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Pre-Invasive Cervical Disease and Cervical Carcinoma

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Abstract: Until a few years ago cervical cancer was one of the commonest type of cancer in women worldwide. Its incidence decreased dramatically following the implementation of the Papanicolaou (Pap) smear as a screening procedure. The Pap smear can detect a wide range of abnormalities of the cervix from benign cellular changes to precancerous conditions. Part of this review, will focus on this issue, specifically the abnormal and/or possibly precancerous findings that can be found in a Pap smear result. These will be classified according to the Bethesda system. One must emphasize here that most of these abnormalities regress on their own and do not need specific treatment. Yet, findings like the High-grade Squamous Intraepithelial Lesion (HSIL) have a high rate of progression to cancer and necessitate immediate management. The other half of this review will focus on cervical cancer in itself, a malignant and therefore invasive disease which, like all other cancers, can be fatal if left untreated. The extent of spread of the cancer is determined by the staging system, here described according to the International Federation of Gynecology and Obstetrics (FIGO). Staging is an important means of evaluating the treatment plans used.

Key words: HPV, Pap smear, Bethesda system, carcinoma, invasive, recurrent

INTRODUCTION

Nearly 500, 000 women each year develop cervical cancer (Parkin *et al*., 1993) and a quarter of a million women die each year from it (Craus *et al*., 2005). Cervical cancer, that is, cancer of the cervix or neck of the uterus, is the second most common type of cancer in women in developed countries and the second most common cause of death from cancer (Lowy and Schiller, 2006) following breast cancer. It is also the most common type of cancer in women in developing countries and the most frequent female genital cancer in many states worldwide.

Infection by sexually-transmitted, oncogenic subtypes of Human Papillomavirus (HPV) is the main cause of cervical cancer. Human papillomavirus (HPV) the DNA of which is found in 100% of histologically confirmed cervical cancers (Craus *et al*., 2005) is the most common sexually transmitted virus. It is estimated that 75% of sexually active adults transmit HPV at some instance during their life (Palefsky, 2002).

A woman's sexual behavior may increase her risk of becoming infected with the virus. In fact, the risk factors for acquiring HPV infection are the following: Sexual activity at an early age, having multiple sexual partners, having a partner who has many sex partners, having an uncircumcised partner and having a partner with penile cancer (Tatti, 2003). In young women, the cervix is still maturing and the transformation zone is vulnerable to becoming infected with HPV (Palefsky, 2002). It has also been found that older women develop an immune response against the virus, whereas younger ones do not (Tatti, 2003). Uncircumcised men are more likely to harbour the virus. HPV is also associated to a certain degree with penile cancer.

However, being infected with the virus does not necessarily mean that a woman will develop cervical cancer. Other risk factors must be present that increase a woman's chance that her infection will result in neoplastic changes in her cervix. These are:

- Low socio-economic status and/or inadequate screening.
- Smoking-nicotine has been found in the cervical mucus of women who smoke (Tatti, 2003).
- Number of live births/multiple pregnancies.
- Long-term use of oral contraceptives-these alter the way an HPV infection can progress (Tatti, 2003).
- Immunosuppression, either due to drug treatment, secondary to haematological malignancies or due to HIV infection (Cubie, 2007).
- Infection with *Chlamydia trachomatis*-this organism makes the cervix more prone to the cellular changes induced by HPV (Palefsky, 2002).
- Use of hormonal drug diethylstilbestrol (DES).
- Family history of cervical cancer-this increases the risk of developing dysplasia (Palefsky, 2002).

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The introduction of the Papanicolaou (Pap) smear and the treatment of Cervical Intraepithelial Neoplasia (CIN) are mainly responsible for the decrease in the incidence of cervical cancer that has been observed over the last decades. Screening women aged 35-64 years every 5 years leads to an 84% reduction in cervical cancer incidence. If screening is done every three years, there will be a higher reduction; but if screening is done more often, the incidence of cervical cancer will not decrease any further (Busuttil *et al.*, 2006).

The incidence of cervical cancer will not decrease if <70% of a particular population is screened (Quint *et al.*, 2006). It is for this reason that cervical cancer remains the most frequent cancer amongst women in developing countries. Developing countries do not have the resources to sustain screening programmes. Also, women in developing countries lack awareness of cervical cancer symptoms and most importantly they do not know how cervical cancer can be prevented. Adequate knowledge about cervical cancer among health workers in Ibadan, for example, is lacking and the Pap smear is unpopular (Ayinde and Omigbodun, 2003). Screening high-risk women in developing countries once or twice in their lifetime might be an effective beginning (Adesina *et al.*, 2003).

