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Young age as a prognostic factor in cervical cancer: analysis of population based data from 10 022 cases

CLIVE A MEANWELL, KRYSTYNA A KELLY, SUSAN WILSON, CLAUDIA ROGINSKI, CIARAN WOODMAN, ROD GRIFFITHS, GEORGE BLACKLEDGE

Abstract

The effect of young age on survival in cervical cancer is not fully known, although evidence has suggested that it is a poor prognostic factor and that young patients should therefore be treated differently from older patients. All 10 022 cases of invasive cervical cancer in the west Midlands during 1957-81, which comprised 10% of the cases in England and Wales, were analysed to determine the prognostic effect of age. Univariate analysis showed a median survival time of 54 months for all cases, with survival rates at five years of 69% for patients aged under 40 and 45% for those aged 40 or older (χ_1^2 (log rank)=331·4; p<0·0001). This difference remained significant after stratification for stage (χ_1^2 (log rank)=7·1; p=0·008). Cox regression analysis with nine covariables, including age and year of registration, reaffirmed the importance of conventional prognostic factors such as stage of disease, size of tumour, state of lymph nodes, and differentiation of the tumour. After allowance was made for the effects of other prognostic factors young age was found to be a small but significant favourable factor that did not change during the period of the study. Estimated survival distributions obtained from the Cox model showed that for women presenting with the common characteristics associated with stage Ib disease who were treated with radical radiotherapy the survival rate at five years fell non-linearly from 71% in the group aged 25-29 to 65% in the group aged 65-69.

Young age alone is not a reason to alter existing policies for treatment for patients with invasive cervical cancer.

West Midlands Cancer Research Campaign Clinical Trials Unit, Queen Elizabeth Hospital, Birmingham B15 2TH
CLIVE A MEANWELL, MB, CHB, research fellow
KRYSTYNA A KELLY, PHD, senior statistician
GEORGE BLACKLEDGE, MD, PHD, director

Birmingham and West Midlands Regional Cancer Registry
SUSAN WILSON, BA, statistician
CLAUDIA ROGINSKI, BSC, deputy director
ROD GRIFFITHS, MD, FFCM, acting director

Department of Social Medicine, University of Birmingham
CIARAN WOODMAN, MB, MRCOG, registrar

Correspondence to: Dr Meanwell.

Introduction

Recent changes in mortality from cervical cancer in women aged under 40[1] have prompted speculation about the prognostic importance of young age in patients diagnosed since the mid-1970s. Research has suggested that, stage for stage, cervical cancer in young women has a poor prognosis,[2] that young women with stage Ib disease as defined by the International Federation of Obstetrics and Gynaecology (1976)[3] are particularly at risk of early death, and that treatment policies for these women should be changed.[4]

The aims of this study were to examine the relation between age and survival in women with invasive cervical cancer treated in the west Midlands, taking account of other prognostic factors, and to determine whether this relation changed from 1957 to 1986.

Methods

Regional demography and population at risk—Data were taken from records held at the Birmingham and West Midlands Regional Cancer Registry, which have been based on the general population since 1957 and covers the whole of the five original counties in the west Midlands: Warwickshire, Worcestershire, Staffordshire, Shropshire, and Herefordshire. The outer regional boundaries were not altered during the period studied, and demographic characteristics of the region are representative of those of England and Wales as a whole.[5] The population at risk, which constitutes around 10% of the female population of England and Wales, increased from 2·2 million women in 1957 to 2·6 million women in 1981 with only minor alterations in the distribution of age.[6-8]

Registration and collection of follow up data—The study group comprised all 10 022 cases of invasive malignancy of the uterine cervix diagnosed between 1 January 1957 and 31 December 1981 in residents in the west Midlands. Notifications of cases were obtained from hospitals, pathology laboratories, general practitioners, coroners, and the Office of Population Censuses and Surveys and details were abstracted by registry staff. Various

systems of cross checking were used to prevent duplication of data, and the efficiency of registration has been estimated to exceed 98%.[5] Follow up information was gathered yearly for five years, at seven years, at 10 years, and every five years thereafter, and the outcome of hospital follow up visits was notified to the registry. Registry staff implemented an active follow up procedure when hospital follow up ended, patients failed to attend for hospital follow up, or patients moved away from the region. Cases obtained by way of death certificates from the Office of Population Censuses and Surveys were included in the analyses only when corroborative diagnostic information was available from other sources. Table I shows the classification of patients at diagnosis into successive five year age groups. Table II shows their other characteristics.

