Role of Pap smear in early diagnosis of cervical cancer- A Case Study of women in Saudi Arabia

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Abstract: The fifth most common and deadly cancer amongst women worldwide is Cervical cancer. Cervical cancer mostly affects younger women and during the last two decades the incidence in younger age groups has further increased. The EU established principles for organised population-based cervical screening to control and decrease the incidence of cervical cancer. 1941, Papanicolaou described cervical mass screening for early detection of cervical cancer. The Pap smear has proved valuable for mass screening and enabling lesions detection at an early enough stage for effective treatment and has an incidence of reducing squamous ICC by at least 80%. Organized screening has not been introduced in Saudi Arabia hence the reasons for the Pap smears (n=1475) performed were one or a combination of vaginal discharge, vaginal itching, lower genital tract burning, suspected urinary tract infection by the patient and age of the patient where the doctor performed the pap smear because the patient was in the age range for cervical cancer. For 83% this was their first Pap smear. The total number of abnormal cervical smears was 43. i.e. 2.91% of all screened cytology cases. Our research indicated a high prevalence of CIN 1 and CIN 3. Pap smears play a substantial role in not only detection but also prevention of cervical cancer. Success of organized screening programme is possible when Family physicians at family clinics will be properly trained in performing Pap smears.

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Key words: pap smear, cervical cancer, ICC, cytology, colposcopy.

1. Introduction

Worldwide, cervical cancer is twelfth most common[1] and the fifth most deadly cancer in women.[1] It affects about 16 per 100,000 women per year and kills about 9 per 100,000 per year.[1] Approximately 80% of cervical cancers occur in developing countries. Worldwide, in 2008, it was estimated that there were 473,000 cases of cervical cancer, and 253,500 deaths per year.[1]

Clinical stages and prognosis

The International Federation of Gynecology and Obstetrics staged Cervical cancer as tabulated below.

The stage distribution differ in different parts of the world and this is most likely a reflection of the presence or lack thereof of screening programmes that spot early stage disease. However introduction of effective screening can lead to overestimation of survival estimates as some cases will be diagnosed at an earlier stage (lead time bias).

Treatment

For early stage cervical cancer (I–IIA) the usual treatment is radical hysterectomy and pelvic lymphadenectomy occasionally followed by radiotherapy and chemotherapy but this deprives females of their fertility. Mostly stages IB2 and IIA, are best treated by a combination of radiotherapy and chemotherapy.[2]

Hysterectomy is used to treat the Microinvasive cancer stage IA1 but in order to preserve fertility it is done by one excision of the lower part of the cervix.[3]

For females at stage IA2 or IB1 the following methods may be used; in case of no lymph node metastasis, fertility sparing surgery is opted. The lymph nodes can be taken away laparoscopically and if negative nodes, the cervix is radically removed by a vaginal approach.[4]

The last technique, abdominal approach, requires extensive experience and speciality. Abdominal approach is pelvic lympadenectomy and radical trachelectomy - leaving the uterus.[5]

Etiology

Human papillomavirus

Continual infection with a carcinogenic papillomavirus (HPV), which is a double-stranded circular DNA viruss that infects many species, is a basic cause of squamous cell carcinoma and adenocarcinoma.[6-8]

Risk factors

The following have been identified as co-factors that can raise the risk of precancer and cancer between 3-5 times amongst women already infected by HPV; long term use of oral contraceptives [9-10] high parity, multiple parity [11-12] and smoking.

Since HPV is sexually transmitted hence the sexual behavior, number of sexual partners of the woman and /or her partners both notably impact the risk of ICC [12-13].Some studies show that male

circumcision reduces the risk of ICC in female partners.[14-17]

Protection from condom use is varied as it shows protection in some studies, but not significantly so in several studies. [18-19]

Cervical neoplasia

Carcinogenesis

HPV infections have a high spontaneous clearance, irrespective of the age. Approximately 50% of the infections clear within 6 months, 66.6% within 12 months, and around 80% within two years.[20] The longer the infection lasts, the more it increases the probability that it will continue and cause precancer/cancer. [20] In 20-30% females persistant infections over 12 month period have lead to CIN2+.[20-21]

Cervical screening

Following the World Health Organisation (WHO) definition of screening as "the presumptive identification of unrecognised disease by means of tests or examinations that can be applied rapidly".[18]

Since the precancer time period for cervical cancer is longer as compared to other female cancers hence the mortality rate is comparatively high as well. Also treatment of precancer or early stage ICC usually leads to healthier outcome than late treatment.

