CANCER FORUM

FORUM

Cervical cancer

OVERVIEW: A NEW ERA OF CERVICAL CANCER PREVENTION

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The story of cervical cancer control is a drama of epic proportions. It has chapters on basic science, viral infection and carcinogenesis, epidemiology and the successful integration of multimodality cancer therapy. It is the story of the most successful cancer screening project in human history, having reduced the most common cancer in women to a rare event in many populations. Australia now has the lowest mortality from cervical cancer in the world. And finally, with universal vaccination programs we have the prospect of completely eradicating a whole range of human papillomavirus (HPV) related disease.

This edition of *Cancer Forum* celebrates and reviews the achievements and remaining challenges of cervical cancer control in Australia. Cathryn Wharton and colleagues summarise the current status of cervical cancer in Australia. Despite the successes of the screening program, there are still challenges and Penny Blomfield and Marion Saville address the problem of glandular lesions – a type of cervical cancer that has had little impact from screening in any jurisdiction.

Women still develop the disease and there are treatment challenges for clinicians working in the area. Jim Nicklin summarises the current state of the art in relation to treatment. Kim Hobbs acknowledges and addresses the unique psychosocial dimensions of this cancer - due to the demographics of the population who develop the disease and to its largely preventable nature, women who are diagnosed with cervical cancer will often face uniquely distressing circumstances. Encouragingly, the small cohort of young women who develop cervical cancer will gain hope from the prospects of fertility preserving surgery discussed by Alison Brand.

The viral aetiology of this cancer has opened the prospect of a new population based approach to cancer control. The Australian National HPV Vaccination program means that Australian women will be among the first cohort of young women in the world to be vaccinated against a whole range of HPV diseases. Into the future, there is the prospect of vaccines to treat these diseases: these prospects are discussed by Merja Ruutu and colleagues from the University of Queensland, all of whom have been instrumental in the development of the prophylactic vaccines.

Finally, Margaret Davy reviews some of the history of the cervical screening program, which is a case study in successful collaboration across various stakeholder groups that has extended over decades.

Cervical cancer prevention has traditionally been based on cervical cytologic surveillance detecting a wide range of cellular abnormalities. Cervical cytology has been successful despite its poor sensitivity and specificity. It has recently been supplemented by the HPV vaccination program, which will eventually dramatically worsen the sensitivity of cytology.

The time is now right for a completely new approach to cervical cancer prevention in Australia. Having these twin pillars of cervical cancer prevention in place, along with the immense infrastructure and expertise that has developed in the area, Australia has a unique opportunity to now seek the best way to prevent cervical cancer in its population into the future. We have an opportunity to build on the twin pillars, incorporate new technology and algorithms and develop a highly sophisticated and comprehensive re-engineered program.

However, this will not be simple, as cervical cancer prevention is characterised by diverse and often-conflicting interests. Previous attempts to introduce change have been resisted fiercely. The current screening program is not sustainable for a whole range of reasons. Cytologic techniques are too valuable a resource to be wasted on screening and there are more efficient techniques available, such as molecular testing for HPV, that need to be efficiently and safely incorporated into our prevention paradigm.

The challenge for the cancer control community is to bravely move into the future, embrace new technologies, build on the scientific evidence base and provide a comprehensive cervical cancer prevention program.

WHERE ARE WE TODAY WITH CERVICAL CANCER IN AUSTRALIA?

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Abstract

Cervical screening has had a significant impact on the incidence and mortality of cervical cancer in developed regions of the world, particularly where organised screening programs have been implemented. In Australia, the National Cervical Screening Program was established in 1991. The two-year participation rate for Australian women in 2004-2005 was estimated to be 61% and has been relatively constant over the last decade. Australia currently has the lowest mortality rate (1.9 women per 100,000) and second lowest incidence rate (9.1 women per 100,000) from cervical cancer in the world. However, this largely represents a reduction in incidence of squamous cell carcinomas, which are more readily preventable by screening than adenocarcinomas. The incidence of cervical cancer plateaus after the age of 35 years and increases again for older women (11.6 women per 100,000 age 75 years and over). The mortality from cervical cancer for Aboriginal and Torres Strait Islander women is more than four times that of non-Indigenous women. The National Cervical Screening Program has been highly successful in reducing both incidence and mortality from cervical cancer in Australia, however inequities in the burden of disease exist, particularly for Indigenous women.

Widespread cervical screening, based on the Pap test, has been very successful at identifying pre-cancerous cervical lesions and reducing cervical cancer incidence and mortality worldwide.[1-7] Since the introduction of the organised cervical screening program in Australia, mortality from cervical cancer has declined markedly and is now the 18th most common cause of cancer mortality in Australian women. Australia has the lowest mortality rates from cervical cancer in the world.[8-9] Although cervical screening became available through Government funded opportunistic screening in Australia in the 1960s, the National Cervical Screening Program was introduced in 1991 and Pap test registries and cancer registries in each Australian state and territory monitor the incidence and mortality from cervical cancer.

National Cervical Screening Program

In 1988, the Cervical Cancer Screening Evaluation Steering Committee reviewed cervical screening in Australia and recommended that cervical screening would be most effective through an organised approach. The Organised Approach to Preventing Cancer of the Cervix was established in 1991 and renamed the National Cervical Screening Program in 1995. The program aims to: increase participation rates; support the establishment of reliable smear taking and assessment services; improve management of screen detected abnormalities; as well as monitor and evaluate these processes.[10] The program targets all 18 to 69 year-old Australian women and encourages them to have Pap tests every two years.

The program has overseen the establishment of Pap test registers in each state and territory. These are confidential databases of Pap test results for the purposes of issuing reminder letters to women when Pap tests are due and providing a safety net for the follow-up of women with abnormal Pap tests. The registers also provide information to laboratories, in the form of screening histories, to assist in the reporting of current tests, and quantitative data to manage quality assurance activities.

With the inception of the organised approach to cervical screening, a national policy around the target ages, screening intervals and management of screen detected abnormalities was developed.[11] These guidelines have recently been updated within an evidence-based framework, to reflect the current state of cervical cancer in Australia and our understanding of the natural history of cervical cancer.[12] The 2005 National Health and Medical Research Council's guidelines introduced the Australian Modified Bethesda System 2004 for the reporting of low and high-grade squamous intraepithelial abnormalities (LSIL and HSIL) and management recommendations that are appropriate to their differing neoplastic potential.

Because gynaecological cytology reporting involves human interpretation, it is prone to error and it is important to monitor accuracy and maintain uniform standards of performance across Australian laboratories. The most meaningful interpretation of laboratory quality is achieved through aggregate performance measures, as these reflect day-to-day reporting practices. In July 1999 it became mandatory that Australian cytology laboratories present annual data relating to quantitative national performance measures, as part of the triennial accreditation to retain government (Health Insurance Commission) funding.[13] The laboratory performance measures have been aimed at the main reporting processes of a cytology laboratory, addressing the profile of cytology reporting categories, the accuracy of cytology reports that predict a high grade abnormality and the accuracy of negative cytology reports.[13] State and territory cervical cytology registries facilitate the process of laboratory compliance with performance standards, through the provision of

relevant data. The high quality of education and training for Australian cytologists, laboratory accreditation processes and mandatory laboratory performance standards have ensured a high standard of cervical cytology and contributed to the success of the National Cervical Screening Program.

Participation in the National Screening Program

Over the last decade, participation in the National Screening Program, as measured by two-year participation rates, has remained relatively consistent. The national participation rate for the two-year period 1996-1997 was 61%. This increased to 63.4% for the period 1998-1999, but then stabilised to around 61% from 2002-2006.[8]

While the participation rates within each state and territory have been relatively consistent, there has been some variation in the participation rates between states and territories. The highest two-year participation rate for the period of 2004-2005 for any state or territory was 65.4% in Victoria, whereas the lowest was 58.2% in NSW (Figure 1).

The vast majority of women have their repeat test within 24 months. The proportion of women undergoing early re-screening (defined as more than one test over a 21 month interval) has declined from 32% in 1999 to 26.2% in 2004.[14]

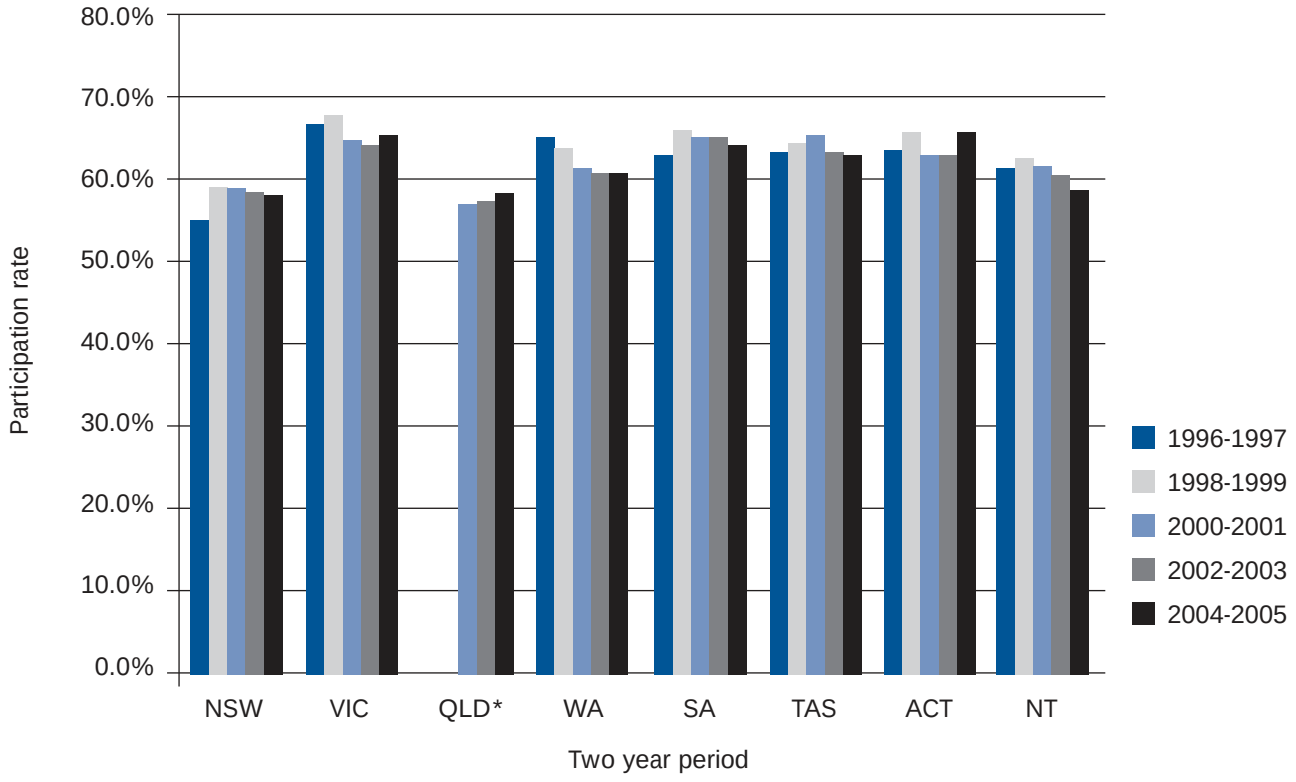
Detection of pre-cancerous cervical lesions

Cervical screening is effective in reducing mortality from cervical cancer because it detects cervical lesions at an early stage, when they are amenable to treatment. Under the new cytology coding schedule (Australian Modified Bethesda System 2004), cervical squamous abnormalities may be broadly grouped into low-grade and high-grade categories. Low-grade abnormalities on cytology are quite common in Australia, particularly among young women, because of the higher prevalence of HPV infection in young women and the frequent screening interval in Australia. In 2002, 4.3% of cytology reports in NSW were low-grade abnormalities, with the highest rate of 9.4% in women aged 20-24 years.[12] However, overall in Australia in 2005, the incidence of histologically confirmed low-grade lesions was much lower at 0.8 per 100,000 women. The incidence of histologically confirmed high-grade lesions was 7.5 per 100,000 women for the same time period. This rate was highest in women aged 20-24 (19.2 per 100,000) and declined markedly after the age of 30 years.

International incidence and mortality from cervical cancer

The world age-standardised incidence rate of cervical cancer is 16.2 women per 100,000, and the mortality rate is 9 per 100,000 women.[9] However, the incidence and mortality from cervical cancer around the world

Figure 1: *Participation of women in the National Cervical Screening Program*



*Queensland registry not operational until 1999

Source: Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2004–2005. Cancer series No. 38. Cat. No. CAN 33. 2007: Canberra.

varies greatly. It is estimated that 83% of new cases of cervical cancer occur in developing countries where screening programs are not well established or effective.[3] Eastern Africa has the highest incidence and mortality rates of cervical cancer, followed by other regions of Africa, Melanesia, Central America, Polynesia, Asia, Europe and then Australia and New Zealand (Table 1).

Table 1: *Incidence of cervical cancer and mortality rate per 100,000 women for world regions, 2002*

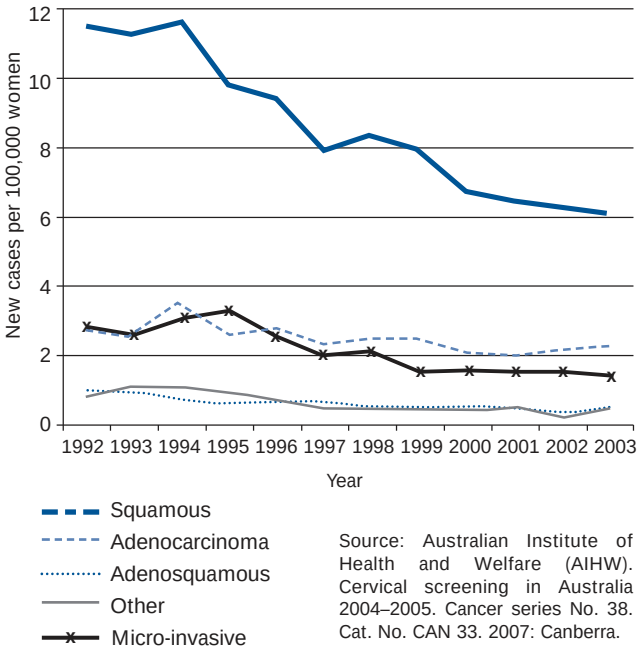
Region	ASR (w)	
	Incidence	Mortality
Eastern Africa	42.7	34.6
Southern Africa	38.2	22.6
Melanesia	38.1	21.7
Caribbean	32.6	16.0
Central America	30.6	15.0
Western Africa	29.3	23.8
South America	28.6	12.9
Middle Africa	28.0	23.0
South-Central Asia	26.2	15.0
South-Eastern Asia	18.7	10.2
Central and Eastern Europe	14.5	7.1
Northern Africa	12.1	9.8
Southern Europe	10.7	3.3
Western Europe	10.0	3.4
Northern Europe	9.0	3.6
Northern America	7.7	2.3
Eastern Asia	7.4	3.7
Australia and New Zealand	7.4	2.0
Western Asia	5.8	2.9

ASR (w)= age standardised rate (world standard population)
Source: GLOBOCAN 2002 database. (www-dep.iarc.fr/)

Compared to other countries with cancer registration systems, Australia now has the second lowest incidence rate of cervical cancer in the world.[12] The age standardised incidence rate of invasive cervical cancer in Australia (using the Australian population) in 2003 was 9.1 per 100,000 women, representing 6.1 per 100,000 for squamous cancers, 2.2 per 100,000 for adenocarcinomas and 0.8 per 100,000 for other types of cervical cancer.[8] The actual number of new cases of cervical cancer declined from 896 invasive cervical cancers (including 650 squamous, 146 adenocarcinomas and 100 other types) and 154 microinvasive cancers in 1991,[14] before the commencement of organised screening in Australia, to 578 invasive cancers (including 391 for squamous, 137 adenocarcinomas and 50 other types) and 80 microinvasive cancers in 2003.[8]

The reduction in cervical cancers from 1991 to 2003 has been predominantly due to a decrease in squamous cell carcinomas, with relatively little decline in the incidence of adenocarcinomas (Figure 2). The incidence of adenocarcinomas since the inception of the program declined only modestly from 2.7 per 100,000 women in 1992 to 2.2 per 100,000 in 2003.[8] Cervical screening is most effective for the prevention of squamous cancers, as cytology is less effective in detecting cervical adenocarcinomas, in part because of the difficulties of sampling glandular lesions in the endocervical canal and difficulties in interpretation of cytologic abnormalities.[12]

Figure 2: *Incidence of cervical cancer by histological type for women aged 20-69 years, 1992- 2003*



Source: Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2004–2005. Cancer series No. 38. Cat. No. CAN 33. 2007: Canberra.

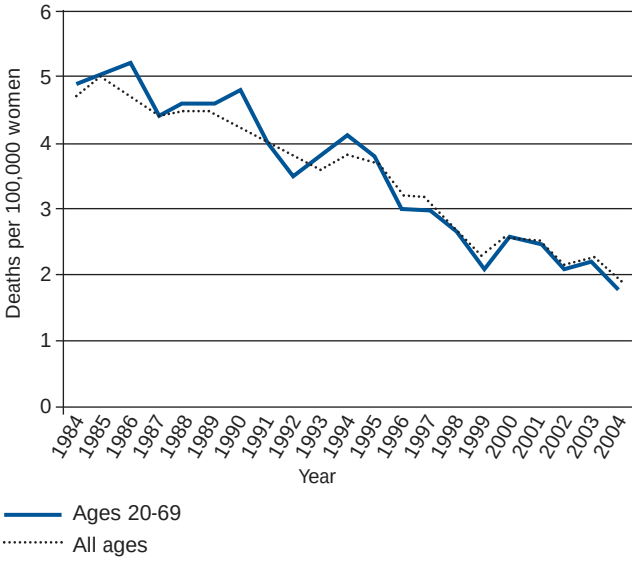
In 2004, cervical cancer accounted for 212 deaths of Australian women. The age-standardised mortality rate (to Australian population) from cervical cancer declined from 4.7 deaths per 100,000 women in 1984 to 1.9 in 2004 (Figure 3).[8] These low mortality rates are largely attributed to the success of the National Cervical Screening Program.

The incidence of invasive cervical cancer continues to rise with age (18.3 women per 100,000 aged 80-84 years) with a modest plateau in incidence in the 45 to 49 year age group (Figure 4). On the other hand, the incidence of micro-invasive cervical cancer peaks in the age group of 30 to 34 years at 2.7 women per 100,000, but then gradually declines with age. Micro-invasive cancers are a reflection of early detection in the screening program.

Mortality from cervical cancer rises dramatically after age 60 years and is highest in older age groups with the age-standardised mortality rate for ages 75 years or older being 11.6 women per 100,000 (Figure 4).

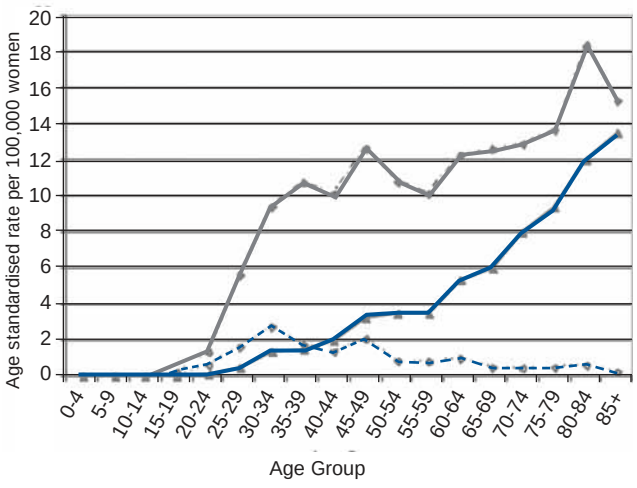
It is interesting to note that the low mortality from cervical cancer in Australia, which currently has a two

Figure 3: *Mortality from cervical cancer in Australia, 1985-2004*



Source: Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2004–2005. Cancer series No. 38. Cat. No. CAN 33. 2007: Canberra.