Prognostic variables used in analysis—The registry records overall stage classification (stage I, II, III, or IV) but does not consistently record substage classifications (substages a and b) for invasive cervical cancer. A retrospective review of case notes was therefore performed to categorise cases according to the criteria of the International Federation of Obstetrics and Gynaecology (1976)[3] when possible. Case notes of all 4855 patients registered in 1970-81 and those of 1325 patients registered before then were reviewed by one of us (CAM) and compared with computerised records. A substage was assigned only if (*a*) the substage had been recorded by the clinician at the time of diagnosis; (*b*) a detailed clinical report was available including results of intravenous urography, cystoscopy, and sigmoidoscopy; or (*c*) in cases classified as preclinical invasive disease—that is, stages Ia and Ib (occult)—

TABLE I—*Numbers of cases of cervical cancer by age group and year of first treatment or, if not treated, year of diagnosis (anniversary year)*

Anniversary year	Age group																
	20-24	-29	-34	-39	-44	-49	-54	-59	-64	-69	-74	-79	-84	-89	-94	≥95	Total
1957		1	13	31	34	41	45	42	35	29	24	8	5	1	1		310
1958		4	15	32	20	36	36	32	41	29	29	21	8	3			306
1959		6	21	44	41	55	40	39	46	35	23	14	7	4	1		376
1960		2	12	48	39	52	41	57	31	35	32	22	10	3			384
1961		2	11	34	53	51	39	43	54	39	33	21	11	10		1	402
1962		3	16	34	58	39	49	48	36	34	29	20	13	6	2	2	389
1963		2	10	36	71	65	47	41	24	38	16	20	7	5		1	383
1964	2*	4	15	42	78	68	64	54	41	32	35	13	15	8	3	1	475
1965	3	4	6	33	66	54	61	52	41	32	25	18	7	4			406
1966	3	8	13	42	48	69	67	51	38	40	24	16	9	6			434
1967	1	5	8	34	78	94	56	55	48	29	31	22	12	7			480
1968	2	7	18	31	60	88	61	45	42	21	24	14	9	3	1	1	427
1969	1	5	19	21	42	59	46	65	44	27	29	18	11	5	3		395
1970	2	6	14	21	43	56	61	49	45	31	30	15	12	8			393
1971	2	10	14	19	30	56	67	56	38	26	25	24	8	1	1		377
1972	4*	3	16	22	30	65	65	55	51	38	32	16	12	8			417
1973		12	14	22	34	44	68	53	42	36	28	19	8	4	2		386
1974	1†	10	23	27	37	47	56	45	52	28	25	10	6	9	2		378
1975	1	11	21	24	27	48	59	52	65	36	37	17	11	9	2	1	421
1976	4*	16	27	22	27	43	58	59	50	26	30	17	11	5	2	1	398
1977	5	28	36	34	24	34	56	65	48	39	22	10	9	5	3		418
1978	2	22	43	47	29	29	46	63	41	33	29	17	7	4			412
1979	4	26	35	41	22	29	36	69	45	45	27	17	10	6	2		414
1980	5†	20	39	40	29	31	39	59	57	49	29	27	11	7			442
1981	2*	23	40	41	53	34	30	47	42	40	25	10	4	6	2		399
Total	44	240	499	822	1073	1287	1293	1296	1097	847	693	426	233	137	27	8	10022

*One patient was aged 15-19 years.
†One patient was aged 10-14 years.

TABLE II—*Characteristics other than age of patients with cervical cancer. Values are numbers (percentages) of patients*

Characteristic	Total group (n=10 022)	Group used in multivariate analysis (n=7879)
Main site of primary tumour:		
Endocervix	859 (8·6)	683 (8·7)
Not specified	9163 (91·4)	7196 (91·3)
Stage of disease:		
I	3440 (34·3)	3294 (41·8)
II	2648 (26·4)	2518 (32·0)
III	1793 (17·9)	1587 (20·1)
IV	715 (7·1)	480 (6·1)
Found at necropsy only	60 (0·6)	
Unknown	1366 (13·7)	
Lymphadenopathy:		
Present	477 (4·8)	356 (4·5)
None known	9545 (95·2)	7523 (95·5)
Metastases:		
Present	422 (4·2)	216 (2·7)
Not documented	9600 (95·8)	7663 (97·3)
Histological type of tumour:		
Squamous cell carcinoma	7868 (78·5)	6972 (88·5)
Adenocarcinoma	662 (6·6)	558 (7·1)
Anaplastic carcinoma	411 (4·1)	349 (4·4)
Other carcinomas (includes mixed types)	238 (2·4)	
Unknown	843 (8·4)	
Intention of treatment:		
Curative	8379 (83·7)	7081 (89·8)
Non-curative*	1643 (16·3)	798 (10·1)
Primary treatment:		
Radiotherapy	6423 (64·1)	5463 (69·3)
Surgery	1261 (12·6)	1003 (12·7)
Radiotherapy and surgery	1208 (12·0)	963 (12·2)
Systemic, incomplete, or none	1130 (11·3)	450 (5·8)

*Includes exploratory treatment and no treatment.

there was both a copy of the original pathological report indicating that invasion had occurred and a statement that no clinically detectable disease was evident at the time of diagnosis. No attempt was made to differentiate between stages Ia and Ib (occult) disease as this classification system was not in use for most of the years included in the study. The overall stage of disease was determined for 8596 cases; but in 1366 cases no stage was recorded and insufficient clinical information was available for a classification to be made; the remaining 60 cases were diagnosed only at necropsy. Other variables used in the analyses were duration of symptoms related to cancer before diagnosis; year the disease was first treated or, if it was not treated, year of diagnosis (anniversary year); age at diagnosis; main site of disease; size of tumour; histological type of tumour; intention and type of primary treatment; and presence and site of diseased lymph nodes or other metastases (see tables II and III).