Although screening started in Saudi Arabia in 1984 there was and still exists a lack of organized cancer screening programmes that led to lack of trends available hence there was no proper estimation till the study of WHO in September 2010.[23]

Many studies have also shown that the effect of screening programmes has yielded different results across different countries, which may be attributed to differences in the implementation of screening. [18,23-24] Hence the aim of the screening test should be 'high sensitivity' i.e. to permit as few as possible with the disease to get through undetected .

Even though in 1985, the National Board of Welfare recommended screening every third year in ages 20-59 to date there still exists the enormous challenge worldwide to execute organised cervical screening.[25]

Cytologic tests

Conventional cytology

In 1941, Papanicolaou[26] described cervical mass screening for sexually active women for early detection of cervical cancer. For the Pap smear, cells are collected from the surface of the uterine cervix and the cervical canal, smeared on a glass slide, and analysed in a microscope.

According to the American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer[27] a combination of the extended tip spatula and the endocervical brush provides optimal sampling of the ectocervix, T-zone, and endocervix, and has the lowest false-negative rate.

The Pap smear has proved valuable for mass screening and enabling lesions detection at an early enough stage for effective treatment and has an incidence of reducing squamous ICC by at least 80%.[28] The Pap smear does have its limitations among them the most important being its 47-62% limited sensitivity and the subjective interpretation of the results. [28]

Liquid based cytology

In the Liquid-based cytology known as LBC the cellular material is immersed in a container with a special liquid but it needs to be performed in a special equipment lab.[29] Since the sample is not smeared on a slide the possibility of representative smears and of less obscuring factors (blood, mucus, inflammatory cells) increases. It allows less time for sample interpretation and most importantly the same sample can be used for other analyses (hrHPV, Chlamydia).

Although a meta-analysis of international studies found no evidence of improved accuracy (sensitivity and specificity) with LBC compared to conventional cytology however despite the higher cost, LBC has largely replaced conventional cytology in several countries,[22] and the method is recommended by the Swedish Society for Obstetrics and Gyneacology.[30]

Classification System

In 1988 the Bethesda System (TBS) was introduced in order to standardize cytology reporting. The past decade saw important changes and updates in gynecologic cytology like LBC and (HPV) DNA testing that led to minor amendments in 1991 and a new redefined version of TBS in 2001.

The Bethesda System 2001[31] is as follows:

1) Negative for intraepithelial lesion or malignancy

a) Organisms

Trichomonas vaginalis

Fungal organisms morphologically consistent with *Candida* spp.

Shift in flora suggestive of bacterial vaginosis

Bacteria morphologically consistent with *Actinomyces* spp.

Cellular changes consistent with Herpes simplex virus.

b) Other non-neoplastic findings

Reactive cellular changes

Atrophy

2) Epithelial cell abnormalities

a) Squamous cell

• Atypical squamous cells

Of undetermined significance (ASC-US)

Can not exclude HSIL (ASC-H)

• Low grade squamous intraepithelial lesion (LSIL) encompassing: human papilloma virus (HPV)/mild dysplasia/CIN 1

• High grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia,

CIS/CIN 2 and CIN3 with features suspicious for invasion (if invasion is suspected)

• Squamous cell carcinoma

b) Glandular cell

Atypical

Endocervical adenocarcinoma in situ

Adenocarcinoma

3) Other malignant neoplasms

Specimen adequacy

As per TBS 2001 the minimum requirement for adequacy for a conventional cytology is 8000-12000 visible squamous cells but for LBS only 5000 cells are sufficient. [29,31]

A satisfactory sample means atleast 25% visible squamous cells, but in case atypical cells can be indentified irrespective of the percentage of visible cells then the smear is abnormal'. [31] For the purpose of research the reason for an unsatisfactory sample should always be stated. The unsatisfactory samples can be obscured by blood or inflammatory cells.[29] The sample collected might have very few cells or it could have cells that are poorly fixed.