Figure 4: *Age standardised incidence and mortality rates of cervical cancer, 2000-2003*



Source: Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2004–2005. Cancer series No. 38. Cat. No. CAN 33. 2007: Canberra.

year screening program, is similar to some Northern European countries, which have three to five year screening intervals. In a recent paper by Canfell et al, screening uptake and changes in cervical cancer incidence and mortality were compared between Australia and the UK, which has a predominantly three year screening interval.[4] Lifetime participation in the screening program was found to be similar at around 90% and incidence and mortality fell by similar proportions in both countries, 33% and 36% respectively. The authors concluded that the policies in both countries were of similar effectiveness despite a shorter screening interval in Australia.

There are variations in mortality rates from cervical cancer between metropolitan, regional and rural areas within Australia. Although the death rate for cervical cancer has reduced in recent years overall, it remains higher in remote and rural areas than in metropolitan areas. The 2000-2003 age standardised mortality rate was 2.4 for remote areas and 2.5 for regional areas, compared with 1.9 for metropolitan areas.[8]

There are inequities in the burden of disease for Australia's Indigenous population. During the period 2001-2004 the age standardised mortality rate for cervical cancer for Aboriginal and Torres Strait Islander women aged 20-69 years was more than four times the rate for non-Indigenous women, at 9.9 per 100,000 (95% CI 6.0-15.3) for indigenous women compared to 2.1 per 100,000 for non-indigenous women (95% CI 1.9-2.5).[8] As a greater proportion of Indigenous women reside in remote areas, the higher rates in remote areas largely reflect the increased rates for Indigenous women.

Diagnosis of advanced cervical cancer has also been found to be more common for Indigenous women. For Indigenous women with cervical cancer, 37% had advanced disease at diagnosis (regional or distant spread) compared with 24% of non-Indigenous women with cervical cancer.[15-16] The five year cancer survival rate for Indigenous women was also much lower at 27.1% compared with 70% for non-Indigenous women.[16]

Similar disparities have been seen on an international level with ethnic groups (such as non-Hispanic white women, African Americans, American Indians and Vietnamese Americans).[17] Although data on participation in the Australian screening program by Indigenous status are not available in all jurisdictions, these inequities are largely believed to be due to reduced access to screening services for Indigenous women and lower participation in the screening program.[18-21] To improve participation of Indigenous women in the screening program, inequalities need to be addressed in limited resources, access to health care and social and cultural barriers to screening.

The National Cervical Screening Program has been highly effective in reducing cervical cancer mortality and morbidity in Australia. However, it is informative to consider the screening histories of women who continue to be diagnosed with cervical cancer in Australia to determine whether these cancers are primarily failures of detection or failure to participate in screening. Studies have found that the proportions of non-compliant women or women with no Pap test history are higher for cervical cancer cases than controls.[22-28]

Data from Victoria suggests that approximately 94% of women diagnosed with invasive squamous cervical cancer between 2002-2004 have either no screening history or an inadequate screening history in the 10 years prior to diagnosis, whereas for glandular cancers this proportion was 73%.[29] This indicates that the primary reason for diagnosis with cervical cancer in the

current screening program is inadequate participation in screening.

It has been estimated that in 2003, approximately 70% of squamous carcinomas were prevented by cervical screening in Australia, compared to earlier estimates of 46% in 1989. This improvement has been attributed to the improved follow-up of cytologic abnormalities, improved laboratory quality assurance and an increase in participation in the screening program by Australian women.[2]

Conclusion

Over recent decades the Australian National Cervical Screening Program has been highly successful in reducing the impact of cervical cancer in Australia, resulting in the lowest mortality rates in the world. Since the beginning of the program, the incidence of squamous cell carcinoma has almost halved, although there is some recognition that the program has not been as effective at reducing incidence of glandular cervical cancers.

Despite the program's success in Australia, mortality among Indigenous women is substantially higher than non-Indigenous women and these inequities in screening participation need to be addressed. With the recent implementation of the HPV vaccination program, participation in the screening program needs to be carefully monitored in the years ahead to ensure that women continue to participate and that cervical cancer incidence continues to decline.

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OUTSTANDING PROBLEMS – GLANDULAR LESIONS

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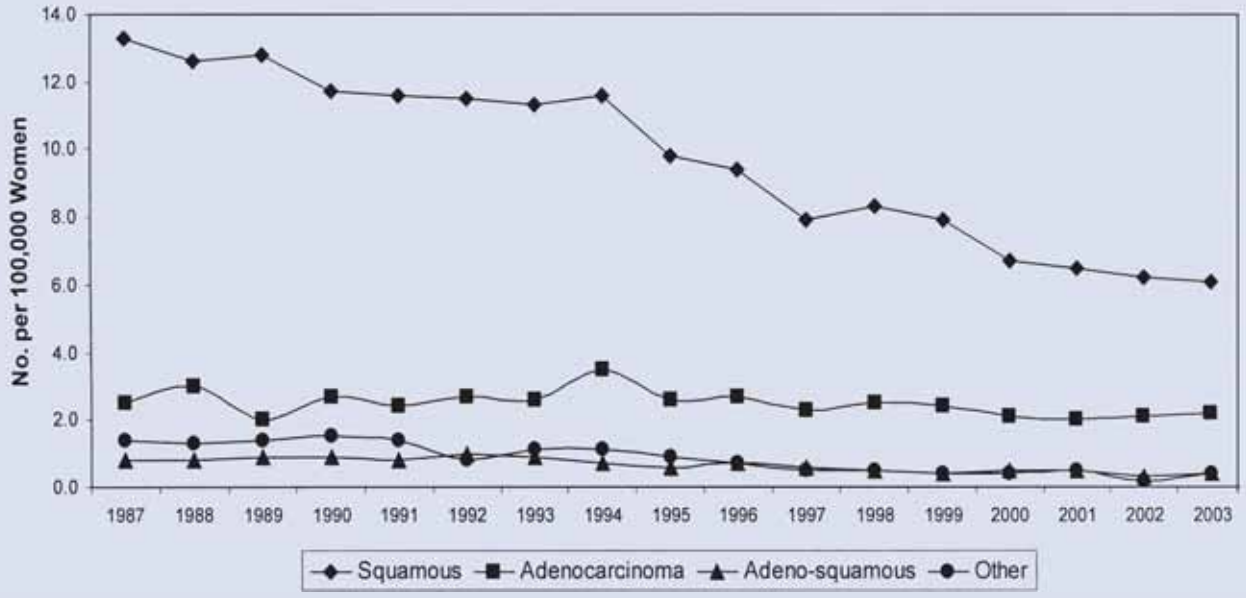
Abstract

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.

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AN OVERVIEW OF TREATMENT FOR INVASIVE CERVICAL CANCER

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Abstract

Treatment of cervical cancer varies depending on stage and patient factors. Comprehensive management is best provided within a well resourced multidisciplinary team. Micro-invasive disease is largely managed surgically.. Treatment for stage IA2 disease involves radical clearance around the primary disease and pelvic lymphadenectomy. Stage IB1 and non-bulky stage IIA disease can be treated with radical hysterectomy or chemoradiation. Important developments in the surgical management of patients with this stage of disease include radical trachelectomy, nerve sparing and laparoscopic techniques, and sentinel node identification and resection. For patients with stage IB2 and bulky stage IIA disease there are four valid management options. These include primary chemoradiation, radical hysterectomy and lymphadenectomy +/- adjuvant chemoradiation, neoadjuvant chemotherapy followed by radical surgery and chemoradiation followed by completion hysterectomy. The mainstay of treatment for patients with stage IIB – IVA disease is chemoradiation. Timely completion of treatment and the maintenance of haemoglobin between 12-14 g/dL are associated with optimal results. The role of surgery in advanced disease is controversial. There may be some role for the resection of bulky pelvic and para-aortic lymph nodes prior to chemoradiation. With the advent of sophisticated imaging modalities of CT, MRI and PET scanning, the role of pre-treatment surgical staging via a retro-peritoneal or laparoscopic approach is more controversial. There is some role for primary exenerative surgery in selected patients with stage IVA disease involving either bladder or bowel mucosa. Treatment of patients with stage IVB and recurrent disease is highly individualised and may involve surgery, chemotherapy or radiotherapy.

The treatment of cervical cancer varies, depending upon stage of disease and patient factors. Comprehensive management of the full spectrum of disease can only be provided in the context of a well resourced multidisciplinary team, including specialist gynaecologic pathologists, subspecialty trained surgeons, medical oncologists, radiation oncologists, palliative care specialists, nursing and allied health professionals.

Micro-invasive disease (FIGO stage IA1 and IA2)

Micro-invasive disease is by definition microscopic disease, usually arising in a background of high grade intra-epithelial neoplasia. The diagnosis can be subtle and cannot be made on anything less than a cone biopsy or equivalent excisional treatment. Ideally, the entire cone specimen should be extensively embedded and sectioned and reviewed by an expert gynaecological pathologist. Stage IA1 is defined as measured invasion of stroma no greater than 3mm in depth and no wider than 7mm. Stage IA2 is defined as invasion of stroma greater than 3mm, but no greater than 5mm, and width no greater than 7mm.[1] The distinction is quite important with respect to the risk of nodal involvement. FIGO staging does not distinguish between squamous and glandular lesions.

For patients with stage IA1 disease, the risk of pelvic nodal disease is less than 1%.[2-7] Patients can be treated with a simple hysterectomy or cone biopsy if reproductive potential is required. Conisation alone is safe therapy where the cone margins are negative, there is no lymph-vascular space invasion and the endocervical curettings are negative. Cumulative data would suggest that these recommendations can be safely applied to both squamous and glandular lesions.[8]

For patients with stage IA2 disease, there is a larger tumour volume and greater depth of invasion. The risk of pelvic lymph node involvement is of the order of 4-8%.[2-7] There is an imperative to ensure not only an adequate margin around the primary tumour, but to also treat the pelvic lymph nodes. It may be possible to achieve an adequate margin around the primary tumour with cone biopsy or hysterectomy, however commonly a modified radical hysterectomy or trachelectomy (depending upon reproductive requirements) is performed to ensure adequate clearance. A pelvic lymphadenectomy is also necessary because of the risk of nodal disease.

Stage IB1 and non-bulky IIA disease

There are two main options for treatment of stage IB1 and non-bulky IIA disease; surgery or chemoradiation. The benchmark for surgery is radical hysterectomy and pelvic lymphadenectomy. This operation refers to an en bloc excision of the uterus with the parametrium to the level of the internal iliac artery, the uterosacral ligaments one third to half way to the sacrum, and the upper part of the vagina. The pelvic lymphadenectomy includes all the fibro-fatty-lymphatic tissue between the internal iliac/obliterated umbilical artery, the obturator nerve, the deep circumflex iliac vein, the genito-femoral nerve and the common iliac nodes +/- sacral nodes. A modified radical hysterectomy may be used for smaller primary lesions and is defined as resection of the parametrium to the level of the ureters and the uterosacral ligaments, divided some 2-3cm from the cervix and a smaller cuff

of vagina. The extent of surgery can be largely tailored to the size of the tumour, with a view to attaining margins of at least 1cm.

Recent developments in the surgical management of cervical cancer include the incorporation of minimal access and laparoscopic techniques. Laparoscopic assisted radical vaginal hysterectomy and total laparoscopic radical hysterectomy (including the incorporation of robotics) have been demonstrated to be feasible with reduced blood loss, longer operating times, shorter hospitalisation, and faster recovery.[9] A randomised trial comparing laparoscopic radical hysterectomy and open surgery has recently commenced (www.ClinicalTrials.gov, Identifier: NCT00614211). Another development in the surgical management is the nerve-sparing radical hysterectomy. The technique involves identification and clearance of the hypogastric nerve under the ureter and lateral to the uterosacral ligaments, the inferior hypogastric plexus in the lateral parametrium and the distal inferior hypogastric plexus in the posterior vesico-uterine ligament.[10] This latter technique is reportedly associated with less voiding, defaecation and sexual dysfunction.[10]

An option for patients who are desirous of retaining reproductive potential, is radical trachelectomy (in conjunction with a pelvic lymphadenectomy). This provides radical clearance around the primary tumour without removing the corpus. Radical trachelectomy is usually confined to smaller cancers <2cm with no lymph-vascular space invasion and can be performed via either a vaginal or abdominal approach. A more detailed review of this treatment has been included elsewhere in this issue. There are no randomised trials comparing radical trachelectomy with standard surgical treatment, however retrospective observational series have demonstrated the procedure to be safe and feasible with an acceptable "take-home baby rate".

A novel, experimental approach to the management of the pelvic lymph nodes is sentinel node biopsy. The rationale for this approach is the belief that there is an orderly sequence of metastatic spread from the primary site to identifiable sentinel nodes and then to second echelon and subsequent nodal groups. This approach has become increasingly accepted in the management of breast cancer, cutaneous melanomas and even vulval cancer. In the context of treating cervix cancer, technetium-99 radiocolloid and Patent Blue vital dye is injected around the tumour. The sentinel node is identified at the time of surgery by colour and increased radioactivity on a gamma probe.[11] Several studies have demonstrated that detection and removal of sentinel nodes is feasible and safe, particularly in patients with smaller tumours.[12] Although over 800 have been reported in the world literature, this is an experimental surgical protocol and randomised trials comparing it with full pelvic lymphadenectomy are still some way off.

The second option for treatment of early stage disease is primary chemoradiation. The survival outcomes for surgery and radiotherapy are identical. There has been only one randomised study comparing hysterectomy and tailored adjuvant radiotherapy with primary radiotherapy alone for women with stage IB1 to IIA disease. In the study, 109 out of 228 (47.8%) patients had bulky disease >4cm and were stratified by cervical diameter. There was a very high rate of adjuvant radiotherapy in the surgery arm (64%) and the five year survival rates and disease free survival were not significantly different (83% and 74%). There was a significantly higher rate of severe morbidity (predominantly urological and gastro-intestinal) in the surgery (plus tailored radiotherapy) v the radiotherapy arm (28% v 12%, p = 0.0004).[13]

The superiority of chemoradiation over radiation alone in treating women with both early and advanced cervical cancer has been demonstrated in several randomised trials and in a meta-analysis. Consequently, chemoradiation has become the standard of care. Of note, few patients in the combined trials had early stage disease such as in the population under consideration. Survival is so good in this group that the addition of chemotherapy provides a small marginal benefit.

The advantage of surgery is as follows:

1. Preservation of ovarian function in pre-menopausal women.
2. Preservation of vaginal function and length.
3. More comprehensive evaluation and capacity for resection of bulky pelvic lymph nodes.
4. Determination of extent of nodal metastases allows individualisation of radiotherapy field.

The advantage of primary chemoradiation is as follows:

1. Avoids the demonstrated morbidity of combined radical treatments.
2. Avoids the need for surgery, particularly for patients with significant medical co-morbidities.

Treatment decisions in this group ultimately come down to patient factors, patient and physician preference and local resources and expertise.

Stage IB2 and bulky stage IIA

For patients with bulky stage IB and IIA disease there are four valid options for management:

1. Primary chemoradiation.
2. Radical hysterectomy and lymphadenectomy, plus adjuvant chemoradiation.
3. Neoadjuvant chemotherapy followed by radical surgery.
4. Chemoradiation followed by completion hysterectomy.

Primary chemoradiation is a predominant mode of treatment in the developed world. The addition of concurrent chemotherapy to radiotherapy has been associated with significant survival benefits in many randomised studies. The benefits of the addition of chemotherapy are more marked for earlier stage disease.[14] A more detailed discussion of chemoradiation is included in the next section.

Primary surgery followed by chemoradiation allows removal of large, potentially radiation resistant tumours,

may obviate the need for brachytherapy, allows for removal of bulky retroperitoneal lymph nodes, and may allow for transposition and preservation of ovarian function and tailored adjuvant chemoradiation. The risk of major morbidity is increased with the combination of radical therapies. To minimise the risk of morbidity the following techniques have been advocated:

1. Restricting lymphadenectomy to debulking of enlarged nodes only, on the understanding that radiation to the nodal bed will sterilise the vast majority of microscopic metastases.
2. Limiting the radiation to a smaller central field where a comprehensive lymphadenectomy has been performed and no nodal metastases found.
3. Use of carefully planned conformal radiotherapy field and belly board to minimise gut morbidity.

The rationale of neoadjuvant chemotherapy is sound. Numerous non-randomised studies demonstrate that squamous cell carcinoma of the cervix is usually sensitive to cisplatin-containing regimens. Delivery of these regimens is feasible and safe and is associated with downsizing of tumours with increased resectability of bulky tumours. A recent Cochrane meta-analysis from 18 trials involving 2074 patients found a high degree of heterogeneity in chemotherapy regimes and trial design. However, it was noted that trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m^2/week tended to show a survival advantage for neoadjuvant chemotherapy. The authors concluded only that timing and dose intensity of cisplatin-based neoadjuvant chemotherapy had an important impact on benefits for women with locally advanced cervical cancer and that further investigation was warranted.[15]

Historically, a completion hysterectomy following radiotherapy was often planned in this patient population in the era before chemoradiation. The rationale was that bulky, often hypoxic tumours were found to extend laterally and superiorly to the tumouricidal, isodose radiation curves of the brachytherapy devices post external beam radiation. Up to one half of specimens were found to contain viable tumour at the completion of radiation. A single randomised study comparing radiation with and without extra-fascial hysterectomy demonstrated a trend towards a lower recurrence rate in the surgery arm (15 v 27%), with much stronger trends for larger tumours, but the difference was not statistically significant.[16] Consequently, even before chemoradiation replaced radiotherapy alone as the standard of care, the routine practice of completion hysterectomy largely fell out of favour. However, Nijhuis et al advise careful evaluation for viable tumour and biopsy of the cervix eight to ten weeks post treatment to identify patients who may benefit from salvage surgery.[17] Multiple series have subsequently been published reporting the role of completion hysterectomy following chemoradiation in patients with disease ranging from stage 1B1 to IVA.[18] This treatment certainly has a role in the multi-modality management of cervical cancer, most notably in patients with surgically-resectable, viable disease post-chemoradiation, in patients with anatomical distortions of the lower genital tract due to fibroids or tumour which may compromise brachytherapy and possibly in larger tumours.

Stage IIB, III and IVA disease

The mainstay of treatment for patients with locally advanced disease is combination external beam irradiation and brachytherapy with concomitant sensitising chemotherapy. The superiority of chemoradiation over radiation alone has been demonstrated in multiple randomised studies and a meta-analysis.[14,19-23] The optimal chemotherapy regimen has not been determined as the radiation regimen used in each of the trials was different. The conclusion of the Cochrane review was that radiation with sensitising chemotherapy, whether with or without cisplatin, was associated with a significantly improved overall survival and progression free survival, with a significant reduction in both loco-regional and distant recurrence rates. There was a significantly greater incidence of haematological and gastro-intestinal toxicity, with poor reporting of late effects of treatment. Treatment related deaths were rare. The greatest beneficial effect was noted in trials that included the higher proportion of patients with early stage disease.[14]

From several retrospective studies it is apparent that timely completion of chemoradiation is associated with improved local control of disease and survival.[24-28] Ideally, treatment should be completed within six to eight weeks. Treatment durations of greater than eight to ten weeks were shown to be associated with higher rates of loco-regional recurrence and poorer survival.[24-28]

Anaemia is common in patients with advanced cervical cancer and has been demonstrated to be associated with compromised outcomes.[29] Thus, anaemia is a credible target for therapeutic interventions to improve clinical outcomes. The optimal hemoglobin level during treatment is thought to be between 12 and 14 g/dL.[30] Experimental strategies to correct anaemia during treatment using either blood transfusions or recombinant erythrocyte erythropoietin have been studied.[31-32] Erythropoiesis stimulating agents used in this manner have been associated with increased thromboembolic events. The optimal regimen to maintain haemoglobin levels during treatment is yet to be determined.

