and referred for biopsy examination at King Abdulaziz Medical City, Riyadh, Saudi Arabia between February 2017 and December 2017.

Results: A high risk of cervical cancer in Saudi women was associated with 4 risk factors: family history (adjusted odds ratio [aOR], 4.216; 95% confidence intervals [CI], 1.433–12.400), vaginal bleeding (aOR, 3.959; 95% CI, 1.272–12.318), hypertension (aOR, 4.554; 95% CI, 1.606–12.912), and an abnormal pap smear test (aOR, 13.985; 95% CI, 5.108–38.284). The model yields an adequate utility (area under the curve, 87.5%, 95% CI, 80.9-94.0%) with acceptable goodness-of-fit (p=0.6915).

Conclusion: The pap smear test alone is inadequate to assess high risk for cervical cancer in our center. Early detection of cervical cancer may require consideration of a combination of factors including the pap test. This study has shown that using a combination of abnormal family history, vaginal bleeding, hypertension, and the pap smear test improved the effectiveness of cervical cancer screening.

Address correspondence and reprint request to: Dr. Anwar E. Ahmed, Department of Epidemiology and Biostatistics, College of Public Health and Health Informatics, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia. E-mail: ahmeda5@vcu.edu ORCID ID: orcid.org/0000-0001-8743-6007

Cervical cancer is the second-most common cancer type and the fourth leading cause of cancer-related death among women worldwide and the main cause in low- and middle-income countries.[1,2] Cervical cancer incidence in Saudi Arabia among cancer incidence

increased to 31.4% from 2004 to 2014, and its rank changed from the 11th to the 8th most common cause of cancer-related death in women within 10 years.[3]

The incidence of cervical cancer in developing countries remains high.[1] Approximately 85% of the global burden of cervical cancer occurs in the less-developed countries.[4,5] In Saudi Arabia, approximately 150 cases are reported annually and 30% of these patients die from the disease every year.[3] Many studies have reported factors associated with a high risk of cervical cancer: age at first sexual intercourse;[6] smoking;[7] multiple sexual partners;[8] an immunocompromised state;[8] use of oral contraceptives;[9] multiparty;[8,9] having given birth to 3 or more children; and use of non-barrier methods of birth control.[6-10] Other risk factors for cervical cancer include: a family history of cancer,[1] diabetes,[2,11] hypertension,[2] and obesity.[12] The study by Arbyn et al[1] indicated that routine and early screening decrease the mortality rate by up to 80%. Another study reported that early detection of invasive cancer cells can increase the survival rate to 92%.[8] The papanicolaou (pap) smear test is the main screening procedure used in our center to detect precancerous changes at an early stage. The pap test is recommended for women between the ages of 21 and 65 years, with a frequency of every 3 to 5 years.[9] A large systematic review that included 7 studies of 43,993 women from developing countries found that the pooled sensitivity of the pap test was 59% (95% confidence intervals [CI], 56-62%), while specificity was 94% (95% CI, 94-94%).[10] A study in the United States reported a sensitivity of 78.1% (95% CI, 72.1-83.3%) and a specificity of 69.5% (95% CI, 65.5-73.3%).[13] These studies show that the diagnostic accuracy of the pap test is inadequate for making informed clinical decisions. For instance, necrotic debris and inflammation may limit the accuracy of the pap smear test.[13]

In Saudi Arabia, the practice is to use the pap smear as a routine after delivery or if abnormal discharges occurs.[14] The inadequate performance of the pap test[15] focused our attention on developing a risk assessment tool that could incorporate various information on demographics, symptoms, and clinical and laboratory findings. This combined information may have the potential to significantly improve the screening process by accurately differentiating between patients with malignant and benign cervical tissues. The current study was designed to explore a combination of factors that may improve the screening accuracy of cervical cancer in Saudi Arabia.

Methods. A retrospective cohort study was conducted at the King Abdulaziz Medical City Hospital , Riyadh, Saudi Arabia between February 2017 and December 2017. The study included symptomatic Saudi Arabian women who were suspected to have cervical cancer and referred for biopsy examination during the study period. The study excluded Saudi Arabian women with unavailable biopsy results due to incomplete medical records.