Survival times—Survival was measured in months and defined as the time from the anniversary date to death from cervical cancer. Anniversary date was the date the disease was first treated or, if it was not treated, the date of diagnosis. Data on cause of death in each case were obtained from multiple sources, including family practitioners, hospital case notes, and death certificates from the Office of Population Censuses and Surveys; adjusted survival rates were used—that is, patients were censored from the analysis at the time of death if they died from causes not attributable to cervical cancer, at the time of embarkation if they emigrated, and at the time last seen alive if they were still alive or could not be traced.

Handling of data—Data were stored, and validity checks performed by using in house software, on a DEC PDP11/73 minicomputer in the RSX-11M operating system at the Birmingham and West Midlands Regional Cancer Registry and on a VAX 8730 minicomputer at the West Midlands Cancer Research Campaign Clinical Trials Unit, Birmingham. Statistical analyses were performed with software programs from the Clinical Trials Service Unit in Oxford and the BMDP (biomedical programs) statistical package.[9]

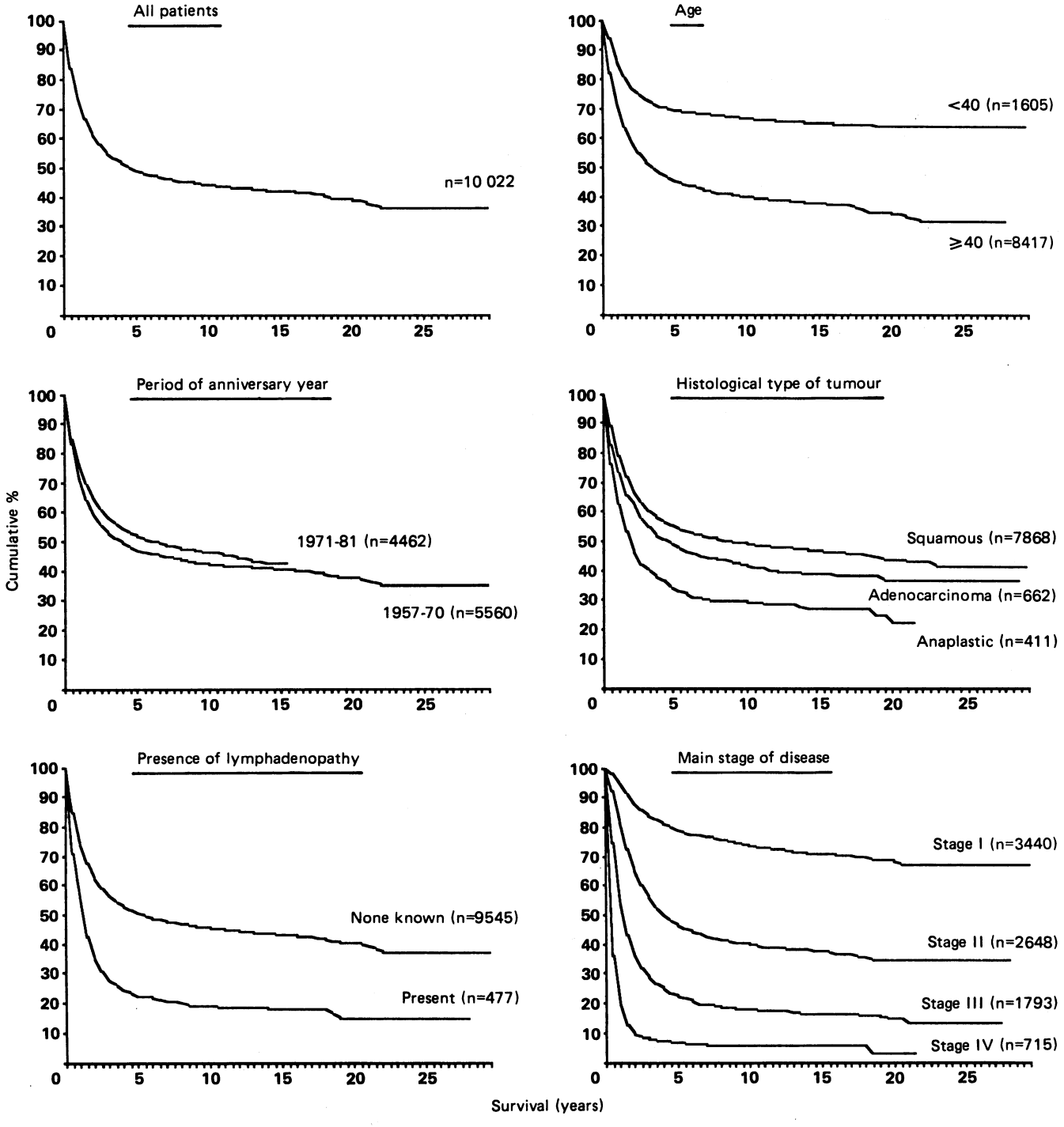

FIG 1—Univariate actuarial survival curves for patients subdivided into various classifications. Test statistics for the curves for age and period of anniversary year are given in the text; those for histological type of tumour, presence of lymphadenopathy, and main stage of disease are given in table IV.

Results

Univariate analyses of survival—The median actuarial survival time for the 10 022 patients was 54 months. Five, 10, 15, and 20 year overall survival rates were 49%, 44%, 42%, and 39%, respectively (fig 1). Cases registered in successively later years were associated with improved survival. The rate of survival at five years increased from 40% in cases registered in 1957 to 52% in cases registered in 1981 (χ_1^2 (linear trend)=49·0, p<0·0001), although there was some evidence of deviations from linearity in this trend (χ_{23}^2=43·5, p=0·006). Five year survival rates were 47% for cases registered before 1971 and 52% for cases registered from 1971 onwards (χ_1^2 (log rank)=19·8, p<0·0001) (fig 1(B)). Table III and figure 1 show actuarial survival distributions for the other prognostic covariables. Cases registered in successively younger five year age groups were associated with improved survival (χ_1^2 (linear trend)=1432·9; p<0·0001) (table IV). With a previously proposed cut off point for age in cervical cancer[1 2 4] five year survival rates were found to be 69% for women under 40 years old and 45% for those aged 40 or more (χ_1^2 (log rank)=331·4, p<0·0001) (fig 1). This difference remained significant after stage of disease was controlled for by stratification[10] whether cases were divided into two age groups (under 40 and 40 and older, χ_1^2 (linear trend)=7·08; p=0·008) or into successive five year age groups (χ_1^2 (linear trend)=95·7, p<0·0001).