The role of surgery in advanced stage disease

Bulky, malignant, retroperitoneal nodes on the pelvic side wall and in the aortic area are potentially resistant to standard doses of (chemo) radiation and a likely site of treatment failure. Retrospective studies of debulking of grossly involved nodes prior to radiation have shown some improvement in outcome compared to radiation treatment alone.[33-34] Although chemoradiation is the new standard of care, it is likely that pre-treatment resection of bulky nodes, particularly via a retro-peritoneal approach, will provide some therapeutic advantage.

With the advent of the sophisticated imaging modalities of CT, MRI and PET scanning capable of detecting occult para-aortic and distant metastases, the place of routine

staging surgery is reduced. Surgical staging may be accomplished via either a trans-peritoneal or extra-peritoneal approach, using either laparoscopy or laparotomy. Multiple studies have demonstrated that such an approach is feasible and potentially more accurate than imaging techniques. However, this must be balanced against the delay in institution of chemoradiation and particularly the GIT morbidity of combined radical modality therapy. A single randomised study comparing clinical staging to pre-treatment surgical staging, via either a laparoscopic or an extra-peritoneal open approach, was terminated prematurely when interim analysis demonstrated significantly worse progression-free and overall survival in the surgical arm.[35]

For selected patients with primary malignant involvement of the bladder or rectal mucosa, particularly with evidence of fistula formation and without evidence of significant distant disease, there is a place for exenterative surgery and reconstruction.

Stage IVB disease

For all intents and purposes, disseminated disease is incurable. Treatment is palliative and quality of life is of paramount importance. Specific treatments are directed at symptom relief. For patients with significant vaginal bleeding, palliative radiotherapy is usually appropriate. Any place for chemotherapy is determined by the extent and type of symptoms and patient wishes.

Recurrent disease

The treatment of recurrent disease is determined by the extent and distribution of disease, the interval to recurrence, the modality used to treat the primary disease and patient wishes. For patients with an isolated central recurrence of disease, particularly following chemoradiation, there is a place for exenterative surgery. Surgery may also be appropriate for isolated, late, pulmonary metastases or nodal metastases. Radiotherapy may be useful to palliate pain or bleeding in the pelvis and at other sites.

Multiple chemotherapeutic drugs, including ifosfamide, paclitaxel, topotecan and vinorelbine have been tested as single agents and in combination with cisplatin in patients with disseminated cervical cancer. Only the combination of cisplatin and topotecan was shown to have a survival advantage over single agent cisplatin (9.4 verses 6.5 months). While there was significantly greater toxicity in the combination regimen, there was no significant difference in quality of life.[36,37]

Conclusions

The treatment of cervical cancer frequently involves carefully integrated, multi-modal therapies which optimise survival and minimise morbidity. Early stage disease is usually amenable to surgery alone. More advanced stage disease will usually require multi-modal therapy often including chemoradiation +/- surgery.

A multi-disciplinary team provides the full spectrum of expertise and services to manage patients with all stages of cervical malignancy. Furthermore, this therapeutic model provides continuity of care, particularly with respect to recurrent disease and complications of treatment.

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PSYCHOSOCIAL DISTRESS AND CERVICAL CANCER

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Abstract

This overview of the psychosocial distress experienced by women diagnosed with cervical cancer addresses the important tasks of individually assessing and managing the impact of the diagnosis and treatment for all women and their caregivers. Distress in the context of a cancer diagnosis is a normal, anticipated response. While the experience of distress is universal, the intensity and duration of distress varies according to prognosis, social circumstances of the patient and the morbidity associated with treatment. Symptoms of elevated distress may persist long after treatment ceases, even for patients who have a favourable prognosis. For cervical cancer patients, there are unique factors associated with their experience of distress. In this article the factors associated with distress are discussed. The socio-demographic characteristics of 90 women treated at a large gynaecological cancer treatment centre in metropolitan Sydney are reviewed. Differences between women who present with early versus late-stage disease are examined. Regardless of disease stage or prognosis, there are long-term consequences of cervical cancer treatment and these are highlighted. The major side-effects of cervical cancer treatments impact on bladder, bowel and sexual function, as well as overall quality of life. Three case studies of women with cervical cancer are presented to illustrate the importance of high quality, individualised psychosocial care as an integral component of the comprehensive cancer care of women with cervical cancer.

The diagnosis of cancer in any site has the potential to be a catastrophic, life-altering event. Immediate responses usually focus on existential issues of survival and impact on family and caregivers. In the longer term the focus shifts to management of treatment side-effects, which may impose a considerable physical and emotional burden.[1] Beyond the impact of the treatment and questions concerning prognosis, the legacy of being a cancer patient is pervasive. Even for long-term survivors, significant numbers report considerable distress associated with the fear of recurrence and adjustment to a new self-concept.[2-4]

In the case of cervical cancer, women may experience a unique emotional and psychological burden for three main reasons: cervical cancer is largely a preventable cancer; there is an effective screening test, readily available to most in the Australian population; and it is associated with a sexually transmitted virus, raising the spectre of guilt and blame, at least in the minds of many women and families if not in the minds of health care providers.[5]

Anecdotally, and at the risk of over-generalising, women with cervical cancer fall into two main groups. The first group are those with (usually) early stage disease for whom the cancer has manifested within the screening interval. Women in this category are often young and usually have an adequate Pap test screening history. A small number of these women are found, on review of pathology, to have had a false negative result on a previous Pap test. Not infrequently, the diagnosis is made in the context of child-bearing; either on routine ante-natal screening, or at post-natal follow-up.

No matter what the circumstances in which women in this group find themselves with an un-anticipated diagnosis of cervical cancer, the dominant issue is profound distress that their best endeavours at attending to their own health have let them down. Often there is anger and a sense of injustice directed at health care practitioners whom women may perceive as having failed to protect them. In these cases, the distress at the diagnosis of cancer and the immediate questions concerning threat to survival may be compounded by worries about future reproductive ability, sexual function and body image,[6] as well as a generalised distrust of health care providers.

The second main group of women are those who have advanced disease at presentation, usually because they have not been adequately screened and in some cases, not screened at all. There are a variety of factors which mitigate against women accessing Pap test screening. These factors include, usually in combination: socioeconomic disadvantage; physical, intellectual or psychiatric disability; history of sexual abuse; family dysfunction; or simply being born in a country where there is no routine screening.[7] For many of these women, the diagnosis of advanced cervical cancer is yet another disaster in a lifetime characterised by catastrophe, impoverishment, neglect and disadvantage; the sense of injustice here relates not so much to individuals as to endemic social injustice.

Impact of treatment

Regardless of the stage of cancer or the circumstances of the woman and her family, beyond the primary concern for survival is the challenge of managing the real impact of the disease, the quality of survival in the context of side-effects and consequences of treatment.

For women diagnosed with early stage disease, treated with surgery alone, the prospects for cure are high,[8] but so too are the prospects for long-term morbidity. While these women can expect to survive their cancer, cure

may come at the cost of infertility, sexual dysfunction, bladder dysfunction, changes to body image and/or lower limb lymphoedema. Ongoing problems with anxiety, depression and relationship difficulties are often reported, as are persistent difficulties with sexual function.[9,10-15] Additionally, there is frequently generalised anxiety and worry associated with fear of recurrence, or development of a new cancer.

Women whose treatment for stage II cervical cancer is primary chemo-radiation and those who have combined surgery and chemo-radiation, have a relatively good chance of cure. However, the morbidity from treatment is usually more significant than for those who have surgery alone. Along with loss of fertility, sexual dysfunction[16] and lower limb lymphoedema, these women may have to contend with the additional burdens of menopausal symptoms (premature for many) and vaginal stenosis, both of which may make more difficult their sexual rehabilitation and resumption of a normal lifestyle. In a small number of cases, even though treatment confers long-term survival or cure, severe bladder and bowel complications may result in the development of fistulae, requiring surgical intervention and the formation of ostomies. Not surprisingly, patients report significant distress associated with persistent bladder or bowel problems.[17] Paradoxically, the cancer may be in abeyance, but the associated existential angst may persist, as does the fear of recurrence.[18]

Treatment for very advanced cervical cancer offers a small chance of cure, but incurs a high rate of severe treatment related complications for many women. Nevertheless, it is offered to and accepted by most women, because it carries the hope of extended survival and is effective in palliating symptoms of pain and vaginal bleeding. Whilst morbidity following treatment is significant, quality of life may be enhanced by the opportunity to have treatment and to optimistically anticipate improved functioning and survival.[19-20]

Cervical cancer in context

Moving on from an abstract discourse about the impact of cervical cancer in a theoretical sense, what is the 'lived experience' of the women themselves? What are the characteristics of women who have recently been treated for the disease in the gynaecological cancer service of a major, capital city teaching hospital?

In the period from January 2005 to July 2007, 90 women with a new diagnosis of cervical cancer presented to Sydney's Westmead Centre for Gynaecological Cancer. So, who are they?

Snapshot summary

Table 1: *Country of birth, n=90*

Australia	59
United Kingdom	10
New Zealand/Oceania	7
Asia	6
Europe	4
Middle East	3
South America	1

Table 2: *Place of residence, n=90.*

Sydney West Area Health Service	70
Rural/regional areas	17
Other metropolitan health services	3

Patients treated in this unit were predominantly English-speaking (78%), with three-quarters of them living in the local area health service. On the face of it, arranging and completing treatment would appear to be relatively uncomplicated for most of these women; they are not impeded by communication barriers and they live within a reasonable distance of the treatment facility. However, for many, their lack of adequate social supports, lack of reliable private transport options, socioeconomic impoverishment, poor performance status at diagnosis and the morbidity associated with several weeks of chemo-radiation, combined to make the treatment course a difficult process.

Table 3: *Clinical stage, n=90.*

Stage 1A	15
Stage 1B	25
Stage 2A	11
Stage 2B	20
Stage 3	12
Stage 4	7

Table 4: *Age at Diagnosis, n=90.*

Less than 30 years	5
30-39 years	22
40-49 years	19
50-59 years	13
60-69 years	16
70-79 years	8
80+ years	7

Encouragingly, almost half the women had stage I disease at presentation, with excellent prospects for long-term survival or cure. However, 20% had very advanced cancers (stages III and IV). This has obvious implications for the increased need of ongoing hospital and community-based health care services, including palliative care services, for both optimal management of difficult symptoms and end of life care.

There was a wide distribution of ages, reinforcing the fact that cervical cancer can occur across the life cycle. Thirty per cent of women were aged less than 40 years at the time of diagnosis, which has potential implications for fertility issues, as well as for coping with the long-term consequences of treatment. At the other end of the spectrum, 16% of women were aged more than 70 years when diagnosed. This has implications for the capacity of these women to maintain an independent living status and flags the potential for them to require increased utilisation of domiciliary aged-care services in their communities. For all age groups,

the support and assistance of partners and family caregivers, if available and competent, is crucial to the ability of these women to manage arduous treatment regimens and long-term follow up.

Psychosocial care

Every woman diagnosed with cervical cancer has a separate and unique story. Recounting the real life stories of three women will demonstrate their complexity and the need for sensitive assessment and service provision on many levels.

Ms M.C. Age: 42

This woman, with a stage III cancer at presentation, lived alone in a remote location. Her dwelling was primitive, with no running water, no land line phone service, inconsistent mobile phone coverage and an unreliable electricity generator. She had a long standing history of mental illness, substance abuse, an addiction to prescription analgesics and several previous suicide attempts. She was scornful and dismissive of the community-based mental health services which had tried on many occasions to engage and assist her. All of her childhood and adult relationships had been characterised by violence and abuse. She had few friends (and those she had were similarly troubled with mental health concerns) and was estranged from her family. She trusted no-one.

It is eight years since her diagnosis and she remains cancer free, discharged from clinical follow-up. However, she has suffered severe radiation enteritis, requiring a bowel resection. She continues to live an isolated existence, with rigid dietary and lifestyle restrictions, along with poorly controlled chronic pain and an ongoing battle with substance addiction.

Mrs A.N. Age: 31

In the early 1960s a six year-old girl, along with her two older siblings, was abandoned by her parents in rural NSW. For the next 10 years she lived in a children's home (otherwise known as orphanage). At age 16 she elected to be placed with a foster family who had visited her regularly and taken her on holidays and to their family home throughout her period in the orphanage. They had wanted to permanently foster her from a younger age, but did not have parental consent. Her education in the children's home had been patchy, but after moving to live with the foster family, she attended TAFE, completed a diploma with distinction and commenced work with a passion to succeed.

At 29, married with two children, she was managing a small business and was well regarded in her local community. She was an active participant in school and sporting committees. She was diagnosed with a stage II cervical cancer, which initially responded well to chemo-radiation. However, her cancer recurred after a brief disease-free interval. She investigated and tried every available option to treat her recurrent disease, displaying the same tenacity and resilience which had seen her survive a disastrous early childhood.

She died, aged 31, leaving a devastated husband, two children and a devoted foster family.

Mrs G.K. Age: 72

This woman, with a long history of paranoid schizophrenia and multiple presentations to her local community health service, was brought by ambulance to the emergency department of a regional hospital after setting fire to her nightdress on a radiator in the dilapidated caravan where she had lived for many years. She was estranged from her family and no longer knew where any of them resided. The community nurse who had been visiting to dress her varicose ulcers was aware of her squalid living conditions and of her chronic health problems, but was unsuccessful in persuading her to attend a medical practice, due to her pervasive suspicion and paranoia.

On arrival at hospital, in addition to her burns, she was found to be in renal failure. Further investigations revealed advanced cervical cancer. A guardianship order was obtained to administer palliative radiotherapy and to prescribe medication to treat her florid psychosis. The radiotherapy was effective in reducing her pain and stopping her vaginal bleeding; medication relieved her psychotic symptoms. Treatment of her burns continued beyond the short course of radiotherapy and at the completion of this she was transferred to a nursing home where she was permitted to take her small dog. She died 18 months later. Efforts to find her family resulted in a son being contacted in another country, but he declined to visit or to correspond with her.

The psychosocial issues which accompany a diagnosis of cervical cancer are frequently long-standing and entrenched. Social workers, clinical psychologists and care coordinators need to be well acquainted with the range of community support services which can be engaged in parallel with the cancer care team, to assist women and their families as they confront the problems associated with the diagnosis and treatment of cervical cancer. There is a diverse range of services and there is variability across regions. Services which can be utilised to assist in the care of these women may include a combination of community nursing, mental health teams, domestic assistance and personal care agencies, meals on wheels, family support, community legal services, women's health centres, disability advocacy services, charitable and church-based organisations, community transport, palliative care teams, support groups and the various programs offered by state and territory Cancer Councils.

All women need individualised, tailored psychosocial care plans, in just the same way as their oncological care plans are individualised and tailored according to disease stage, co-morbidities and histopathology. For many women, the psychosocial distress evident at the time of the cancer diagnosis, relates to more than just the cancer itself. For women who are battling family dysfunction, mental illness, disability, remoteness from home or poverty, the additional challenges posed by an intensive course of treatment are simply overwhelming. High quality, targeted psychosocial care assists in optimising adjustment, coping and compliance even for the most complex cases.[21-22]

Cervical cancer in the future

In spite of successful screening programs and population immunisation programs, cervical cancer will continue to exist, although the number of new cases of cervical cancer is likely to be dramatically reduced as the benefits of immunisation are realised. So, who will develop cervical cancer in future generations? Answer: the most marginal and dispossessed within our society.

Cervical cancer will largely (but not exclusively) be confined to women who have not been immunised, or for whom immunisation comes well after exposure to the human papilloma virus. While cervical cancer in developed countries may eventually be classified as a rare cancer, the special management and care needs of the disadvantaged women who have it will continue to present challenges to the next generation of health care practitioners.

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PRESERVING FERTILITY: NEW SURGICAL APPROACHES TO THE MANAGEMENT OF EARLY CERVICAL CANCER

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Abstract

The diagnosis of cervical cancer is particularly devastating when it occurs in young women who have yet to complete, or even start their family. In the past, the options for treatment, either radical hysterectomy or radical radiotherapy, rendered women infertile. In the 1990s the technique of radical trachelectomy was developed which potentially preserved fertility in these young women while treating their cancer. Experience with this technique has grown in the past 10 years such that there is evidence that in highly select patients, who are highly motivated to preserve their fertility and whose cancers fulfill strict criteria (early stage disease, tumours less than 2cm and otherwise suitable for surgical treatment), survival rates are equivalent to radical hysterectomy. The procedure is not without risk and the pregnancies that may ensue are to be considered high-risk with the incidence of second trimester loss (11%) and the incidence of pre-term birth (18%) more than double that of the general population.

Cancers, in general, are often thought to be diseases of 'old' people. Nothing could be further from the truth with cervical cancer. It has its peak incidence in the 45 to 49 year-old age group and over 30% of all cervical cancers are diagnosed in women in their prime reproductive years (ages 20 to 40).[1] Given the increasing trend for women in Australia and in other developed countries to delay childbearing into their thirties and later, it is not surprising that some patients are faced with a diagnosis of cervical cancer when they have yet to complete or even start their family. For young women, the otherwise successful treatment of early cervical cancer with radical hysterectomy or radical radiotherapy can still be devastating because they are rendered infertile in the process.

It was in response to this difficult clinical scenario that Daniel Dargent first developed the technique of radical vaginal trachelectomy in order to preserve the uterus in women diagnosed with early stage cervical cancer.[2]

Technique

The radical vaginal trachelectomy described by Dargent involved removal of the upper vaginal cuff, paracervical tissue and cervix up to the isthmus of the uterus. A pelvic lymphadectomy was also performed. The lower uterine segment was then rejoined to the vagina. Subsequently, there have been modifications to this technique. Plante and Roy described leaving up to 1cm of upper cervix to try and optimise a woman's reproductive potential.[3,4] Smith et al have described the technique of radical abdominal trachelectomy, stating it is an easier technique to master for surgeons more familiar with the technique of radical abdominal hysterectomy than radical vaginal surgery.[5] As world-wide experience with all these techniques grows it can be said that, for best results, the technique should be limited to women who would otherwise be candidates for radical hysterectomy, but who have a strong desire to preserve fertility and have a tumour size less than 2cm.[3]

For patients who fulfill the above criteria and choose fertility sparing surgery, a pelvic lymphadectomy with frozen section is first carried out, either laparoscopically or via open technique, to ensure that there is no evidence of extra-cervical spread. If the nodes are involved, then the radical trachelectomy procedure is abandoned in favour of definitive surgery or radiotherapy as the preferred treatment as individual circumstances dictate. If the nodes are negative, then radical trachelectomy is performed, with the upper margin of the cervical specimen being assessed by frozen section to ensure a tumour free margin of at least 5mm. Then the upper cervix, or what remains of it, is sutured to the vagina. A catheter may be inserted to prevent scarring and narrowing of the newly formed cervical os and a permanent cervical suture may also be inserted.

Safety

Radical hysterectomy has been a highly successful treatment of early cervical cancer for many years, with five year survival rates of over 90% for small tumours. There is no doubt that when the new technique of radical trachelectomy was described, there were misgivings about the wisdom of meddling with such success. Concerns were expressed that patients undergoing radical trachelectomy would have an unacceptably high central recurrence rate. No randomised controlled trials have been done comparing radical hysterectomy with radical trachelectomy and it would be considered impractical because of low patient numbers. Thus, any information regarding the success of the treatment in oncological terms rests with comparing reported outcomes in patients who have undergone radical trachelectomy with those who have undergone radical hysterectomy.