Visibility of only 25-50% epithelial cells terms the sample as "partially obscured" .[31]

Negative cytology

TBS regroups the category negative for intraepithelial lesion or malignancy for benign or normal alterations.

Abnormal cytology

The two-stage TBS and the three stage system of abnormalities are shown in the tables below.

Although both cytology and histology are fundamentally the same however Cytological interpretation are subjective and they are not always accurate hence the diagnosis should be determined in combination with histopathology.[18,29]

Cytology findings

Saudi Arabia has a population of 6.51 million women ages 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 152 women are diagnosed with cervical cancer and 55 die from the disease.[22]

Cervical cancer ranks as the 11th most frequent cancer among women in Saudi Arabia, and the 8th most frequent cancer among women between 15 and 44 years of age. Data is not yet available on the HPV burden in the general population of Saudi Arabia.[22]

2. Methods and Results

For the purpose of this study data was collected from January 2009 – January 2011 at King Abdul Aziz Hospital & Oncology Centre Jeddah. All Pap smears were performed by the same doctor. This was to ensure that there was no compromise on quality and method of sample collection for Pap smear.

As mentioned earlier organized screening is not prevalent is Saudi Arabia hence the reasons for the Pap smears performed were one or a combination of vaginal discharge, vaginal itching, lower genital tract burning, suspected urinary infection by the patient and age of the patient where the doctor performed the pap smear because the patient was in the age range for cervical cancer. For 83% this was their first Pap smear.

3. Discussion

It has been recognized worldwide, through studies and clinical practices that for early detection of precancerous lesions of cervical cancer the best technique is cytological examination of cervical by Pap smear. This is because an abnormal cervical cytology report show the existence of a precancer lesion which if left untreated mostly progresses to cancer.

There is an international agreement that women with high grade squamous abnormalities and with glandular abnormalities need colposcopy.[18,29] The colposcopy magnifies the cervix 6-40 times and after the application of 3 % or 5% acetic acid solution onto the cervix turns precancer lesions acetowhite. The sensitivity of colposcopy is similar to that reported for Pap smear screening while specificity is lower.[32]

However, because colposcopy relies on subjective visual interpretation, it is crucial to define consistent criteria for suspicious lesions and to train providers to correctly implement these criteria [33] as opposed to Pap smears.

According to one Cochrane review while colposcopy has a reputable role in determining the most suspicious areas for colposcopically directed biopsies and in planning effective treatment, but it is not a diagnostic test and cannot substitute cytological evaluation.

It can be said with great certainty that cytological screening programs play a major role in reducing both the incidence and mortality of ICC. In the US, Canada and Europe widespread introduction of cytological screening decreased the incidence of cancer of the cervix that was paralleled by a reduction in mortality.[32,34-35]

Europe has approximately 55 000 new cases each year and 25 000 deaths. [36]The greater part of these cases are in Eastern Europe where there are no cervical screening programmes.[14]

All abnormal cytology patients were amongst the 83% giving their first Pap smear sample. This indicates that for CIN2 and CIN3, patients earlier Pap smears would have meant earlier detection at the earlier stage leading to an increased rate of recession and hence of mortality.

For patients with CIN1 and early stages of cervical cancer a regular yearly Pap smear would have shown the cellular change and for those with abnormal cytology but non cancerous legions the correlated treatment has begun and their follow-up Pap smear is to be performed after 6 months of the first Pap smear.

4. Conclusion and Recommendations

It is extremely imperative to note that whereas factors like male circumcision and early sexual activity do have a protective affect against HPV transmission many other significant risk factors of cervical cancer are very much prevalent in Saudi Arabia.

The increasing rate of cervical cancer incidence in Saudi Arabia can be greatly reduced, thus increasing the mortality rate, as Pap smears play a substantial role in not only detection but also prevention of cervical cancer. Especially if performed yearly for women after the age of 34 as it is after this age when majority of the incidence cases have been reported in Saudi Arabia.

