OUTSTANDING PROBLEMS – GLANDULAR LESIONS

Penny Blomfield[1] and Marion Saville[2]

1 Gynaecologic Oncologist, Royal Hobart Hospital, Hobart, Tasmania.

2 Victorian Cytology Service, South Carlton, Victoria.

Email: penny.blomfield@dhhs.tas.gov.au

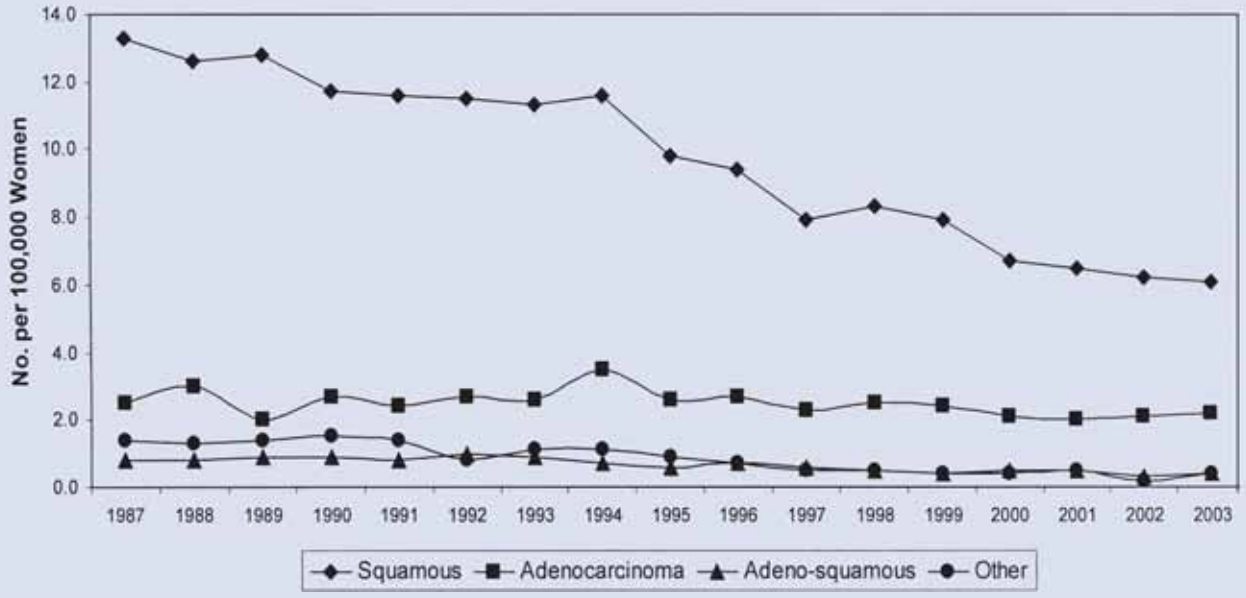
Abstract

Both pre-invasive and invasive cervical glandular lesions remain outstanding challenges. Although the Australian National Cervical Screening Program has led to an accelerated decline in the incidence and mortality from squamous cervical carcinoma, this has not been observed for the subset of women who develop invasive glandular cancers. In addition, the role of cervical cytology, colposcopy and surgery in the management of women with pre-invasive glandular lesions (adenocarcinoma in situ) is far from clearly defined. In this article we have addressed three key questions for the future. Firstly, whether the Australian National Cervical Screening Program is having any impact on the incidence of cervical adenocarcinoma, and if this is the case, can we be more optimistic about the future. Secondly, whether emerging technologies ie. cervical human papillomavirus DNA testing, are likely to play an increasing role in the management of women with pre-invasive glandular lesions. Thirdly, whether there can be any expectation that human papillomavirus vaccination will impact on this disease.

Although the National Cervical Screening Program is applauded for achieving substantial reductions in the mortality from cervical cancer in Australian women, pre-invasive and invasive glandular cervical lesions are considered an outstanding challenge. There has been no substantial impact on the incidence or mortality rates for the subset of women who develop this disease. Historically, invasive squamous cell carcinoma dominated the clinical setting, with 95% of women presenting with this histological subtype. However, the continued decline in the incidence of squamous disease now means 28% (23.7% adenocarcinoma, 4.3% adenosquamous) of women present with glandular cancers (see Figure 1).[1]

Cervical adenocarcinoma is commonly discussed and studied as a single clinical entity, but it must be remembered that there are a large number of histological subtypes that fall under the umbrella of this category of tumour. There are clear differences in clinical behaviour for some of these subtypes, suggesting that it may well be necessary to categorise these tumours further for future study and to allow a clear understanding of the natural history of glandular cervical pathology.