PRE-INVASIVE CERVICAL DISEASE-THE BETHESDA SYSTEM RATING

Atypical squamous cell of undetermined significance: The term Atypical Squamous Cell of Undetermined Significance (ASCUS) (Palefsky, 2002) is sometimes simply called Atypical Squamous Cell (ASC) (IARC, 2005). As shown in (Table 1) this phrase is used when cytological findings are more suspicious than benign changes (Palefsky, 2002) and indicative but not diagnostic of a Squamous Intraepithelial Lesion (SIL).

An ASCUS finding occurs in about 5% of women undergoing cytological screening (Murta *et al.*, 2007). ASCUS indicates some cellular change that could develop into dysplasia, the presence of existing dysplasia and/or the presence of one or more of infections like candida infection, bacterial vaginosis or trichomonas infection. Although, 68% of ASCUS diagnosed regress to normal (Palefsky, 2002) CIN or invasive lesions can still occur in women with a diagnosis of ASCUS. Therefore, immediate review of the thin sections, new cytological tests or colposcopy and rigorous follow-up should be considered (Murta *et al.*, 2007).

ASCUS is divided into two categories: ASC-US (unsatisfactory significance) and ASC-H (cells that cannot exclude HSIL). This subdivision is important because women with ASC-H are at a considerably higher risk for developing Cervical Intraepithelial Neoplasia (CIN) 2 or 3 and of being positive for high-risk HPV DNA than are women with ASC-US (IARC, 2005). The absence of high risk HPV in patients with ASC-H indicates the absence of HSIL and this means that HPV-DNA testing is a means to better select which patients with ASC-H should undergo colposcopic examination (Liman *et al.*, 2005). In fact, reflex HPV DNA testing may be used as an alternative triage method for women diagnosed with ASC-H especially for women older than 30 years of age (Wu *et al.*, 2006). High-risk cases are referred for colposcopy (Manos *et al.*, 1999).

Atypical glandular cell of undetermined significance: The term Atypical Glandular cells of Undetermined Significance (AGUS) can be simply referred to Atypical Glandular Cells (AGC). Although, relatively rare (found in less than 1% of all Pap smears) it may cause diagnostic uncertainty (Mood *et al.*, 2006) and often indicates more serious problems than does ASCUS (Palefsky, 2002) (Table 1). In fact, 56% of the AGC findings are associated with cancerous or precancerous conditions (Scheiden *et al*., 2004) hence, the term AGUS is a misnomer (Disaia and Creasman, 2002). AGUS is diagnosed as favor reactive when it more likely to be overactive cell changes, whilst it is diagnosed as favor neoplasia when cells indicates that a precancerous condition may already have developed (Palefsky, 2002).

Moreover, women younger than 35 years of age with an AGC result have a higher frequency of histopathologic findings, typically squamous lesions. On the other hand, women with an AGC finding who are older than 50 years of age have more glandular lesions than do younger women. Therefore, AGC represents a marker for serious pathologic processes (Geier *et al*., 2001). Because of this, a complete and careful evaluation (Scheiden *et al*., 2004) and follow-up (Mood *et al.*, 2006) is necessary. In fact, the recommendations are colposcopy and endocervical curettage (Palefsky, 2002).

Identifying AGC in pregnancy is particularly difficult. Some cytological changes associated with pregnancy and the postpartum period are benign findings that may be misidentified as an adenocarcinoma. For this reason, the pathologist must know if the patient is pregnant or not (Connolly and Evans, 2005).

