SECTION 3

Cervical cancer and screening

Cervical cancer and screening

Aim of section
The aim of this section is to provide an overview of the epidemiology, the natural history, the risk factors and the role of the Human Papilloma Virus (HPV) in cervical cancer. It also highlights the value of vaccination in preventing disease and the importance of screening.

3.1 Introduction

Recent advances in medical research and practice have greatly enhanced our knowledge of the natural history of cervical cancer with a deeper understanding of the Human Papilloma Virus (HPV) and the role it plays as the necessary, but not sole, causative agent.

3.2 Epidemiology

3.2.1 Introduction

Cervical cancer is a female specific cancer. While all cancer accounts for approximately 20 per cent of deaths in women in Ireland[1] and for 40 per cent of premature deaths, cervical cancer accounts for 1.8 per cent of total cancer deaths. This is a cancer of young women where the mean age of death is 56 years and 50 per cent of all cases are diagnosed in women aged ≤ 46 years. Each woman who dies from cervical cancer loses, on average, 25 years of life. Just over one third of women diagnosed with cancer die within five years.

3.2.2 Incidence of cervical cancer

In Ireland, there is an average of 180 new cases of cervical cancer diagnosed (Table 3.1) and 73 deaths reported each year. In the absence of a full screening programme in Ireland, deaths from cervical cancer have been increasing by an average of 1.5 per cent per year since 1978 (Figure 3.1). The incidence rates fall within the mid-range of rates observed across Europe but exceed that seen in the USA. Ireland is the only region of the British Isles where the mortality rate continues to rise. In particular, the rate of reduction in deaths from cervical cancer in the UK was seen to accelerate when a more stringent call and recall system was introduced in 1988 (Quinn et al, 1999). Prior to the establishment of a National Cervical Screening Programme, it is believed that an appropriate number of smears were taken opportunistically in Ireland. However, as the whole population who are at risk were not being screened, this smear taking activity has had little or no impact on the detection and appropriate management of cervical disease.

The following table provides an outline of the incidence rates of cervical cancer in Ireland between 1994-2005 as documented by the National Cancer Registry Ireland. The increase in the number of cases of cervical cancer has kept pace with our increasing population.

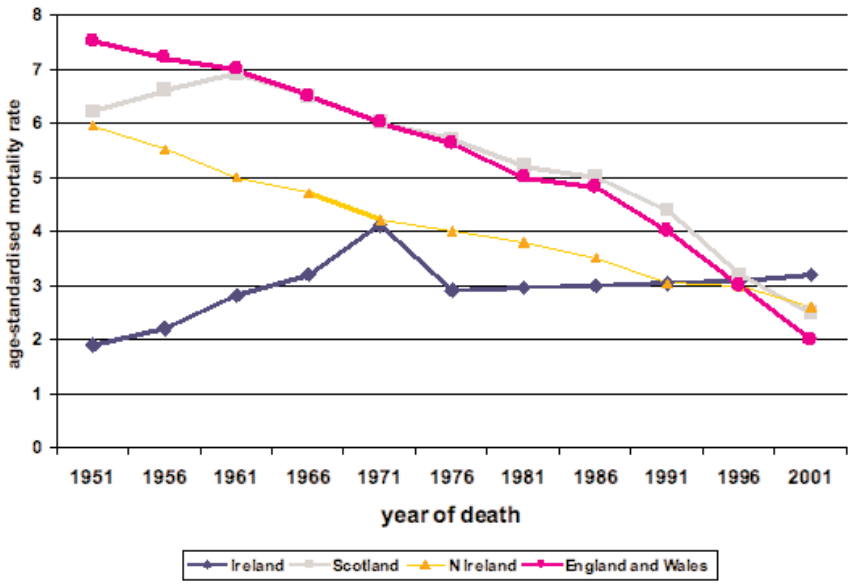
1 *CSO: Vital Statistics, 1999.*

Table 3.1 Incidence of cervical cancer in Ireland, 1994-2005

Year	NUMBER OF CERVICAL CANCER CASES	% OF TOTAL NUMBER OF CASES
1994	174	1.8%
1995	156	1.63%
1996	212	2.09%
1997	173	1.66%
1998	182	1.75%
1999	154	1.45%
2000	189	1.68%
2001	185	1.59%
2002	207	1.71%
2003	203	1.57%
2004	200	1.49%
2005	252	1.81%

Source: The National Cancer Registry of Ireland

Figure 3.1 Deaths from cervical cancer, Ireland & Britain 1951-2002



Source: Comber, H. & A Gavin, A (2004): British Journal of Cancer 91, 1902 -1904

3.3 Natural history

Cervical cancer in most cases develops gradually over a period of time, commencing with early abnormal 'pre-cancerous' changes to the cells in the cervix. These pre-cancerous changes are categorised as mild, moderate and severe dyskaryosis. More than 800 women per year are diagnosed in Ireland with the pre-cancerous abnormality described as *carcinoma in situ* where there is minimal stromal invasion. These women are diagnosed at an average age of 32 years.