To date, the outcome of 548 patients undergoing radical vaginal trachelectomy have been reported.[4, 6-14] With a median follow-up time of 44 months (range 1-176),

there have been 22 recurrences (4.0%) and 14 deaths (2.6%). This is certainly comparable, or even better than, the results expected with conventional treatment. It should be remembered that the patients undergoing radical trachelectomy were highly selected and even included patients who might have been adequately treated with cone biopsy alone. In addition, those with adverse prognostic features such as lymphatic space invasion, tumour size greater than 2cm and high grade histology, were often excluded.

Outcomes with radical abdominal trachelectomy have also been published, however the reported cases are much fewer. In total, three investigators have reported their results on a total of 37 patients who have undergone radical abdominal trachelectomy.[15-17] Follow-up information is available on only 33 patients. With a median follow-up of greater than three years (range 9-75 months), there have been no recurrences and no deaths.

Surgical morbidity, including intra-operative and post-operative complications, appears to be lower in patients undergoing radical vaginal trachelectomy than radical hysterectomy because the procedure is less extensive. Shepherd's group reported that blood loss, analgesic requirements and length of hospital stay were all shorter with the radical vaginal trachelectomy group as compared to radical hysterectomy group.[18] In addition, bladder hypotonia was also less frequent. On the other hand, patients undergoing radical vaginal trachelectomy had more problems with dysmenorrhea (24%), dyspareunia, irregular vaginal bleeding (17%), amenorrhea (7%) and cervical stenosis (10%).

Obstetric outcomes

The 'raison d'etre' for performing radical trachelectomy rather than radical hysterectomy is to allow the patient to successfully carry a pregnancy and deliver a healthy baby. Accordingly, obstetric outcome is of paramount interest. Because the procedure radically compromises the cervix, in its early days there were concerns expressed about the ability of patients to conceive a pregnancy and to carry a pregnancy to viability, let alone term.

Obstetric outcomes have been reported in 484 patients undergoing radical trachelectomy (see Table 1).[13,14,19] Of the 484 patients, less than half (214) have attempted conception with 118 patients succeeding (70%). As shown in Table 2, there have been 213 pregnancies. Ninety-three patients have had a live birth at greater than 36 weeks. Eighteen per cent have had a first trimester loss or spontaneous abortion, which is comparable to the general population. Of concern is that 18% have had a live birth at less than 36 weeks (preterm birth) and 11% have had second trimester losses. This compares unfavourably to the general population, where the incidence of pre-term birth is 7-8% and the incidence of second trimester loss is 3%.

All would agree that these pregnancies should be considered high-risk with a substantial risk of pre-term birth and second trimester loss. This is felt to be related to decreased cervical length, alteration in cervical mucous and presence of a cervical suture leading to infection.[19]

Frequent antenatal visits will be required and some investigators advocate serial cervical length measurement.[20] Given that increased incidence of pre-term birth is felt to be due to ascending infection and premature rupture of membranes, other investigators advocate screening for bacterial infection and use of prophylactic antibiotics.[21] Those with a cervical suture in place will need delivery by caesarean section.

There is little guidance in the literature as to how to best manage these high-risk and much wanted pregnancies.[22] No consensus exists on the timing of the pregnancy or even whether there should be a waiting period after the procedure before attempting pregnancy.

It is interesting to note that less than half of the women undergoing this procedure have actually attempted pregnancy. The reasons for this are varied, however may relate to short follow-up of some studies, lack of partner at follow-up, or early age at diagnosis of cancer, with desire to maintain options or changed circumstances.

The future

Patients who are being evaluated as candidates for radical trachelectomy often have had a cone biopsy prior to definitive treatment to adequately assess their disease and size of tumour. One of the interesting observations from several studies on radical trachelectomy is the high rate of no residual disease on the final trachelectomy specimens. Shepherd, in the largest radical trachelectomy study to date, reported that 63% of patients had no residual disease on final pathology.[13]

This raises the question as to whether even less aggressive surgery may provide similar outcomes to radical trachelectomy in early stage, low volume disease. Rob et al has reported on a less aggressive approach, in which 26 women who underwent large cone biopsy or simple trachelectomy, combined with laparoscopic sentinel pelvic node identification for early stage cervical cancer.[23] With a median follow-up of 49 months, he reported one central recurrence which was treated with chemo-radiation, with no evidence of disease 36 months later. Fifteen out of 26 women planned a pregnancy, with 11 succeeding (15 pregnancies). Of these pregnancies, there were eight children delivered, three of which were pre-term deliveries at 24 weeks, 34 weeks and 36 weeks, respectively.

There have been no other reported studies to date and much larger numbers of patients will be required to determine whether this could be a reasonable option for highly selected patients in the future.

Patient expectations

The option of radical trachelectomy provides hope to a woman diagnosed with invasive cervical cancer that she may still be able to have a child of her own. In the face of a diagnosis of a life-threatening disease, this is often the most positive piece of information she is given. Are the expectations of women in this situation valid, and what are their concerns about their reproductive future?

Carter et al addressed the reproductive concerns of women treated with radical trachelectomy in a study of 29 patients undergoing the procedure.[24] She found that pre-operatively, patients had relative high expectations of successful conception and childbirth in that 85% of patients rated their chances of conceiving at 50% or greater. By six months post-operatively, expectations had declined such that only 63% of patients rated their chances at 50% or greater. Six months post-operatively, 85% of women had concerns about pregnancy and 27% had concerns about time pressures ie. 'clock ticking'. Clearly, while radical trachelectomy offers hope for future fertility, it does not remove anxieties and concerns women may have about future fertility.

Conclusions

Radical trachelectomy is slowly gaining acceptance among the gynaecologic oncology community as a valid option for a highly select group of patients with early cervical cancer who wish to preserve their fertility options. Given that the incidence of cervical cancer in Australia continues to fall, this is not a procedure that will commonly be performed by all gynaecological oncologists. In expert hands, the survival rates following the procedure are comparable to that of radical hysterectomy. However, patients need to be fully informed about the risks of infertility, early pregnancy loss, pre-term delivery and neonatal complications. The challenge for gynaecological oncologists in the future is to recognise how safely we can push the limits of conservative treatment without jeopardising outcome and survival.

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HPV VACCINES AND THE AUSTRALIAN HUMAN PAPILLOMAVIRUS (HPV) VACCINATION PROGRAM

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Abstract

Australia was the first country in the world to commence a national vaccination program against human papillomavirus, using the quadrivalent human papillomavirus vaccine, Gardasil®. This program is soundly based on the natural history of human papillomavirus infection and utilises the vaccine that has been shown to be highly effective in preventing human papillomavirus related diseases. The program is a population-based strategy offering the vaccine to all Australian women, aged between 12 and 26 years. Preliminary evidence suggests that the program has achieved high coverage and high compliance. This foreshadows that Australian women will now form the first cohort of young women in the world to be protected against a wide range of human papillomavirus related diseases.

Australian women will be the first cohort of young women in the world to be vaccinated against a range of human papillomavirus (HPV) related diseases, including cervical cancer. The National HPV Program is funded by the Australian Government and was started in 2007. Under the program, the HPV quadrivalent vaccine, Gardasil®, will be provided free to girls and women aged 12 to 26 years. There are three aspects to the program: an ongoing vaccination program for all 12 year-old girls; a two year catch-up program for school girls aged 13-18; and a general practitioner based program for women aged 19 to 26 years. The school-based program started in April 2007 and the community-based program started in July of that year and will run until June 2009.

This program is expected to have a significant impact on the incidence of HPV infection and markedly reduce the clinical burden of HPV related disease in Australia. Boys and men are not included in the program at this stage because there is not yet enough clinical effectiveness data available in males, despite the public health grounds for including them.

The human papillomavirus

HPV infection is very common, with around 70% of both males and females showing evidence of HPV infection within five years of becoming sexually active. In 70 to 90% of cases, the infection will resolve within 36 months.[1] Infection with certain types of HPV is the major cause of invasive cervical cancers and their precursor lesions.[2] HPV infection itself is generally asymptomatic and is usually not recognised until patients are diagnosed with cervical dysplasia, cancer or genital warts.

Up to 79% of women worldwide are infected with HPV at some point in their lives. The peak incidence of infection is within the first five years of commencing sexual activity and studies in the US and UK have shown high rates of acquisition in young women. A woman's lifetime number of sexual partners is the most important risk factor, but the high transmission rate shows that even minimal sexual contact can result in infection.

Human papillomaviruses are small, non-enveloped DNA viruses that can affect cutaneous and mucosal epithelial tissues. Over 100 different types of HPV have been isolated and up to 40 of these types of HPV can infect the anogenital epithelium. HPV causes a variety of diseases in humans, ranging from benign warts to cancer of the epithelia (including the cervix, vagina, vulva, anus and oropharynx). Those HPV types associated with the development of cancer are called 'high risk' for oncogenicity. Other HPV types, such as HPV types 6 and 11 associated with genital warts, are considered 'low risk' for oncogenicity. HPV can be transmitted by direct skin-to-skin contact during all types of sexual activity. The viruses contain outer capsid components, referred to as the L1 and L2 viral components.

After infection, the protein products of two HPV genes, E6 and E7, bind to host cell growth proteins that have tumour suppressor functions and stop the normal arrest of cell division. In some cases of persistent infection, the HPV genome inserts into the host genome in a process known as integration.[3-4] After integration, E6 and E7 may be over-expressed, causing host squamous epithelial cells to proliferate in a less orderly fashion and acquire the cellular appearance of a high-grade squamous epithelial lesion (HSIL). A small proportion of HSIL clones of cells, which harbour persistent and commonly integrated HPV, become fully malignant and over time, manifest as invasive squamous cell carcinoma.[5]

HPV types are classified as high risk (oncogenic) or low risk (non-oncogenic) according to their risk of promoting oncogenesis. Approximately 15 high risk types have been linked to cervical, vaginal, vulval, anal, penile and head and neck cancers. Persistent infection of the

cervix with some high risk HPV types can cause cell changes that may lead to cervical cancer over a period of usually more than 10 years. High risk HPV types 16 and 18 are linked to 70 to 80% of cervical cancers and about 50% of high grade cervical pre-cancers in Australia.[6-7] HPV types 16 and 18 also account for about 25% of low grade cervical abnormalities.[8] Low risk HPV types include types 6 and 11, which are linked to approximately 90% of genital warts cases and around 10% of low grade cervical abnormalities. These HPV types can also cause recurrent respiratory papillomatosis, a rare but debilitating condition characterised by repeated growth of warts in the respiratory tract requiring surgery.

HPV vaccines

There are two vaccines currently available in Australia – a quadrivalent vaccine against types 6/11/16 and 18 called Gardasil® and a bivalent vaccine against 16 and 18 called Cervarix®. Both have been developed by recombinant genetic technology that allows expression of the major structural protein of HPV, the L1 protein that spontaneously assembles into virus-like particles (VLPs) which are both type specific and highly immunogenic.

Both vaccines contain VLPs, but the products differ in the types of HPV L1 proteins included as antigens, substrates used for production, adjuvant properties and in the final formulation. Antibodies raised to the VLPs provide protection against HPV infection, probably by transudation of IgG from serum to local mucosal/epithelial areas, especially at sites of trauma where HPV can otherwise gain access to basal epithelial cells.[9] Published efficacy studies suggest subtle but probably insignificant differences in prevention of type-specific HPV infections and disease.[10-11] The vaccines are not infectious, as they do not contain viral DNA, and Gardasil® has been safely administered to more than 22 million people worldwide. The vaccines prevent infection through the development of mucosal neutralising antibodies. They are prophylactic – not therapeutic – vaccines, and have no impact on pre-existing or previous infection. To date, Gardasil® is the only vaccine to be included on the Australian National HPV Vaccination Program.

High levels of antibodies have also been shown in young males and females following vaccination.[12-13] Immunogenicity responses one month after the three-dose vaccination regimen with Gardasil® show that the seroconversion rate is ≥99.5%, with antibody levels highest in 9 to 17 year-old boys and girls and 18 to 26 year-old women. There is currently no clinical efficacy data available in boys or men older than 15 years and only preliminary data showing efficacy of Gardasil® in women older than 26 years.

Bridging immunogenicity studies were conducted to link efficacy in young women aged 16 to 26 years to the younger populations. In most jurisdictions, recommendations for vaccination have been made for girls aged approximately 12 years, as this population will mount a very effective immune response to the vaccine and will be most unlikely to have prior exposure to HPV infection. Several jurisdictions, including Australia, have also recommended catch-up programs for women aged 13-26 years.

Rationale for the Australian HPV vaccination program

Implementation of a vaccination program for 12 to 26 year-old women has shown to be cost-effective in Austalia.[14] It is estimated that the vaccination program will reduce the lifetime risk of cervical cancer by 48%, compared to the current screening system. This estimate is based on data from the National Cervical Screening Program in Australia, 100% vaccine effectiveness, lifetime duration of efficacy and 80% coverage. The vaccine should also substantially reduce the incidence of cervical precursor lesions and the related interventions.

The administration of all three doses is important for optimal protection from the vaccine, so compliance needs to be encouraged. Logistics around the school based program have involved teams of trained nurses visiting schools on an organised rotational basis. The school-based program has been administered over the course of a single school year to reduce the potential for missed doses. Preliminary information regarding the program suggests that high coverage rates have been achieved in the school vaccination program, with high levels of compliance with second and third doses.[15]

No new vaccine has ever entered clinical practice with a known duration of protection. Therefore, the exact duration of protection from the current vaccines will not be known for many years. However, to date, research has shown that Gardasil® confers protective immunity and efficacy for at least five years and there is no indication currently that boosters will be needed. In addition, there is evidence of an immune memory response, so long-term protection is likely. Clinical trials are continuing and the results will be monitored to determine whether booster doses will be needed in the future.

A National HPV Vaccination Program Register is being developed by the Australian Government to collect data about the program. Personal details identifying the patient will be kept confidential and information will not be sought about the patient's sexual history. Personal information collected will be used to evaluate the impact of the HPV Vaccination Program on cervical cancer rates, to issue reminders if the course is incomplete, to issue confirmation the course is complete and to contact vaccine recipients should booster doses become required.

Conclusion

The National HPV Vaccination Program represents an additional prevention strategy against cervical cancer and other HPV-related diseases and will complement the National Cervical Screening Program. All eligible women should be encouraged to participate in the program and obtain the benefits of this highly effective vaccine.

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THERAPEUTIC VACCINATION AGAINST CERVICAL CANCER – ARE WE NEAR?

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Abstract

Therapeutic vaccines developed to target the papillomavirus antigens that are expressed by cervical cancer induce immune responses, but have yet to show clinical efficacy. Transplantable tumour models expressing human papillomavirus antigens do not predict vaccine outcome in the clinic. Understanding how immune responses are influenced in a tumour antigen experienced host, and what surrogate marker or markers reflect the potential efficacy of therapeutic vaccines in the clinic, will be necessary to provide new approaches to immunotherapy for cervical cancer.

Human papillomavirus (HPV) causes cervical cancer

HPV infections are very common and it has been estimated that the lifetime risk for genital HPV infection is over 50% for sexually active women.[1] Human papilloma viruses are the main etiological agent in cervical cancer and more than 99% of cervical cancers contain human papillomavirus DNA.[2] Worldwide it is estimated that there are about 500,000 cancers of the cervix uteri diagnosed each year and 270,000 deaths, mainly in developing countries. Cervical cancer is the second most common malignant disease in women, with nearly 80% of the cases arising in developing countries[3]. Despite the fact that millions of women have papillomavirus infection every year, most of them clear the infection within 18 months (Fig 1).[4-6]

More than 100 different HPV types have been described and they can be grouped into high and low-risk types, depending on their oncogenicity.[7] Of these, about 30 types infect genital tract or other mucosal sites. In cervical cancer, HPV16 is the most prevalent (50-60%), followed by types 18, 31, 33 and 45[8-10]. Papillomavirus infection can also lead to anal, vulvar, penile, oral and tonsillar cancers.[11-12]

Papillomavirus oncogenes as targets for immunotherapy

Human papillomaviruses are small DNA viruses that infect the basal cell layer of epidermis and their protein coding sequences (open reading frames) can be divided into early (E1-7) and late (L1, 2) according to their expression in the viral life cycle. L1 and L2 code for viral capsid proteins and are expressed only in differentiating keratinocytes. HPV has two major oncogenes, E6 and E7. These genes are expressed early in the basal layer of the epidermis and are the major targets for therapeutic approaches. E7 has been shown to be more highly expressed in cancer cells and is more immunogenic than E6 and is widely used in therapy models.[13]

The effectiveness of human papillomavirus oncogenes lies in the fact that they prevent the infected epithelial cells from differentiating. E6 protein binds to p53 and E7 to pRb preventing exit from the cell cycle. Cells continue to divide, permitting ongoing replication of the virus genome. Papillomavirus is a non-lytic virus that divides only in epithelial keratinocytes and encodes mainly short-lived proteins in the cells in which the virus replicates. These characteristics make it a hard target for immunotherapy.

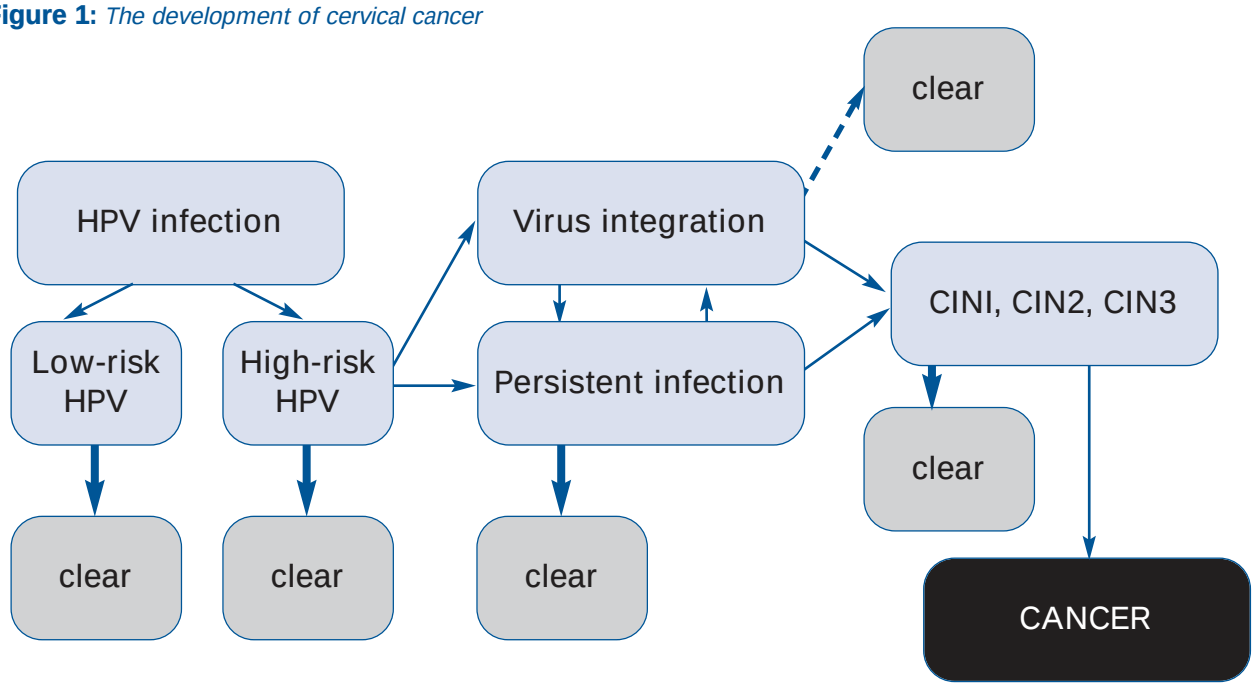
Prophylactic vaccines (Gardasil® HPV6/11/16/18; Cervavix® HPV16/18), in which L1 capsid protein of the virus is used as an antigen, have been so far efficacious in clinical trials, providing 100% protection against infection with the HPV types incorporated in the vaccines.[14] About 30% of cervical cancers are due to HPV types other than HPV16/18. However, these vaccines do not assist with the virus in already infected women. The duration of protection is not currently known and there are millions of HPV-infected women in the world who cannot benefit from the prophylactic vaccine. HPV is prevalent already in newborn babies and the effect of this early infection on prophylactic vaccine efficacy is unknown.[16-18]

An HPV therapeutic vaccine would therefore assist to help reduce the global burden of papillomavirus-related cancers. There are several challenges for development of therapeutic vaccines. These include viral and tumour determined immune escape mechanisms, poor immunogenicity of some viral antigens and the immuno-compromised state of cancer patients.