Figure 1. *Age-standardised incidence rates of cervical cancer, by histological type, women aged 20–69 years, 1987–2003*



*Rates are expressed per 100,000 women and age-standardised to the Australian 2001 population.
Source: National Cancer Statistics Clearing House, Australian Institute of Health and Welfare.

In this article three key questions will be addressed. Firstly, whether the Australian National Cervical Screening Program is having any impact on the incidence of cervical adenocarcinoma. Secondly, whether emerging technologies ie. cervical human papillomavirus (HPV) DNA testing are likely to play an increasing role in the management of women with preinvasive glandular lesions. Thirdly, whether there can be any expectation that HPV vaccination will impact on this disease.

Epidemiology

Cervical adenocarcinoma is rare, with fewer than 200 women in Australia diagnosed in 2003.[1] The median age at diagnosis is 43 years. Cervical adenocarcinoma shares many risk factors with squamous disease, with some exceptions. Personal risk rises with increasing numbers of sexual partners, early age at first intercourse, increased parity and early age of first birth, as well as use of the oral contraceptive pill. Body mass index and smoking do not influence disease development.[2] Cervical infection with high risk HPV DNA has also recently been confirmed as necessary for the development of most cervical adenocarcinomas.[2-4] Compared to squamous disease, infection with HPV 18 DNA appears responsible for a higher percentage of cases (35% v 16%) and HPV 16 for fewer cases (40% v 56%).[2] The E6 and E7 oncoproteins encoded by high risk HPV utilise the ubiquitin-proteosome system to degrade and inactivate p53 and Rb tumour suppressor gene products and cell cycle deregulation follows.

Role of cervical cytology and colposcopy in the identification of pre-invasive glandular lesions

Pre-invasive squamous disease is readily identified by repeated cervical cytology and colposcopy and the success of the National Cervical Screening Program has resulted from an organised approach using these tools. The role of cervical cytology and colposcopy and targeted biopsy is far less clearly defined in identifying asymptomatic women with high-grade pre-invasive glandular abnormalities, known as adenocarcinoma in situ. This is thought to result from sampling deficiencies because of the anatomical situation of cervical glands, as well as difficulties of cytological interpretation. These challenges are clearly reflected in the considerable variation in rates of reporting of cervical glandular abnormalities on Pap smear between different Australian states and laboratories.[5] In addition, glandular abnormalities reported on Pap smear are rare.

There are four main categories of Pap smear reports relating to glandular abnormalities. Outcome data for women with Pap smears suggesting a high grade glandular abnormality, suggests the majority of women do have histological evidence a glandular cancer or a high grade glandular preinvasive lesion. This is not the case for the more frequently reported lower grade abnormalities (see table 1). Very few of these women have adenocarcinoma in situ and most women have no significant abnormality. Indeed, the significance of lesions labelled as low-grade glandular dysplasia or atypia by pathologists remains unclear.

Adenocarcinoma in situ is diagnosed infrequently. Data from Victoria suggested an incidence of 0.12 per 1000 women screened for 2002.[6] Adenocarcinoma in situ has no reliable colposcopic features and its prevalence in women is unknown. Histological diagnosis is sometimes reached because of suspicion of a glandular abnormality on the Pap smear report. Equally, frequently the diagnosis is made during the management of squamous pre-invasive disease, which commonly coexists with adenocarcinoma in situ.

Management and treatment of adenocarcinoma in situ

Although the entire endocervical canal can be the site of adenocarcinoma in situ, in young women most lesions

TABLE 1. *Outcome data after a cytological prediction of a glandular abnormality on Pap smear using Australian Pap test registry data.[5]*

Grade of index* Pap smear (Australian modified Bethesda system 2004)	**Outcome over 24 month follow-up based on final histological and cytological diagnosis N=1313**						
	Number of women	Cervical cancer	Endometrial cancer	Adenocarcinoma in situ	High grade squamous intraepithelial lesion	Low grade intraepithelial lesion	Normal or benign
Adenocarcinoma in situ	792	14.3%	1.6%	41.3%	12.7%	11.9%	18.3%
Possible high grade glandular lesion	298	4.4%	0.8%	9.7%	10.4%	14.4%	60.0%
Atypical glandular cells of uncertain significance	126	0.8%	0.0	1.6%	7.8%	16.2%	73.6%

