Original Article

Incidence, Mortality and Five-year Relative Survival Ratio of Prostate Cancer among Chinese Residents in Singapore from 1968 to 2002 by Metastatic Staging

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Abstract

Introduction: This paper examines the incidence, mortality and survival patterns among all Chinese residents with prostate cancer reported to the Singapore Cancer Registry in Singapore from 1968 to 2002 by metastatic staging. Materials and Methods: This is a retrospective population-based study including all prostate cancer cases aged over 20 reported to the Singapore Cancer Registry (SCR) from 1968 to 2002 who are Singapore Chinese residents. Follow-up was ascertained by matching with the National Death Register until 2002. Metastatic status was obtained from the SCR. Age-standardised incidence and mortality rates, as well as the 5-year relative survival ratios (RSRs), were obtained for each 5-year period and grouped by metastatic stage. A weighted linear regression was performed on the log-transformed age-standardised incidence and mortality rates over the study period. Results: In the most recent period of 1998 to 2002, the age-standardised incidence and mortality rates (per 100,000) for prostate cancer among the Chinese were 30.9 (95% CI, 29.1 to 32.8) and 9.6 (95% CI, 8.6 to 10.7), respectively. The percentage increase in the age-standardised incidence and age-standardised mortality rates per year were 5.6% and 6.0%, respectively, for all Chinese Singapore residents. There was an improvement in the 5-year RSRs for Chinese diagnosed with non-metastatic cases from 51.3% in 1973 to 1977, to 76.1% in 1998 to 2002. However, the RSR remains poor (range, 11.1% to 49.7%) for Chinese diagnosed with metastatic prostate cancer. Conclusions: Both age-standardised incidence and mortality rates for prostate cancer among Chinese Singapore residents are still on the rise especially since the 1990s. Since the 1990s, the improvement in RSRs was substantial for the Chinese non-metastatic cases.

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Introduction

Prostate cancer is now the third most common cancer among Singapore males, with a world age-standardised incidence rate (ASIR) of 23.9 per 100,000 from 2003 to 2007.[1] The average annual rate of increase between 1968 and 2002 was 5.6%, with a steeper increase seen in the last 10 years.[2] Signorello and Adami[3] noted that Western countries have a higher prostate cancer incidence than Asian countries. From *Cancer Incidence in Five Continents*,[4] the incidence rate of prostate cancer in Singapore (ASIR of 28.7 per 100,000) was much lower than that of Western countries such as the United States (ASIR of 197.4 per 100,000), but higher compared to other Asian countries such as China, Shanghai (ASIR of 11.6 per 100,000) and India, Mumbai (ASIR of 11.5 per 100,000).[5]

Interestingly, in spite of the increasing incidence of prostate cancer in many countries, a substantial reduction in prostate cancer mortality has been reported in the United Kingdom, the United States, Austria, Canada, Italy, France, Germany, Australia and Spain.[6] One of the possible reasons that have been proposed for the reduction in prostate cancer mortality is the widespread use of prostate-specific antigen (PSA) screening in some of the developed countries, especially in the United States. In contrast, PSA screening is

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not routinely done in Singapore. It will be useful to compare the time trends in Singapore prostate cancer incidence and mortality rates between metastatic and non-metastatic cancers, with that of some developed countries which may reveal an association between prostate cancer mortality and the frequency of PSA screening.

In order to better elucidate the progress against cancer,[7] survival trends will be interpreted simultaneously with the trends in incidence and mortality. In our earlier paper, we demonstrated ethnic differences in the prostate cancer incidence, mortality and 5-year relative survival among resident Singapore Chinese, Malays and Indians.[8] Therefore, this study will examine the effect of metastasis on the incidence, mortality and survival patterns unique to the Singaporean Chinese prostate cancer cases diagnosed from 1968 to 2002.

Materials and Methods

Study Population

This is a retrospective population-based study using data from the Singapore Cancer Registry which was established in 1968. All medical practitioners and pathology laboratories voluntarily notify the registry of any incident cancers, and registry staff also review hospital discharges and death certificates against registered cases to ensure completeness of cancer reporting.

