## SECTION 1
## cervical cancer and screening



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## 1.1 Epidemiology

Cancer is responsible for approximately 20% of deaths in women in Ireland each year and for approximately 40% of premature deaths. Female-specific cancers account for a considerable proportion of cancer deaths in women (Figure 1)[1]. Deaths from cervical cancer account for approximately 2% of female cancer deaths. The crude mortality rate is 4.6/100,000.

| CAUSES OF DEATH IN WOMEN | NUMBER OF DEATHS | PROPORTION |
|---|---|---|
| All causes | 15,203 | - |
| Malignant neoplasm's | 3,430 | 22.5% of total deaths |
| Breast | 638 | 18.6% of cancer deaths |
| Trachea, bronchus & lung | 525 | 15.3% of cancer deaths |
| Colon | 309 | 9% of cancer deaths |
| Cervix uteri | 75 | 2.2% of cancer deaths |

*Figure 1: Deaths from malignant neoplasms in Irish women, 1999[1]*

There were 152 cases of invasive carcinoma and 906 carcinoma in-situ in 1999[2]. Given that there were 75 deaths from cancer of the cervix uteri, this represents a mortality/incidence ratio of 49%. The incidence of invasive cervical cancer peaks in the 40-44 year age group (Figure 2).

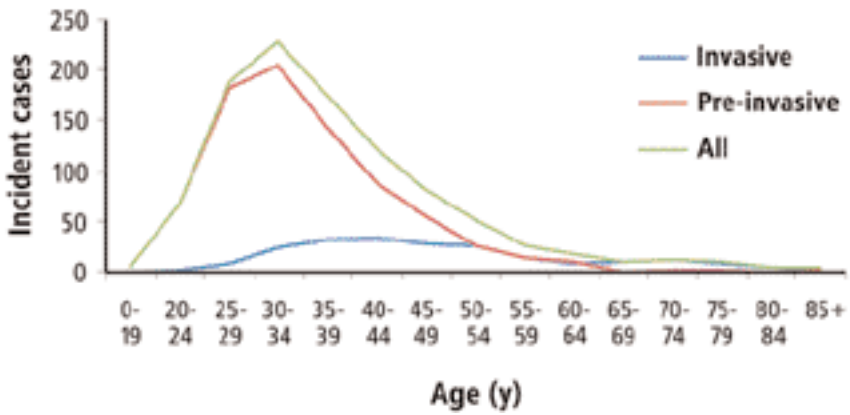


*Figure 2: Age specific incidence of cervical cancer in Ireland, 1996*

## 1.2 Natural History

Despite the fact that it has been widely accepted for more than half a century that cervical cancer is preceded by pre-malignant cellular changes that can be easily detected by a smear test, the natural history of the condition is not well understood.

Most cervical cancers arise in the transformation zone between the squamous and columnar epithelium, close to the os. Approximately 85% of cervical cancers are squamous cell carcinomas and the remaining 15% are adenocarcinoma (glandular) or mixed types. The apparent rise in the incidence of glandular or mixed types in recent times may be due to a true rise in its incidence, a greater awareness of the cell type within cervical cancer or because cytological screening is better able to detect pre-cancerous squamous lesions and thus the relative incidences has changed.



Cervical intraepithelial neoplasia (CIN) is the descriptive term used for squamous cell changes but the cellular changes occurring in glandular or mixed types are not described by the CIN nomenclature and will not necessarily be detected by cervical smear testing. About 40% of adenocarcinomas may be picked up by chance but there is no suitable screening procedure for this type of cervical cancer.

The precise causation of the pre-malignant cellular changes is as yet unknown. A number of theories have been widely promoted and subsequently discredited over the years. The underlying assumption is that it is associated with agents potentially transmitted by sexual intercourse[3]. Most experts currently believe that human papillomavirus (HPV) is necessary for the development of cervical cancer[4]. However, other factors may be necessary for cancer to occur[5]. HPV types 16 and 18[6] are considered high risk uncogenic types.

