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Changing character of cervical cancer in young women

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Abstract

To examine the hypothesis that the pattern of cervical cancer is changing data on women presenting with the disease over 34 years were studied retrospectively. During 1953-86, 2628 women with cervical cancer were referred to a large tertiary referral hospital in Sydney; 418 were aged 35 or less. During the period of review the proportion of young women with the disease increased from under 9% in the 1950s and 1960s to about 25% in the 1970s and 1980s; a similar but less pronounced trend was apparent for the whole of New South Wales in the 1970s and 1980s. The prevalence of less common morphological types of cervical cancer increased throughout the period, particularly in the young. Pelvic lymph node metastases were identified in younger patients with stage Ib and IIa tumours more commonly in the later years of the study, suggesting that the disease was becoming more severe. Overall rates of recurrence improved over time, but an apparent increase in early recurrences was observed in young patients with Ib and IIa tumours and without nodal disease. The results suggest that the clinical and pathological behaviour of cervical cancer changed over the period of review.

Introduction

For some years gynaecologists managing cervical cancer have thought that the pattern of the disease has been changing. The use of Papanicolaou smears had led to earlier detection of clinical and preclinical lesions so that fewer patients were presenting with locally advanced disease. More recently, however, the disease has become more common and apparently more severe among young women. Epidemiological reports in the past 15 years have mostly confirmed this impression and indicated that cervical cancer is now both more common and associated with an increasing mortality in younger women.¹⁻¹⁷ The proportion of cases of cervical cancer in young women varies in different reports, from 7-14% in Scandinavia to up to 25% in a small series from the United States.¹⁸⁻²⁰ These variations

presumably reflect differing referral, demographic, geographic, racial, and social patterns.

To check the validity of theories on the increase in cervical cancer in younger women we analysed the patterns of cervical cancer in patients admitted to a large tertiary referral hospital in Sydney during 1953-86.

Patients and methods

The study comprised 2628 patients with cervical cancer admitted to King George V Hospital, Sydney, for part or all of their primary treatment during 1953-86. The histological characteristics of the tumours were reviewed by two gynaecological pathologists (PR and PB). Tumours were classified into the following types: adenocarcinomas and keratinising, non-keratinising, small cell squamous, adenosquamous, undifferentiated small cell (oat cell), adenoid cystic or adenoid basal, and unclassified carcinomas.

Radical hysterectomy with pelvic lymphadenectomy was the preferred treatment for stage Ib and IIa disease and some early stage IIb tumours. During 1953-69, surgery was usually preceded by intracavitary radium treatment. Those women with node metastases generally received postoperative external pelvic radiotherapy. From the early 1970s all lymphoid tissue was embedded in paraffin blocks and step sectioned six times to permit improved detection of microscopic metastases. Radical pelvic irradiation (external and intracavitary) was generally used for stage IIb to stage IV tumours.

Preclinical cancers were defined as those requiring colposcopically directed punch or cone biopsy to establish the diagnosis and those clinically unrecognised or unsuspected lesions found on routine histological examination of uteruses or cervixes removed for supposed benign disease. These preclinical cancers were subdivided into a microinvasive subgroup, in which the tumour had penetrated less than 5 mm into the stroma measured from the surface of the cervical epithelium, and an occult subgroup, in which invasion exceeded this limit, irrespective of the volume of the

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tumour, lymphatic permeation, and degrees of differentiation. The policy of management for women with occult stage Ib tumours was radical hysterectomy with pelvic lymphadenectomy; with microinvasive disease there was a strong trend away from radical surgery towards more conservative management after 1969.

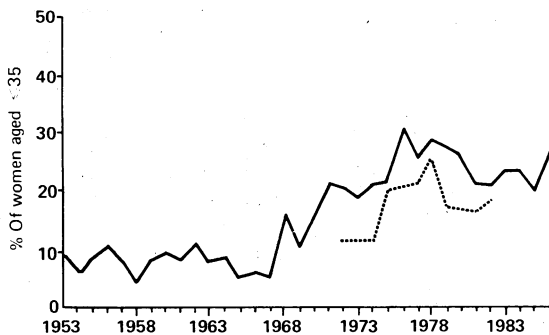
Proportions were compared with χ^2 and Fisher's exact tests. Multivariate analyses of time to relapse or death used the proportional hazards model. All *p* values were two sided, and no adjustment was made for multiple comparisons.

Results

Table I shows the age distribution of the women by stage of disease; a total of 418 women were under 36. During 1953-69 the number of new admissions each year was fairly constant, and women aged 35 or less comprised less than 9% of the total. During 1970-86 the proportion of new cases in women aged ≤ 35 increased each year until young women comprised nearly 25% of the total. The same trend was seen in the figures for the whole of New South Wales during 1972-83²¹ (figure).