See **Section 5** for further information on the Classification Systems

These pre-cancerous abnormalities do not produce symptoms, cannot be seen by the naked eye but can be detected by screening. The benefits of screening are that these and less severe changes can be identified and treated before they cause symptoms, resulting in an earlier diagnosis of cervical cancer than otherwise might have occurred. Screening tests offer the best opportunity to detect cervical cancer at an early stage when successful treatment is likely, and actually prevent most cervical cancers by detection and treatment of abnormal cervix cell changes before they have a chance to develop into a cervical cancer.

The first changes occur at the squamo-columnar junction. Both invasive squamous cell cervical cancer and the preceding pre-malignant cellular changes occur at the transformation zone of squamo-columnar junction. At cytology, the first changes are seen in the nuclei i.e. Borderline Nuclear Abnormality or BNA with more extensive cellular dysplasia becoming evident at a later stage. These changes may also be reported as viral changes and represent infection by and immunological response to the HPV.

See **Section 5** for further information

More severe changes are termed dysplasia or Cervical Intraepithelial Neoplasia (CIN) or squamous intraepithelial lesion depending on the terminology adopted by the laboratory (Table 3.2). These changes represent long term viral persistence.

Table 3.2 Grading schemes for pre-invasive histological abnormalities of the uterine cervical squamous epithelium

DYSPLASIA CLASSIFICATION	Cervical Intraepithelial Neoplasia	BETHESEDA CLASSIFICATION SYSTEM
Mild Dysplasia	CIN 1	LGSIL
Moderate Dysplasia	CIN 2	HGSIL
Severe Dysplasia	CIN 3	HGSIL
Cacinoma in Situ	CIN 3	HGSIL

Source: IARC Handbook of Cancer Prevention Vol 10. Cervix Cancer Screening 2005

Table 3.3 represents the continuum of disease changes and range of outcomes. Outcomes for example relating to rates of regression of CIN 1 appear to be up to 60 per cent with progression in only 10 per cent. Studies have indicated that it is safe to monitor women in this category with cytological follow-up (Ostor, 1993). Treatment with excision is indicated with lesions of CIN 2 and CIN 3 where regression is less common.

Table 3.3 Outcomes relating to CIN classifications

Dysplasia Classification	CIN 1	CIN 2	CIN 3
Regress	57%	43%	32%
Persist	32%	35%	56%
Progress	11%	22%	-
Ca in Situ (Invasive)	1%	5%	>12%

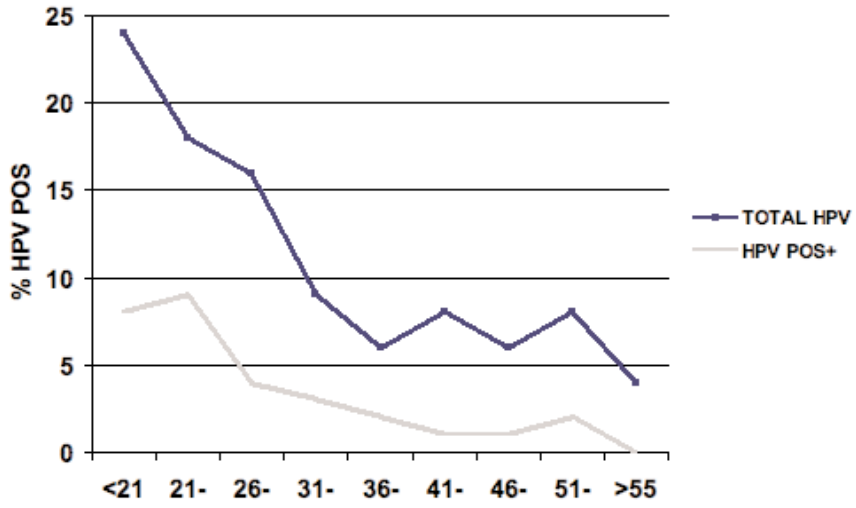
Source: Ostor (1993)

3.4 Risk factors and the role of the HPV

3.4.1 Infection with HPV

It is now understood that cervical infection with one of approximately fifteen types of HPV is the necessary but not the only pre-requisite cause of cervical cancer worldwide. HPV is an extremely common sexually transmitted infection that occurs in most sexually active women. It is estimated that 80% of sexually active women become infected with HPV (Winer et al, 2003). However, most women either clear or immunologically "contain" the viral infection and only a small percentage of those infected go on to develop cervical cancer.