Low-grade squamous intraepithelial lesion: A Low-grade Squamous Intraepithelial Lesion (LSIL) is equivalent to mild dysplasia or CIN I. (Cervical Intraepithelial Neoplasia grade I). Most mild dysplasias are associated with oncogenic HPV types (Palefsky, 2002, as shown

Table 1: Different classifications of cellular changes within the cervix and their relation to HPV (Palefsky, 2002)

Class system rating (Pap smears)	Bethesda system rating (Pap smears)	Dysplasia system rating (tissue biopsies)	Cervical intraepithelial neoplasia (CIN) system rating	HPV relationship rating
0	Unsatisfactory	Unsatisfactory	Unsatisfactory	Not enough evidence to study
1	Within normal limits	Negative	Negative	Not directly linked to HPV
1	Benign cellular changes	Negative	Negative	Not directly linked to HPV
2	ASC-US or AGUS favor reactive	No term	No term	May or may not be linked to HPV
2	ASC-H or AGUS favor neoplasia	No term	No term	May or may not be linked to HPV
3	LSIL	Mild	CIN 1	Directly linked to HPV
3	HSIL	Moderate	CIN 2	Directly linked to HPV
3	HSIL	Severe	CIN 3	Directly linked to HPV
4	HSIL	Carcinoma *in situ* (CIS)	CIN 3	Directly linked to HPV
5	Carcinoma	Carcinoma	Carcinoma	Directly linked to HPV

ASC-US = Atypical Squamous Cell of Undetermined Significance; AGUS = Atypical Glandular cell of Undetermined Significance; ASC-H = Atypical Squamous Cells; LSIL = Low-grade Squamous Intraepithelial Lesions; HSIL = High-grade Squamous Intraepithelial Lesions

in Table 1. In fact, the cytological features that define CIN I overlap with the cellular changes that HPV causes. These changes include multinucleation, perinuclear halos, nuclear atypia, irregular nuclear outlines and hyperchromasia. These features are together referred to as koilocytosis (IARC, 2005).

No symptoms are usually present and the changes are fully reversible. Yet still, some cases of mild dysplasia are associated with low-risk types like HPV 6 or 11, in which case, warts on the cervix may be present (Palefsky, 2002). Colposcopy and directed biopsy are indicated in cases of repeat LSIL smears. Local excision can be performed after diagnosis, but treatment may not be needed because 60% of cases regress on their own (Disaia and Creasman, 2002).

High-grade squamous intraepithelial lesion: A High-grade Squamous Intraepithelial Lesion (HSIL) possesses a wide variation in its cytological appearance and usually indicates moderate and severe dysplasia of the cervix, both of which, but especially the latter, have a high probability of progression to cancer (Palefsky, 2002) (Table 1). HSIL of the moderate dysplasia type contains cells similar to those seen in LSIL. In severe dysplasia, the overall size of the cells is reduced, but because the cells show minimal differentiation, the nuclear: Cytoplasmic ratio is greatly increased (IARC, 2005). HSIL nearly always indicate the presence of a high-risk HPV type. Colposcopy and directed biopsy are indicated in cases of repeat HSIL smears (Disaia and Creasman, 2002). Treatment involves the performance of Loop Electrosurgical Excision Procedure (LEEP), conization or cryotherapy (Palefsky, 2002).

CERVICAL CANCER

Type of tumour: There exist a wide variety of malignant cervical tumours as shown in Table 2 85-90% of cervical cancers are squamous cell carcinomas. Most of the other tumours, are usually adenocarcinomas arising from the endocervical mucous-producing glandular cells. These create what are known as barrel-shaped lesions, large neoplasms that expand throughout the cervical canal. Local recurrence is more common in these lesions maybe because they are more radioresistant or due to the bulky nature of these lesions. Neuroendocrine small cell cervical cancers occur infrequently and have a poor prognosis. More rare cancers include cervical sarcomas, cervical leimyomyomas and cervical melanomas (Disaia and Creasman, 2002).

Table 2: Malignant tumours of the uterine cervix. Adapted from Buckley *et al*. (1993)

Squamous carcinoma	Well differentiated, keratinizing
	Moderately well differentiated, focally keratinizing
	Poorly differentiated, large cell, non-keratinizing
	Poorly differentiated, small cell, non-keratinizing
	Verrucous carcinoma
	Papillary squamous carcinoma
Adenocarcinoma	Endocervical adenocarcinoma
	Minimal deviation adenocarcinoma
	Papillary serous adenocarcinoma
	Endometriod adenocarcinoma
	Clear cell adenocarcinoma
	Mesonephric adenocarcinoma
	Enteric adenocarcinoma
Mixed tumours	Adenosquamous carcinoma
	Glassy cell carcinoma
	Adenoid cystic tumours
Small cell carcinomas	Neuroendocrine tumours
	Adenoid basal carcinoma
	Subcolumnar reserve cell carcinoma
Undifferentiated carcinoma	Metastatic carcinoma
	Malignant melanoma
Malignant non-epithelial tumours	Sarcoma
	Lymphoma