Progression rates for CIN changes have been estimated[7,8]. While almost 60% of low-grade lesion will regress, it is likely that the majority of CIN 3 / CIS lesions, if left untreated, will progress (Figure 3).

| | CIN 1 | CIN 2 | CIN 3 |
|---|---|---|---|
| Regress | 57% | 43% | 32% |
| Persist | 32% | 35% | 56% |
| Progress | 11% | 22% | - |
| Carcinoma in situ (invasive) | 1% | 5% | >12% |

*Figure 3: Natural history of CIN*

The development of a low-grade lesion does not mean invariable progression to an invasive cancer. For those lesions which do progress it is estimated from trial data that the average time from development of low grade dysplasia to carcinoma in situ is twelve years with invasive disease taking a further 5 or more years[8].

## 1.3 Risk Factors

**Regular cervical smears protect against the risk of developing cervical cancer. It is not the smear but its investigation when abnormal which protects the few women at risk of developing cervical cancer.**

While a number of risk factors have been directly or indirectly associated with cervical cancer, the strength of each individual association is relatively weak, apart from the presence of oncogenic HPV (Figure 4)[9].

| RISK FACTOR | LOW RISK | HIGH RISK | RELATIVE RISK |
|---|---|---|---|
| Sexual partners | Few | Many | 4+ |
| Age at first intercourse | Old | Young | 4+ |
| Social class | Non-manual | Manual | <2 |
| Smoking | No | Yes | 2-4 |
| Sexually transmitted infection | Never | Ever | <2 |
| Oral contraceptive use | <5 years | 5 years + | <2 |
| Cervical smear | Ever | Never | 4+ |
| Age | Young | Old | 4+ |
| Geographical location | Developed world | Developing world | 4+ |

*Figure 4: Risk factors in developing cancer of the cervix*

**It is important that we do not confuse epidemiological risk factors with value judgements on a woman's behaviour (or that of her partner) as this is likely to be inaccurate in the individual case and will, undoubtedly, deter women from attending for screening.**

## 1.4 The Role Of Human Papilloma Virus (HPV) [10]

Up to 98% of cervical cancers are associated with infection with one of the oncogenic human papilloma viruses (HPV). These high-risk viruses include types 16, 18, 31, and 45 and there is significant geographic variation in the prevalence of different types. While they are linked to the subsequent development of cervical cancer, an altered immune response locally is probably necessary. Adenocarcinoma is associated with HPV type 18, and squamous cell carcinoma is associated with the more common type 16.

HPV typing is not routinely carried out as part of international national screening programmes at present.

- **Many types of HPV can cause visible warts.**
- **Women with oncogenic HPV will not necessarily have visible warts.**
- **Eradication of visible warts does not alter the risk.**
- **More frequent screening cannot be justified for women with a history of genital warts.**

## 1.5 Prevention Of Cervical Cancer - The Case For Screening

Screening has been defined as the examination of asymptomatic people, in order to classify them as likely or not likely to have the disease that is the object of the screening process[11]. Although the smear test is a good tool for screening for pre-cancerous changes of the cervix, no technique or protocol is perfect. Consequently, some women will develop invasive cervical cancer despite adherence to accepted screening protocols.



While the precise cause of cervical cancer remains unknown, primary prevention is not feasible. Cervical cancer screening, by smear testing, aims to identify cervical intraepithelial neoplasia, the pre-invasive stage of cervical cancer. There is evidence that early treatment improves survival rates (Figure 5)[12,13]. No randomised control trials have been undertaken in cervical screening. However, observational studies and computer simulation models have reported the effectiveness of cervical screening.

| SCREENING SCHEDULE | CUMULATIVE RATE 20-64 PER 100,000 | REDUCTION IN RATE (%) | NO. OF TESTS | NO. OF CASES PREVENTED PER 100,000 TESTS |
|---|---|---|---|---|
| None | 3311.5 | | | |
| Every 10 years, 25-64 | 1298 | 61 | 4 | 503 |
| Every 10 years, 35-64 | 1476 | 55 | 3 | 612 |
| Every 10 years, 45-64 | 1895 | 43 | 2 | 708 |
| Every 5 years, 20-64 | 544 | 84 | 9 | 308 |
| Every 5 years, 30-64 | 630 | 81 | 7 | 383 |
| Every 3 years, 20-64 | 303 | 91 | 15 | 201 |
| Every year, 20-64 | 216 | 93 | 45 | 69 |

From IARC Working Group (1986) assuming incidence rates from Cali, Colombia. The first screening test is assumed to be 70% sensitive. D. M. Parkin, Cancer Screening, UICC 1991

*Figure 5: Effect of different screening policies on incidence of cervical cancer*

Screening sceptics would argue that trends in mortality have been downward in the developed world, irrespective of the existence or effectiveness of formal screening programmes[14,15,16]. However, in the UK, the death rate from cervical carcinoma prior to 1987 was falling at a rate of just 1.5 % per year and since the late eighties when the call and recall system was introduced has been falling by 7% per year[17]. There is also concern about the potential hazards of over treatment of early disease, which might spontaneously have reverted to normal without intervention.