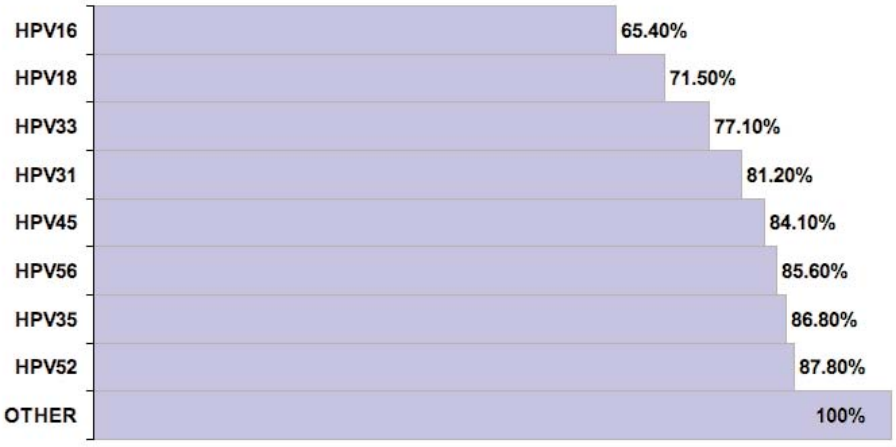
Figure 3.2 HPV prevalence by age



Source: ARHP (2001) Permission kindly granted by Article author.

Immunological data show that those women who develop cervical disease have a persistence of both viral DNA and are serologically positive. Certain HPV types are noted to be more oncogenic than others. 87.8 per cent of cancers are caused by eight particular types; four types account for 81.2 per cent of cervical cancers i.e. types 16, 18, 31 and 33 (Figure 3.3).

Figure 3.3 HPV types by related levels of oncogenicity

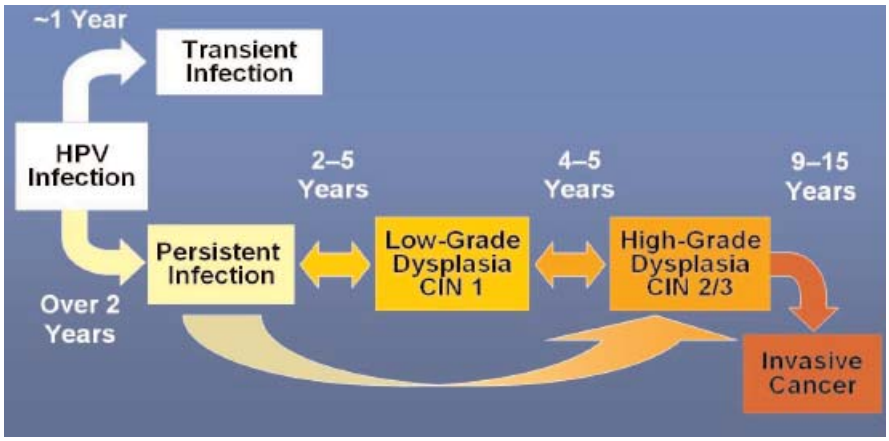


Source: Adapted from Muñoz (2000)

Multiple epidemiological studies (McIntyre-Seltman et al, 2005) have identified secondary risk factors (HPV co-factors) that are associated with the development of CIN 3 such as long duration of oral contraceptive use, multi-parity, smoking (Ho et al, 1998), host immune function and possibly non-HPV sexually transmitted infections.

Research has shown that cervical lesions CIN 3 and cervical cancer is a smoking-related disease with an odds ratio of 1.5 with both an increase of incidence and greater likelihood of progression of the disease in those who smoke (Gram, 1992). Immuno-compromised patients, for example those with HIV or on immunosuppressant medication, are also at greater risk of cervical cancer.

Figure 3.4 Natural history of high risk HPV infection & progression to cervical cancer



Source: Pagliusi SR (2004), Aguado MT. Vaccine. 23:569-578

Figure 3.4 shows the possible relationship of a HPV infection and outcomes with the probable timeline relationship depending on the individual's immune reaction to HPV.

3.5 Prevention by vaccination

Recognition of the role played by HPV in the genesis of cancer of the cervix prompted the development of a vaccine against the most commonly recognised oncogenic types. The first quadrivalent vaccine has been developed from Virus Like Particles (VLP) and offers protection from infection by HPV 6, 11, 16 and 18. The first two types cause visible warts and the latter, HPV16 and HPV18, have been estimated to cause 71 per cent of cervical cancer.