**Index Pap smear was defined as a women's first cytology report as known to Australian Pap test registries in 1999. Only pure glandular abnormalities identified by cervical Pap smear were included in this study.[5]*

lie within 1cm of the squamocolumnar junction and skip lesions are infrequent occurrences.[7] Cold knife cone biopsy is the gold standard for diagnosis and treatment. Conservative fertility-sparing surgery can only be contemplated once adequate and clear endocervical and ectocervical margins are obtained. Women must be informed that close follow-up is necessary, although there are well-recognised limitations to colposcopy, biopsy and endocervical cytology as previously discussed. Hysterectomy is recommended upon completion of childbearing.

Recurrent disease is subsequently identified in as many as 15-19% of women when cone margins are free of disease and rises to more than 50-65% if the margins are involved.[8-9]

Is the Australian screening program having any impact on the incidence of cervical adenocarcinoma?

Women are informed that cervical screening only leads to prevention of approximately 80% of cervical cancer and cytopathologists would be very wary of suggesting efficient identification of adenocarcinoma in situ. It remains uncertain as to whether cervical screening programs will eventually lead to a reduction in incidence rates of cervical adenocarcinoma, however, there is limited data to suggest a positive effect from cervical screening.

From 1970 through to the mid-1990s many countries, including Canada, the US and the UK, documented an increase in incidence rates of cervical adenocarcinoma, particularly among younger women (especially <55years).[10-12] This was thought to be the result of a cohort effect, with women born in the early 1960s experiencing a considerably increased risk of cervical adenocarcinoma compared to women born before 1935. These observations are possibly the result of changing sexual mores leading to greater exposure to high risk HPV infection in women during this period.[12] Conversely, since the mid-1990s, several countries have reported a halt in the rise or decline in incidence rates of cervical adenocarcinoma, especially in younger women[10-12] and this is attributed to an effect of cervical screening. All countries reporting these changes have organised cervical screening programs with substantial population coverage that have been in place for many years ie. Ontario, UK, Denmark and Sweden. In many countries emphasis has been placed upon techniques and sampling devices that encourage practitioners to adequately sample the cervical transformation zone, collecting both squamous and glandular cells. In Australia, laboratories are required to give feedback to practitioners concerning their individual performance in this regard.

Plaxe and Saltzstein estimated, using SEER data from the US, an average of 13 years for the progression of adenocarcinoma in situ to invasive adenocarcinoma, suggesting that there is opportunity to detect and treat this precursor.[13] Furthermore, several studies have recently been published which suggest that for Australian women, cervical screening may offer some protection against invasive cervical adenocarcinoma. Mitchell et al concluded that adenocarcinoma in situ is predominantly a screen-detected disease by demonstrating that women who are diagnosed with adenocarcinoma in situ have a screening history very similar to that of healthy control women.[6] This group also demonstrated a decreased risk of invasive adenocarcinoma in women with a recent negative Pap smear.[14] Other groups have also now confirmed this.[2]

Lastly, there have been few estimates of the sensitivity of detection of adenocarcinoma in situ using cervical cytology. Schoolland from Western Australia found that a single cervical smear had the sensitivity of approximately 50% for the detection of adenocarcinoma in situ.[15] This level of sensitivity is not dissimilar the lower estimates for cervical cytology performance in the presence of pre-invasive squamous lesions.[16]

Role of new technologies in the management of glandular lesions

In recent years, adenocarcinoma in situ has also been shown to be linked to the presence of high risk HPV DNA and surrogate markers of viral oncogene activity ie. overexpression of p16INK and p53. Recent studies suggest as high as 100% of adenocarcinoma in situ lesions are positive for high-risk HPV DNA.[17]

There are several situations in which testing for cervical high-risk HPV DNA may assist in the investigation and management of women with glandular abnormalities on Pap smear. In Australia, women reported as having either a possible high-grade glandular lesion or atypical glandular or endocervical cells of undetermined significance on Pap smear, have a 60% and 74% chance respectively of having no significant pathology. For squamous disease the negative predictive value for cervical high-risk HPV DNA is extremely high and it would be reasonable to postulate that when investigating women with possible glandular pathology, high-risk HPV testing is more likely to be negative for women without significant cervical pathology. However, what remains unknown is whether testing for high-risk HPV DNA in cervical specimens in the presence of glandular disease is likely to be as reliable in terms of identifying women who do have significant pathology. Unfortunately, Ruba et al suggested sampling errors are the main cause of false negative cervical cytology reports in cases of adenocarcinoma in situ.[18] If this is the case then this may be a major hindrance to utilising HPV testing in this situation.