The study was approved by the Institutional Review Board of the Ministry of National Guard - Health Affairs, approval #IRBC/177/17. Due to the nature of the study design, informed and publication consent were not required as per the ethical committee at the Ministry of National Guard - Health Affairs. In order to protect the privacy and confidentiality of patients the studied data were anonymized.

A structured data collection form was used to collect relevant data on women. The following demographic information was collected when available: age, height (m) and weight (kg). We extracted the following data on comorbidities and risk factors: chronic diseases (yes or no; diabetes, hypertension, depression, asthma), use of contraceptives (yes or no), and family history of cancer (yes or no).

We retrieved data on cervical cancer symptoms (yes or no): vaginal bleeding, vaginal discharge, post-coital bleeding, pelvic pain, unexplained weight loss, and fatigue. We retrieved data on the results of the pap smear test as normal or abnormal findings. Abnormal pap smear test includes cervical intraepithelial lesion, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, atypical glandular cells, and atypical squamous cells of undetermined significance.[4]

Statistical analysis. The data analysis was performed using Stata 12 software (StataCorp, College Station, TX, USA). The overall summary of the sample population is presented in **Table 1**. Bivariate analyses (Chi-square, independent samples t-test, and the simple binary logistic model) were applied to identify individual factors associated with a high risk of malignant cervical tissue (**Table 1**). The predictive accuracy of the pap smear test in discriminating malignant from benign cervical tissues was summarized by the area under the curve (AUC),

sensitivity, and specificity. The stepwise binary logistic model was applied to identify multiple factors that were associated with a high risk of malignant cervical tissue (**Table 2**). The adjusted risk was presented in adjusted odds ratios (aOR) and CI. The discriminatory power of the final model was summarized by AUC and 95% CI. The goodness-of-fit was evaluated for the final model using the Hosmer–Lemeshow test. Internal validation was performed in 200 samples with replacement using a bootstrapping approach and reported as optimism-corrected AUC.[16] We used DeLong et al[17] algorithm to assess the performance of the risk prediction model compared with individual factors. Index algorithm was applied to define optimal cutoff probability.[18-20]

Results. Data from 300 women with suspected cervical cancer were analyzed (mean age 51.7 ± 12.8 years). Of these women, 15.4% had a family history of cancer. The most common symptom was vaginal bleeding (51.4%), followed by vaginal discharge (28.5%), and post-coital bleeding (13.9%). The details can be found in **Table 1**. In the

subgroup analysis, 8 factors were associated with a high risk of malignant cervical tissue: age, family history of cancer, vaginal bleeding, vaginal discharge, weight loss, diabetes, hypertension, and an abnormal pap smear test ($p \leq 0.05$). The pap smear test had an accuracy of 73.3%, a sensitivity of 57.1%, and a specificity of 89.5%.

The stepwise multivariate binary logistic analysis showed 4 factors that independently associated with a high risk of malignant cervical tissue: family history of cancer (aOR, 4.216; 95% CI, 1.433-12.400), vaginal bleeding (aOR, 3.959; 95% CI, 1.272-12.318), hypertension (aOR, 4.554; 95% CI, 1.606-12.912), and an abnormal pap smear test (aOR, 13.985; 95% CI, 5.108-38.284).

This model showed powerful discrimination of malignant cervical tissue from benign cervical tissue (AUC=87.5%, 95% CI: 80.9-94.0%) with acceptable goodness-of-fit (p=0.6915). The model was found to be internally valid in 200 bootstrapping samples with an optimism-corrected AUC of 83.9%. This model showed significantly better predictive accuracy than individual factors alone ($\chi 2$ (4) = 143.04, p=0.001)(**Figure 1**).

Table 1 - Individual factors associated with high risk malignant cervical tissue (N=300).