Staging: The extent of cervical cancer is usually described by the staging system shown in Table 3. Staging is determined by clinical examination, that is, rectovaginal examintion, radiography, colposcopy,

Table 3: Staging for cervical cancer, according to the International Federation of Gynecology and Obstetrics (IARC, 2005)

Stage	Description
0	Carcinoma in situ, preinvasive carcinoma
I	Invasive carcinoma, strictly confined to cervix
IA	Invasive carcinoma identified microscopically
IAI	Measured invasion of stroma 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
IA2	Measured invasion of stroma >3.0 mm but mo >5.0 mm in depth and 7.0 mm or less in horizontal spread
IB	Clinically visible lesion confined to cervix or microscopic lesion greater than stage IA2
IB1	Clinical lesions of 4.0 cm or less in size
IB2	Clinical lesions >4.0 cm in size
II	Carcinoma extending beyond cervix but not to pelvic side wall; carcinoma involves vagina but not its lower third
IIA	No parametrial involvement
IIB	Parametrial involvement
III	Carcinoma extending onto pelvic wall; the tumour involves lower third of vagina. All patients with hydronephrosis or non-functioning kidney are included unless known to be the result of other causes
IIIA	Involvement of lower third of vagina; no extension of pelvic sidewall
IIIB	Extension to pelvic sidewall and/of hydronephrosis or non-functioning kidney
IV	Carcinoma extends beyond true pelvis or clinically involves mucosa of bladder or rectum.
IVA	Spread of growth to adjacent organs
IVB	Spread to distant organs

cystoscopy, proctosigmoidoscopy, Intravenous Pyelography (IVP) and/or barium studies of the lower colon and rectum. Staging is an important means of evaluating the treatment plans used. Other factors influencing the treatment given are the age and general health of the patient and the presence and nature of any complicating abnormality (Disaia and Creasman, 2002).

MICROINVASIVE CERVICAL CARCINOMA

In 1973, the Society of Gynaecologic Oncologists (SGO) defined a microinvasive lesion as one in which a neoplastic epithelium invades the stroma in one or more places to the depth of $3 mm below the base of the epithelium and in which there is no visible lymphatic or vascular involvement. In 1994, the International Federation of Gynaecology and Obstetrics (FIGO) better defined microinvasive cervical cancer by classifying it as stage I (a/b) in the FIGO staging for cervical cancer (Table 3). Vascular and/or lymphatic space involvement would not exclude a patient from this definition. Patients with FIGO stage Ia1 can be treated with simple hysterectomy, or, if continued fertility is desired, conisation of the cervix is performed. Therapy for stage Ia2 is by radical hysterectomy and pelvic lymphadenectomy (Disaia and Creasman, 2002).

INVASIVE CERVICAL CARCINOMA

Symptoms: The first symptom of early cervical cancer is a thin, watery, blood-tinged vaginal discharge that frequently goes unnoticed by the patient, whilst the classic symptom is intermittent, painless metorrhagia or spotting only postcoitally or after douching. As the malignancy enlarges, the bleeding episodes become heavier and more frequent. The patient may notice this as an increase in the amount and duration of her menstrual flow; ultimately, the bleeding becomes continuous.

Late symptoms include the development of pain referred to the flank or to the leg. This is usually secondary to the involvement of the ureters, pelvic wall or sciatic nerve routes. Many patients complain of dysuria, haematuria, rectal bleeding or constipation resulting from bladder or rectal invasion. Distant metastasis and persistent oedema of one or both lower limbs as a result of lymphatic and venous blockage as a result of pelvic wall disease are late manifestations of primary disease or of recurrent disease. Massive haemorrhage and the development of uremia with profound inanition may also occur (Disaia and Creasman, 2002).

Routes of spread: The main routes of spread of carcinoma of the cervix are:

- Into the vaginal mucosa.
- Into the myometrium of the uterus.
- Into the paracervical lymphatics which travel to the obturator, hypogastric and external iliac nodes.
- Direct extension into adjacent structures or parametria, which may reach the obturator fascia and the walls of the true pelvis. The bladder and rectum can also become involved.