In addition, because glandular abnormalities are uncommon there is a paucity of data regarding the utility of HPV testing in assisting to define women with clinically significant disease. In recent small studies only 75% and 90% of women with histological evidence of adenocarcinoma in situ tested positive for high-risk HPV DNA in cervical cytological specimens.[19-20] Clinicians also need to be mindful of several situations in which high-risk HPV DNA is likely to be absent in the presence of serious pathology. This includes women with endometrial cancer and a small number of women with rare glandular cancers such as adenoma malignum.

HPV testing may also assist in the management of women diagnosed with adenocarcinoma in situ and microinvasive glandular cancers, who seek to preserve

fertility and who are treated by cone biopsy alone. Rates of persistent and recurrent disease are high (15-65%) and it has been difficult for clinicians to reassure women during follow-up because of the limitations of cytology and the difficulties of assessing what is commonly a scarred stenosed post treatment cervix.

Costa et al reported a multi-centre European study assessing the performance of HPV testing in predicting recurrent or residual disease.[9] High-risk HPV testing was a significantly stronger predictor of disease persistence and clearance than cervical cytology. Of the 42 women treated by cone biopsy in this study, 13 had further cone biopsies and a further 18 went on to hysterectomy. Persistent disease was found in a total of 17 women, mostly within the first 24 months post treatment. High-risk HPV testing performed at six and 12 months, post initial cone biopsy, was found to be more sensitive but less specific than cervical cytology. Used in combination, these tests were reported at one year to give a sensitivity of 100%, specificity of 52.6% and a negative predictive value of 100%. Although these results are encouraging, adenocarcinoma in situ is occasionally diagnosed in women in their twenties who need follow-up over many years. In this study all residual/recurrent disease was identified in the first 18 months, so it is difficult to make comment on the long-term outcomes.

Will HPV vaccination impact on the incidence and mortality from cervical adenocarcinoma?

High risk HPV infection is now clearly demonstrated as a necessary cause for most cervical adenocarcinomas and has been identified in the majority of lesions labelled as adenocarcinoma in situ. Immunisation with the quadrivalent vaccine Gardasil® has been shown to significantly reduce the risk of persistent cervical HPV infection with both HPV 16 and 18, and to prevent development of both squamous and glandular high-grade pre-invasive disease (CIN2, CIN3 and adenocarcinoma in situ). Data is now published with follow-up out to three years. The bivalent vaccine Cervarix® has been shown to significantly reduce the risk of persistent infection with HPV 16. Risk of persistent HPV 18 infection was reduced, but not significantly.

As with squamous disease, HPV 16 and 18 are linked to two thirds of invasive cancers. It is anticipated that we may well observe a reduction in the incidence of both squamous and glandular cervical cancer in the generations of women immunised prior to commencing sexual activity.

Conclusion

Caring for women with abnormal cervical cytology suggesting glandular abnormalities or histologically confirmed glandular disease continues to remain an outstanding challenge. Glandular pre-invasive abnormalities are rare and women need to be managed by an expert colposcopist or gynaecologic oncologist, in conjunction with pathologists familiar with this disease. There remain many uncertainties as to how to best advise women. There are indications that there may be a positive effect from cervical screening and there is certainly an anticipated benefit from HPV vaccination in the longer term. The role of HPV testing in guiding management is less clear and future research in this area is required.

