ORIGINAL ARTICLE

A population-based analysis of incidence, mortality, and stage-specific survival of cervical cancer patients in Hong Kong: 1997-2006

CME

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Objectives To determine the trends in incidence and mortality of cervical cancer patients diagnosed during 1997 to 2006, and to describe stage-specific survival using population-based cancer registry data.

Design Retrospective, population-based study.

Setting Hong Kong.

Patients All patients diagnosed with cervical cancer between 1997 and 2006. Patients eligible for survival analysis were followed up till 31 December 2007.

Main outcome measures Age-standardised incidence and mortality rates and average annual percent changes in these parameters were calculated using the Poisson regression model. Survival was expressed as relative survival rate using a period approach. Hazard ratios of mortality including 95% confidence intervals for certain variables were estimated using the Cox proportional hazards model.

Results During the 10-year period of the study, overall annual incidence and mortality rates decreased by 4.2% and 6.0%, respectively. Significant rates of reduction were observed in all age-groups except those younger than 45 years. The reduction in incidence of squamous cell carcinoma (3.6% annually) was less than that of adenocarcinoma (5.2%) and other histological types (6.8%). In all, 3807 (86.4%) of the patients were included in survival analysis. The overall 5-year relative survival rate was 71.3% (95% confidence interval, 69.5-73.1%), while the values for stages I, II, III, and IV were 90.9%, 71.0%, 41.7%, and 7.8%, respectively. Age, stage, and histology were independent prognostic factors. Survival of stage IA patients was as good as that of the general population.

Conclusions As in other industrialised countries, the incidence and mortality rate of cervical cancer were decreasing. Stage-specific population-based cancer survival was available for the first time, and was useful as an indicator of cancer control. Collaboration between public and private sectors to further improve the follow-up data could provide more comprehensive surveillance information.

Key words
Epidemiologic studies; Incidence; Prevalence; Survival analysis; Uterine cervical neoplasms

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Introduction

In 2007, cervical cancer was the third most common gynaecological cancer and the eighth most common women's cancer in Hong Kong.[1] The median age at diagnosis was 52 years. Squamous cell carcinoma (SCC) was the most common, followed by adenocarcinoma (ADC) [including adenosquamous carcinoma], each accounting for 74.4% and 15.5% of all cases, respectively.

The Hong Kong Cancer Registry (HKCaR) is a population-based registry established in 1963, and covered the entire population in the region. The collected data attained the quality and completeness criteria for inclusion in the last six volumes of "Cancer Incidence in Five Continents" edited by the International Agency for Research on Cancer.[2] Basic data like demographics, the anatomical site, and the pathology of cancer were recorded. Cancer death data were also included. Completeness of the coverage was demonstrated by the

1997至2006年香港子宮頸癌患者的發病率、死亡率和癌症分期存活率：以人口為基礎的研究

目的 透過涵蓋全港人口為本的癌症登記資料庫數據，檢視1997至2006年期間確診子宮頸癌患者的發病率和死亡率的趨勢，並描述患者的分期存活率。

設計 回顧性、以人口為基礎的研究。

安排 香港。

患者 1997至2006年期間所有確診子宮頸癌患者，並跟進合乎存活分析的患者至2007年12月31日。

主要結果測量 年齡標準化發病率和死亡率，及利用卜瓦松（Poisson）迴歸模型計算年度平均百分比變化。患者存活率則按癌症分期的相對存活率顯示。部份變數的死亡率風險比及其95%置信區間則以Cox比例風險模型估計。

結果 在進行研究的10年期間，整體年度發病率和死亡率分別減低4.2%和6.0%。除45歲以下的年齡組別，其他組別的上述比率均顯著減低。鱗狀細胞癌發病率減低的幅度（每年3.6%）不及腺癌（5.2%）和其他類型癌腫（6.8%）。研究共為3807名（86.4%）患者進行存活分析。整體5年的相對存活率為71.3%（95%置信區間：69.5-73.1%），而各階段的存活率如下：第I期90.9%、第II期71.0%、第III期41.7%、第IV期7.8%。年齡、癌症分期和癌腫類型是獨立預後因素。第IA期患者存活率理想，跟一般人口相若。