The first bivalent vaccine contains VLPs of HPV 16 and 18. The vaccine results in almost 100 per cent seroconversion and subsequent protection to the development of CIN 2 and more severe cytological changes (Paavonen et al, 2007). Results from the Phase IIb and III trials show that these vaccines offer women who were not yet exposed to HPV, a very high level of protection from persistent infection and cervical intra-epithelial lesions. Phase IV studies are required to show protection against cervical cancer and verify duration of protection. These phase IV studies are also required to define future policies of screening of vaccinated cohorts. Furthermore, there is a danger that there may be an increased prevalence of other HPV oncogenic types i.e. the occurrence of cancers by non-vaccine types. 29 per cent of cervical cancers are caused by other types of HPV for which there is no vaccine at this time.

Following a request from the National Cancer Screening Service Board, the Health Information and Quality Authority agreed in July 2007 to carry out a Health Technology Assessment (HTA) on the role of vaccination against HPV in reducing the risk of cervical cancer in Ireland. The Authority asked the National Centre for Pharmacoeconomics to undertake the HTA. The purpose of this assessment was to establish the cost-effectiveness of a combined national HPV vaccination and cervical cancer screening programme compared to a cervical cancer screening programme alone.

The results of this cost-effectiveness analysis show that universal HPV vaccination of 12 year old females would be cost-effective in Ireland. At older ages, the vaccine becomes less effective due to an increased likelihood of females being exposed to the virus before vaccination.

3.6 The case for screening

Screening has been defined as the examination of asymptomatic people in order to detect their probability to having or developing the disease. The following figure outlines the key principles of screening as applied to cervical cancer.

Figure 3.5 Screening as applied to cervical cancer

KEY PRINCIPLES OF SCREENING	AS APPLIED TO CERVICAL CANCER
The condition should pose an important health problem.	Cervical disease is a growing killer of young women.
The natural history of the disease should be well understood and should have a recognisable early stage.	It is possible to recognise cervical cell changes that are asymptomatic by smear testing. The presence of CIN can be inferred from the degree of dysplasia seen on a smear test.
There should be a suitable and acceptable test.	The cervical smear is reliable, valid, safe and is largely acceptable to the eligible population.
Treatment of the disease at an early stage should be of greater benefit than that started at a later stage.	Relatively simple treatment eradicates the disease in those with cell changes detected on smear testing.
There should be adequate facilities for the diagnosis and treatment of the abnormalities detected.	Facilities have been put in place to manage the outcomes of cervical screening, including diagnostic and treatment facilities.
The test should be repeated at intervals where the disease is insidious.	The screening interval for cervical cancer has been well studied internationally.
The chance of physical and psychological harm to those screened should be less than the chance of benefit.	While there is a chance of over-treatment of lesions that might well regress if left alone, the physical dangers of over-treatment are minor compared to the disease outcome. The psychological sequelae can be managed by appropriate counselling.

Adapted from Wilson, J.M.G. & Junger, G. WHO (1968)

Reports on the incidence of cervical cancer where screening programmes have been organised illustrate a fall in the rate of new cases. Organised screening programmes report a decrease in the incidence of and mortality from cervical cancer whereas opportunistic smeartaking appears to have little impact. In Finland, the decrease in mortality was of the order of 60 per cent (Hakama, 1988). Similar results have been reported from the UK (Quinn et al, 1999) and British Colombia (Anderson et al, 1988).

3.7 The screening interval

While the greatest risk of cervical cancer is never having a smear test, one smear test gives only a 20 per cent risk reduction and regular smear tests are required to make a meaningful impact on the disease (Miller, 1992).

Table 3.4 Screening as applied to cervical cancer

INTERVAL BETWEEN SMEARS IN A (YEARS)	REDUCTION IN CUMULATIVE INCIDENCE RISK (%)	NUMBER OF SMEARS 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

Ref: Miller, WHO (1992); Hakama, et al, IARC (1986)

Three-yearly smear tests will give a reduction in cumulative risk of 91 per cent which would involve a woman having 11 smears during her screening lifetime (25-60 years). Annual smears confer a risk reduction of 95 per cent but at a cost of women having 35 smears in their lifetime.

See **Section 1** for further information on screening intervals and the Call Process.

CervicalCheck screening interval

The current screening interval policy of CervicalCheck (informed by the McGoogan Report 2004) for women aged 25 to 44 years is at three-yearly intervals and for women aged 45 to 60 years is recall at every five years.

Key point:
The danger of developing cancer remains higher in those who have had treatment for CIN 3. Recent evidence from Sweden (Strander, 2007) suggests that this surveillance may need to be extended to 20 years or longer. Smeartakers are advised to follow the colposcopy discharge recommendations.