It is therefore recommended that as part of an organized screening after 34 years of age a yearly Pap smear should be made mandatory as part of the primary health care system in Saudi Arabia and its results recorded in patients' permanent files.

The yearly Pap smear should be performed irrespective of whether any of the before mentioned symptoms exist or not. In case of abnormal but non cancerous cytology a follow-up Pap smear after six months should be performed.

Success of organized screening programme is possible when Family physicians at family clinics will be properly trained in performing Pap smears. It is also essential to educate women over 34 about Pap smear, this can be done by the family physician one 34 years age has been reached and also through pamphlets.

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Abbreviations and Definitions

AGC	Atypical glandular cells
AGUS	Atypical glandular cells of undetermined significance
AIS	Adenocarcinoma in situ
ALTS	ASCUS-LSIL Triage Study
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	Atypical squamous cells, high-grade squamous lesion cannot be excluded

ASCUS Atypical squamous cells of undetermined significance
CGIN Cervical glandular intra-epithelial neoplasia
CIN1-3 Cellular intraepithelial neoplasia grade 1-3
CIS Cancer in situ
DNA Deoxyribonucleic acid
EC Endocervical cells
ECC Endocervical curettage
Effectiveness The extent to which the programme, when deployed in the field in routine circumstances, does what it is intended to do for a specified population
FIGO International Federation of Gynecology and Obstetrics
HC Hybrid Capture
HPV Human papillomavirus
hrHPV High-risk HPV type
HSIL High grade squamous intraepithelial lesion
ICC Invasive cervical cancer
IQR Inter-quartile range
LBC Liquid based cytology
Lead time Period between the detection of a lesion by screening and the time point that it should have progressed, in the absence of screening, to a clinically recognised cancer
LEEP Loop electrosurgical excision procedure
LLETZ Large loop excision of the transformation zone
LSIL Low grade squamous intraepithelial lesion
NETZ Needle excision of the transformation zone
NPV Negative predictive value; i.e. the extent to which subjects are free of the disease in those that give a negative test result
Pap Papanicolaou
PPV Positive predictive value; i.e. the extent to which subjects have the disease in those that give a positive test result
RCT Randomised clinical trial
SAS Statistical analysis system
SNOMED Systematized nomenclature of medicine
Sojourn time Duration of the detectable pre-clinical phase.
Stage IA Microinvasive
Stage IB Localised cancer
Stage II+ Advanced cancer

Table 1. International Federation of Gynecology and Obstetrics Clinical Staging of Cervical Carcinoma and Corresponding MRI Findings

FIGO stage	Description	MRI findings
I	Tumor confined to cervix	
IA IA1 IA2	Microscopic invasive tumor Stromal invasion ≤3 mm; width ≤7 mm Stromal invasion >3 mm but ≤5 mm; width ≤7 mm	No evidence of tumor
IB IB1 IB2	Clinically visible invasive tumor or preclinical tumors > stage IA Tumor ≤4 cm Tumor >4 cm	Intermediate SI mass against low SI of the background cervical stroma
II	Invasion beyond uterus but not to pelvic sidewall or lower third of vagina	
IIA IIA1 IIA2	No parametrial invasion, upper two-thirds of the vagina Tumor ≤4 cm Tumor >4 cm	Loss of the normal low SI of the vaginal fornix or wall, usually contiguous with the primary cervical tumor mass
IIB	Parametrial invasion	Breach of the low SI ring of the cervical stroma
III	Tumor extends to pelvic sidewall and/or involves the lower third of vagina	
IIIA	Tumor extends to lower third of vagina but not to pelvic sidewall	Loss of the normal low SI of the vaginal wall in the lower third of the vagina
IIIB	Extension to pelvic sidewall and/or hydronephrosis or nonfunctioning kidney	Presence of tumor within 3 mm of internal obturator, levator ani and pyriformis muscles or the iliac vessels. Additional signs include increased SI and/or retraction of pelvic muscles, presence of hydronephrosis owing to ureteral obstruction at the level of the primary tumor or nodal metastasis
IV	Tumor extends outside true pelvis or invades bladder or rectal mucosa	
IVA	Invasion of bladder or rectal mucosa	Tumor nodules protruding into the bladder/rectal lumen
IVB	Distant metastasis	Tumor involving organs outside the true pelvis, includes the para-aortic and inguinal nodes

FIGO: International Federation of Gynecology and Obstetrics; SI: Signal intensity.