Factor	Overall n=300	Benign 261	Malignant 39	*P*-value	OR	95% CI
Age (22–101 yrs.) (mean ± sd)	51.7 ± 12.8	50.8 ± 11.7	57.9 ± 17.6	0.002*	1.042	1.016 - 1.069
BMI (15.7–58.9) (mean ± sd)	31.7 ± 6.5	31.8 ± 6.4	30.9 ± 7.5	0.414	0.978	0.926 - 1.032
Family history	46 (15.4)	33 (12.7)	13 (34.2)	0.001*	3.577	1.667 - 7.673
Use of contraceptives	45 (15.4)	42 (16.5)	3 (8.1)	0.199	0.447	0.131 - 1.525
Vaginal bleeding	151 (51.4)	122 (48.0)	29 (74.4)	0.003*	3.138	1.468 - 6.708
Vaginal discharge	85 (28.5)	68 (26.3)	17 (44.7)	0.021*	2.274	1.133 - 4.564
Post-coital bleeding	41 (13.9)	39 (15.1)	2 (5.4)	0.128	0.321	0.074 - 1.389
Pelvic pain	19 (6.5)	16 (6.3)	3 (7.9)	0.701	1.286	0.356 - 4.639
Fatigue	30 (10.1)	26 (10.0)	4 (10.5)	0.920	1.059	0.348 - 3.221
Weight loss	14 (4.7)	9 (3.5)	5 (13.2)	0.015*	4.192	1.325 - 13.265
Diabetes	109 (37.0)	83 (32.7)	25 (65.8)	0.001*	3.962	1.929 - 8.137
Hypertension	111 (37.5)	85 (32.9)	26 (68.4)	0.001*	4.410	2.122 - 9.166
Depression	31 (10.5)	30 (11.7)	1 (2.6)	0.123	0.204	0.027 - 1.539
Asthma	54 (18.4)	47 (18.4)	7 (17.9)	0.942	0.968	0.403 - 2.327
Abnormal pap test	41 (15.5)	25 (10.5)	16 (57.1)	0.001*	11.307	4.806 - 26.601

Values are presented as number and percentage (%). *Significant at $p \leq 0.05$, CI - confidence intervals, SD - standard deviation, BMI - body mass index

Table 2 - Multiple factors associated with high risk of malignant cervical tissue (n=300)

Factor	Beta	Standard error	*P*-value	aOR*	95% CI for aOR
Family history	1.439	0.550	0.009*	4.216	1.433 - 12.400
Vaginal bleeding	1.376	0.579	0.018*	3.959	1.272 - 12.318
Hypertension	1.516	0.532	0.004*	4.554	1.606 - 12.912
Abnormal pap test	2.638	0.514	0.001*	13.985	5.108 - 38.284
Constant	-5.082	0.728	0.001	0.006	0.001 - 0.026

*Adjusted odds ration (aOR)

At an optimal cutoff probability of 0.18, the model yielded a sensitivity of 65.4% and specificity of 91.3%.

Discussion. Cervical cancer is a life-threatening disease for women worldwide,[21] particularly in Saudi Arabia.[1] This study has established a risk prediction model to identify women at high risk of cervical cancer among symptomatic women in Saudi Arabia. Subsequently, the study evaluated the utility of the proposed model as a potential screening tool for cervical cancer and compared its accuracy with each of the independent risk factors, separately. In particular, the model was compared with the pap test because this is the main screening tool for cervical cancer in our center. The study showed that using a combination of multiple predictive factors including the pap test (with an accuracy of 87.5%) outperforms the pap test alone (with an accuracy of 73.3%) and therefore improves the effectiveness of classification.