TABLE I—Clinical stage by age group in 2628 women presenting with cervical cancer, 1953-86. Values are numbers (percentages)

Stage	Age ≤ 35	Age ≥ 36
Ia	145 (35)	287 (13)
Ib Occult	47 (11)	93 (4)
Ib	137 (33)	772 (35)
IIa	36 (9)	286 (13)
IIb	33 (8)	360 (16)
III	15 (3)	308 (14)
IV	5 (1)	104 (5)
Total	418 (100)	2210 (100)



Proportions of women with invasive cervical cancer aged 35 or less referred to King George V Hospital (—) during 1953-86 and reported to Central Cancer Registry of New South Wales (---) during 1972-82

HISTOLOGICAL FINDINGS

The relative proportions of the different histological types of cervical cancer changed during the period studied. During 1953-69 there were 41 microinvasive carcinomas in the young age group (those aged ≤ 35), of which two (5%) were adenosquamous carcinoma. During 1970-86 there were 104 microinvasive cancers, of which 2 (2%) were adenocarcinoma and 11 (11%) adenosquamous carcinoma.

Table II shows the histological characteristics in 2196 cases of cervical cancer (stages Ib-IV) over the 34 years. Among the young women the prevalence of less common cell types—adenocarcinoma, adenosquamous carcinoma, and small cell squamous lesions—increased from 1970, when undifferentiated small cell (oat cell) carcinoma and adenoid cystic tumours were first documented.

TABLE II—Histological types in 2196 cases of stage Ib occult to stage IV cervical cancer by age group and period of presentation

Period	Cell type									Total
	Non-keratinising squamous	Keratinising squamous	Small cell squamous	Adenocarcinoma	Adenosquamous	Undifferentiated small cell (oat cell)	Adenoid cystic or adenoid basal	Unclassified squamous	Unclassified	
<i>Age ≤ 35</i>										
1953-69	46	20	2	3	3			1		75
1970-86	113	33	16	14	13	6	2	1		198
Total	159	53	18	17	16	6	2	2		273
<i>Age ≥ 36</i>										
1953-69	440	369	20	93	26	8	2	55	15	1028
1970-86	383	265	66	73	48	8	7	21	24	895
Total	823	634	86	166	74	16	9	76	39	1923

Among the 418 younger patients, including those with microinvasive cancers, the prevalence of less common cell types (other than keratinising and non-keratinising squamous tumours) increased progressively and significantly from 10/116 (9%) during 1953-69 to 65/302 (22%) during 1970-86 ($p=0.002$). The prevalence of these less common cell types also increased from 160/1139 (14%) to 221/1032 (21%) in patients aged 36 or over in whom cell type was known ($p<0.001$).

LYMPH NODE STATE

Pelvic lymphadenectomy was performed in 275 of the younger and 1191 of the older women with stage Ia-IIb tumours (table III). Among the patients with preclinical lesions none of the 39 younger and three of the 93 older patients with microinvasive tumours had pelvic lymph node metastases. Among the patients with clinical cancers, however, the proportion with nodal disease was significantly higher stage for stage in the younger patients (table III).

TABLE III—Nodal disease by age group and clinical stage, 1953-86

Stage	No of patients who had lymphadenectomy		No (%) of patients with nodal disease	
	Age ≤ 35	Age ≥ 36	Age ≤ 35	Age ≥ 36
Ia	39	93		3 (3)
Ib Occult	42	58	10 (24)**	3 (5)
Ib	137	650	47 (34)**	153 (24)
IIa	35	199	19 (54)*	65 (33)
IIb	22	191	15 (68)*	86 (45)
Total	275	1191	91 (33)	310 (26)
Grand total	1466	401 (27)		

* $p<0.05$, ** $p<0.01$ Compared with corresponding stage in older patients.

The relative incidence of pelvic node metastases in stages Ib and IIa tumours significantly increased from 1970 in the younger ($p=0.02$) but not older patients. Before 1970 the incidence was 13/57 (23%) and 120/499 (24%) in the young and old respectively; subsequently the incidence remained stable at 101/408 (25%) in older patients but rose to 63/157 (40%) in younger women.