Advantages of immunotherapy

The main advantage of antigen specific immunotherapy is that it is specific towards tumour cells and does not harm healthy cells. The body's immune system can, in principle, recognise a tumour as non-self and attack cells expressing tumour specific antigen. Systemic immune responses can target microscopic metastases anywhere in the body. William Coley is often regarded

Figure 1: *The development of cervical cancer*



After papillomavirus infection, most infections clear between 9-18 months. A small group of women either get persistent infection or the virus gets integrated into the genome. It is unclear how these two events impact each other or which comes first more often. It is not known if and how cells, where virus has been integrated, are cleared. Part of persistent infections progress to cervical precancerous lesions. Of these, most CIN1 lesions regress, also some of CIN2 lesions, but few CIN3 lesions regress and eventually this leads to cervical cancers years or decades later.

as the father of immunotherapy and developed immuno-therapeutics which activate the innate immune system.[19] He treated sarcomas with massive bacterial infection and immune effector mechanisms associated with bacterial infection were able to control tumour growth. After his time, several researchers tried to treat cancers with similar non-antigen specific immunotherapy with limited success. Animal models of specific immune compromise have however, established that the innate and adaptive immune systems play a role in controlling the development of some tumours.[20-21]

What would be the clinical opportunity for using a HPV therapeutic vaccine? Cervical cancer develops through precancerous lesions, called cervical intraepithelial neoplasia (CIN). Most CIN1 lesions regress spontaneously and some CIN2 lesions regress. New vaccines are relatively expensive and the cost/benefit-ratio might be very high if early CIN lesions, that could regress naturally, are treated. However, trials of HPV therapeutic vaccines in cervical cancer have shown poor results and this may be due to initiation of treatment when patients are already severely immuno-compromised. Recent vaccine trials have aimed to treat CIN2/3 lesions and have shown more encouraging results. It could be beneficial to direct immunotherapy to CIN2/3 lesions since after conventional surgical excision, recurrence occurs in about 5-20% of patients.[30-31]

Route and adjuvants

Muscle is not well provided with antigen presenting cells and novel methods are being considered to create better immune response for therapeutic vaccines.[32] Since skin and mucosa contain greater numbers of dendritic cells, the transdermal route may be a better method of vaccine delivery. Many of the recent clinical trials (Table 1) have used subcutaneous immunisation.

Most vaccines have adjuvants that enhance the immunogenicity of the vaccine. Proteins and peptides are weakly immunogenic and adjuvants are needed to stimulate a strong immune response and possibly to help break the tolerance to tumour antigens. Aluminium hydroxide is widely used in prophylactic vaccines, but biases immune responses toward antibody production, and new adjuvants will be needed for therapeutic approaches, which will require activation of cytotoxic T lymphocyte (CTL) responses. QS-21, a refined saponin from the bark of *Quillaja Saponaria*, can induce strong T Th1 (T helper 1) type responses in animal models.[33] Certain cytokines (eg. IL-2,IFNy) that direct T cells towards a Th1 type response, might also be considered.

Clinical trials against HPV-induced diseases

Previously, clinical trials have been done in late stage cervical cancer patients who are often already immuno-suppressed and results from these trials have been poor; no clinically significant responses have been seen and immune responses were worse than with later clinical trials.[20-21,30-35] Nowadays, the clinical trials have been directed to earlier, pre-cancerous CIN lesions.

One problem with clinical trials for therapy for CIN is that after the vaccination period, patients with high grade CIN cannot be observed long before treatment for CIN lesion

Table 1. *Clinical trials with HPV therapeutic vaccines from latest three years.*

Patients	Controls/placebo	Vaccine	How efficacy was measured	Results in patients	Reference
30 males with flat condylomas	20 males with flat condylomas	MVA E2 (vaccinia virus Ankara [MVA] expressing the E2 gene ***VV**	Colposcopy, histology, HPV test, ab response, CTL response against HPV+ cancer cells	28/30 clearance of condylomas, 30/30 had ab against vaccine, no recurrence in a year. In control group, 13/20 clearance, 3 recurrences in 3 months, no abs were detected	Albarran et al 2007[22]
58 women with CIN3	None	Hsp(65)E7 (SGN00101) ***P**	Histology, colposcopy	13/58 responded (to CIN1 or clearance), 32/58 reduction of lesion size, 1 1/58 no response	Einstein et al 2007[23]
26 women with CIN2/3 (14 high dose and 12 low-dose vaccine). All were HPV16+	13 women with CIN2/3. All were HPV16+	HPV16L1E7 ***P**	Histology, Ab response for L1, CTL response against E7, HPV test	5/23 showed CTL response against E7. All had ab against L1, seroconversion in 10/25, none in placebo group, 10/17 showed reduction in lesion size in vaccine group, 3/5 in placebo group, HPV16 DNA clearance in 6/16 in vaccine group, 1/7 in placebo group	Kaufmann et al 2007[24]
21 women with CIN2/3	None	Hsp(65)E7 (SGN00101) ***P**	Histology, HPV test	7/20 clearance, 1/20 regression to CIN1, 11/20 no response, 1/20 progression, IFNg-ELISPOT positive 9/20	Roman et al 2007[25]
29 women with AGIN3, 27 of them HPV16+	None	Prime TA-CIN, boost TA-HPV ***P,VV**	Histology, visual measurement of size	1/29 clearance, 5/29 reduction of lesion, 18/29 no change, 5/29 progression. 4/29 clear from HPV DNA	Fiander et al 2006[26]
34 women with CIN2/3	None	MVA E2 ***VV**	Colposcopy, histology, Ab response for E2, CTL response against cancer cells, HPV test	Colposcopy:19/34 clearance, 11/34 reduction of lesion, 4/34 minimal reduction, histology: 20/34 clearance, 11/34 reduction in lesion size, 3 downgrade to CIN2/1, ab against E2 in all patients, CTL response against cancer cells in all patients, HPV viral load reduced in all patients	Garcia-Hernandez et al 2006[27]

Table 1. *Clinical trials with HPV therapeutic vaccines from latest three years (continued)*

Patients	Controls/placebo	Vaccine	How efficacy was measured	Results in patients	Reference
161 patients with anogenital warts positive for HPV6/11	159 patients with anogenital warts positive for HPV6/11	HPV6L2E7 ***P**	Photography of warts, HPV test, ab response against L2E7	No change of recurrence rate was seen in vaccine v placebo groups. All vaccinated patients had ab response to L2E7	Vandepapeliere et al 2005[28]
10 patients with CC (stage IB)	None	DC pulsed with HPV16 or HPV18 E7 and KLH (as carrier protein) ***DC**	ELISA, ELISPOT, DTH	10/10 showed ab against E7, 5/10 had no previous ab, 5/10 showed increase in E7 ab levels, 10/10 showed ab against KLH	Santin et al 2008[29]

**VV=HPV antigens delivered by viral vectors, P=protein vaccine, DC=dendritic cell vaccine*

has to be undertaken for ethical reasons. Generally, patients are vaccinated and after a short follow-up period, they are treated with conventional methods eg. loop excision of the cervix transformation zone.

Table 1 shows some recent clinical trials of HPV immunotherapy for women with CIN2 or CIN3 or genital warts. Where placebo controls have been used, there has been no evidence of significant efficacy. Comparison between trials is difficult since responses are measured with different indicators. In general, the results have not been astounding and many therapeutic approaches that have succeeded in animals (murine models), have failed in humans.

Vaccine types

There are several vaccine strategies available today. Below, a few of the strategies are discussed briefly.

Peptide-based vaccines

Peptide-based vaccines have been used in clinical trials against human cancers,[36,37] however the problem is their weak immunogenicity, generating low affinity CTL responses and Th1 stimulation. Peptides from either E6 or E7 oncogenes are used in therapeutic vaccines against HPV-related cancers and pre-cancers. Recently, animal models have shown that cytokines might serve as effective adjuvants, increasing the efficacy of the vaccine.[38] This has also been detected in clinical trials with peptide-based melanoma vaccines.[39] Vaccines with long E6 and E7 peptides have been successfully tested with animals,[40-41] and a phase I trial of immunogenicity and safety of these vaccines in humans has just been published.[42] The trial showed that more than 50% of patients had specific CTL response against E6_E7 long peptides, but of 43 patients only one had complete response and five remained stable with a disease.

Protein vaccines

Protein vaccines have mainly used E7 protein fused to heat-shock protein (hspE7) or HPV L2 and E6 (TA-CIN) and they are safe vaccines. Several trials have been done recently,[13,43-44] however the clinical results have not been plausible. Studies by Frazer and Hallez showed reduction in HPV DNA and viral load was seen as well as some CTL responses, however this didn't correlate with clinical outcome (1/23 in CIN2/3 at Frazer, 0/5 in CIN3 at Hallez, cleared the lesion). Goldstone and colleagues showed that three out of 14 patients with warts cleared the lesion.

Dendritic cell vaccines

Dendritic cell (DC) vaccines are cell-based vaccines where patients own naïve antigen presenting cells are pulsed with antigens and cultured to maturity with specific cytokines. These mature dendritic cells are introduced to the patient and theoretically they have the potential to induce both tumour-specific effector and memory T cells. The basics of DC therapy have been reviewed elsewhere.[45] DC vaccines are highly effective at inducing immunity but difficult and expensive to produce. Animal experiments with DC vaccines against cervical cancer have given poor results.[46] Two small DC therapy trials have been conducted against cervical cancer, CTL and/or antibody responses were seen in 3/11[47] or 4/4[48] patients, however neither study showed any clinical responses, possibly due to late stage of the disease. Recently, a phase I clinical trial has been done in cervical cancer patients to test the efficacy and safety of DC therapy vaccine (Table 1)[29] and it remains to be seen if DC therapy proves to be effective in treatment of CIN lesions or early stage cervical cancer.

Plasmid DNA and recombinant viral vector vaccines

Plasmid DNA and recombinant viral vector vaccines contain protein-coding DNA that produces immunologically active antigens in live cells. These vaccines can induce antibody and CD4+ T cell helper responses and they induce strong CD8+ T cell responses because they express antigens intra-cellularly, introducing them directly into the MHC class I

antigen processing and presentation pathway. Most promising results have been achieved with these viral vector vaccines, however only a few studies have been published.

A group of women were treated with MVA E2 (modified virus Ankara + E2, recombinant papillomavirus vaccine) vaccine and 20/34 showed complete response and 11/34 reduction in lesion size. All patients showed CTL and ab responses.[27] In another study, 30 males with condylomas were treated with the same vaccine (MVA E2) and 28/30 showed complete responses; all had antibody responses and no recurrences were detected within a year.[22]

However, all vaccines face the need to break immunological tolerance by vaccination, MHC class I and antigen loss on tumour cells, systemic defects in dendritic cells and secretion of immunosuppressive cytokines etc.[49] More basic immunology studies are needed to clarify the immunological reactions behind the tumour development.

Animal models for cervical cancer vaccine

There are currently three animal models commonly used for studying cervical cancer immunotherapy. Most studies have been done with a model in which E6 and E7 expressing transformed mouse cells (TC-1) are injected into mice.[50] These cells form tumours in normal mice and vaccines can be tested for their ability to prevent, or more preferably to cure, tumours. A problem with the TC-1 model is that it is "too successful"; therapeutic protocols have worked with this mouse model but human studies with the same therapy have shown very poor results.

A further animal model is a mouse that expresses papillomavirus oncogenes E6 or E7 or the whole HPV16 genome in epithelial cells from the keratin 14 promoter. Mice develop spontaneous tumours in old age,[51] and tumours can be also induced by estrogen treatment. A problem with this mouse model is that the viral genes are expressed in all basal epithelial cells of all organs, including the thymus. The animals are therefore partially tolerant of these proteins[52-53] and the model is a tough test for a vaccine.

A third model is a skin graft model where skin from E7 transgenic mice (previous model) is grafted on to a normal mouse. E7 skin grafts are not rejected. Since E7 is presented to the immune system in HPV infections, it is used in this setting as a model antigen. Therapeutic approaches are tested for ability to reject E7 skin graft. A problem in this model is the site of lesion (skin instead of cervix). However, we believe it is a good model to study some of the requirements for, and effectiveness of immunotherapy, because the antigen is expressed in the correct cell types, without the problems of tumour induced immunosuppression, and the efficacy of immunotherapy can be evaluated over the life of the animal.[54-55]

Future directions for therapeutic vaccines against cervical cancer

Efficacy of therapeutic vaccines for cervical cancer remains to be demonstrated by clinical trials. However, there are several approaches that might increase the success of therapeutic vaccines which are discussed below.

1. Increasing effector T cell functions

Cytotoxic T cells specific to tumour antigens are the key players in tumour regressions. Enhancing the effector T cell function by either increasing the efficacy or the number of tumour specific T cells might lead to better eradication of the lesion. It is also possible to use cytokines, like IL-15, that prolong the life span of T cells.[56]

2. Overcoming the suppressive effect of regulatory T cells and macrophages

It is widely accepted that regulatory T cells (Treg) exist and prevent effective immune responses. Treg cells have been described to control autoimmune diseases, infection and transplantations and to regulate immune responses of tumours.[57] They suppress immune responses either through direct cell to cell contact or through secreting suppressive cytokines such as IL10.[58] A further regulatory population of myeloid suppressor cells seen in epithelial cancer are also able to prevent T cell effector function.

Tumour specific regulatory T cells

Tumour specific regulatory T cells have been identified and cell lines established from tumour patients. CIN and cervical cancer patients have increased Treg cell frequencies in peripheral blood and CD4(+) T cell fraction.[59] Also, HPV E6 specific Treg cells have been identified in cervical cancer patients.[60] In a study using TCR transgenic T cells specific for influenza virus hemagglutinin (HA) antigen, it was shown that immunotherapy will amplify the tumour specific regulatory T cells and thus reduce the effectiveness of immunotherapy.[61] Similar results were obtained by using dendritic cell immunisation and targeting antigen through specific pathways.[62]

Vaccine induced T regulatory cells

Chimeric papillomavirus like particles have been candidate vaccines for the treatment of cervical cancer,[63] however it has been demonstrated in a clinical trial that no efficacy has been observed.[24] We have shown that vaccination with chimeric PV VLPs can induce Treg cells and this might explain the unresponsiveness for the therapy.[64] Others have also shown that immunisation through stimulate TLR4 also induce regulatory T cells.[65]

Collectively, these results suggest that immunisation may induce and expand existing tumor specific regulatory T cells, inhibiting cytotoxic T cell responses. In future, it needs to be considered how to overcome the inhibition of vaccine induced and expanded regulatory T cells. Current methods to eliminate regulatory T cells are to deplete these cells using antibodies, such as anti-CD25, anti-GITR. However, conventional T cells can change into regulatory T cells, and as currently no specific markers for regulatory T cells have been identified, antibody depletion might also deplete activated cytotoxic T cells. We found that when IL10 is neutralised at the time of vaccination, cytotoxic cells are not inhibited by regulatory cells.[64-66] Recently, this concept has been tested in a mouse chronic viral

infection model (HCMV), where immunisation plus neutralising IL10 can clear HCMV infection. This may provide a method for the development of therapeutic vaccine against chronic HPV infection and cervical cancer.

3. Increasing tumour cells' sensitivity to effector T cells

Clinical trial results often show successful generation of effector T cells that kill tumour cells in vitro but fail to demonstrate efficacy in vivo, even when effector T cells travel to the tumour site. Although increasing effector T cell trafficking to a tumour site is a focus of therapeutic vaccination, it has been well demonstrated that tumour micro-environment is suppressive to the effector T cells.[67-68] Tumour micro-environment contains suppressive cells including regulatory T cells, suppressive macrophages and high levels of IL10 and TGF beta. Recent results have demonstrated that local administration of pro-inflammatory agents such as TLR agonist (like imiquimod) will boost tumour rejection, although its effect could be at boosting effector T cell function at effector stage.[69] At the same time, sensitivity of tumour cells to effector T cells increases, which may be another mechanism.

Suppressive molecules on tumour cells, PD-1/PD-L1, belong to newly identified B7-CD28 family members which regulate the balance between the stimulatory and inhibitory signals for immuno-regulation.[70-72] PD-L1 expression on peripheral tissues prevents autoimmunity.[73] Tumour cells can use PD-1/PD-L1 pathway to facilitate immune evasion. PD-L1 expression on tumour cells is correlated with poor clinical prognosis of many types of cancers and has been found in many tumour tissues including squamous cell carcinoma;[74] all 18 squamous cell carcinoma tumour samples tested express PD-L1. Tumour derived PD-L1 can promote tumour specific T cells apoptosis, through an unidentified receptor on effector T cells, thus resistant to the killing by effector T cells. More inhibitory molecules expressed on tumour cells have been identified and studies on how to overcome the suppressive functions by these molecules will provide better outcomes for therapeutic vaccines.

Interestingly, it was demonstrated that IFNg promotes the expression of PD-L1 on tumour cells.[75] IFNg is also a critical component for tumour killing. Therefore, IFNg may play a dual role for the rejection of established tumour tissues. IFNg can enhance MHC class I restricted antigen presentation by tumour cells and increase T cell effector function. However, at the same time, it has been demonstrated that IFNg promotes the generation of Foxp3+ regulatory T cells, prevents inflammatory cells trafficking and promotes Th1 cell apoptosis in a tumour model.[76-78] More recently, we have shown that IFNg signalling promotes the secretion of IL10 by VLPs induced regulatory T cells and prevents the rejection of tumour antigen expressing skin graft in our tumour model (unpublished data). More work is needed to find out how to reduce the suppressive signals at the same time as trying to amplify tumour killing components like IFNg.

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WHERE WE HAVE TRAVELLED IN CERVICAL CANCER PROTECTION

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Abstract

Cervical cancer was described in the time of Hippocrates, and it was commented that it had a grim prognosis. Over the centuries, various theories regarding aetiology and also treatments were proposed – in vain in the majority of cases. More and more aggressive treatments were advocated to treat those unfortunate women who were diagnosed with cervical cancer. It is only now, in the 21st century that a pre-malignant phase has been identified and means for investigation have been perfected.

In 1925, Hinselman developed the colposcope, a binocular magnifying instrument, and described vascular patterns associated with malignancy and pre-malignant conditions of the cervix.[1] Papanicolaou and Traut described the cytology changes which have led to the Pap test as we now know it.[2]

These two pioneered the work that has taken us to the point where we can now prevent cervical cancer by detecting and treating precancerous changes. By the 1960s screening by the use of exfoliative cytology and then investigation by colposcopy to identify the lesion was well recognised and accepted. Colposcopy units were established in most public hospitals in Australia. The main problem was that screening was opportunistic only and those women at most risk of developing the disease missed out.

Cytological classifications

Papanicolaou devised a class system, which was meant to express the degree of suspicion of the presence of cancer. Over time, laboratories used descriptive terms, borrowed from histological classifications of pre-invasive squamous lesions. This led to changes in the classifications over the decades, to better reflect the expected or known natural history of the abnormal smear.

1. Pap Class I-V[3]

This initial classification had no bearing on either the ultimate histology or the natural history of the disease process.