Only Chinese Singapore residents aged 20 years and above with prostate cancer diagnosed from 1968 to 2002 (n = 2834) were included in the analysis. The median age of diagnosis was 73 years, with interquartile range of 67 to 79. The distribution of prostate cancers from the registry was as follows: 1186 non-metastatic (N) (41.8%), 533 metastatic (M) (18.8%) and 1115 unknown metastatic (U) cases (39.3%) from the information obtained from the registry. The U group consisted of prostate cancer cases that were not staged either because: (i) the case was not investigated further to determine if metastasis had occurred, or (ii) the notifier did not make this information available to the cancer registry.

Statistical Analysis

The prostate cancer incidence and (cause-specific) mortality rates were age-standardised using the world standard population with 5-year age groups (20-24, 25-30, …, 75-79, 80+) and 7 calendar periods (1968-1972, …, 1998-2002). The denominators for both incidence and mortality rates were the total number of person-years from the Singapore resident population. Confidence intervals for the ASRs were computed using the gamma distribution approach.[9] To test for any linear trend over time in the log-transformed ASRs, we performed a weighted linear regression using the inverse of the variance as weight, and performed a Wald test. We used the coefficient of determination (R^2) to assess the goodness-of-fit of the regression.

Relative survival was used to measure the survival of prostate cancer patients. It is computed by taking the ratio of the observed survival of patients and the expected survival of a comparable group (in terms of attained age and year of diagnosis) in the general population. The expected survival rates, which were estimated from all causes of death in the general Singapore population, were computed using the Ederer II method.[10] A period-based approach was adopted to give a more up-to-date estimate on cancer survival.[11,12] Age-standardisation of the relative survival ratios (RSRs) to the World Standard Cancer Population[13] was performed using Brenner's approach,[11] with age being categorised into 4 groups (20-54, 55-64, 65-74, 75+ years) for all prostate cancer cases and 3 groups (20-64, 65-74, 75+ years) for prostate cancer sub-groups.

Results

From 1968 to 2002, the ASIR of prostate cancer (per 100,000) among the Chinese was 18.7 (95% CI, 18.0 to 19.4). In the most recent period of 1998 to 2002, the ASIR was 30.9 (95% CI, 29.1 to 32.8). The percentage increase in ASIRs per year from 1968 to 2002 was 5.6%, (P <0.0005). A linear regression model provided a good fit to the data (R^2 = 99%). From 1968 to 2002, the age-standardised mortality rate (ASMR) of prostate cancer (per 100,000) among the Chinese was 7.8 (95% CI, 7.3 to 8.2). In the most recent period of 1998 to 2002, the ASMR (per 100,000) was 9.6 (95% CI, 8.6 to 10.7). The percentage increase in ASMR per year from 1968 to 2002 was 6.0% (P <0.0005). A linear regression model provided a good fit to the data (R^2 = 99%).

There were significant upward trends in the ASMR among the N (P = 0.001) and the M (P = 0.002) cases (Table 1 and Figs. 1a, 1b). The percentage increases in ASMR per year from 1968 to 2002 were 6.8% and 4.7% for N and M cases, respectively. The survival experience (i.e. 5-year RSR) of the Chinese N cases in post-1990 was higher than pre-1990 (Table 1 and Fig. 1a). The 5-year RSRs for N cases seemed to have reached a plateau since 1990. The RSRs for M cases did not show any improvement over the years, but the number of cases was small in general (Table 1). The 5-year RSRs for U cases followed a similar pattern as that of the N cases (Table 1 and Fig 1c).

Discussion

Our analysis showed that the incidence and mortality rates of prostate cancer had been on the rise in Singapore Chinese over the last few decades and have risen more rapidly since the 1990s.