結論 香港子宮頸癌的發病率和死亡率正逐漸改善，情況跟其他工業化國家相若。這是首個以全港人口為基礎及按癌症分期的存活率研究，並可視作癌症控制的指標。公營和私營機構的合作可進一步強化隨訪期數據，提供更加全面的監測信息。

very low (<1%) rate of 'death-certificate only' cases in recent years. For some cancers including cervical cancer, stage information was collected since 2001. The aim of the Registry was to identify, as completely and accurately as possible, all newly diagnosed cases of cancer in the territory. The Registry obtains information from: (1) reports on patients referred to oncology or radiotherapy centres in both public and private hospitals; (2) pathology reports from all public and most private hospitals; (3) electronic in-patient and out-patient records from all public hospitals; (4) death certificates kept by the Government; and (5) voluntary notification from medical practitioners. A quarter-century collection of population-based cancer statistical information on incidence and mortality is readily accessible on the internet. While the public hospital information was relatively comprehensive and easily accessible, private practice follow-up data were based on voluntary notification and subject to private practice agreement.

Survival information has long been recognised as an important indicator for monitoring the success of cancer-control activities.[3] Important prerequisites to obtaining valid survival estimates on a population-based level are that the follow-up data should be complete and of high quality.[4] The majority of such information was available from either the electronic Patient Record system of the public health care system (containing information on over 90% of cancer patients in Hong Kong), or from routine record linkage of data on all deceased persons provided by the Government's Births and Deaths General Register Office.

The purpose of the current study was to estimate for the first time, the incidence and mortality rates, as well as stage-specific population-based survival rates of patients with cervical cancer in Hong Kong. The study also examined survival patterns of different patient groups according to age, stage, and histology. These data could provide valuable information for future planning and evaluation of interventions against cervical cancer, such as those resulting from implementation of the mass Cervical Screening Programme provided by the Department of Health in 2004.

Methods

This retrospective study was limited to individuals newly diagnosed to have cervical cancer and registered in the HKCaR from 1997 to 2006, because this facilitated retrieval of relevant details; information on death from causes other than cancer was not available prior to that time. Apart from patient demographic characteristics, the following data were collected/verified: date of diagnosis (accurate to the month), tumour site, histological type (according to the International Classification of Diseases for Oncology), and tumour staging as per the Federation Internationale de Gynecologie et d'Obstetrique (FIGO), and the International Union Against Cancer 6th edition.[5] For histological types, cases were divided into SCC (large-cell nonkeratinising type, large-cell keratinising type SCCs), ADC (adenocarcinoma and adenosquamous carcinoma) and others. Patients were divided into the following age-groups for analysis: younger than 45, 45-59, 60-74, and 75 years or older.

A total of 4407 patients with invasive cervical cancer were registered during the study period, of whom 97.8% were verified microscopically; 2.1% were clinically diagnosed and less than 0.1% were based on death certification only. The annual incidence and mortality rates were standardised by the direct method using the world standard population.[6] Trends in incidence and mortality over 10-year periods were analysed for the four age-groups and each histological type (if known). The annual percent change was calculated using the Poisson regression model, by fitting a regression line to the natural logarithm of the annual standardised rates, using calendar year as a regressor variable (ie $y = mx + b$ in which $y = \ln$ (rate)

and x = calendar year). The estimated annual percent change (EAPC) was then equal to 100* (e^m–1).

Of the 4407 incident cases, 600 (13.6%) were excluded from the survival analysis for the following reasons: other pre-existing or coexisting primary malignancies; diagnosis based on death certificate only; unknown age at diagnosis; aged ≥100 years; and loss to follow-up. Survival analyses were based on the cohort of the remaining 3807 (86.4%) patients followed up until 31 December 2007. The end-point of each analysis was: (1) the date of death; (2) the censored date of last follow-up, or (3) termination of the study.