Lymph node involvement in stage 1 is between 15-20%; in stage 2 between 25 and 40% and in stage 3, at least 50% of the nodes are involved. The metastasis status of pelvic lymph nodes (PLNs) seems to be a predictive factor of survival. The presence of HPV DNA and other biological markers in PLN may indicate a subclinical early metastasis, but it may be associated to an active immune reaction (Landro *et al*., 2008).

Treatment

Surgical management: Radical hysterectomy was introduced in 1944 following dissatisfaction with radiotherapy. It involves the removal of the uterus, the upper two-thirds of the vagina, the uterosacral and uterovesical ligaments, all of the parametrium on each side and and pelvic node dissection encompassing the

obturator, ureteral, hypogastriic and iliac lymph node chains. Metastasis to the ovaries is rare and hence these structures can be preserved.

The major complication following this technique is postoperative bladder dysfunction. This arises due to direct injury to the sensory and motor nerve supply of the detrusor muscle of the bladder and is usually manifested as a loss of the sense of urgency to void and an inability to empty the bladder completely. For this reason, long periods of constant bladder drainage may be necessary post-operatively and patients may need to be taught intermittent self-catheterization. Another complication is pulmonary embolism. The operative period is the most dangerous period for the formation of a thrombus in the leg or pelvic veins. For this reason the pelvic veins should be carefully dissected for minimal thrombus formation in these structures. Other complications, all of which are preventable, include the development of ureteral fistulas and lymphocysts, pelvic infection and haemorrhage. Whilst antibiotics prevent pelvic infection, they contribute to fistula formation. Finally, recurrence is expected in 10-20% of patients treated with radical hysterectomy and bilateral lymphadenectomy (Disaia and Creasman, 2002).

Radiotherapy and adjuvant chemotherapy: Radiation therapy is successful if the cancer cell has a greater sensitivity to a normal cell to ionizing radiation; if the normal tissue has a greater ability to recuperate after irradiation and if the patient is in a reasonably good physical condition. The maximal effect of ionizing radiation on cancer is obtained in the presence of a good and intact circulation and adequate tissue oxygenation. Consideration must be given to the tolerance of the normal tissues of the pelvis, which are likely to receive high doses during the course of treatment of cervical malignancy. A general principle of radiotherapy states that the normal tissue tolerance of any organ is inversely related to the volume of the organ receiving irradiation (Disaia and Creasman, 2002).

Five large randomized controlled trials showed that survival of patients with cervical cancer is improved if adjuvant chemotherapy is used in combination with radiation. Primary radiotherapy is delivered as a combination of external-beam teletherapy and brachytherapy and given with concurrent cisplatin-based chemotherapy (Gray, 2008). The addition of weekly cisplatin to radiotherapy is recommended for patients with high-risk early stage cervical cancer who undergo a radical hysterectomy and pelvic lymphadenectomy (Liu *et al*., 2000). This technique improves long-term PFS and OS (Rose *et al*., 2007) and gives the best results if the dose and delivery time of the radiation are carefully controlled (Pearcey *et al*., 2002).

RECURRENT AND ADVANCED CERVICAL CARCINOMA

Definition: Approximately, 35% of patients with invasive cervical cancer will have recurrent or persistent disease after therapy. Recurrence after surgery is defined as evidence of a tumour mass after all gross tumour has been removed and the margins of the specimen were free of disease. Persistent disease after surgery is defined as persistence of gross tumour in the operative field or local recurrence of tumour within one year of initial surgery. A new cancer of the cervix would be a lesion that occurs locally at least ten years after primary therapy.

The definition of persistent disease after radiation therapy is the evidence of a portion of the tumour that was clinically present before treatment or else, the development of a new demonstrable tumour in the pelvis within the treatment period. The definition of recurrence after radiation therapy is a regrowth of the tumour in the pelvis or distally, which is noted after complete healing of the cervix and vagina (Disaia and Creasman, 2002).

Locations of recurrence: After radical hysterectomy, about one fourth of recurrences occur locally in the upper part of the vagina or the area previously occupied by the cervix. Twenty seven percent of recurrences occur in the cervix, uterus or upper vagina; 6% in the lower two-thirds of the vagina; 43% in the parametrial area, including the pelvic wall; 16% distant and 8% unknown (Disaia and Creasman, 2002). Skin metastasis is a late manifestation in cervical cancer patients and indicates widespread metastasis of the disease (Chen *et al*., 2007).