Table 1. Chinese (Aged 20 Years and Above) Age-adjusted Incidence and Mortality Rates, and 5-year Relative Survival Ratios of Prostate Cancer from 1968 to 2002

	Period	Incidence rate (per 100,000)		Mortality rate (per 100,000)		Relative survival ratio (%)	
		Total	Rate (95% CI)	Total	Rate (95% CI)	Total*	Ratio (95% CI)
Non-metastatic	1968-1972	33	3.1 (2.0-4.4)	5	0.5 (0.1-1.4)	-	-
	1973-1977	40	3.0 (2.1-4.2)	10	0.8 (0.4-1.6)	11.6	51.3 (31.8-72.0)
	1978-1982	61	3.5 (2.6-4.5)	17	1.0 (0.6-1.6)	10.1	47.7 (28.4-68.0)
	1983-1987	82	4.1 (3.3-5.1)	28	1.4 (0.9-2.1)	30.7	55.7 (39.9-72.0)
	1988-1992	146	5.8 (4.9-6.9)	34	1.3 (0.9-1.8)	41.2	76.5 (61.9-90.1)
	1993-1997	306	10.3 (9.2-11.6)	54	1.8 (1.3-2.3)	81.4	76.3 (65.1-86.8)
	1998-2002	518	14.7 (13.5-16.0)	100	2.8 (2.3-3.4)	179.5	76.1 (69.0-82.9)
Metastatic	1968-1972	24	2.0 (1.2-3.2)	8	0.6 (0.3-1.3)	-	-
	1973-1977	22	1.6 (1.0-2.5)	10	0.6 (0.3-1.2)	6.4	11.1 (2.5-29.3)
	1978-1982	24	1.3 (0.9-2.0)	11	0.6 (0.3-1.2)	9.1	49.7 (25.8-75.2)
	1983-1987	41	2.0 (1.4-2.8)	11	0.5 (0.3-1.0)	5.3	16.9 (5.3-35.6)
	1988-1992	95	3.6 (2.9-4.5)	41	1.6 (1.1-2.2)	15.4	43.0 (27.1-60.2)
	1993-1997	147	4.9 (4.2-5.8)	89	2.9 (2.3-3.6)	22.5	23.4 (15.0-33.5)
	1998-2002	180	5.1 (4.4-5.9)	120	3.4 (2.8-4.1)	39.5	33.7 (25.1-43.0)
Unknown metastatic status	1968-1972	17	1.3 (0.8-2.1)	5	0.3 (0.1-0.8)	-	-
	1973-1977	42	3.0 (2.1-4.1)	10	0.7 (0.3-1.4)	5.1	25.8 (5.7-58.7)
	1978-1982	94	5.7 (4.6-7.1)	24	1.5 (0.9-2.3)	15.9	41.9 (27.1-58.3)
	1983-1987	134	6.6 (5.5-7.8)	36	1.7 (1.2-2.3)	29.6	50.5 (36.3-65.4)
	1988-1992	170	6.8 (5.8-7.9)	73	2.7 (2.1-3.4)	54.1	51.7 (40.8-62.9)
	1993-1997	265	8.8 (7.8-9.9)	96	3.1 (2.5-3.8)	63.8	50.6 (41.0-60.5)
	1998-2002	393	11.1 (10.0-12.3)	122	3.4 (2.8-4.1)	91.5	59.8 (50.8-68.6)

95% CI: 95% confidence interval
*The effective number at risk in the fifth year of period survival analysis

Generally, prostate cancer incidence and mortality rates are higher in Western countries than Asian countries. Among the Singaporean Chinese, the ASIR was 30.9 and ASMR was 9.6 per 100,000 in the period 1998 to 2002.[8] These rates are still much lower than those found in the United States (ASIR of 197.4 and ASMR of 21.6 per 100,000) and the Nordic countries (e.g. Finland: ASIR of 137.8 and ASMR of 29.7, Sweden: ASIR of 141.0 and ASMR of 35.8 per 100,000) for the same period.[4,14] One possible risk factor for the increasing incidence in Singapore is the adoption of a westernised diet that generally has a higher intake of animal fats. The upward trend seen in the prostate cancer incidence rates in Singaporean Chinese has also been reported in Asian countries such as Japan, China-Hong Kong and China-Shanghai,[15] whose affluence has also led to the adoption of more westernised diets.

A few studies have reported that Asian diets may offer some protection against prostate cancer.[3,16,17] For example, legumes have been shown to confer protection against prostate cancer in a recent multi-ethnic case-control study.[18] Many studies have attempted to elucidate the nutritional aetiology of prostate cancer but definitive answers have not been found. Hence, this will be an interesting and useful avenue of research.