2. Dysplasia/carcinoma-in-situ[4]

This incorporated the concept of dysplasia (abnormal development or growth). It also led to an international agreement on histological terminology.[5] It also presented anomalies. The treatment algorithm for "severe dysplasia" was cone biopsy. However, if the pathology report was "carcinoma-in-situ" then hysterectomy was called for.

3. Cervical Intraepithelial Neoplasia (CIN)[6]

In the 1960s Ralph Richart challenged the duality of Carcinoma – in-situ and dysplasia. He intimated there was an inexorable and orderly progression from CIN I through CIN II to CIN III, implying that there had been a failure of the screening process if CIN III was detected.

4. Australian modification of Bethesda system[7]

Kurman et al proposed the Bethesda System in the mid-1990s, which was not widely accepted in Australian laboratories.

This final stage which has come about as we appreciate the role of human papillomavirus (HPV) in the genesis of cervical abnormalities. Low grade epithelial abnormalities are the product of an active and productive HPV infection; the majority will resolve without the need for any intervention. It is only the long-term persistence of HPV which is potentially serious. High grade epithelial abnormalities do have a true malignant potential, although not all will progress to malignancy if not treated.[8]

Organised screening

In the late 1970s to early 80s the world began to appreciate the value of organised screening.

Finland was out early, screening woman every five years, and reported massive decreases in the incidence of invasive cervical cancer.[9] In Australia, pilot demonstration programs were set up under the auspices of the Federal Government, in the mid 1980s, after it was appreciated that only 30% of women were regularly screened.[10]

After an initial meeting convened by Cancer Council Australia, then the Australian Cancer Society, a national policy was developed in 1991 and consensus guidelines were established, Screening for the Prevention and Management of Cervical Cancer.[11] The policy stated: "Routine screening with Pap smears should be carried out every two years for women who have no symptoms or history suggestive of cervical pathology. All women who have ever been sexually active should commence having Pap smears between the ages of 18 to 20 years, or one to two years after first sexual intercourse, whichever is the later. In some cases, it may be

appropriate to start screening before 18 years of age. Pap smears may cease at the age of 70 years for women who have had two normal smears within the last five years. Women over the age of 70 years who have never had a Pap smear, or request a Pap smear, should be screened."

Governance of the screening process

Over the next decade, several important committees were established to oversee the screening process. These were under the auspices of the Commonwealth Department of Human Services and Health and various publications resulted.

Cervical cancer screening in Australia: options for change 1990[12]

The main recommendations from this group, chaired by Heather Mitchell, were that there should be a nationally organised screening program at two yearly intervals along with a backup register.

Robert Rome chaired the committee which produced *Making the Pap smear better*[13] in 1993. This addressed issues of quality assurance in:

- smear taking
- cytology reporting
- laboratory QA
- notification of results and follow-up
- recommendations for cytology registries, including medico-legal aspects.

Edith Wiseman's committee produced *Guidelines for the management of screen-detected abnormalities,*[14] which was endorsed in 1994. Again, these guidelines were a consensus, not evidence-based.

There were several groups looking at quality assurance aspects.

- 1993 – National Pathology Accreditation Advisory Council (NPAAC) established guidelines for reporting cytology.
- 1994 – Royal Australian College of Obstetricians and Gynaecologists established a colposcopy project.
- In 1997 NPAAC revised its guidelines.

Indigenous people were not forgotten in this flurry of activity. *Early detection and management of breast and cervical cancer in Aboriginal and Torres Strait Islander Women: supporting the role of the General Practitioner*[15] was published in October 2002, commissioned by the Royal Australian College of General Practice (RACGP) and carried out through James Cook University. The *Aboriginal and Torres Strait Islander Women's Project*[16] evaluation report was published in January 2003, again under the auspices of the RACGP.

How is success measured?

The aim of the program was to decrease the incidence of invasive cervical cancer by detecting and treating precancerous lesions of the cervix. The state run Cervical Cytology Registers offered the best means of assessment of the success of the program.

Prior to the organised program, participation rates for screening were below 50%.[17]

The first report of the Australian Institute of Health and Welfare on *Breast and Cervical Cancer Screening in Australia 1996-97*[18] (1998) reported a national participation rate of 62.4%, whilst the next publication, 1997-98, reported an increase to 63.9%. This was an increase of over 12% on the pre-screening rates. Mortality rates in the target group fell from 4.9/100,000 women in 1985 to 2.8/100,000 in 1997. Much of this improvement has been ascribed since 1989 to the screening program. Most of the women who now die from cervical cancer, have not had a Pap smear in the recommended screening interval.

Quo Vadis?

The original *Guidelines for the Management of Screen Detected Abnormalities*[19] had recommended a review after five years. In 2000, they were rescinded and a new committee established. This was chaired by Ian Hammond, and the remit was to establish evidence-based guidelines. The new guidelines – *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen-detected abnormalities* – were accepted in 2005.[8] The main features have now been adopted by the medical profession and are being put into practice. They are:

- Changes in terminology, to reflect current knowledge of the natural history of cervical lesions. This has led to the acceptance of the Australian Modified Bethesda System 2004, as the gold standard for reporting.
- Acknowledgement of the pivotal role HPV infection plays in the genesis of cervical abnormalities and the interpretation of the significance of low grade epithelial abnormalities as a mark of HPV infection, not a precancerous lesion per se.

These guidelines, in time, will also be subject to evaluation.

We have come a long way, but we should not forget that there are still women who die from cervical cancer – usually because they have not been screened. The future lies in reaching them, and the challenge is how.

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ARTICLES

DEVELOPMENTS IN CANCER CARE: A PERSONAL RETROSPECTIVE

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The Tom Reeve oration was presented at the Clinical Oncological Society of Australia's Annual Scientific Meeting in November 2007.

I am privileged to deliver the 3rd Tom Reeve Oration, honouring the most important figure in the evolution of cancer care in Australia over the past 15 years. I acknowledge the immense wisdom, experience and commitment that he brought to the role of Executive Officer of the Australian Cancer Network and to the management committee of the National Cancer Control Initiative. I am encouraged to note that Tom Reeve was already 69 when he took on these roles, an age to which I still aspire. In his earlier life he had a distinguished academic surgical career and had been President of the Royal Australasian College of Surgeons.

Martin Tattersall

I propose to reflect on my medical training and to identify factors contributing to my career choices and path. I will identify individuals and events that influenced my experiences in cancer care and research. My medical career has involved periods in England, Canada, the US and latterly Australia. The move to Australia in 1977 was consequent on a ghastly mistake, in that the IRA bomb which killed Gordon Hamilton Fairley, a distinguished haematologist/oncologist at the Marsden and St Bartholomews' Hospital in London, was intended to kill a British politician who lived next door. In 1975, Gordon had been asked to consider moving to Sydney to establish a cancer research unit funded by the Ludwig Institute for Cancer Research and the day after his return from visiting Sydney he was killed. I was 'the 2nd cab off the rank', and in 1976, I was invited to consider moving to Sydney.

I have been fortunate to work with many extremely able individuals in the UK, US and Australia, who have been influential in global developments in cancer care over the past 40 years. My experience leads me to propose some 'take home messages' which I hope may be of interest and guidance to young people commencing a career in cancer care and cancer research.

Why medicine?

Both my mother and father were doctors, as was my grandfather and two of my father's brothers. I went with the flow and was not attracted to other paths. I studied natural sciences at Cambridge and subsequently I entered medical school at University College Hospital (UCH), London, graduating in 1965.

Exposure to cancer patients was not a memorable aspect of my undergraduate clinical education. There was no recognisable cancer syllabus, though cancer was a significant component of the pathology lectures and practicals. There was a radiotherapy department at UCH which was closely aligned with surgery. I was allocated to a medical 'firm' for six months run by two physicians, one with an interest in gastroenterology and the second was recently appointed Professor of Clinical Haematology.

The Professor of Medicine at UCH, Max Rosenheim, was an impressive clinician and educator whose teaching rounds and outpatient clinics were extremely popular with students. I learned much medicine and clinical skills from observing senior consultants in outpatients. Medical grand rounds on Saturday mornings was always well attended. Max Rosenheim, a bachelor, whose life was medicine and fishing, was an influential role model. I remember him recommending a research topic stating "let a textbook fall open, read the first sentence that catches your attention and then prove it is wrong!" He became President of the Royal College of Physicians. When he was elevated to the peerage, several medical students sent him a cable stating simply "Good Lord!"

Medical student elective

I spent my three month medical student elective in West Africa at the MRC Research Station in the Gambia. This was a fantastic experience exposing me to clinical and epidemiological research and caring for people with malaria, hookworm, hepatitis and measles. My emerging interest in haematology got off to a bad start when I diagnosed malaria in my medical student colleague after examining a thick film of his blood. I was embarrassed to be told by one of the technicians that my 'malaria' parasite was a platelet.

After graduation, I spent six months as a house physician at UCH, which was hard work, living in the doctors' residence most of the time because of being on call two nights in three. The second six months I was a house surgeon and during that time I was surprised how much I enjoyed surgery. Hence for my third job, I embarked on a surgical career, working at the Birmingham Accident Hospital. This involved care of major trauma patients and patients with burns. At the end of these six months, I decided I would not continue surgical training and felt I needed to travel. I also came to recognise the dangers of 'specialised' hospitals. One of my 'trauma' patients very nearly died of a ruptured appendix, because we did not think of it. My parents were horrified by my 'dropping out' and my father remarked to my mother: "He has the world at his feet and he's throwing it away". I have sometimes felt like saying the same about our children!

Travel: 1967-1970

I left the UK with a pack on my back and returned two and a half years later, having travelled overland through the Middle East, Afghanistan, India and then to Thailand, Cambodia, Vietnam (during the TET offensive), Formosa, Japan and then to Canada. I ran out of money in Canada and worked as a doctor in Vancouver and the Yukon. With finances restored I spent six months travelling in Latin America and then to the UK. This 'dropping out' experience was enormously helpful in sorting out my ideas – obtain the MRCP and then train in clinical haematology. I got a job in Birmingham and passed the MRCP thanks to being away from my friends in London and a good training experience. Then I had to get on a haematology training program. Luck was on my side, since at the interview for a registrar job at the Postgraduate Medical School, the bulk of the discussion was about my CV entry "Physician" to the Yukon!

Why cancer? Specialist and research training 1970-75

In the early 70s, the Royal Postgraduate Medical School (RPGMS) at Hammersmith Hospital was a most stimulating environment, with a large group of leading research clinicians and a talented group of younger staff drawn from all over the Commonwealth. Included among them were many Australians, including Val Beral, subsequently at Oxford and responsible for the million women studies. John Dacie FRS was head of haematology and an impressive intellect. A component of the haematology unit was the MRC Leukaemia Research Unit, headed by David Galton, with younger staff building their careers including John Goldman and Danny Catovsky. I spent much time resuscitating febrile neutropenic patients and the concept of empirical antibiotic therapy evolved during my time as registrar. John Dacie recognised my interest was clinical rather than laboratory-based and advised me to join the newly emerging field of medical oncology. This advice influenced my choice of research topic for my higher degree. My wife was training at the RPGMS, sharing a house with Val Beral and several other Australians. After we married in 1971, the notion that we would move to Australia was not on our radar.

I undertook research training in biochemical pharmacology with Victor Hoffbrand at RPGMS and Ken Harrap at the Institute of Cancer Research. I shared a lab with Australians Dick Fox and Ray Lowenthal. After completing my MD, we planned a year in Boston, being offered a job by Sidney Farber supported by an MRC Travelling Fellowship. Just before leaving for Boston, I was appointed as a Consultant Physician at Charing Cross Hospital and I negotiated a year's leave of absence.

When we arrived in Boston in 1973, Sidney Farber had died and Tom Frei was the boss. George Canellos was head of medical oncology and among the oncology fellows were Herb Abelson (of Abelson leukaemia virus fame), Fred Li (of Li Fraumeni fame) and Craig Henderson, Bob Mayer and Stephen Sallan, all of whom have been major figures in oncology over the past 30 years. Tom Frei was a dynamo, keen to support young ideas and people. This was the era of high dose methotrexate (MTX)/folinic acid in osteogenic sarcoma. He gave me a lab and support to explore the clinical pharmacology of high dose MTX, and to investigate thymidine as a modulator of MTX activity.

The work environment was stimulating, and it seemed that Nixon was going to win the war on cancer. We worked hard, but also found time to explore New England. We left Boston with happy memories, an increasing CV and many friends. We negotiated a three month delay of starting work at Charing Cross Hospital and this enabled us to backpack around Latin America, including presenting an invited plenary paper at the World Congress of Paediatrics in Buenos Aires. During this meeting, my wife Sue received a telegram offering her a job at the RPGMS and we had to reply in Spanish! It wasn't until our arrival back in England that we learned our telegram had been understood.

Charing Cross Hospital 1975-76

I was one of the first medical oncologists appointed in the National Health Service. I joined Ken Bagshawe's department, which had pioneered the systematic approach to the medical management of trophoblastic tumours and established the mole registry and follow-up protocols in the UK (for which he was elected FRS). With his support I expanded the interest of the department to a broader range of tumours and established a small pharmacology research lab. I developed an interest in liposome encapsulation of anti-cancer drugs and investigated the effect of liposome composition on distribution/selective uptake. In early

1976, I was approached about moving to Sydney and after three visits to 'case the joint' and after speaking to my ex bosses etc (who without exception said I would be crazy not to go), I accepted a five year contract in Sydney. My wife and I left London in late December with our six month old son.

Sydney 1977 – Recruitment and training of the new generation of medical oncologists

One of my first and smartest moves was to recruit Dick Fox to join me in establishing the unit in Sydney. Not only was he an ex-Royal Prince Alfred/University of Sydney graduate, but was then based in Melbourne. Thus I was able to bring him back to his alma mater, where he was much admired for his clinical and research achievements. He had overlapping biochemical pharmacology research interests with me and we established two labs which explored the mode of action and basis of toxicity of nucleic acid antimetabolites and antifolates. I was able to recruit Rob Sutherland to set up a research lab investigating aspects of endocrine response and together we built a substantial clinical and laboratory research program which attracted bright young people to join us.

Among the first flush of individuals to join us in the clinic and/or the lab were some who were to make their names in the field of cancer care and research, namely Alan Coates, John Simes, Rick Kefford, Michael Friedlander, Roger Reddell, Graham Mann and later Michael Boyer, Geoff Lindeman, Paul Harnett, Nicholas Wilcken and Martin Stockler. We were fortunate to attract young clinical cancer research people from the UK to spend a year or more, and notable among these were Stan Kaye (now Professor of Medicine at the Royal Marsden) and David Hedley (now at Princess Margaret Hospital, Toronto). The only other medical oncologist in Sydney in the late 1970s was John Levi, recently returned from US to a new job at Royal North Shore Hospital.

During the 1980s medical oncologists who had trained with me began to create new departments and to expand pre-existing units. Rick Kefford established the thriving department at Westmead, Dick Fox returned to Melbourne as head of haematology/oncology at the Royal Melbourne Hospital and Michael Friedlander went to the Prince of Wales Hospital via a stint at North Shore. John Simes established the National Health and Medical Research Council clinical trials centre and recruited Martin Stockler to oversee the cancer trials.

Fostering the development of clinical trials, medical oncology and multidisciplinary training

The opportunity to establish clinical cancer research protocols and organisations was wide open in the late 1970s. I was involved in the creation of the Ludwig Breast Cancer Study Group (later the International Breast Cancer Study Group) and the ANZ Breast Cancer Trials Group was born in my office. With the support of the Clinical Oncological Society of Australia (COSA), at the time a head and neck surgeon/radiation oncologist society, a number of clinical trials groups evolved, including the ANZ Breast Cancer Trials Group and the COSA Gynaecological Cancer Group. COSA also created and funded a clinical trials centre at the Peter MacCallum Cancer Centre and this later stimulated the development of the National Health and Medical Research Council clinical trial centre. An umbrella group of medical oncologists was formed within COSA, the Australian Society of Medical Oncologists (ASMO) and a specialist advisory committee in medical oncology was created to advise/oversee the training of medical oncologists. Inevitably, I played some role in these developments.

Alan Langlands established the Department of Radiation Oncology at Westmead in the early 1980s and we developed a close and respectful relationship. Both of us were keen to foster the development of an integrated training program for medical and radiation oncologists, but ultimately this was not to be. However early on, it was a requirement of medical oncology trainees that they spent six months gaining experience in malignant haematology and six months in radiation oncology. The establishment of a medical oncology clinic at RPAH and the increasing use of chemotherapy led to the need to develop and support training of nurses in chemotherapy administration and supportive care. Several of the initial recruits to the chemotherapy staff at RPAH have played a crucial role in the development of chemotherapy nurse specialists, notably Keith Cox OAM, and Letitia Lancaster.

Medical student education about cancer

When I arrived in Sydney, the university gave me the title of Professor. The university initially proposed that my title should be Professor of Cancer Studies or Cancer Research, but I preferred and they agreed Cancer Medicine. I viewed my university role to include medical student education about cancer, but this seemed not to be part of the faculty's expectations. With Alan Langlands' support (soon to be given the title Professor of Radiation Oncology) we attempted to influence undergraduate medical student education about cancer and ensure that medical students were exposed to a cancer curriculum.

We published a series of articles in the 1980s concerning medical student education about cancer, including a proposed curriculum. After this was published, Michael Baum, a leading breast cancer surgical academic in the UK told me that he had implemented the Sydney curriculum in London University. I had to tell him that we had been unable to implement it in Sydney. Subsequently, with the support of the Australian Cancer Society (ACS) and COSA, we undertook surveys of medical student education at all Australian medical schools and published the results internationally. In due course this work set the scene for Michael Barton and others, with the support of the ACS, to develop the *Ideal oncology curriculum for medical students*, a landmark publication, now endorsed by the International Union against Cancer (UICC) and used in many parts of the world.

Life after the Ludwig Institute for Cancer Research (LICR) 1988-2008

In 1987, after my contract for a third five-year term as Director of the Sydney Cancer Therapy Branch of the LICR had been renewed, I was informed the branch was to be closed (as were other branches in Cambridge, Toronto and at the Royal Marsden). My wife and I decided that our three sons were 'aussified' and that we would stay in Sydney. The university agreed to continue funding a few salaries and RPAH assumed funding of some clinical staff including Alan Coates.

Over the next few years, the 'wet' laboratory research program reduced to a small biochemical pharmacology group and the magnetic resonance spectroscopy group lead by Carolyn Mountford. She moved her group to North Shore after a while and after I experienced a nasty life threatening skiing injury, I reappraised my priorities and decided to cease most administration and 'wet' laboratory research and to focus on clinical research, teaching and patient care.

My clinical research evolved to focus on investigating the cancer consultation and aspects of informed consent. I was fortunate to have a most creative interaction with Stewart Dunn and with Phyllis Butow, one of his research fellows. After Stewart moved to North Shore, Phyllis and I established the Medical Psychology Research Unit in the Department of Medicine and when she was appointed to a Chair in Psychology, the unit spanned the two faculties. This research group has been highly productive and we have been fortunate to recruit extremely able young people to work with us. These include medical oncologists (Natasha Leighl, Peter Ellis), psychologists (Melina Gattellari, Rebecca Hagerty, Richard Brown), nurses (Heather Shepherd, Rhonda Devine) and palliative care physician (Joey Clayton). We have collaborated with cancer clinicians throughout Australia and interacted extensively with the emerging cancer consumer groups.

Interest in the cancer patient perspective arose in the early 1980s and Alan Coates published a series of widely quoted papers entitled *On the receiving end*. The relevance of monitoring breast cancer patients' quality of life during cancer chemotherapy evolved and a paper in the *New England Journal of Medicine* by the ANZ Breast Cancer Trials Group documented the relevance of these measures in clinical cancer research. My personal experience of being a patient after my skiing injury stimulated my interest in estimating and talking about prognosis. This research has been productive.