Rationale for multivariate analysis of survival—Variables used in the univariate analyses were not independent—for example, women under 40 years of age were more commonly registered as having the early stages of the disease, more commonly treated with curative intent, and less commonly classified as having adenocarcinomas than older women. To determine the independent prognostic effects of young age and other factors Cox regression analysis was performed[11 12] on data from 7879 cases with complete records for nine covariables (age group, year of registration, histological type of tumour, main site of primary tumour, stage of disease by the criteria of the International Federation of Obstetrics and Gynaecology (1976),[3] intention of

primary treatment, method of primary treatment, and the presence or absence of clinically evident lymphadenopathy and metastases). Table II shows the characteristics of these cases. Stratification of cases by each of the covariables in turn gave no evidence to suggest violation of the proportional assumption of risk. Appropriate scales that provided linear relations between each covariable and the function of risk were selected. Various models, which included linear and non-linear components and cut off points for age groups, were fitted to explore the relation between age and risk of death from cervical cancer. The optimal model included a non-linear relation between age and the function of risk which was consistently monotonic, increasing with age. There was no evidence to suggest that women under 40 years of age or subgroups of women under 40 had a worse prognosis than any older subgroups.

Stepwise analysis with optimal description of covariables—As expected from the univariate analysis all the covariables except main site of primary disease were significant prognostic factors at step 0 of the stepwise multivariate analysis. At step 1 stage of disease (approximate χ^2 to enter=2537·8), the most significant independent prognostic covariable, was entered into the model; early stages were associated with best survival. After stage of disease was controlled for at the end of step 1 year of registration was no longer a significant prognostic covariable (approximate χ^2 to enter=1·9) whereas main site of disease (approximate χ^2 to enter=14·6) became a significant covariable. Subsequent steps of the analysis identified as significant independent prognostic variables the primary method of treatment (surgery better than radiotherapy); policy of treatment (curative intention better than palliative); lymph node state (negative better than positive); histological type (squamous cell carcinoma better than adenocarcinoma, which was in turn better than anaplastic carcinoma); age group (young better than old); clinical metastases (absent better than present); and main site of disease (endocervical better than unspecified). Complete data for the nine covariates used in the main analysis and for primary tumour size and duration of symptoms were available for only 320 cases. The assumptions implicit in the Cox regression model were also tested for these data, and stepwise analysis was performed. Although this analysis was performed on data from a subgroup of cases, results suggested that the documented size of the primary tumour was second in importance only to stage of disease as an independent index of the risk of death from cervical cancer.