In contrast to figures from the United States where a peak was observed in the 1990s, the ASIRs for Singaporean Chinese were still increasing during 1998 to 2002.[19] One possible reason could be the slower uptake and routine use of PSA testing in Singapore. In the United States, 1.2% of white men received a PSA test in 1988. The percentage increased to nearly 40% in 1994.[20] There is no comprehensive data to illustrate the extent of PSA testing in Singapore. However, from clinical observation, the uptake of PSA testing in Singapore is still low (Cheng 2008 – personal communication). PSA screening tests are offered to men above 50 years of age as part of their health screening exercise but this optional test comes with an additional cost. This may explain why the trend in the age-adjusted prostate cancer incidence rates from Singapore is similar to that in the United Kingdom where the uptake of PSA

is also slower than in the United States.[19] The increase in public awareness with regard to the possible benefits in early diagnosis of prostate cancer, the increasing use of PSA and digital rectal examination (DRE) and the availability of transrectal ultrasound and extended systematic and sextant biopsies for prostate cancer detection in the late 1990s could have also contributed towards sustaining the upward trend in prostate incidence in our study.[15]

The RSR outlook for the Chinese N cases was more favourable for those diagnosed post-1990 compared to those diagnosed in the 1980s (Fig. 1a). This improvement in prognosis is probably related to earlier diagnosis which results in stage migration of the disease and the better treatment modalities. Overall, the ASMR for Singapore has declined over the years: 7.70 per 1000 in 1970, 5.95 per 1000 in 1980 and 4.59 per 1000 in 1990.[21] The 40% decline of the rates between 1970 and 1990 may be attributed to social and economic growth, as well as improvement in medical services and management, and may also contribute to the RSRs reported in this study.

For Chinese patients diagnosed with M prostate cancer, no obvious improvement in RSRs was observed and their corresponding ASIR and ASMR were tracking each other over time (Fig. 1b). This reflects the fatality of M prostate cancer and the lack of long-term effective treatment for M cases. In the early 1990s in the United States, there was a decline in the age-adjusted prostate cancer mortality rate in white men with distant metastasis, after a progressive rise from the 1970s.[22] The difference is most likely due to the use of PSA testing, which leads to earlier diagnosis of patients with asymptomatic metastasis, resulting in a seemingly decline in mortality. Other possible reasons could be over-diagnosis and a benefit from screening; if screening using PSA test is, in fact, effective. There could also be misclassification in staging as some of the asymptomatic patients with "positive bone scan" (based on a few suspicious hot spots) might not actually harbour any secondary at all.

The strength of our study is the high quality data – using Death Certificate Only (DCO) as a measure of completeness