APPENDIX 3

References & further reading

Anderson, G.H., Boyes, D.A., Benedet, J.L., Le Riche, J.C., Maistic, J.P., Suen, K.C., Worth, A.J., Millner, A., Bennett, O.W.: *Organisation and Results of the Cervical Cytology Screening Programme in British Columbia 1955-1985*. BMJ 1988 296: 975-978.

Arbyn, M. & Dillner, J. (2007): *Review of Current Knowledge on HPV Vaccination: An Appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening*. Journal of Clinical Virology, Volume 38, Issue 3, Pages 189-197.

ARHP (2001): Human Papillomavirus (HPV) and Cervical Cancer. ARHP Clinical Proceedings®. The Association of Reproductive Health Professionals, Washington, US.

CSO: *Vital Statistics,* 1999.

Gram, I.T., Austin, H. & Stalsberg , H. (1992): *Cigarette Smoking and the Incidence of Cervical Intraepithelial Neoplasia, Grade III, and Cancer of the Cervix Uteri*. American Journal of Epidemiology Vol. 135, No. 4: 341-346.

Hakama M, & Louhivuori K. (1988): *A Screening Programme for Cervical Cancer that Worked*. Cancer Survey7(3):403-16.

Hakama, M., Miller, A.B., Day, N.E. (1986): *Screening for Cancer of the Uterine Cervix*. IARC Press, Lyon.

Ho, G.Y., Kadish A.S., Burk R.D., Basu, J., Palan, P.R., Mikhail M., & Romney S.L. (1998): *HPV 16 & Cigarette Smoking as Risk Factors for High-grade Cervical Intra-epithelial Neoplasia*. International Journal of Cancer, Volume 78 Number 3: Pages 281-285.

IARC Handbooks of Cancer Prevention (2005): *Volume 10 Cervix Cancer Screening*. IARC Press, Lyon.

McGoogan, E., (2004): *Report on the Irish Cervical Screening Programme*. ICSP, Limerick.

McIntyre-Seltman, K., Castle, P., Guido, R., Schiffman, M., Wheeler, C. (2005): *Smoking is a Risk Factor for Cervical Intraepithelial Neoplasia Grade 3 among Oncogenic Human Papillomavirus DNA–Positive Women with Equivocal or Mildly Abnormal Cytology*. Cancer Epidemiology Biomarkers & Prevention Vol. 14, 1165-1170.

Miller, A.B. (1992): *Cervical Cancer Screening Programmes: Managerial Guidelines*. WHO, Geneva.

Muñoz, N., Bosch, F.X., Chichareon, S., Eluf-Neto, J., Ngelangel, C., Caceres, E., Rolón, P.A., Bayo, S., Chaouki, N., Shah, K.V., Wallboomers, J.M., & Meijer, C.J. (2000): *A multinational case-control study on the risk of cervical cancer linked to 25 HPV types: which are the high risk types?* In: Castellsagué, X., Bosch, F.X., de Sanjosé, S., Moreno, V. & Ribes, J., eds, International Papillmavirus Conference – Program and Abstracts Book, Barcelona, Thau S.L., p 125 (Available online: www.hpv2000.com).

Paavonen, J., Jenkins, D., Bosch, F.X., et al. (2007): *Efficacy of a Prophylactic Adjuvanted Bivalent L1 Virus-like-particle Vaccine against Infection with Human Papillomavirus Types 16 & 18 in Young Women: An Interim Analysis of a Phase III Double-blind, Randomised Controlled trial*. Lancet 369:2161.

Quinn M, Babb P, Jones J, Allen E (1999): *Effect of Screening on Incidence & Mortality From Cancer of Cervix In England: Evaluation on Routinely Collected Statistics.* BMJ 318: 904-5.

Ostor A. G. (1993): *Natural History Of Cervical Intraepithelial Neoplasia: A Critical Review*. Int. Journal Gynecol. Pathol., 12: 186-192.

Strander, B., Andersson-Ellström, A., Milsom, I., & Sparén, P. (2007): *Long Term Risk of Invasive Cancer After Treatment for Cervical Intraepithelial Neoplasia Grade 3: Population Based Cohort Study.* BMJ 335;1077.

Winer, R.L, Lee S-K, Hughes, J.P., Adam D.E., Kiviat ,N.B., & Koutsky, L.A. (2003): *Genital Human Papillomavirus Infection: Incidence & Risk Factors in a Cohort of Female University Students*. American Journal of Epidemiology, Vol. 157, No. 3 157: 218-226.

Notes