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Table 2. Risk factors associated with cervical cancer wikipedia

Sexual Activity
Number of sexual partners
Early sexual activity (especially less than 16 years of age)
Sexually transmitted diseases
Human papilloma virus (HPV)
Herpes simplex virus
Early age of first pregnancy
Parity
Cigarette smoking
HIV
Immunosuppression from any cause
Vitamin deficiencies
Interval since last Pap smear
Oral contraceptive use

Table 3

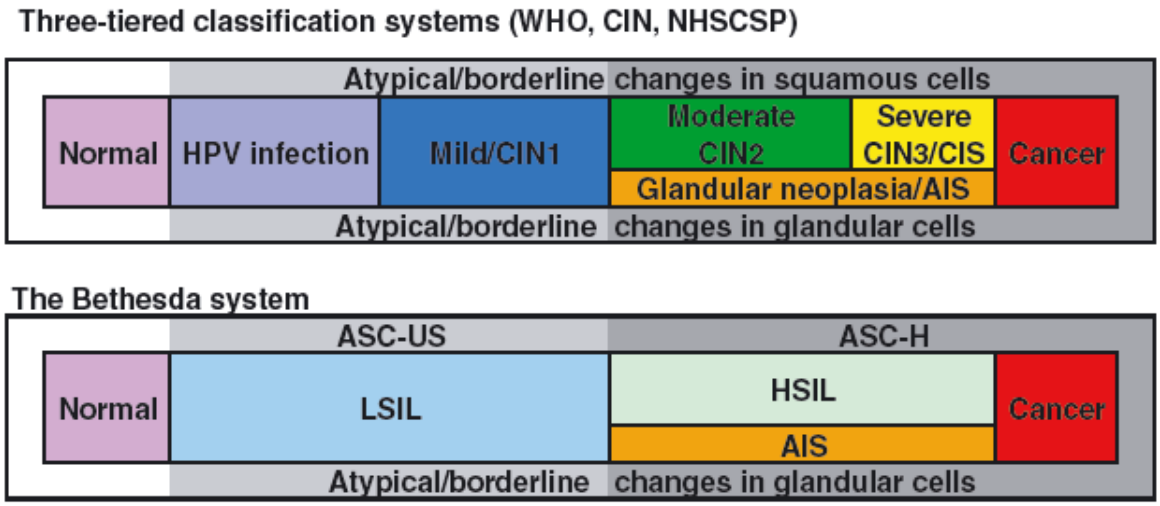


Table 4: Key Statistics on Saudi Arabia (WHO, 2010)