RECURRENCE OF TUMOURS AND SURVIVAL

Results of follow up are presented for all patients seen in 1953-81 and for patients aged 35 or less seen in 1953-86. Table IV shows the rates of recurrence by clinical stage, nodal disease, and age group in the 2175 patients treated in or before 1981. Multivariate analysis of time to recurrence in a proportional hazards model indicated that tumour stage and node state were highly significant ($p<0.0001$) independent prognostic factors. Examination of both time to recurrence and duration

TABLE IV—Recurrence by clinical stage, nodal disease, and age group in 2175 patients presenting during 1953-81

Stage	No of patients	No (%) with recurrence	Nodes affected		Nodes not affected	
			No of patients	No (%) with recurrence	No of patients	No (%) with recurrence
Age ≤35						
Ia	118	2 (2)			35	
Ib Occult	38	8 (21)	8	7 (88)	25	1 (4)
Ib	96	32 (33)	29	21 (72)	67	11 (16)
IIa	26	9 (35)	15	7 (47)	10	1 (10)
IIb	26	20 (77)	13	11 (85)	6	3 (50)
III	11	10 (91)				
IV	4	4 (100)				
Age ≥36*						
Ia	229	15 (7)	3	2 (67)	80	7 (9)
Ib Occult	76	14 (18)	3	1 (33)	47	5 (11)
Ib	619	169 (27)	117	67 (57)	411	68 (17)
IIa	223	92 (41)	48	31 (65)	114	31 (27)
IIb	296	181 (61)	81	63 (78)	96	40 (42)
III	253	222 (88)				
IV	85	82 (96)				

*Seventy five patients whose recurrence state was unknown are omitted.

of survival by decade of presentation showed an improved outcome in 1973-81 ($p=0.02$). When node state was allowed for age group was not an independent prognostic factor for recurrence or death.

Time to recurrence in the 418 younger patients seen in 1953-86 suggested that those presenting during 1983-6 had a significantly worse outcome ($p=0.037$), but other divisions of accrual time yielded results that were not significant. Within the 76 young patients with stage Ib and IIa tumours and affected nodes there was evidence of fewer recurrences in patients accrued in more recent periods. This was significant if the time was divided into 10 year ($p=0.014$), five year ($p=0.013$), or two year ($p=0.027$) periods. Experience with patients whose nodes were not affected showed an opposite trend. Among the 138 young patients with stage Ib and IIa disease whose nodes were not affected recurrence occurred in six out of 44 (14%) of those who presented in 1953-69 (four pelvic, one distant, one both), seven out of 64 (11%) of those who presented in 1970-82 (three pelvic, four distant), and seven out of 30 (23%) of those who presented in 1983-6 (three pelvic, two distant, two both). Of the 22 young women with stage Ib and IIa disease seen in 1985-6—two out of nine (22%) with nodal disease and six out of 13 (46%) without developed recurrences ($p=0.06$). Whether this trend in women without nodal metastases is apparent or real remains to be resolved.

Discussion

This analysis of the clinical and histological characteristics of patients with cervical cancer referred to our unit for treatment during 1953-86 confirms the clinical impression that the disease is changing its character and behaviour, with a rising incidence in young women. The histological types of cervical cancer have also changed. Whereas keratinising and non-keratinising squamous tumours remain the most common, the relative proportions of the other histological types have been greater in young women since 1970 and these other types have contributed an increasing proportion of the total since 1970. This increase in unusual histological tumour types has also, however, been observed, though to a less extent, in older women and in those with preclinical cancers.

Although clinical stage is an important prognostic factor, the state of pelvic lymph nodes provides additional prognostic information. Our data indicate that lymph node metastases became more common in young women after 1969, again suggesting that the disease is changing its character.

Our patients with stage Ib and IIa cervical cancer and affected nodes were treated with adjuvant external

pelvic radiotherapy, and there was a progressive reduction in rates of recurrence during 1953-86. This probably reflects improved surgical techniques, a more detailed examination of lymph nodes, and more effective postoperative radiation treatment. From 1982 some of these women also received adjuvant combination chemotherapy,²² but the impact of this additional treatment on rates of recurrence cannot yet be assessed.

A more worrying development has been an apparent worsening of the prognosis in young women without histologically affected pelvic lymph nodes: six of the 13 who did not have nodal disease and presented during 1985-6 have already had a recurrence. Though the numbers are small, this development prompted us to consider the use of adjuvant treatment (radiation or chemotherapy, or both) for all younger patients regardless of pelvic node state.

A recent report examined the prognostic importance of age in women with cervical cancer treated by radiotherapy during 1971-8.²³ Young patients (≤ 35) with stage Ib disease fared somewhat better than older patients ($p=0.02$), but this group included patients with stage Ib occult tumours. No analysis of changing histological patterns of the disease was reported and no information about node state given.

Our analysis of cervical cancer provided substantial evidence that the disease is changing. It has become more common in young women, the histological characteristics have changed, and in young women lymph node metastasis is more common. The roles of papillomavirus infection, changing sexual practices, and smoking²⁴ are not yet clear. Nevertheless, there is a clear need for vigilance in reviewing results of treatment and considering new therapeutic approaches.

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