Independent prognostic effects of anniversary year and age group—The nine covariables used in the main analysis were fitted to the data simultaneously. With this model estimated survival functions were computed and predicted

TABLE III—*Univariate analysis of survival for subgroups of cases*

Variable	No of cases		Estimated survival		χ^2*	df	p Value
	Total	Censored	At five years (%)	Median (months)			
Stage:							
I	3440	74·8	79	NR			
II	2648	40·8	47	47			
III	1793	19·1	22	13			
IV	715	<0·1	7	3	3609·1	3	<0·0001
Main site of primary tumour:							
Endocervix	859	47·2	52	79			
Not specified	9163	45·0	48	52	4·9	1	0·0272
Histological type of tumour:							
Squamous carcinoma	7868	49·8	54	95			
Adenocarcinoma	662	42·1	47	49			
Anaplastic carcinoma	411	29·9	33	19	110·3	2	<0·0001
Lymphadenopathy:							
None known	9545	46·4	50	62			
Present	477	20·1	22	14	203·3	1	<0·0001
Metastases:							
None known:	9600	46·7	50	64			
Present	422	11·4	12	3	475·4	1	<0·0001
Intention of treatment:							
Curative	8379	52·8	57	154			
Non-curative	1643	0·1	7	3	5038·0	1	<0·0001
Method of treatment:							
Surgery	1261	80·6	85	NR			
Surgery and radiotherapy	1208	62·9	68	NR			
Radiotherapy	6423	41·4	45	45			
Other	350	18·6	20	6			
None	780	<0·1	2	1	5142·5	4	<0·0001
Duration of symptoms (months)†:							
<1	1381	42·1	47	46			
-<2	1185	39·7	44	36			
-<3	1095	39·5	44	36			
-<6	1802	40·9	46	41			
-<12	1248	42·1	47	46			
-<24	528	41·1	45	39			
-<36	111	45·9	51	64			
≥36	203	42·9	49	52	4·6	7	0·7094
Diameter of primary tumour (cm)‡:							
<2	37	75·6	77	NR			
-<2	63	50·1	57	95			
-<3	102	49·0	52	98			
-<4	75	46·7	50	67			
-<5	56	30·4	34	24			
≥6	73	24·7	25	14	45·7	5	<0·0001

NR=Median estimated survival time not reached.
*Log rank test.
†For 7553 patients with symptoms.
‡In 406 cases for which data were available.

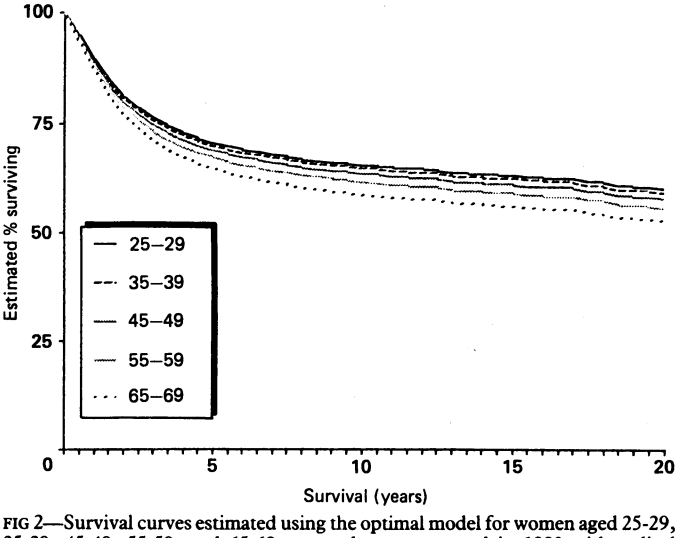

FIG 2—Survival curves estimated using the optimal model for women aged 25-29, 35-39, 45-49, 55-59, and 65-69 years who were treated in 1980 with radical radiotherapy for stage Ib non-endocervical squamous carcinoma of the cervix and had no known lymphatic or other metastatic disease.

survival curves drawn for hypothetical groups of cases. Identical survival curves were obtained from one of these computations for young women with the same set of patient characteristics diagnosed as having the disease in 1960, 1965, 1970, 1975, and 1980. The favourable prognostic effect of young age was shown in other computations: for women aged 25-29, 35-39, 45-49, 55-59, and 65-69 who were treated in 1980 with radical radiotherapy for stage Ib, non-endocervical squamous carcinoma, and had no known lymphatic or other metastatic disease, estimated survival rates at five years were 71%, 70%, 69%, 67%, and 65%, respectively (fig 2). A similar effect of age on prognosis was also found after computing estimated survival distributions for women with typical disease characteristics associated with stage IIIb who were treated with radical radiotherapy (table IV).