In order to allow for deaths due to other causes, survival was expressed as a relative survival rate, which is the ratio between observed survival and expected survival. Hence, the probability of surviving was compared with a group of the general population with same age distribution and birth cohort. Expected survival rates were estimated according to the Hakulinen's method,[7] using Hong Kong population life tables.[8] The calculations were carried out using the SURV3 analysis programme.[9] The Multivariate Cox proportional hazards model[10] was then used to assess the impact of covariates on survival and estimate adjusted relative risks and 95% confidence intervals (CIs), after adjusting for other covariates. These calculations were performed using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US). All tests were two-sided and P values of less than 0.05 were considered statistically significant.

Results

Incidence and mortality

Between 1997 and 2006, there were on average 441 women diagnosed with cervical cancer each year (4.5% of all cancers in women). The crude rates of incidence and mortality were 12.8 and 3.8 per 100 000 women, respectively. Stage distribution was: I, 42.0%; II, 27.7%; III, 16.8%; IV, 4.7%; and unstaged, 8.8%. Average annual rates by age-groups, histological types, and calendar year of diagnosis are shown in Table 1. Overall, age-standardised incidence rates decreased annually by 4.2% (P<0.001) and 6.0% in mortality (P=0.001) during the period. There were significant decreases in both incidence and mortality in almost all age-groups, except those diagnosed when younger than 45 years. There was a greater decrease in mortality than incidence in almost all age-groups, except in those diagnosed aged 75 years or older. The greatest drop in incidence rates was in patients 75 years or older, while it was static in the youngest age-group. Figure 1 shows the change in age-specific incidence rates over the three periods. For the most recent period, the age-specific incidence

TABLE 1. Cervical cancer incidence and mortality per 100 000 women in Hong Kong, 1997-2006

Categories	No. of new cases	1997-1999	2000-2002	2003-2006	EAPC (%)*	P value
		Mean annual incidence				
Age-group (years)						
<45	1273	5.7	5.6	5.5	-0.6	0.353
45-59	1320	24.7	22.4	18.4	-4.4	0.004
60-74	1157	40.3	31.6	29.6	-4.3	0.005
≥75	653	47.1	38.9	27.6	-7.4	0.001
All ages†	4407‡	10.9	9.2	8.1	-4.2	<0.001
Histology§						
SCC	3277	7.9	6.9	6.1	-3.6	0.008
ADC	683	1.7	1.5	1.2	-5.2	<0.001
Others	447	1.2	0.8	0.8	-6.8	0.006
	No. of deaths	Mean annual mortality				
Age-group (years)						
<45	182	0.9	0.8	0.7	-2.0	0.170
45-59	328	7.3	4.7	4.5	-5.8	0.039
60-74	399	15.2	10.7	9.4	-6.5	0.005
≥75	409	26.4	23.3	19.6	-4.2	0.005
All ages†	1318	3.4	2.4	2.1	-6.0	0.001

* EAPC denotes estimated annual percent change over the 10-year period
† Rates were age-adjusted to the world standard population
‡ Includes four cases with unknown age
§ SCC denotes squamous cell carcinoma, and ADC adenocarcinoma

curve shows a peak at 65-69 years, which was 10 years earlier than in previous periods. There were also changes in the proportion of these various cervical cancers with respect to the histological diagnosis; the incidence being significantly decreased for SCC (EAPC, -3.6%; P=0.008), ADC (EAPC, -5.2%; P<0.001) and other rare tumours (EAPC, -6.8%; P=0.006).