Signs and symptoms: These are:

- Unexplained weight loss.
- Leg oedema-due to progressive lymphatic obstruction, occlusion of the iliofemoral vein system or both.
- Pain radiating to the upper thigh or to the buttock. Sometimes, it may be pain in the groin or a deep-seated central pelvic pain.
- Vaginal bleeding and a watery smelly discharge-suggest a central recurrence.
- Ureteral obstruction.
- Enlargement of supraclavicular lymph nodes especially on the left side.
- Cough, haemoptysis and chest pain due to pulmonary metastasis (Disaia and Creasman, 2002).

Management: Radical hysterectomy is the therapy for small recurrent cervical carcinoma following radiation. In cases of bone metastasis, external irradiation in moderate

doses can relieve the pain. Radiation is also used in cases of recurrence after radical hysterectomy has been performed. Patients with bilateral ureteral obstruction should be considered for urinary diversion followed by radiation. Pelvic exenteration-removal of many pelvic viscera-can be performed in cases of recurrent pelvic cancer; however, only a few patients are suitable for this operation and can lead to fatal complications (Disaia and Creasman, 2002). Anterior pelvic exenteration with the formation of an ileal conduit allows radiotherapy to be used to treat recurrent disease (Barrington *et al*., 1997).

Various studies have been conducted to establish the benefits of chemotherapy in advanced and recurrent cervical cancer. Response to combined chemotherapy varies from 16-69% depending on the size of the lesion and previous radiotherapy (Alberts *et al*., 1998). Using cisplatin and 5-flourouracil, dose-cumulative neuro-toxocity develops as a side-effect (Chiara *et al*., 1988). Nephrotoxicity, mucositis and diarrhoea are the main potential toxicities from this type of treatment. Nephrotoxicity can be prevented by prehydration and by reducing the duration of infusion (Kish *et al*., 1985). Toxicity can also be improved by the use of growth stimulating factor (Ghaemmaghami *et al*., 2003).

Recent data suggests that topotecan, a semisynthetic camptothecin which exerts its cytotoxic effect through inhibition of DNA topoisomerase I (Randall-Whitis and Monk, 2007), when used concurrently with cisplatin, may be the new standard of care for the management of recurrent or advanced cervical cancer. Although, single-agent cisplatin-based chemoradiotherapy is the standard of care for high-risk or locally advanced cervical cancer, topotecan, when used concurrently with cisplatin and/or radiation therapy, produces high objective response rates, improved overall survival and progression-free survival (Ackermann *et al*., 2007).

CONCLUSION

Cervical cancer is a preventable disease. Its aetiology and associated risk factors have been well documented in the literature. Its relation to HPV is unquestionable.

Until a few years ago, most emphasis as to how prevent cervical cancer was based on screening tests. The efficacy of the smear test, which was and is still used to detect precancerous changes in the cervix, has been improved by the implementation of liquid-based cervical cytology. Also, HPV DNA testing is now used as an adjunct to cervical cytology for women aged 30 years and older. For maximum benefit, screening programmes in all countries must be organized and not done haphazardly.

For those women who unfortunately have been diagnosed with invasive cervical cancer, or who will be diagnosed with this disease in the future, it is important that correct evaluation of the lesion/s and appropriate treatment be given. The lesion should be defined according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. Prior to treatment, histopathological evaluation of the lesion and appropriate tests on the patient must be performed, what is known as pre-treatment evaluation. Treatment in itself, on the other hand, must be based on several factors, most importantly the size of the lesion. Follow-up must be done on patients who have been treated for invasive cervical cancer, because they remain at risk of recurrence. As regards recurrent cervical cancer, the treatment chosen is usually based on the localization of the site of recurrence and of the extent of the disease.

Emphasis should be placed as to how decrease cervical cancer incidence in developing countries. Here, cervical cancer is still the most frequent cancer amongst women and a major cause of death. In the literature one finds lots of studies carried out about the female situation in these regions. It is in these countries, which are not few in number, that many women are encountering the disease, are not treated for it and die from it. It is also in these countries that women are not aware of how cervical cancer can be prevented because they are not educated about it. Even health care workers living in these places lack adequate knowledge about the disease.

Developing countries lack adequate resources and finances to sustain regular screening programmes. They also lack specialists involved in the interpretation of results. In order to organize an effective screening programme in developing countries, there need to be adequate financial resources, the infrastructure must be developed and the necessary people must be trained (Adesina *et al*., 2003).

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