TABLE IV—*Estimation of rates of survival at five years according to age group by univariate analysis and after controlling for other covariates by using the multivariate Cox model*

Age group (years)	Univariate analysis: No of cases: Total	Univariate analysis: No of cases: Censored	Univariate analysis: Actuarial survival (%)	Multivariate Cox model*: Patients with stage Ib disease (%)	Multivariate Cox model*: Patients with stage IIIb disease (%)
10-14	2	2	100	71·0	29·4
-19	4	3	75	70·9	29·3
-24	38	25	63	70·8	29·1
-29	240	180	75	70·6	28·8
-34	499	372	75	70·3	28·4
-39	822	505	65	69·9	27·8
-44	1073	599	60	69·4	27·1
-49	1287	628	52	68·8	26·3
-54	1293	593	50	68·0	25·2
-59	1296	548	47	67·1	24·1
-64	1097	451	48	66·0	22·6
-69	847	293	40	64·6	20·9
-74	693	196	32	62·9	19·1
-79	426	78	22	61·0	17·1
-84	233	42	15	58·7	14·9
-89	137	13	7	56·1	12·7
-94	27	1	10	53·1	10·4
>95	8	0	0	49·5	8·1

*Estimates derived for patients with non-endocervical squamous cell carcinomas with no known lymphadenopathy or metastases treated in 1980 with curative radiotherapy.

Discussion

The idea that young women with cervical cancer have a poor prognosis is not new; as long ago as 1913 Zweifel suggested that, "Je junger die Frauen sind um so rapider der Verlauf,"[13] (the younger the women the faster the course), and since then his suggestion has often been discussed. Most investigators have failed to show that age has an effect on survival,[14-23] but some have concluded that young age has a favourable effect[24 25] and others that it has an unfavourable one.[26 27] Few of these reports described long term actuarial survival data or investigated the independent effects of age on prognosis. None of them used population based data.

Considerable interest has been shown recently in the prognosis of cervical cancer in relation to age. Results reported from one regional referral centre for gynaecological cancer in the United Kingdom included a five year survival of below 50% for patients under the age of 40 with stage Ib cervical cancer treated with radical surgery; only 6% of this group had well differentiated keratinising tumours and one third had metastases in the pelvic lymph nodes.[4] These data, supported by anecdotal observations,[2 28] have led to the view that young women (under 40) with invasive cervical cancer that has been recently diagnosed have a poor prognosis; Ward *et al* suggested that they should be treated with chemotherapy.[4] This view was partially refuted in a study of 2870 patients treated with radiotherapy in Manchester, England, from 1971 to 1978, which showed that the prognosis for patients under 35 or 40 was better than that for older age groups, only 318 of the patients studied, however, were under 40, and when the effect of stage of disease was considered the difference in survival between young and old patients was of only borderline significance.[23] Furthermore, the effects of other prognostic covariables possibly related to age were not examined in these patients who were treated in hospital.

Our study reports data on survival for about 10% of patients with invasive cervical cancer treated in England and Wales from 1957 to 1981. The data were population based, included details relating to most of the recognised prognostic factors in cervical cancer,[29] and were based on at least five years of follow up to 1986. The survival rates at five, 10, 15, and 20 years for all patients were 49%, 44%, 42%, and 39%, respectively, and the median survival time was 54 months. The survival rate at five years for patients treated with curative intent was 57%, and these figures agree with those in most previously published series. Overall five year survival rates improved from 1957 to 1981 and with decreasing age, but these trends were mediated by other prognostic covariables such as stage of disease.

In contrast to results recently reported by Russell *et al*,[23] our results showed that young age confers a highly significant advantage in terms of survival, even after stage of disease was controlled for by stratification.[10] Nevertheless, to account for other possible factors dependent on age a Cox regression analysis of survival was performed using data from 7879 cases. Results indicated that young age had a small but significant favourable prognostic effect—for example, for women with characteristics of stage Ib disease who were treated with radical radiotherapy the survival rate at five years fell, in non-linear fashion, from 71% in the age group 25-29 to 65% in the age group 65-69 (table IV). Furthermore, the prognosis of young or old patients with cervical cancer did not change during the period of the study. These observations do not support the view that the disease may be more virulent in young compared with old women or that the pattern of cervical cancer in young women has changed recently as the result of aetiological, immunological, or hormonal effects.[27 28 30]

Our study reaffirms that more advanced stage of disease, large primary tumours, anaplastic histology, lymphatic or metastatic dissemination at the time of diagnosis, and treatment with palliative radiotherapy are unfavourable prognostic factors in cervical cancer. Diseased lymph nodes had a profound effect on survival: the estimated five year survival for women aged 25-29 with stage Ib squamous cell carcinoma with no metastases treated with radical radiotherapy was 70% if there was no lymphadenopathy and 35% if there was. These data are consistent with those reviewed by Morgan and Nelson, which indicated that five year survival rates in patients with early clinical disease and diseased lymph nodes were about half of those in patients with no lymphatic spread.[29] Tumour size is a prognostic factor independent of stage,[31] and in a subgroup of patients we found that the size of the primary lesion was an independent prognostic variable second in importance only to stage of disease; thus the size of the primary tumour should be estimated and recorded before treatment. Finally, although several studies have indicated that poorly differentiated squamous cell or anaplastic carcinomas are associated with a poor prognosis,[32-37] the relative prognosis of women with adenocarcinoma of the cervix has not yet been resolved.[38 39] Our data support the view that anaplastic cervical cancer carries a poor prognosis and suggest that squamous cell carcinomas may carry a better prognosis than adenocarcinomas. These observations must, however, be interpreted with care as we did not review histological material.