Survival

Among the 3807 incident cases of cervical cancer patients selected for the survival analysis, 28.6% were aged below 45 years and 14.3% were aged 75 years or above. There was no significant difference in stage distribution between those in the survival analysis group and those who were excluded. The mean follow-up time was 51 months (range, 1-132 months). Table 2 summarises the 5-year relative survival rates of cervical cancer patients according to stage and histology. The overall 5-year relative survival rate of all patients was 71.3% (95% CI, 69.5-73.1%). Relative survival rates at 5 years according to FIGO staging were: 90.9%, 71.0%, 41.7%, and 7.8% for stages I, II, III, and IV, respectively. There were considerable differences in survival rates among different substages (Fig 2). The prognosis of patients with stage IA was nearly the same as that of the general population and the survival of those with stage IIA and IIB cancers were similar. The multivariate Cox proportional hazards model also confirmed that age-group, stage, and histology had a significant impact on survival (Table 3).

Discussion

This study was the first report based on the HKCaR

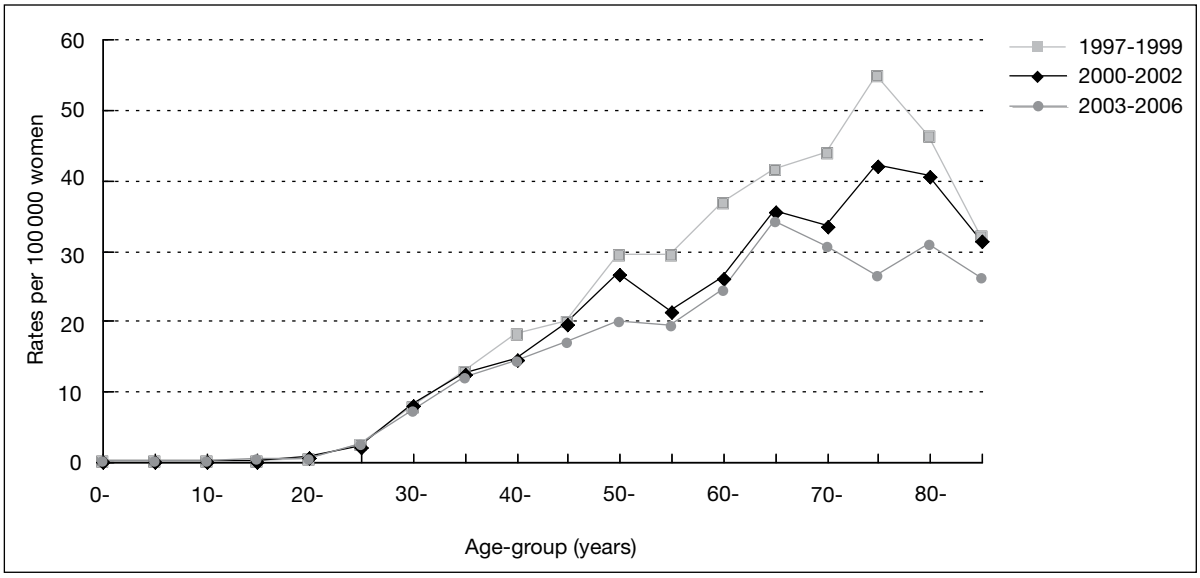

FIG 1. Age-specific incidence rates for cervical cancer in Hong Kong

TABLE 2. Survival of patients with cervical cancer according to stage and histology

Categories	No.	Survival rate (%)					95% Confidence interval for 5-year survival
		1 Year	2 Years	3 Years	4 Years	5 Years	
All	3807	90.6	81.0	76.6	73.2	71.3	69.5-73.1
Stage							
I	1598	98.3	95.1	93.4	91.7	90.9	89.0-92.7
II	1062	95.1	83.7	78.3	74.5	71.0	67.5-74.5
III	643	81.6	63.1	52.7	44.4	41.7	36.9-46.4
IV	179	39.9	18.9	14.5	9.8	7.8	2.8-12.9
Unstaged	325	83.8	72.0	67.5	65.6	63.6	56.2-69.1
Histology*							
SCC	2978	91.8	82.6	78.0	74.6	72.6	70.6-74.6
ADC	533	90.3	80.0	75.9	72.7	70.5	66.0-75.1
Others	296	79.8	67.7	63.7	60.4	60.0	53.4-66.5

* SCC denotes squamous cell carcinoma, and ADC adenocarcinoma

on incidence, mortality, and stage-specific survival rates for cervical cancer. The strength of this study is that it is population-based, comprising virtually all cases in Hong Kong and covering different hospitals, districts, and social classes.