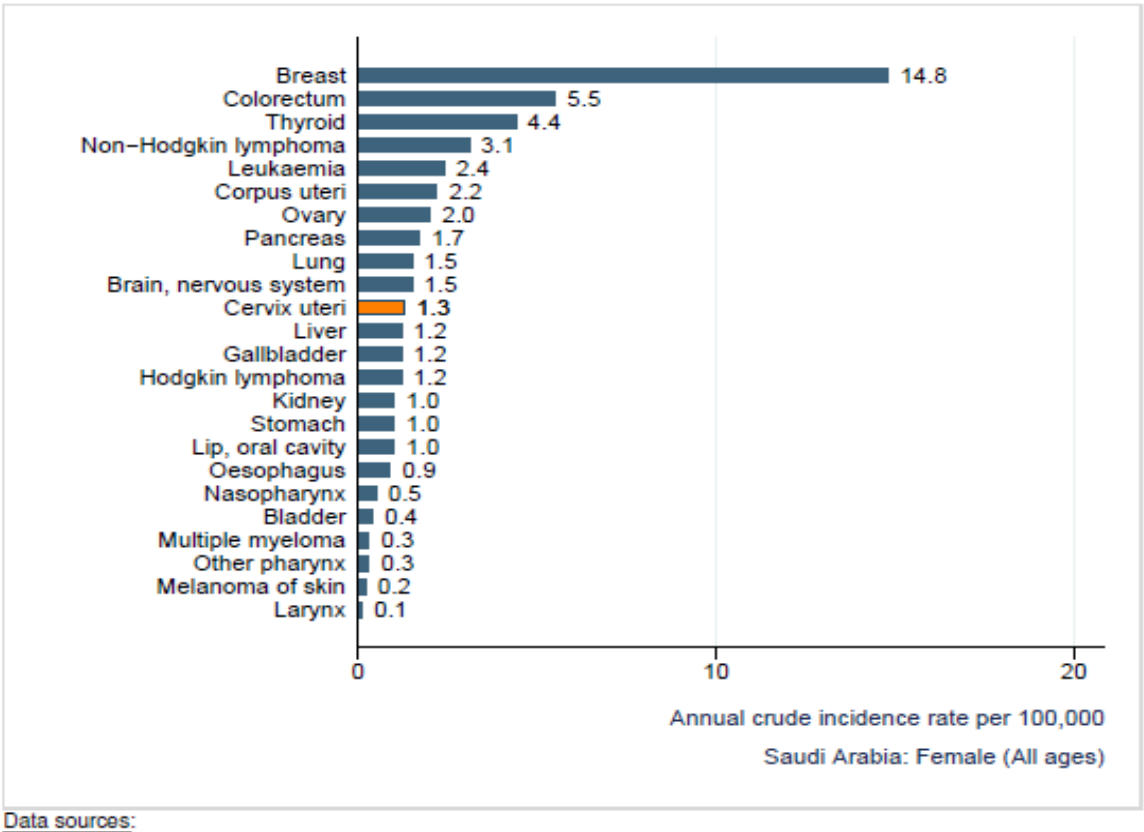
Population	
Women at risk for cervical cancer (Female population aged >=15 yrs)	6.51 millions
Burden of cervical cancer and other HPV-related cancers	
Annual number of cervical cancer cases	152
Annual number of cervical cancer deaths	55
Other factors contributing to cervical cancer	
Smoking prevalence (%), women	3.2
Total fertility rate (live births per women)	3.1
Oral contraceptive use (%)	19.6

Table 5: Incidence of cervical cancer in Saudi Arabia, Western Asia and the World

Indicator	Saudi Arabia	Western Asia[a]	World
Crude incidence rate[1]	1.3	3.6	15.8
Age-standardized incidence rate[1]	2.1	4.5	15.3
Cumulative risk (%). Ages 0-74 years[1]	0.2	0.5	1.6
Annual number of new cancer cases	152	3931	529828