References

1. Australian Institute of Health and Welfare 2007. Cervical screening in Australia 2004–2005. Cancer. Series no.38. Cat.no. CAN 33. Canberra: AIHW
2. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer. 2007 Feb 15;120(4):885-91.
3. Castellsagué X, Díaz M, de Sanjosé S, Muñoz N, Herrero R, Franceschi S et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006 Mar 1;98(5):303-15.
4. Cifford GM, Smith JS, Pummer M, Munoz N, Franchesci S. Human Papillomavrus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003;8863-73.
5. Appendix 8. Outcome after a cytological prediction of glandular abnormality in 1999. Author Dr Heather Mitchell. Screening to prevent Cervical Cancer: Guidelines for the management of asymptomatic women with screen detected abnormalities. Available from the NHMRC website www.nhmrc.gov.au/publications.
6. Mitchell H, Hocking J, Saville M. Cervical cytology screening history of women diagnosed with adenocrcinoma in situ of the cervix. A case control study. Acta Cytologica 2004;48:595-600.
7. Nicklin J, Wright RG, Bell JR, Samaratunga H, Cox NC and Ward BG. A clinico-pathological study of adenocarcinoma in situ of the cervix. The influence of HPV infection and other factors and the role of conservative surgery. Aust and NZ J Obstet Gynaecol 1991;31(2):19-183.
8. Souter WP, Haidopoulos D, Gornall RJ, McIndoe GA, Fox J, Mason WP et al. Is conservative treatment of adenocarcinoma in situ of the cervix safe? Br J Obstet Gynaecol 2001;108 (11):1184-1189.
9. Costa S, Negri G, Sideri M, Santini D, Martinelli G, Venturoli S et al. Human papillomavirus (HPV) test and PAP smear as predictors of outcome in conservatively treated adenocarcinoma in situ (AIS) of the uterine cervix. Gynecol Oncol. 2007 Jul;106(1):170-6.
10. Bray F, Carstensen B, Møller H, Zappa M, Zakelj MP, Lawrence G et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev. 2005 Sep;14(9):2191-9.
11. Howlett RI, Marrett LD, Innes MK, Rosen BP, McLachlin CM. Decreasing incidence of cervical adenocarcinoma in Ontario: is this related to improved endocervical Pap test sampling? Int J Cancer. 2007 Jan 15;120(2):362-7.
12. Sasieni P, Adams J. Changing rates of adenocarcinoma and adenosquamous carcinoma of the cervix in England. Lancet 2001;357:1490-93.
13. Paxe SC, Saltzstein SL. Estimation of the duration of the preclinical phase of cervical adenocarcinoma suggests there is ample opportunity for screening. Gynaecol Oncol 1999; 75: 55-61.
14. Mitchell H, Hocking J, Saville M. Improvement in protection against adenocarcinoma of the cervix resulting from participation in cervical screening. Cancer (Cancer cytopathol) 2003; 99:336-41.
15. Schoolland M, Segal A, Allpress S, Miranda A, Frost FA, Sterrett GF. Adenocarcinoma in situ of the cervix. Cancer. 2002 Dec 25;96(6):330-7.
16. Smith HO, Padilla LA. Adenocarcinoma in situ of the cervix: sensitivity of detection by cervical smear: will cytologic screening for adenocarcinoma in situ reduce incidence rates for adenocarcinoma? Cancer. 2002 Dec 25;96(6):319-22.
17. Zielinski GD, Snijders PJ, Rozendaal L, Daalmeijer NF, Risse EK, Voorhorst FJ et al. The presence of high-risk HPV combined with specific p53 and p16INK4a expression patterns points to high-risk HPV as the main causative agent for adenocarcinoma in situ and adenocarcinoma of the cervix. J Pathol. 2003 Dec;201(4):535-43.
18. Ruba S, Schoolland M, Allpress S, Sterrett G. Adenocarcinoma in situ of the uterine cervix: screening and diagnostic errors in Papanicolaou smears. Cancer. 2004 Oct 25;102(5):280-7.
19. de Oliveira ER, Derchain SF, Sarian LO, Rabelo-Santos SH, Gontijo RC, Yoshida A et al. Prediction of high-grade cervical disease with human papillomavirus detection in women with glandular and squamous cytologic abnormalities. Int J Gynecol Cancer. 2006 May-Jun;16(3):1055-62.
20. Derchain SF, Rabelo-Santos SH, Sarian LO, Zeferino LC, de Oliveira Zambeli ER, do Amaral Westin MC et al. Human papillomavirus DNA detection and histological findings in women referred for atypical glandular cells or adenocarcinoma in situ in their Pap smears. Gynecol Oncol. 2004 Dec;95(3):618-23.
21. The Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like -particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grad3 and adenocarcinoma in situ; a combined analysis of four randomized clinical trials. Lancet 2007;369:1861-68.