It is hard now to imagine clinical research without major consultation with consumer groups, yet this was the norm before the late 1980s. Our research of the cancer consultation and means of assisting patients to participate in their care has involved developing and evaluating question prompt lists for patients and carers, the use of audio-recordings of the cancer consultation and communication skills training for oncologists. It is gratifying to see the increasing adoption of these consultation aids internationally.

Take home messages

As I approach the age at which Tom Reeve commenced his leadership of interdisciplinary cancer care in Australia, I have taken this opportunity to reflect on factors impacting on my cancer career and its course. My career started before medical oncology was conceived. I believe its developments have been impacted by my contemporaries, some of whom I have had the privilege to work with and perhaps influence. I believe the main factors guiding my career have been chance, the role models of my early bosses and the opportunity to train with and recruit into cancer research and care extremely able people. I hope my beliefs that cancer medicine is about people with cancer and not only the molecular biology of cancer cells, will impact young cancer clinicians commencing their careers.

AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

Centre for Health Research and Psycho-oncology (CHeRP), New South Wales

The Cancer Council NSW Telephone Support Group Evaluation

In an effort to fill gaps in the provision of support to those affected by cancer, the Cancer Council NSW established telephone support groups during 2000. The groups operate in a similar way to a face-to-face group with three to seven members and two professional facilitators. They run for approximately one hour each fortnight or month. The current format is an open group structure, whereby members can join the group at any time and the number of group sessions is unlimited.

This study aims to evaluate the service in terms of its acceptability to members and facilitators, impact on members' psychosocial wellbeing and cost-effectiveness. Participants are former, current and new members of the telephone support groups and the group facilitators. Telephone support group members have completed a computer assisted telephone interview, assessing acceptability of the groups in terms of access, structure, content, leadership and perceived benefits. New members also complete a pen and paper survey assessing their psychosocial wellbeing (health related quality of life, anxiety, depression, self-efficacy, perceived social support) prior to their first telephone support group session and 12 weeks later. Group facilitators have completed a pen and paper survey assessing their work-related burnout and a face to face semi-structured interview about the group's structure, mode of delivery and content, as well as training and support needs. The results will help to guide the future delivery of this innovative service to ensure it meets the needs of both members and facilitators.

Australian pension funds and tobacco investments

Until now there has been no systematic examination of issues surrounding pension funds and their tobacco shareholdings. Two studies designed to document the tobacco investment policies and practices of pension funds and to assess community and fund member attitudes to pension fund shareholdings in the tobacco industry were recently carried out by researchers at CHeRP.

Chief executives of Australian pension funds were mailed questionnaires. Of 241 eligible funds, 107 (44.4%) returned questionnaires, representing about 61% of total Australian primary superannuation accounts. Twelve per cent indicated that they did not currently hold tobacco investments, 30% held tobacco shares and 58% did not know or failed to answer. Overall, 6% of respondents said that they held no tobacco investments and would not consider future investments; 2% had formal policies precluding tobacco investments. Funds with 10,000 or more members were found to be more likely to report tobacco investments, with external fund manager advice the most important factor influencing the funds' position.

In the second study, a sub-sample of consenting subjects from 12,000 households randomly selected from the NSW electronic White Pages completed phone interviews. Over three-quarters (77.4%) of all respondents (n=1158) disagreed that pension fund investments in tobacco were ethical. Approximately two-thirds (63.6%) of fund members agreed that their funds should not make tobacco investments.

Published recently in the journal *Health Promotion International*, the results of these studies have received widespread interest from the news media, including investment media. The results highlight the need for strong advocacy efforts by cancer organisations to eliminate tobacco investments by superannuation funds in line with community opinion.

Behavioural Research and Evaluation Unit (BREU), South Australia

In addition to other ongoing evaluations and research run by the BREU in South Australia, results were recently reported for several key studies.

Prostate Cancer Call-in

The prostate cancer call-in was held on 13 September 2007 (6pm to 9pm). There were 166 callers and 68 of these participated in a one-month follow-up. Participants most frequently reported they called the service to obtain general information or because they showed symptoms. The majority reported their information needs were met, they found it beneficial talking to someone and were satisfied with the service. Few participants had used The Cancer Council Helpline prior to the prostate cancer call-in. However, most reported they would use the helpline again and they would recommend it to someone else. Overall, the results of the prostate cancer call-in were informative and generally positive.

Cancer Connect evaluation

The Cancer Connect program offers peer-support by telephone to people affected by cancer. Sixty-four Cancer Connect volunteers were surveyed about their experience. While over half of the participants were satisfied with the number of matches received, many reported they would prefer more matches. Participants considered the type of treatment, cancer site and type of surgery as the most important factors in matches and reported they most commonly talked about personal experiences/feelings and treatment options with recipients. Overall, most participants reported they were satisfied with the experience of being a volunteer and with the level of support they had received from the Cancer Council.

Cancer Information Centre

The Cancer Council South Australia hosts a Cancer Information Centre at the Royal Adelaide Hospital in SA. This centre provides cancer patients, their families and carers information and support at key times throughout the cancer journey. An evaluation of this service revealed that the information centre has been well received by both staff and patients, however requires changes to work optimally. Results along with anecdotal feedback suggest that more promotion is needed to increase staff, patient and carer awareness of the centre and the services it provides, and changes need to be made to the physical environment of the centre to differentiate it from other areas of the hospital and make it more welcoming to users.

Tobacco Use Prevention and Cessation Program for Oral Health Professionals

Quit SA in conjunction with the University of Adelaide and TAFE SA delivered a multidisciplinary, educational course titled *A Tobacco Use Prevention and Cessation Program for Oral Health Professionals.* The sample consisted of 28 students in their 2nd year of a Bachelor of Oral Health degree at the University of Adelaide and 15 TAFE SA Advanced Diploma of Oral Health students. The program consisted of eight sessions ranging in duration from $1^1/_2$ hours to $3^1/_2$ hours. Preliminary results detected significant improvements in participants' knowledge, attitudes and experience between pre and post measures. Specifically, students took responsibility for addressing tobacco use with dental patients. It is suggested that by offering a program specifically tailored to educating health professionals about the risks of tobacco use, and the skills necessary to assist in offering cessation services, dental health professionals may be more able to support patients who use tobacco.

Cancer Prevention Research Centre (CPRC), Queensland

Logan Healthy Living Program: a telephone counselling intervention for physical activity and dietary behaviour change

Logan Healthy Living Program is one of the first large-scale Australian studies to evaluate a telephone counselling intervention for physical activity and diet. It targeted patients with type II diabetes and hypertension from a disadvantaged community.

Using a cluster-randomised design, 10 general practices were randomised to a telephone counselling intervention or usual care. Electronic medical records were used to identify condition-eligible patients. Telephone counselling participants received a workbook, pedometer and 18 tapered calls over 12 months. Data were collected via telephone at baseline, four and 12 months, using validated measures for physical activity (total min/wk; Active Australia) and diet (total fat, saturated fat, serves of vegetables/ fruit, fibre; ACCV Food Frequency Questionnaire).

Four hundred and thirty four patients consented to participate. Analysis of 12 month data (n = 341) revealed that 91% of telephone counselling participants received $\geq$ 10 of 18 calls. Significant intervention effects (telephone counselling v usual care) at 12 months were found for percentage energy from total fat, saturated fat, serves of vegetables and fruit. At 12 months, telephone counselling and usual care participants both increased total physical activity similarly.

Physical Activity in Localities and Community Environments (PLACE) follow-up

This study evaluated a broad-reach intervention modality (structured, behaviourally-based telephone counselling), targeted multiple health behaviour change in a socially-disadvantaged chronic illness sample, collecting detailed implementation data. As such, it makes a unique contribution to the physical activity and dietary intervention literature. Telephone counselling is a promising approach to promoting physical activity and dietary change, with the potential for wider spread application.

CPRC recently undertook a follow-up survey of participants from the PLACE study. The PLACE project, conducted in Adelaide during 2003-04, collected spatially referenced area-level and individual-level data. Supported with National Health and Medical Research Council funding, the study aims to identify relationships between local community environments and adults' physical activity habits. Results of the first two surveys continue to be disseminated through a variety of policy and academic forums.

Eligible responses to the follow-up survey were received from around 1100 (50%) participants in the PLACE Survey II (n = 2194). Respondents were residents of 32 urban neighbourhoods, selected to represent high and low walkable and high and low socio-economic status areas. Categorisation was based on geographic information system data and Australian Bureau of Statistics 2001 Census data. The 12-page follow up questionnaire was mailed in September 2007. Questions were on changes in physical activity and neighbourhood environment, active transport, sedentary and sun protective behaviours, as well as perceived health.

Preliminary descriptive analysis indicates that around half (47%) of respondents thought at least one aspect of their neighbourhood environment had improved since

Survey I in 2003. The most reported improvements were to neighbourhood attractiveness and access to shops and services. A quarter of participants said that their environment had become worse during the period, with decreased safety from crime and loss of neighbourhood attractiveness. Slightly fewer than half the respondents (50% of women and 42% of men) had gained at least one kilogram. Those under 50 years at Survey I (2003) were more likely to have put on weight than older participants.

Centre for Behavioural Research in Cancer (CBRC), Victoria

Association between commercial television exposure and fast food consumption among adults

This study aimed to examine the association between television advertising exposure and adult fast food consumption using a cross-sectional telephone survey. Questions regarding frequency of fast food consumption at different meal times and average daily hours spent watching commercial television were asked of 1495 Victorian adults (41% response rate).

Twenty-three per cent of respondents usually ate fast food for dinner at least once a week, while 17% consumed fast food for lunch on a weekly basis. The majority of respondents reported never eating fast food for breakfast (73%) or snacks (65%). Forty-one per cent of respondents estimated spending one hour/day watching commercial television (low viewers); 29% watched two hours/day (moderate viewers); 30% watched ≥ three hours/day (high viewers). After adjusting for demographic variables, high viewers were more likely to eat fast food at least once weekly for dinner compared to low viewers. Both moderate viewers and high viewers were more likely to eat fast food at least once weekly for snacks compared to low viewers. Commercial television viewing was not significantly related to fast food consumption at breakfast or lunch.

Our results suggest cumulative exposure to television food advertising is linked to adult fast food consumption. Additional research is needed to gain a greater understanding of the mechanisms driving this association.

Scully M, Dixon H, Wakefield M. *Public Health Nutrition.* (in press, accepted February 2008).

Can population-based tobacco control policies change smoking behaviors of adolescents from all socio-economic groups? Findings from Australia: 1987-2005

This study aimed to examine whether socio-economic status (SES) was associated with changes in smoking prevalence among Australian adolescents during three phases of tobacco-control activity between 1987 and 2005. Triennial cross-sectional national studies of representative random samples of secondary students aged 12–17 years have been conducted since 1987. Numbers range from 19,203 in 1987 to 29,853 in 1996. Self-report anonymous surveys assessed cigarette use in the past month, week (current), and on at least three of the previous seven days (committed). Students' residential postcode was collected and the Index of Relative Socio-Economic Disadvantage associated with each postcode determined socio-economic status quartiles.

Between 1987 and 2005, smoking prevalence decreased in all socio-economic status groups. Tobacco-control activity level was associated with changes in smoking prevalence and whether changes were consistent across socio-economic status groups. In a period of low tobacco-control funding (1992–1996) and activity, smoking prevalence increased among 12 to 15 year-olds, the increase being greatest among low socio-economic status students. In a period of high tobacco-control activity (1997–2005) smoking decreased and reductions were generally consistent across socio-economic status groups. It was concluded that well-funded, population-based tobacco control programs can be effective in reducing smoking among students from all socio-economic status groups.

White VM, Hayman J, Hill DJ. *Cancer Causes and Control* (in press, accepted Jan 2008).

Influence of narrative content and context of anti-smoking public health messages

Mass media has been used for public health campaigns with varying degrees of success. Based on narrative transportation theory, the aim of this PhD is to investigate the extent to which narrative versus non-narrative anti-smoking messages might influence smoking-related attitudes and behaviours, and encourage interpersonal discussion. A quasi-experimental study rating the narrativity of existing anti-smoking messages and two forced-exposure experiments will be conducted. A series of field studies will also be conducted, which will examine smokers' short-term responses to narrative and non-narrative television ads viewed within their home environment during the actual ad-launch weeks.

Centre for Behavioural Research in Cancer Control (CBRCC), Western Australia

Reducing overweight and obesity in mothers with young children

Among women, the childbearing years are associated with increases in weight. Furthermore, weight retention following childbirth has been identified as being a significant predictor of long-term obesity. The aim of this study was to conduct theory-based formative research looking at the barriers and facilitators to physical activity, as well as assessing the feasibility of implementing a nutrition and physical activity program with mothers attending playgroups (social and support groups for first-time mothers and their young children).

Eight focus groups were conducted with mothers at playgroups. The results highlighted the mothers' low priority of adopting healthy physical activity and nutrition behaviours in the face of the difficulties surrounding childbearing demands, fatigue, lack of time and childcare. Guided by these findings, a community-based

intervention focusing on improving the nutrition and physical activity behaviours of mothers with young children is currently being developed and will be piloted over the next six-months.

Point-of-sale tobacco displays

In WA, all forms of tobacco product advertising are banned and point-of-sale product displays restricted to one square metre, accompanied by prominent health warning signs. However, there is an argument that any display of tobacco products remains a form of advertising, so there are calls for tobacco products to be removed from the public eye altogether and be restricted to under the counter storage.

CBRCC is currently undertaking exit interviews with smokers who have just purchased cigarettes at retail outlets to assess the contribution that the point-of-sale displays make to such purchases. Preliminary results suggest that removing tobacco products from eye sight would reduce impulse purchases of tobacco products – a particularly important consideration for early smokers.

Smoking cessation pharmaceuticals

CBRCC is currently halfway through a two-year longitudinal investigation of the effectiveness of smoking cessation pharmaceuticals, such as nicotine replacement therapy and Zyban, in real-life settings. A sample of 1200 smokers was interviewed at the beginning of 2007 and follow-up interviews have been conducted every three months and will continue until the beginning of 2009. Incidental quit attempts with and without the benefit of pharmaceutical smoking cessation aids are being tracked.

Preliminary results were presented at the Behavioural Research in Cancer Control conference in Melbourne in April this year. They suggest that pharmaceutical aids are far less effective in real-life settings compared to randomised controlled trials, because many quitters stop using them after about two to three weeks as they think they have successfully quit and no longer need them. However, manufacturers' recommended period of use is usually 12 weeks and many seemingly successful quitters relapse before this time in the period after they stopped using the pharmaceutical aids. The implication is that more quit attempts using pharmaceutical aids may be successful if smokers can be persuaded to use the aids for the complete 12 week regime – analogous to finishing an entire course of antibiotics even if 'cured'.

Viertel Centre for Research in Cancer Control (VCRCC), Queensland (Psycho-Oncology Research Unit)

Colorectal cancer and quality of life study

Colorectal (bowel) cancer is the most common invasive cancer in Australia, with latest figures showing 12,977 new cases and 4,068 deaths in 2004. The risk of developing colorectal cancer increases with age, and is greatest in those over 50. As the Australian population ages, the number of people diagnosed with colorectal cancer will rise accordingly. Little is known about the long-term outcomes, needs and concerns of the 60% of patients who survive colorectal cancer.

The Colorectal Cancer and Quality of Life study is a collaboration between the Psycho-oncology Research Unit and the Epidemiology Unit of the Viertel Centre for Research in Cancer Control. The project is following 2000 people for five years after diagnosis. The study examines in detail how people fare after treatment for colorectal cancer and identifies factors that influence quality of life following diagnosis. This information will help us to understand the needs of colorectal cancer patients, so that we can advise clinicians and other health professionals of the sort of information and support patients require. Findings of this study will also help the Cancer Council Queensland to develop more effective supportive care programs to address the physical and psychosocial problems faced by people living with colorectal cancer.

We have now completed collection of data from participants who were three years post-diagnosis. Results from the study to date have been published in a number of scientific journals and presented at national conferences. Preliminary results from the Colorectal Cancer and Quality of Life study have also informed the development of a psychosocial and lifestyle intervention for colorectal cancer survivors (CanChange) that was recently presented at the Behavioural Research in Cancer Control Conference in Melbourne and will be tested this year.

Lynch BM, Youlden D, Fritschi L, Newman B, Pakenham K, Leggett B, Owen N, Aitken JF. (2008) Self-reported information on the diagnosis of colorectal cancer was reliable but not necessarily valid. *Journal of Clinical Epidemiology*,61(5),498-504.

Lynch BM, Steginga SK, Hawkes AL, Pakenham K, Dunn J. (2008) Describing and predicting psychological distress after colorectal cancer. *Cancer*, 112(6),1363-1370.

CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA: ADOLESCENT AND YOUNG ADULT CANCER FORUM

The Clinical Oncological Society of Australia (COSA) has identified the management of Adolescent and Young Adult (AYA) Cancer in Australia as a priority area for review. This paper reports on a national forum convened by COSA, ANZ Children's Haematology and Oncology Group (ANZCHOG) and CanTeen to develop a shared understanding of the issues and challenges in the treatment and care of adolescents and young adults with cancer and to agree on the key elements of appropriate models of care.

Key issues in AYA cancer

AYA cancer patients are a significant population with particular medical, psychosocial, social and information needs that necessitate age-appropriate therapy, care and support.[1,2] These distinctive needs include developmental needs, loss of independence, fertility preservation, financial and economic dependency concerns, peer support/integration, as well as the management of the return and transition to school and work. Currently AYA patients are achieving less than optimal outcomes, such as lack of improved survival rates, delayed diagnosis and poor access to clinical trials.[1,3] An improved focus on AYA cancer will be achieved through recognition of AYA cancer as a sub-speciality and a collaborative approach to combine resources and expertise.

AYA forum

COSA, ANZCHOG and CanTeen jointly convened a one-day AYA Cancer Forum in May 2007. The forum, supported by Cancer Australia, Cancer Council Australia and the Cancer Institute NSW was attended by 78 participants from a range of backgrounds with an interest in AYA cancer. It included presentations from national and international experts and consumers, panel discussions, as well as small group work and plenary discussions.

Background presentations

A series of presentations provided the context for the discussion. Ms Emma Sayers and her mother, Clare Sayers, spoke of their personal experiences as an AYA patient and carer, highlighting issues such as the loss of independence, emotional vulnerability, the need for practical support and assistance, career interruptions and return to work issues.

Dr Karen Albritton, Director, AYA Oncology at the Dana Farber Cancer Institute in the US, provided an outline of key issues in AYA cancer, many of which result from AYA cancer being treated in paediatric and medical oncology settings, while not being a specific focus of either.

Key issues highlighted by Dr Albritton included:

- lack of improvement in survival rates, which is in part, a result of delays in diagnosis;
- lack of clinical trial participation;
- the impact of service delivery on health outcomes;
- lack of understanding of the biology of AYA cancer;
- current unmet needs of AYA patients.

Three speakers provided an overview of current approaches to AYA cancer.

Dr Robin Corbett, Medical Director, South Island Child Cancer Service at the New Zealand Ministry of Health, outlined New Zealand initiatives including specific objectives and strategies in the New Zealand Cancer Control Strategy. Dr Corbett described service specifications developed through an AYA Working Party, which include having a multidisciplinary care team involving diagnostic, treatment and fertility specialists, as well as physical and psychosocial support disciplines, located in each treatment centre and linked by videoconference. The service specifications also include a cancer key worker with a case management and care co-ordination role, including co-ordination of the multidisciplinary care team meetings. Decisions about where treatment will be delivered is determined by the multidisciplinary team based on factors such as the patient's age, needs and wishes, cancer type and the patient's maturation stage (puberty, cognition, need for family support and living arrangements).