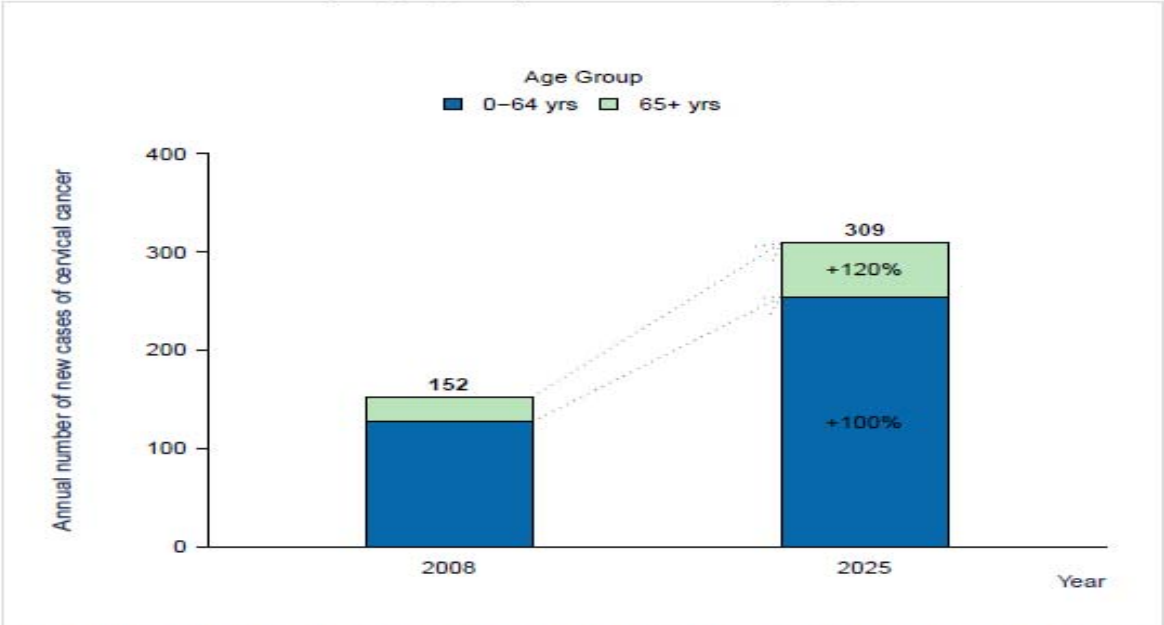
Data sources:
IARC, Globocan 2008. (Specific methodology for Saudi Arabia: National incidence rates (1999-2005, Saudi and non-Saudi populations) were projected to 2008. The rates were 'scaled' using -site, -sex and age-specific percentages of microscopically verified cases, obtained as the mean of the percentages observed in Oman, Omani (1998-2001), Kuwait (1998-2002) and Bahrain, Bahraini (1998-2002) cancer registries. For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=682.)

Table 6: Incidence of cervical cancer compared to other cancers in women of all ages in Saudi Arabia



Data sources:
IARC, Globocan 2008. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Table7: Estimated number of new cases of cervical cancer in Saudi Arabia in 2008 and projected in 2025



Projected burden in 2025 is estimated by applying current population forecasts for the country and assuming that current incidence rates of cervical cancer are constant over time.
Data sources:
IARC, Globocan 2008.

Table8: Reasons for performance of Pap smear

Reason/Symptom	% of total (n=1475)
Vaginal discharge	37.6%
Vaginal itching	21.3%
Lower genital tract burning	9.06%
Suspected urinary infection	3.04%
Age	29%

A total of 1475 cases, ages 30-64 years, were available for the study. The total number of abnormal cervical smears was 40. i.e. 2.706% of all screened cytology cases. The median age of the patients was 47 years.

Table 9: Age, size and cytological distribution of sample size

Age range	Number of patients	Number of abnormal cytology
30-34	200	1
35-39	325	5
40-44	378	9
45-49	255	11
50-54	120	3
55-59	147	7
60-64	50	4
Total	**1,475**	**40**

All the abnormal smears were re-examined and then classified according to the Bethesda System of TBS diagnosis Table 1o below.

Table 10: The disease categories listed with their percentages compared to the total number of cervical smears performed during the period of the study (Jan. 2009 – Jan. 2011)

Disease Category	Age range	Number of Patients	Prevalence of disease (n=1475)
Benign Cellular Changes/infection Herpes	30-34	1	0.068%
Benign reactive changes Cervictis/inflammation Atrophy Radiation Repair	45-49	1	0.068%
Epithelial cell abnormalities ASCUS	40-59	4	0.27%
LSIL CIN1+HPV	35-59	15	1.02%
HSIL CIN2+CIN3+CIS	35-64	13	0.88%
Invasive squamous cell	45-50	3	0.20%
AGUS Adenocarcinoma	40-64	3	0.20%
Total		**4o**	**2.706%**

Table 11: Richart (1966)[37] Cervical cancer Conversion chart

Conversion	Time in Years (approximately)
CIN1 to CIN 3	5
CIN 2 to CIN 3	2
CIN 1 and CIN 2 to CIN 3	4

Comparing our percentage of categorized diagnoses indicates that there is a high prevalence of CIN 1 and CIN 3.