European consensus guidelines on cancer screening recommend that cervical smears should be used for cervical screening among a core age group of women aged 30-60, and the screening interval should be 3-5 years[17]. If resources are available, screening could be offered to a wider age group, but is not recommended for women under 20[18].

**It is important to realise that it is not possible to directly monitor the sensitivity and specificity of a screening test during a normal screening programme. It is also important not to confuse the performance of the screening test with the performance of the screening programme because the programme consists of a complex number of steps.**

## 1.6 Rationale For Screening Intervals

The selection of the screening interval for a cervical screening programme must balance clinical considerations and cost effectiveness. Cervical screening programmes around the world have chosen various screening intervals[19]. The impact of screening interval on reduction in cumulative incidence risk and the number of smears a woman is required to have is detailed in Figure 6.

The ICSP offers 5 yearly screening with a repeat of the first ever smear after 1 year. This is in line with the EU recommendation that cervical cancer screening should be offered at least every fifth year[20]. Screening every fifth year with high quality and high compliance is preferable to screening every third year, where resources are limited[4]. Screening more frequently than every 3 years is not cost effective[21].

| INTERVAL BETWEEN SMEARS (YEARS) | REDUCTION IN CUMULATIVE INCIDENCE RISK (%) | NUMBER OF SMEARS IN A LIFETIME (25-60 YRS) |
|---|---|---|
| 1 | 93.3 | 35 |
| 2 | 92.5 | 17 |
| 3 | 91.2 | 11 |
| 5 | 83.6 | 8 |
| 10 | 64.1 | 3 |
| Single smear at age 40 | 20 | 1 |

*Figure 6: The impact of smear interval on reduction in cumulative incidence risk and the number of smears in a lifetime [19,22].*

Estimates suggest that 6% of smears will show some abnormality and less than 2% will require referral to colposcopy.

## 1.7 Understanding Terms Commonly Used In Screening

**False positive** This results where the screening test reports a positive (abnormal) finding although the person being screened does not have the condition.

**False negative** This results where the screening test reports a negative (normal) finding although the person being screened has the condition.

**Validity** This refers to the accuracy of the screening test in distinguishing those who do have the disease being searched for and those who do not, in the asymptomatic population.

**Sensitivity** This is the probability of the test being correct for subjects who truly have the disease in question. A test with 100% sensitivity will detect every subject with the disease state among those tested. The sensitivity of the cervical smear test is defined as the proportion of women with cervical intraepithelial neoplasia (CIN) whose smear tests are interpreted as positive.

**Specificity** This is the probability of the screening test being negative in subjects who do not have the disease being sought. A test with 100% specificity will correctly identify as normal all those subjects who do not have the disease being assessed. The specificity of the cervical smear test is defined as the proportion of women without CIN whose smear tests are interpreted as negative.



**Positive predictive value** The positive predictive value of a screening test refers to the ratio of lesions, which are truly positive to those, which are test positive. It is intimately affected by the prevalence of the condition under study.

Refer to Appendix 4 for more terminology.

## 1.8 Invasive Cervical Cancer

**Symptoms and signs:**

It is unusual for women to have any symptoms associated with the pre-cancerous state or early cancer. Symptoms of post-coital bleeding, inter-menstrual bleeding and an unusual discharge are associated with more advanced cancer but can be produced by other causes. Invasive cancer can present as an ulcerated cervix.