The utility of the model depends on 4 predictive factors: a family history of cancer, vaginal bleeding, hypertension, and an abnormal pap test. A family history of cancer was associated with a 4-fold higher risk of cervical cancer. None of the previous reports on cervical cancer in Saudi Arabia have investigated the link between family history and the risk of cervical cancer. However, a study in the USA recognized that a family history of cervical cancer increased the risk of cervical cancer.[4] The impact of family history on the risk of cervical cancer should be further explored in previously unstudied populations as a systematic review of 5 studies reported no correlation between family history and risk of cervical cancer.[1]

Certain chronic conditions such as diabetes, hypertension, and obesity have been shown in the literature to increase the risk of cancer in general and cervical cancer in particular.[2] While 2 studies by Lacey et al[22] and Nappi et al[23] demonstrated a significant association of obesity with cervical cancer, our study did not find a significant relationship between these conditions. On the other hand, diabetes and hypertension were correlated in our study with a high risk of cervical cancer. This result is consistent with a study by Oberaigner et al[24] who concluded that patients with diabetes and hypertension have an increased risk for all types of cancer.

While most of our sample were investigated for cervical cancer, 3 symptoms which are vaginal bleeding, vaginal discharges, and unexplained weight loss proved to have a significant association with the occurrence of the disease. Vaginal bleeding was the main symptom, and increased the risk of carrying the disease by up to 3 times. These symptoms have previously been proven in the literature and described in reference books.[25]

Finally, this study reported a moderate accuracy for the pap smear test of 73.3%, a sensitivity of 57.1%, and a specificity of 89.5%. This result is consistent with a systematic review and meta-analysis including women from developing countries,[10] which found a pooled sensitivity for the Pap test of 59%, while specificity was 94%. The pooled diagnostic odds ratio was 22.49.

On the basis of this study and previous studies, we found that it is beneficial to develop a risk prediction model that includes all significant risk factors in order to help clinicians identify high risk patients for further investigations. In Saudi Arabia as well as most of the developed countries, the pap smear test remain the first and easiest tool for cervical cancer screening.[14] In this study, we quantified the risk of cervical cancer in symptomatic Saudi Arabian women. According to our assessment tool, if symptomatic women at high risk for cervical cancer, clinician may request examination of cervix.

Study limitations. The limitations of this study were due to its retrospective nature and also the small number of cases. Findings were based on data from only one center, and correlation does not necessarily mean causation. In addition, certain factors were not included in this study such as infection with human papilloma virus,[26] smoking status, and lifestyle as they may improve the predictive value of the risk assessment tool in screening for cervical cancer.

The pap smear test alone is inadequate to assess high risk for cervical cancer in our center. Early detection of cervical cancer may require consideration of a combination of factors including the pap test. This
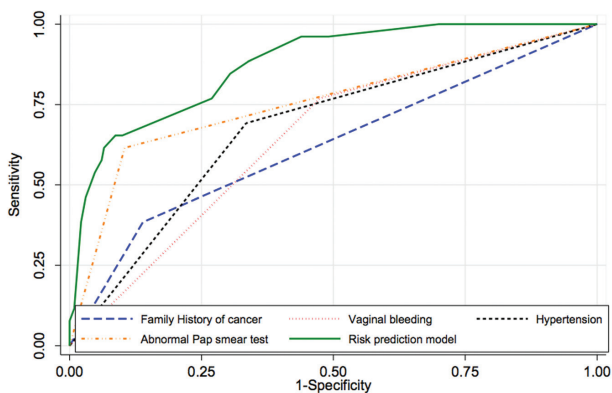

Figure 1 - Differences in Receiver operating characteristics curves between the risk prediction model and individual factors.

study has shown that using a combination of abnormal family history, vaginal bleeding, hypertension, and the pap smear test improved the effectiveness of cervical cancer screening. The proposed model had substantial predictive power and should be validated using external data.

References

1. Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol* 2011; 22: 2675-2686.

2. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1893-1907.

3. Alhamlan FS, Al-Qahtani AA, Al-Ahdal MN. Current studies on human papillomavirus in Saudi Arabia. *J Infect Deve Ctries* 2015; 9: 571-576.

4. Munoz N, Bosch FX, De Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348: 518-527.

5. Al-Darwish AA, Al-Naim AF, Al-Mulhim KS, Al-Otaibi NK, Moris MS, Aleem AM. Knowledge about cervical cancer early warning signs and symptoms, risk factors and vaccination among students at a medical school in Al-Ahsa, Kingdom of Saudi Arabia. *Asian Pac Jof Cancer Prev* 2014; 15: 2529-2532.