The multivariate analyses of survival give no obvious reason why a woman under 40 with cervical cancer should have a worse prognosis than one who is older. Some authors have suggested, however, that young women are more likely to show unfavourable characteristics of the disease such as large and poorly differentiated tumours. The evidence for this is scanty, and our data did not corroborate it. During 1957-81 the proportions of patients aged under 40 registered with anaplastic tumours and that of patients under 40 treated surgically who were found to have diseased lymph nodes did not increase. Similarly, there was no evidence to suggest that these unfavourable characteristics were commoner in young women than old women (unpublished data held at the Birmingham and West Midlands Regional Cancer Registry). We conclude that young age alone is not a reason to alter existing treatment policies in patients with cervical cancer. Systemic treatment may benefit patients (of any age) with advanced stage or large anaplastic tumours in whom lymph node disease is highly suspected or known to be present at the time of primary treatment, but further studies are required to confirm this and identify other characteristics of patients

at high risk of death. Thereafter the value of adjuvant chemotherapy should be tested in a randomised, prospective trial.

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References

1 Cook GA, Draper GJ. Trends in cervical cancer and carcinoma in situ in Great Britain. *Br J Cancer* 1984;**50**:367-75.
2 Hall SW, Monaghan JM. Invasive carcinoma of the cervix in younger women. *Lancet* 1983;ii:731.
3 Shepherd JH. Surgical management of early invasive cervical cancer. *Clin Obstet Gynecol* 1985;**12**:183-202.
4 Ward BG, Shepherd JH, Monaghan JM. Occult advanced cervical cancer. *Br Med J* 1985; **290**:1301-2.
5 Waterhouse JAH. *Cancer handbook of epidemiology and prognosis*. Edinburgh: Churchill Livingstone, 1974.
6 General Register Office. *Census 1961 England and Wales*. London: HMSO, 1963. (Table 6 in county reports for Herefordshire, Shropshire, Staffordshire, Warwickshire, and Worcestershire.)
7 Office of Population Censuses and Surveys. *Census 1971 England and Wales*. London: HMSO, 1973. (Table 8 in part 1 of county reports for Herefordshire, Shropshire, Staffordshire, Warwickshire, and Worcestershire.)
8 Office of Population Censuses and Surveys. *Census 1981 England and Wales*. London: HMSO, 1982. (Table 6 in part 1 of county reports for Hereford and Worcester, Shropshire, Staffordshire, Warwickshire, and West Midlands.)
9 Dixon WJ, ed. *BMDP statistical software*. Berkeley: University of California Press, 1983.
10 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;**35**:1-39.
11 Cox DR. Regression models and life tables. *Journal of the Royal Statistical Society [Series B]* 1972;**34**:187-220.
12 Hopkins A. Survival analysis with covariates—Cox models. In: Dixon WJ, ed. *BMDP statistical software*. Berkeley: University of California Press, 1983:576-94.
13 Zweifel E. Comments during discussion of paper by Graff-Wien E. (Über den Einfluss der Gravidität auf das Wachstum maligner Tumoren). In: *85 Versammlung zu Wien, September 1913. Verhandlungen der Gesellschaft deutscher Naturforscher und Ärtze*. Leipzig: F C W Vogel, 1914:477.
14 Truelsen F. Cancer of the uterine cervix. Copenhagen: University of Copenhagen, 1949. (Dissertation.) Cited in: Lindell A. Carcinoma of the uterine cervix; incidence and influence of age; statistical study. *Acta Radiologica [Stockh]* 1952;**92** (suppl):1-102.
15 Kamnicker H. Das weibliche Genitalkarzinom bei Jugendlichen. *Wien Med Wochenschr* 1939;**89**:415-7.
16 Decker DG, Fricke RE, Pratt JH. Invasive carcinoma of the cervix in young women. *JAMA* 1955;**158**:1417-20.
17 Adcock LL, Julian TM, Okagaki T, *et al*. Carcinoma of the uterine cervix FIGO stage I-B. *Gynecol Oncol* 1982;**14**:199-208.
18 Baltzer J, Koepcke W, Lohe KJ, Ober KG, Zander J. Age and 5-year survival rates in patients with operated carcinoma of the cervix. *Gynecol Oncol* 1982;**14**:220-4.
19 Dodds JR, Latour JPA. Relationship of age to survival rate in carcinoma of the cervix. *Am J Obstet Gynecol* 1961;**82**:33-6.
20 Kyriakos M, Kempson RL, Perez CA. Carcinoma of the cervix in young women. *Obstet Gynecol* 1971;**38**:930-44.
21 Mann WJ, Levy D, Hatch KD, Shingleton HM, Soong S. Prognostic significance of age in stage I carcinoma of the cervix. *South Med J* 1980;**73**:1186-8.
22 Carmichael JA, Clarke DH, Moher D, Ohlke ID, Karchmar EJ. Cervical carcinoma in women aged 34 and younger. *Am J Obstet Gynecol* 1986;**154**:264-9.
23 Russell JM, Blair V, Hunter RD. Cervical carcinoma: prognosis in younger patients. *Br Med J* 1987;**295**:300-3.
24 Gauwerky F. Ergebnisse und Erfahrungen bei der Behandlung des Uteruskarzinoms. *Strahlentherapie* 1948;**77**:325-48.
25 Ashley DJB. Evidence for the existence of two forms of cervical carcinoma. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1966;**73**:382-9.
26 Lindell A. Carcinoma of the uterine cervix; incidence and influence of age; statistical study. *Acta Radiologica [Stockh]* 1952;**92** (suppl):1-102.
27 Stanhope CR, Smith JP, Wharton JT, Rutledge FN, Fletcher GH, Gallager HS. Carcinoma of the cervix: the effect of age on surival. *Gynecol Oncol* 1980;**10**:188-93.
28 Singer A. Cancer of the cervix; diagnosis and treatment. *Clin Obstet Gynecol* 1985;**12**:ix-x.
29 Morgan LS, Nelson JH. Surgical treatment of early cervical cancer. *Semin Oncol* 1982;**9**:312-30.
30 Campion MJ, Singer A, Mitchell HS. Complacency in diagnosis of cervical cancer. *Br Med J* 1987;**294**:1337-9.
31 Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstet Gynecol* 1975;**46**:507-10.
32 Wentz WB, Reagan JW. Survival in cervical cancer with respect to cell type. *Cancer* 1959;**12**:384-8.
33 Wentz WB, Lewis GC. Correlation of histologic morphology and survival in cervical cancer following radiation therapy. *Obstet Gynecol* 1965;**26**:228-32.
34 Swan DS, Roddick JW. A clinical pathological correlation of cell type classification for cervical cancer. *Am J Obstet Gynecol* 1970;**116**:666-70.
35 Van Nagel JR Jr, Donaldson ES, Parker JC, *et al*. The prognostic significance of cell type and lesion size in patients with cervical cancer treated by radical surgery. *Gynecol Oncol* 1977;**5**:142-51.
36 Chung CF, Stryker JA, Ward SP, Nahhas WA, Mortel R. Histologic grade and prognosis of cancer of the cervix. *Obstet Gynecol* 1981;**57**:636-41.
37 Beecham JB, Halvorsen T, Kolbenstvedt A. Histologic classification, lymph node metastases and patients survival in stage IB cervical cancer: an analysis of 245 uniformly treated cases. *Gynecol Oncol* 1978;**6**:95-105.
38 Shingleton HM, Gore H, Bradley DH, *et al*. Adenocarcinoma of the cervix. I. Clinical evaluation and pathologic features. *Am J Obstet Gynecol* 1981;**139**:799-814.
39 Rutledge FN, Galakatos AE, Wharton JT, *et al*. Adenocarcinoma of the uterine cervix. *Am J Obstet Gynecol* 1975;**122**:236-45.