- **A smear test may be negative in the presence of invasive carcinoma**
- **Where suspicion of an invasive carcinoma exists, urgent referral should not await smear test results**
- **A woman with symptoms or signs suggestive of cervical cancer should be referred for diagnostic colposcopy, regardless of the actual smear result**

Well-advanced invasive carcinoma may only show necrotic material on sampling and, similarly, a cervix having CIN3 may appear normal macroscopically, but the following features can be present

- Contact bleeding
- Raised irregular contour (Figure 7)
- Friable easily detached epithelium
- Palpable mass at the vaginal vault

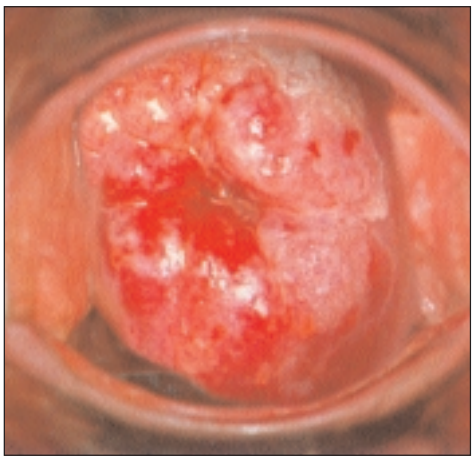

*Figure 7: Grossly abnormal nodular appearance*

## 1.9 Investigation

Abnormal clinical findings need investigation. Colposcopy, where the cervix is viewed under a microscope, plays a central role in determining management of pre-invasive cervical carcinoma. The diagnosis of preinvasive disease is usually made when patients undergo colposcopically directed biopsies following an abnormal smear test.

Both ablative and excisional procedures are employed when preinvasive disease is found. The laser loop excision of the transformation zone (LLETZ) allows excision of the required area with least morbidity. Cone biopsy is associated with long-term morbidity (cervical stenosis and incompetence) but is indicated for women with CIN3 on smear testing and no colposcopically detected visible abnormality or for women where the full extent of the lesion cannot be visualised colposcopically.

## 1.10 Treatment Of Invasive Carcinoma Of The Cervix

The management of women with invasive disease depends on the FIGO (Federation Internationale de Gynecologie Obstétrique) stage and status of the patient (Figure 8). This is a prognostic classification where stages 1a2, 1a2, 1b1 and 11a are considered "early" disease and 11a-1Va are considered locally advanced disease.

| | |
|---|---|
| **Stage 1** | **The cancer is confined to the cervix** |
| Stage 1a | Microinvasive disease |
| Stage 1a1 | Stromal (connective tissue) invasion less than 3 mm |
| Stage 1a2 | Stromal invasion 3-5 mm, not in excess of 7 mm in horizontal spread |
| Stage 1b | Lesions greater than 7 mm in horizontal spread |
| **Stage 2** | **Involvement extends beyond the cervix, including the vagina except for the lowest third, or infiltration of the parametrium (connective tissue near the uterus) but not out to the pelvic sidewall** |
| Stage 2a | Involvement of the upper two-thirds of the vagina, without lateral extension into the parametrium |
| Stage 2b | Lateral extension into the parametrial tissue but not out to the pelvic sidewall |
| **Stage 3** | **Involvement of the lowest third of the vagina or the pelvic sidewall or causes hydronephrosis (nonfunctioning kidney)** |
| Stage 3a | Involvement of the lowest third of the vagina |
| Stage 3b | Involvement of the pelvic sidewall or hydronephrosis |
| **Stage 4** | **Cancer extends beyond the reproductive tract** |
| Stage 4a | Involvement of the bladder or rectal mucosa |
| Stage 4b | Distant metastasis (cancer that spreads to other parts of the body away from the original, primary site) or disease outside the true pelvis |

*Figure 8: FIGO classification for cervical carcinoma*



Stages 1a1 is treated by cone biopsy or hysterectomy, depending on whether fertility is desired. Other stages of early disease are treated with radical hysterectomy (removal of the uterus, cervix, cuff of the vagina, parametrial tissues and pelvic lymph nodes). Less fit women with early disease and women with locally advanced disease are best treated with radical radiotherapy (external beam radiation or brachytherapy where radioactive isotopes are placed within or adjacent to the tumour). These patients have a high risk of nodal disease and would need radiotherapy. Dual treatment with both radiation and surgery is associated with increased morbidity[12].

The 5-year survival of most recent advances in treatment is shown in Figure 9[13].

5-YEAR SURVIVAL ACCORDING TO STAGE

| | |
|---|---|
| Stage 1a | 95% |
| Stage 1b1 | 80% |
| Stage 11a | 66% |
| Stage 11b | 63% |
| Stage 111 | 35-50% |
| Stage 1Va | 17% |
| Stage 1Vb | 9% |

*Figure 9: Cervical cancer stage and survival rates*