The 5-year relative survival rate of cervical cancer in Hong Kong appears comparable to reported rates in other developed countries (Table 4[11-16]). The 5-year survival rate for Hong Kong patients (71.3%) was higher than that of Singapore (64.7%), United Kingdom (65.2%), and Sweden (71.0%), but slightly lower than that of Japan (71.5%), the US (73.3%), and Australia (73.6%). These results, however, should be interpreted with caution due to differences in the

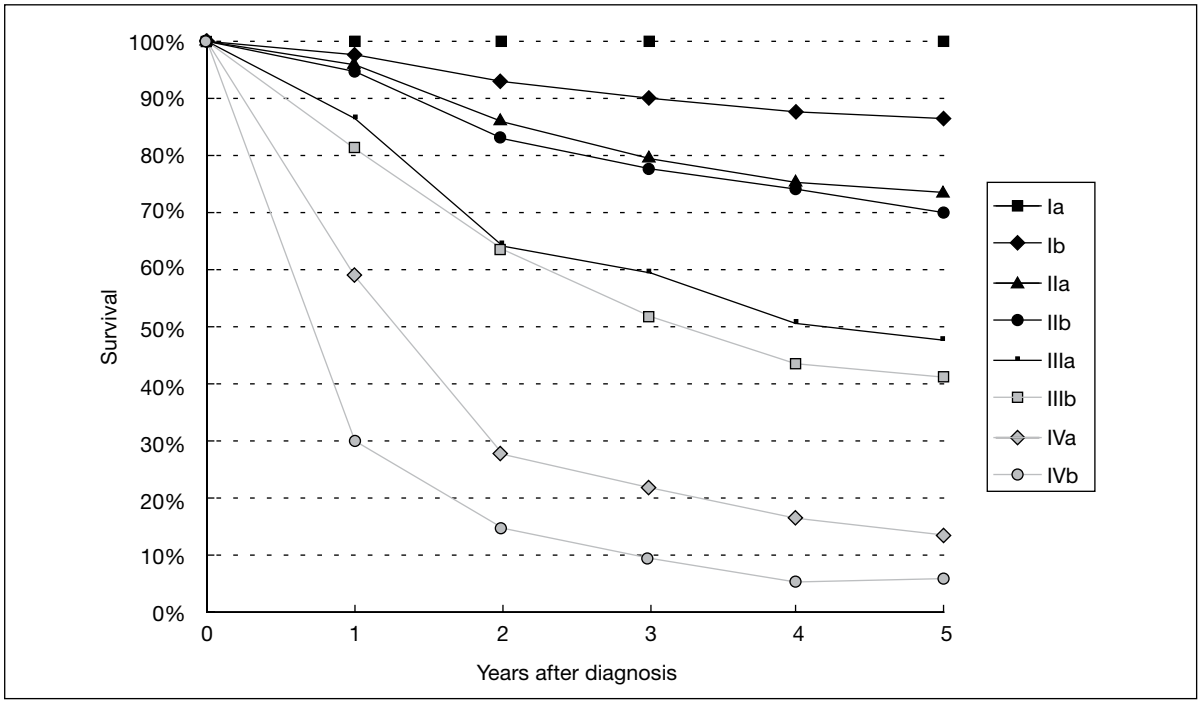

FIG 2. Survival of patients with cervical cancer in Hong Kong according to their FIGO substage
FIGO denotes Federation Internationale de Gynecologie et d'Obstetrique

TABLE 3. Univariate and multivariate analyses of overall survival for cervical cancer patients