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Passive smoking and lung cancer: a publication bias?

JAN P VANDENBROUCKE

Abstract

To assess the likelihood of publication bias in a recent review of the effect of passive smoking on lung cancer the evidence from the reviewed papers was visualised on a "funnel" plot. In such a plot if the relative risks from various studies are plotted according to sample size they should scatter round some underlying true value, the scatter being greatest where the studies have the lowest statistical power—thus showing a "funnel" pattern. If there is publication bias and studies with non-significant results are not being published there should be a "gap" in the plot. The logarithm of the relative risks was plotted against the standard error of the logarithm of the relative risk (which was used instead of sample size as a measure of statistical uncertainty). The resulting plot was compatible with a publication bias but only in studies on men.

Further studies of passive smoking and lung cancer in men seem to be warranted.

Department of Clinical Epidemiology, University Hospital, PO Box 9600, 2300 RC Leiden, The Netherlands
JAN P VANDENBROUCKE, MD, PHD, professor of clinical epidemiology

Introduction

A recent review on passive smoking and lung cancer by Wald *et al* concluded, in line with other reviews, that passive smoking causes a 30% extra risk of lung cancer—that is, a relative risk of 1·30.[1] This conclusion was challenged by Mantel, who held, among others, that publication bias was responsible for this result and concluded, "Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice."[2]

The objection of publication bias is interesting, since it is amenable to statistical analysis by the use of "funnel plotting."[3]

Methods and results

The principle is straightforward. When a diverse number of estimates of some value exist one expects some scatter around the underlying truth. The scatter will be largest, however, for the studies which contain the smallest number of subjects—that is, those which have lowest statistical power.