6. Szostek S, Klimek M, Zawilinska B, Kosz-Vnenchak M. Genotype-specific human papillomavirus detection in cervical smears. *Acta Biochim Pol* 2008; 55: 687-692.

7. Walboomers JM, Jacob MV, Manos MM, Bosch FX, Kummar JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189: 12-19.

8. Sehgal A, Singh V. Human papillomavirus infection (HPV) & screening strategies for cervical cancer. *Indian J Med Res* 2009; 130: 234-240.

9. Moyer VA, U.S. Preventive Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012; 156: 880-891.

10. Chen C, Yang Z, Li Z, Li L. Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. *Int J Gynecol Cancer* 2012; 22: 908-921.

11. National Institutes of Health. Cervical cancer: NIH consensus statement. *Bethesda: National Institutes of Health.* 1996. p. 1-38.

12. Ferri FF. Ferri's Netter Patient Advisor. [Updated 2016 January 28th]. Available from: https://www.elsevier.com/books/ferris-netter-patient-advisor/ferri/978-0-323-39324-9

13. Zhao L, Wentzensen N, Zhang RR, Dunn ST, Gold MA, Wang SS, et al. Factors associated with reduced accuracy in Papanicolaou tests for patients with invasive cervical cancer. *Cancer Cytopathol* 2014; 122: 694-701.

14. Nasser H, AlAyyaf M, Atallah A, Aminulislam M, Rizwan L, Aodah A, et al. Eleven-year review of data on pap smears in Saudi Arabia: we need more focus on glandular abnormalities!. *Ann Saudi Med* 2017; 37: 265-271.

15. Cardenas-Turanzas M, Follen M, Nogueras-Gonzalez GM, Benedet JL, Beck JR, Cantor SB. The accuracy of the Papanicolaou smear in the screening and diagnostic settings. *Journal of Lower Genital Tract Disease* 2008; 12: 269-275.

16. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15: 361-387.

17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837-845.

18. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; 3: 32-35.

19. Ahmed AE, Alzahrani FS, Gharawi AM, Alammary SA, Almijmaj FH, Alhusayni FM, et al. Improving risk prediction for pancreatic cancer in symptomatic patients: a Saudi Arabian study. *Cancer Manag Res* 2018; 10: 4981-4986.

20. Ahmed AE, McClish DK, Alghamdi T, Alshehri A, Aljahdali Y, Aburayah K, et al. Modeling risk assessment for breast cancer in symptomatic women: a Saudi Arabian study. *Cancer Manag Res* 2019;11: 1125-1132.

21. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle. (WA): IHME, University of Washington; 2016.

22. Lacey Jr JV, Swanson CA, Brinton LA, Altekruse SF, Barnes WA, Gravitt PE, et al. Obesity as a potential risk factor for adenocarcinomas and squamous cell carcinomas of the uterine cervix. *Cancer* 2003; 98: 814-821.

23. Nappi L, Indraccolo U, Sardo AD, Gentile G, Palombino K, Castaldi MA, et al. Are diabetes, hypertension, and obesity independent risk factors for endometrial polyps? *J Minim Invasive Gynecol* 2009; 16: 157-162.

24. Oberaigner W, Ebenbichler C, Oberaigner K, Juchum M, Schönherr HR, Lechleitner M. Increased cancer incidence risk in type 2 diabetes mellitus: results from a cohort study in Tyrol/ Austria. *BMC Public Health* 2014; 14: 1058.

25. DiSaia PJ, Chaudhuri G, Giudice LC, Moore TR, Smith LH, Porto MM. Women's health review: a clinical update in obstetrics-gynecology. 1st ed. Philadelphia; Saunders/Elsevier; 2012.

26. Almughais ES, Alfarhan A, Salam M. Awareness of primary health care physicians about human papilloma virus infection and its vaccination: a cross-sectional survey from multiple clinics in Saudi Arabia. *Infect Drug Resist* 2018; 11: 2257-2267.