Categories	No. of cases	Univariate*		Multivariate†	
		Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Age-group (years)					
<45	1089	1	Reference	1	Reference
45-59	1163	1.60	1.33-1.93	1.21	1.01-1.47
60-74	1008	2.37	1.98-2.83	1.61	1.34-1.94
≥75	547	5.42	4.52-6.49	3.06	2.52-3.71
Stage					
I	1598	1	Reference	1	Reference
II	1062	3.35	2.80-4.01	2.87	2.39-3.46
III	643	7.58	6.34-9.06	6.24	5.17-7.53
IV	179	26.47	21.29-32.92	21.14	16.90-26.45
Unstaged	325	4.32	3.46-5.40	3.72	2.97-4.65
Histology‡					
SCC	2978	1	Reference	1	Reference
ADC	533	0.99	0.84-1.17	1.72	1.41-2.10
Others	296	1.59	1.31-1.92	2.64	2.14-3.25

* Use of Cox regression on single covariate
† Use of Cox proportional hazards model adjusted for all other factors in the table
‡ SCC denotes squamous cell carcinoma, and ADC adenocarcinoma

TABLE 4. Comparisons with international reports of 5-year survival from cervical cancer

Country or population	Year of diagnosis	5-Year relative survival rate (%)
Hong Kong	1997-2006	71.3
Korea[11]	1998-2002	80.4
Japan[12]	1997-1999	71.5
Singapore[13]	1998-2002	64.7
Australia, NSW[14]	1999-2003	73.6
UK, England[15]	1995-1999	65.2
Sweden[15]	1995-1999	71.0
US[16]	1995-2001	73.3

periods studied and standardisation methods.

Extent of disease at diagnosis is the most important determinant of survival, implying that early detection is a more important outcome than improvement in the treatment modality. The very high survival in early-stage disease suggests that early presentation and rapid referral are essential. Survival of cervical cancer patients varies with age. After multivariate adjustment, patients with ADC had a worse prognosis than those with SCC. This may indicate that women with cervical ADC have an inherently worse prognosis than women with SCC.

There was continuous significant reduction in the incidence and mortality of patients with cervical cancer over the study period, with unadjusted 5-year relative rate improved from 69.6% in 1997-1999 to 73.2% in 2000-2002 before the implementation of an organised screening programme by the Department of Health in 2004. The overall reduction in incidence in these earlier years might be attributed to period and cohort effects[17] and lower incidences might eventually be translated into reduced mortality. On the other hand, the observed drop in incidence could also have been related to an increase in opportunistic screening that mainly identified pre-cancerous lesions. Subsequent organised screening, if successful, could lead to a steeper fall in incidence rates in the ensuing years. Thus, the present incidence data could serve as a baseline for future comparison.

The steadily decreasing incidence and mortality of cervical cancer in Hong Kong was consistent with trends in other industrialised countries.[18] Various studies revealed that widespread use of cervical screening has been associated with the substantial reduction in incidence and mortality rates of cervical cancer.[19-24] Iceland, Finland, Sweden, and parts of Denmark[25,26] achieved almost complete coverage of the target populations, resulting in sharp falls in incidence and mortality. The increasing survival from cervical cancer was at least partly due to the nationwide programme.[27] However, as cervical cancer incidence in Hong Kong has already dropped to a very low level compared to other western developed countries even before the implementation of organised mass screening, the merit of any mass screening programme towards further decrease of cervical cancer incidence is indeed questionable.

This study provides the first population-based investigation of stage-specific survival of a major cancer—cervical cancer—in the territory. As a baseline, it would provide an effective and economical method of evaluating the impact of the organised screening programme through observation of the future changes in cervical cancer incidence, mortality and survival at community level. Further analyses with longer follow-up periods will also enrich the information for planning or evaluation of actions against this disease. Closer collaboration with private practice on follow-up data would certainly perfect the staging and surveillance data.

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