Megan Plaster, a Paediatrics/AYA Cancer Nurse Co-ordinator from the Western Australia Cancer and Palliative Care Network, provided data from an as yet incomplete audit of cancer services in Western Australia. Preliminary results highlight the broad dispersal of AYA cancer patients across the state and the resulting impact on cancer services, which are thinly spread across this group.

Dr David Thomas, Group Leader, Sarcoma Genomics and Genetics Laboratory at the Peter MacCallum Cancer Centre, described a multidisciplinary care team approach to AYA cancers established in 2004 and outlined a series of principles developed:

- Care should be provided as safely and effectively as possible, then as close to home as possible.
- All young people, regardless of cancer type, have in common unique needs which must be met.
- Cancer care is often best delivered in a multidisciplinary setting with the best possible expertise and resources, and should combine paediatric and adult expertise when necessary.

- Patterns of referral should be based on need, which will vary by cancer type.
- Research is critical.

Panel discussion

An expert panel agreed the approach to improving AYA cancer services needed to be embedded in broader cancer initiatives. Data and evidence would be needed to build a case for change in AYA cancer services, including a better understanding of current practice at the practitioner level, such as referral patterns.

The panel agreed that location of delivery of AYA cancer care should be determined in accord with principles of safe delivery of care and that services should place a greater emphasis on psychosocial care.

The panel recommended:

- Harnessing opportunities provided by telemedicine and innovative models of care, recognising the high levels of technological literacy of AYA cancer patients (eg. web, SMS).
- Developing a national process for ethics committee approval to remove what is currently a significant constraint to improved models of care for AYA cancer patients.
- Improving recognition of the distinct needs of AYA cancer patients.
- Combining and concentrating expertise focused on AYA cancer.
- Increasing ownership and recognition of AYA as a separate discipline.

Priorities and outcomes for AYA cancers

The forum identified the following priorities for AYA cancer:

- Improved collaboration, working through organisations such as Cancer Australia, Cancer Council Australia, COSA, CanTeen and others.
- Capacity building strategies such as provision of training and fellowship opportunities and the creation of dedicated senior staff positions for AYA cancer specialists.
- A clear case with supporting data and evidence to present to governments, the community, patients and clinicians for increased resourcing.
- Governance of AYA cancer should be addressed through current organisations.

Other areas identified:

- Improved focus on the distinctive psychosocial needs of AYA patients.
- Development of clear evidence-based clinical pathways.
- Bridging the artificial divide between paediatric and adult cancer services to develop a patient-focused model of care.
- Improved access to clinical trials, including centralised co-ordination and ‘tumour banking’.
- Development of a national cancer registry for AYA cancer.

The forum identified the following desired outcomes by 2012:

- Government will recognise the distinctive needs of AYA cancer and provide dedicated resources.
- A recognised training scheme for AYA cancer will be in place including training and senior staff positions.
- Medical and allied health practitioners will have increased awareness and education (including multidisciplinary and palliative care) through undergraduate, postgraduate and continuing education.
- An agreed and consistent approach across all speciality groups.
- Most AYA patients will have access to a multidisciplinary team including:
  - a diagnosis and treatment team with expertise in each cancer type, where this is critical to outcomes;
  - a psychosocial support team, including appropriate peer support and palliative care as needed;
  - care co-ordination;
  - management of the transition and follow-up of AYA patients from paediatric to other treatment areas, such as a late effects clinic;
  - facilities to support multidisciplinary care.
- An increase in both the number of clinical trials that AYA patients can access and the number of AYA participants.

Constraints and opportunities

A number of constraints and opportunities were identified.

The practice of AYA cancer is currently constrained by the lack of agreed treatment plans and targeted resourcing eg. care coordination and an insufficient depth of expertise.

The current goodwill, interest and support within cancer and medical organisations provide an opportunity to develop AYA cancer models of care and treatment networks. There is also an opportunity to take advantage of other current initiatives in cancer control to focus the effort and ensure effective use of resources.

Specific options for the AYA cancer model of service include:

- Identification of key health workers or care co-ordinators to support the provision of coordinated multidisciplinary care and assist patients in navigating the system.
- Implementation of peer review processes to ensure patients receive appropriate treatment.
- Development of a national approach to clinical trials to increase patient access and participation.

Key principles

The forum identified the following key principles for effective treatment and care of AYA patients.

Access to treatment and care

All AYA cancer patients will have access to appropriate treatment and care regardless of their location. Appropriate treatment will be facilitated by:

- a national approach, including incentives and processes for monitoring and reporting;
- state-based pathways that identify availability of clinical services;
- networks of treatment centres comprising specialist services, primary care and patient support (psychosocial care and peer and family support);
- defined minimum standards of treatment and care.

Patient and family-centred approach

The approach to treatment and care will focus on the needs of AYA cancer patients and their families, characterised by:

- coordination of care provided by a multidisciplinary team;
- treatment supported by clinical practice guidelines;
- education and training, including continuing education, to support the focus on AYA cancer and the coordinated multidisciplinary team.

System-level support

At the system level, AYA cancer treatment and care will be supported by appropriate incentives and processes for monitoring and reporting, including benchmarking. A national approach to clinical trials will ensure patients have access to clinical trials and that their participation in trials is maximised. Approaches will also be supported by targeted research and an evidence base to support effective practice.

Specific incentives and resources should be provided to promote innovative, cross-institutional links between paediatric and adult units that treat similar cancers, aimed at facilitating harmonisation of treatment protocols and approaches and creating a critical mass for clinical trials.

Future directions for AYA cancer

Forum attendees identified future directions for AYA cancer in Australia, including networks of treatment centres, comprising specialist services (including initial diagnostic teams), primary care and support services, including psychosocial care and peer and family support.

These services would be linked and coordinated with specialist advice and consultation available across the network. Communication and collaboration would ensure clear referral pathways and effective linkages between paediatric and adult cancer services. This would require increased awareness of the network and available options and choices for patients by practitioners and the community.

Other future directions identified were:

- coordinated multidisciplinary team care;
- hospital based AYA services;
- consultative service accessing regional tumour streams;
- consultation team servicing multiple hospitals.

Research priorities for AYA cancer

Priorities for research in AYA cancer identified by forum participants included:

- A national database including information on age, diagnosis and outcomes such as access to multidisciplinary care teams and participation in clinical trials.
- Identifying research projects by examining current data (state cancer registries and tumour data) to identify gaps in research and evidence and appropriate research projects.
- Building evidence in relation to models of care, including referral pathways.
- Development of performance indicators, particularly for outcomes and impacts, including surrogate markers (for example screening).
- Monitoring, evaluation and reporting of impacts, including quality of life.
- Promoting recognition of the need for inclusion of AYA within relevant existing disease-specific trials groups, as well as greater co-ordination between trials groups to facilitate quality of life and psychometric outcome measures.

Improved participation in clinical trials

As participation in clinical trials is critical to health outcomes for AYA patients, there is a need to build awareness and support of the structure, process and benefits of clinical trials. To be effective, clinical trials need to be integrated in health care delivery and supported by an effective infrastructure, in particular a national ethics committee or process for approvals and removal of regulatory barriers such as age limits on participation. The infrastructure also needs to include support in the form of data managers and researchers.

The operation of clinical trials also needs greater collaboration and co-operation around standards and consistent processes. Clinical trials can also benefit from interaction and co-operation with international clinical trials groups. This co-operation will not only ensure the effective operation of trials, feedback from co-operative trials groups can also contribute to research and improvements in practice and inform future policy development.

Changes in clinical practice

Workshop participants recommended a series of mechanisms to facilitate change in clinical practice including:

- Secure ownership of the case for change by building recognition and support with governments, the community, practitioners and patients.
- Recognition of AYA cancer as a sub-speciality, including:
  - creation of AYA cancer appointments to bridge and link paediatric and adult cancer practice;
  - setting of accreditation standards for AYA cancer as a separate practice area;
  - development of clinical practice guidelines, linked to accreditation.
- Empowerment of consumers by raising awareness of the availability and benefits of AYA cancer services.
- Use of incentives, including financial incentives, to promote the uptake of AYA cancer services.
- Workforce capacity building by including a stronger focus on cancer competencies, and AYA cancer competencies in particular, in education and training programs.
- Strengthening of clinical trials, including links to accreditation.
- Identification and support for change 'champions'.

Proposed actions

Forum participants agreed that individuals could progress AYA cancer services by:

- Building the focus on AYA cancer in jurisdictions' current and planned cancer control strategies.
- Advocating AYA cancer in the workplace and through professional groups and other networks.
- Using case meetings and other opportunities to bring like-minded people together.
- Developing and implementing local policies, guidelines and practices.
- Identifying a local AYA cancer liaison person/champion.

Sponsoring organisation initiatives included:

- CanTeen – continuing advocacy, information sharing, patient education of clinicians and service providers and funding of AYA cancer pilot projects.
- Red Kite – creation of new positions addressing AYA cancer (music therapy and social worker).
- COSA – development of clinical practice guidelines (with Cancer Australia).
- Cancer Australia – development of clinical practice guidelines (with COSA) and improvements in clinical trials through a national ethics committee process, removal of the age barrier for clinical trials participation and support of the National Clinical Trials Groups.

Acknowledgements

COSA gratefully acknowledges the financial support from Cancer Council Australia, Cancer Australia and the Cancer Institute NSW. COSA also acknowledges the assistance of: members of COSA Council and staff, Ms Lynette Glendinning from PALM Consulting for facilitating the workshop and Mr Douglas Smith from PALM Consulting for developing a workshop report. The contribution of workshop presenters, panel members and participants is greatly appreciated.

Working Group

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BOOK REVIEWS

Bringing Pain Relief to Children: Treatment Approaches

G.A. Finley, P.J. Mcgrath, C.T. Chambers (Eds)
Humana Press, 2006
ISBN: 978-1-588-29-628-3
240 pages
RRP: US$89.50

This book is a treasure trove of information for health professionals who care for children who encounter pain, i.e. all health professionals who care for children.

Wherever possible the authors have incorporated evidence-based knowledge and where, as so often within paediatric specialities evidence is not available, they have addressed current thinking and practice. It encompasses topics related to pain in the community and in outpatient and inpatient settings, ranging from pain related to immunisation and ear infection to end of life care.

As in any such book, some chapters have greater depth than others and from the perspective of someone working exclusively with childhood pain management, some gaps or superficiality were evident. There is no doubt that the chapters related to supporting children and families where recurrent or chronic pain is an issue are comprehensive, offering information on in and out of hospital care and how to support children back to school. They should be compulsory reading for GPs and paediatricians, as the management of children with chronic pain syndromes is a rapidly developing area of practice.

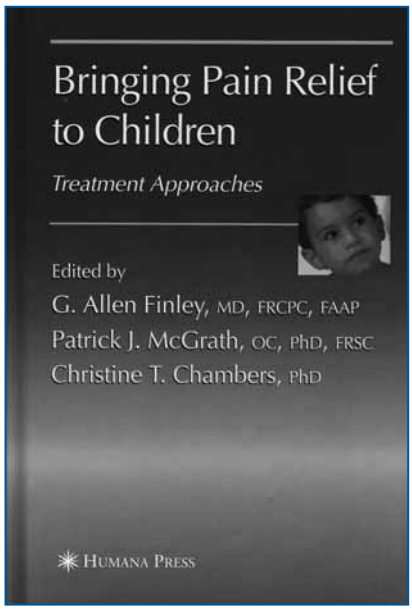
Acute pain management covers the range of analgesic options, but provides limited exploration of managing some of the more complex scenarios such as cancer treatment related pain and burn pain management. Procedural pain management, a significant cause of childhood anxiety, again receives only lip service and yet is so important in building resilience in children who require repeated interventions.

The chapter relating to pain management at the end of life addresses many aspects requiring consideration and an overview of pain management options. For some incomprehensible reason, pain assessment is embedded in the chapter on end of life care. While there are some special considerations here, it should be central to all aspects of paediatric pain management.

Challenges confronting the development of pain management services in countries with less well developed health services, enable us to see how far we have come in first world countries. Coming ahead of the valuable discussion regarding the dilemma of translating current knowledge to practice, it is to be hoped that this will encourage first world health professionals to continue to raise the bar at home and consider ways of supporting pain management services for less fortunate children.

This is not a book of recipes for pain management, but makes much of the current thinking easily accessible to health professionals. There is no doubt that if the wisdom embedded in this book translated into practice, the management of childhood pain would be greatly enhanced.

Gill Bricher, Clinical Nurse Consultant (Pain Management) Children, Youth & Women's Health Service, Adelaide, South Australia.



Cancer Sourcebook 5th Edition

Edited by Karen Bellenir
Omnigraphics (2007)
ISBN: 978-0-7808-0947-5
1133 pages

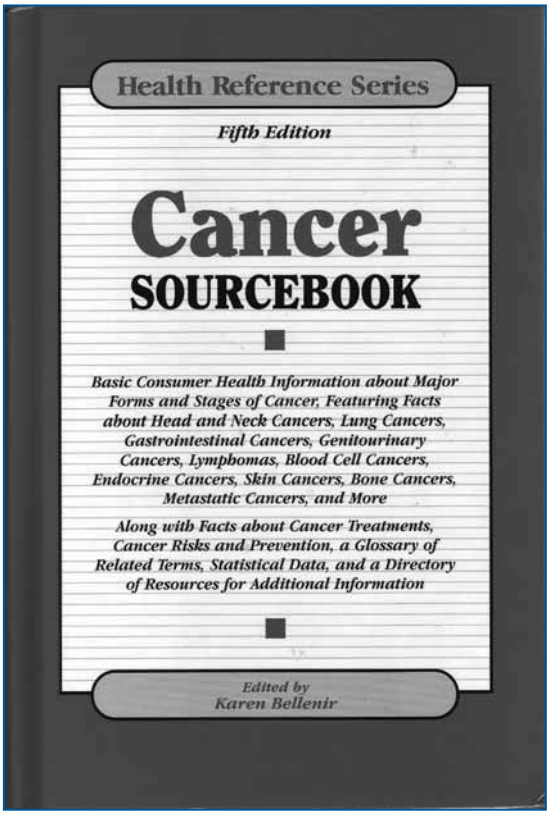
Cancer is expected to affect one in three men and one in four women in Australia by the time they are 75 years. Therefore it is important that we provide relevant information so that the public can make healthy lifestyle choices aimed at preventing cancer and for those diagnosed with cancer to understand the disease process and its many treatment options. The health reference series has published extensively on a variety of topics and this is the fifth edition of the *Cancer Sourcebook.*

The book is aimed at providing basic consumer health information about cancer for patients, families, caregivers and the general public. The table of contents is structured clearly and logically and the book is divided into five parts: cancer risk factors and cancer prevention covering known and suspected factors; types of cancer covering both solid tumour and haematological malignancies; an explanation of the most commonly used cancer treatments; special concerns related to recurrent or advanced cancer including end of life care; and additional help and information covers a glossary of terms and directories for more information about cancer.

The book is well written and is easy to follow, with chapters providing relevant questions on a topic and then covering that topic comprehensively. However, the sections discussing statistical information related to cancer incidence, morbidity and mortality are for the US and would not be relevant to the Australian public. Likewise, the directories for more information relate to organisations found in North America.

This book is not a 'must have' book, although it would be valuable for those dealing with a newly diagnosed or relapsed cancer. It explains what a particular type of cancer is, how it is diagnosed using the relevant tests, and then gives an overview of treatment options with a series of questions which would empower the patient and caregivers to obtain the information they require from health care professionals.

Diana Moore, Mater Private Hospital, Brisbane, Queensland.



Living On – a guide to living on in the thoughts and memories of those you love

J Margo and E Margo
Brandl & Schlesigner (2008)
ISBN: 978-1-876040-91-8
124 pages

Living On – a guide to living on in the thoughts and memories of those you love is a 'self help' book to assist people with life-limiting illnesses to create their own unique 'heart will'. It depicts today's post-modern era where the individual takes some control to lessen the burden of responsibilities for the soon to be bereaved loved ones and to assist in the grief process by reinforcing the relationship after death. Heart wills allow a person who has died to live on in the hearts of those that are important to them by maintaining emotional ties.

This book gives the reader practical ideas about what they may want to say to their loved ones in the future so as to reinforce their emotional self. It outlines different mediums that may be used such as writing letters, cards and short notes, as well as using voice and video recordings. It also draws on Petrea King's work with children around separation anxiety by explaining the 'rainbow ritual', a sensory way of communicating with younger children through imagination.

Although the most important message it conveys is that heart wills do not need to be perfect with an advanced writing style, correct spelling or professional audio and video recordings, it does however use quite articulate examples of heart wills that have been left. It gives useful advice on how to store these in varying different digital formats and also advertises a website www.livingon.net as a type of bank vault to store these messages that is secure and may be accessed by a password. When searching for this site it currently gives the message 'Living on, a new site launching soon', so it was not clear whether there would be a cost associated with accessing this complimentary resource to gather and store precious information.

Overall this book is easy to read and may be helpful to give people with life limiting illnesses ideas of how, when, why and where to leave loved ones heart wills. Its rawness and simplistic format is useful for someone who is unwell, but at the same time it is a very emotive read. Putting these ideas into practice can be both psychologically and emotionally complex for those who are dying. In light of this the book does lack the option of directing people to discuss these issues if they wish with the appropriate members of the multidisciplinary oncology or palliative care team they are associated with.

Jacinta Humphries, Macarthur Cancer Therapy Centre, Campbelltown Hospital, Campbelltown, New South Wales.

Lung Cancer: a Practical Guide

LE Raez and OE Silva
Saunders (2008)
ISBN-13: 9780702028892
256 pages
RRP: $95.00

This book aims to serve readers in three main ways: as a companion to daily practice for a general medical oncology audience; as a succinct introduction to the pathology, management issues and key trials useful for trainees; and as a pilot guide to the relevant literature.

The introductory timeline is an interesting aside before the real business of the handbook, summarising epidemiology, diagnostics and pathology of lung cancers in the first sections, although there is no synopsis of the current or proposed staging systems.

Management is dealt with by division into specific clinical scenarios within broad pathological groups, fitting well with the clinical handbook style, making it easy to extract information tailored to a specific question or case type. There is a broad coverage of management issues across surgery, medical and radiation oncology, as well as chapters on targeted therapies, palliative care and lung cancer in the elderly. Evidence and references are bullet-pointed for clarity and brevity.

This is a book I know I can use to lead me to foundation literature and that I will refer to again as an advanced trainee and beyond as I encounter new clinical problems in lung cancer.

Sandra Harvey, Liverpool Cancer Therapy Centre, Liverpool, New South Wales.

Young People Living with Cancer

A Grinyer
McGraw-Hill Companies (2007)
ISBN: 0-335-22154-8
182 pages
RRP: $62.00

This book is recommended reading for all health care professionals who encounter or are likely to encounter adolescents and young adults with cancer. Although rare, adolescents and young adults with cancer have distinct care needs separate from paediatric and older adult cancer patients.

The book addresses the reasons and the need to understand these differences and how to improve their care. Grinyer describes the cancer journey of adolescents and young adults with cancer through the eyes of 28 patients interviewed. The patients are typical for the adolescents and young adults with cancer population, including patients with testicular cancer, osteosarcomas, Hodgkin Lymphomas and leukaemias.

For easy reference the patients are named with their diagnosis, age and life stage (school, job) at the beginning of the book. The text is then divided into chapters on their experiences of diagnosis, the setting of care, the loss of indepen-dence felt, disruption of their life trajectory with reflection on life plans and friendships and the effect of illness on physical appearance as well as sexuality and fertility.

Collating this at the end are the implications for policy and practice.

Though written from the English health care setting, *Young People Living with Cancer* is applicable to Australian practice. The book does not focus on the palliation of adolescent and young adults with cancer patients which is an area of need in itself.

I found the book easy and rewarding to read over a couple of nights and have recommended it as a valuable resource to others throughout my department.

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