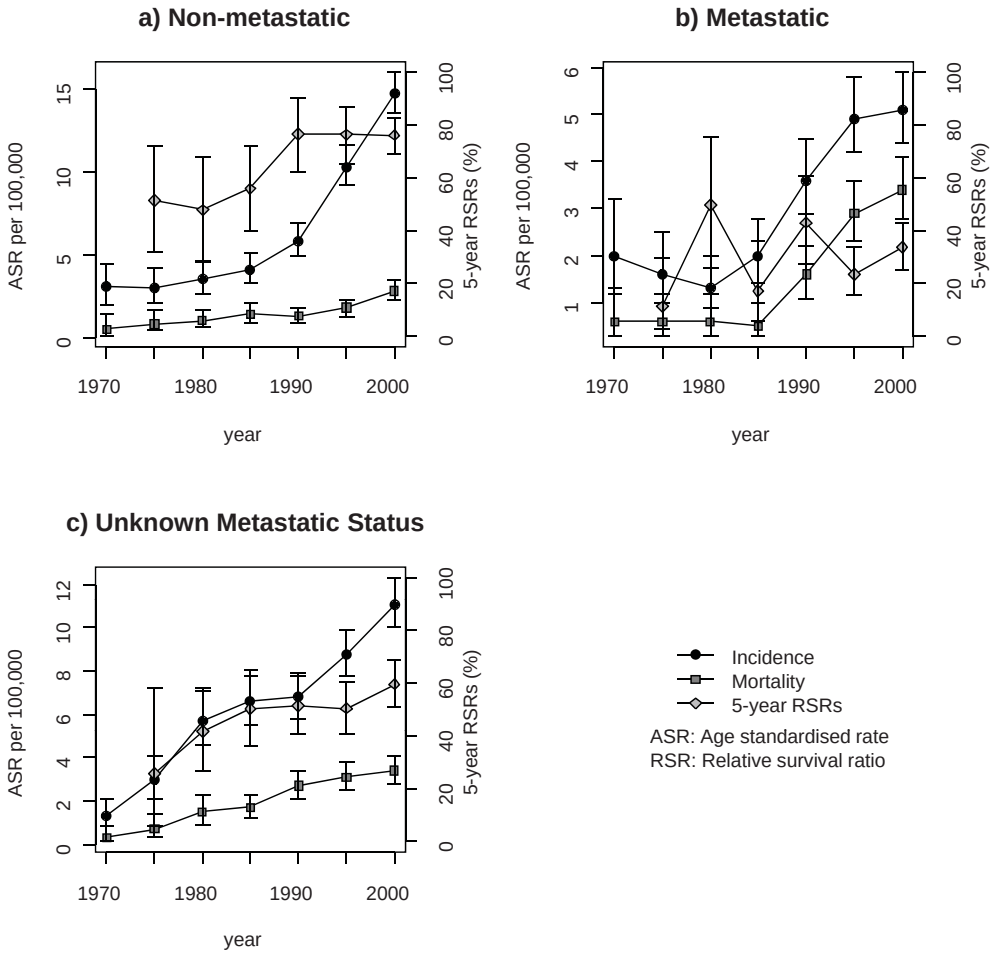

Fig. 1. The incidence (black circle), mortality (dark gray square) and 5-year relative survival (light gray diamond) rates of prostate cancer subtypes among Singapore Chinese residents.

of reporting. The DCO index was approximately 96% in the 1970s and close to 100% in the 1990s. The percentage of microscopic verification was also high, ranging from 72.3% in 1968 to 1972, to 90.6% in 1998 to 2002.[2] The limitation of using DCO as a measure of the quality of the data is that we miss cancers diagnosed and unreported, but that did not lead to death within the study period. However, we expect only very few incident cancers to be missed, as staff from the cancer registry rigorously go through pathology reports from both public and private laboratories to minimise errors.[2] The Registration of Births and Deaths Act in Singapore requires death to be reported within 3 days.[23] Since the emigration rates in Singapore are generally low, emigration of prostate cancer cases is unlikely to affect the study's findings.[24]

A limitation of a study like ours, where data are collected over a time-span of more than 30 years is that, changing diagnostic accuracy is unavoidable. Access to healthcare is also likely to change over time, especially when a country progresses economically, as is the case in Singapore. These factors will not only affect prostate cancer but also cancers at other sites. However, the different incidence patterns reported for site-specific cancers over the last few decades[2] suggest that these factors alone do not explain the steady increase in the incidence of prostate cancer.

Another limitation of our study is that among the Singaporean Chinese, U status constituted 38% of all the incident prostate cancer cases. There were 2 causes for U status: (i) metastatic status was known but not reported (i.e. missing), and (ii) metastatic status was unknown due to lack of adequate information which could arise because patients may be presenting with clinical metastasis and therefore the attending doctor did not send the patient for further investigation (i.e. unknown). Generally, there were no uniform guidelines to the use of proper staging modality such as bone scan especially in the elderly during the early dates. To our knowledge, every effort has been made to reduce the former cause of missing data in the voluntary notification process since besides medical doctors, pathologists and cancer centres in Singapore are also participating in the notification process over the years. To better understand the characteristics of the tumours with U status, we investigated the data recorded concerning the spread of the primary tumour to see if this was changing over time. In contrast to a stable composition illustrating the extent of disease for N cases ($P = 0.127$) and M cases ($P = 0.117$) from 1968 to 2002, there was a significant change among the U cases ($P < 0.0005$) from 1968 to 2002. The incidence and mortality rates of the U group also reflected an increased number of N cases in this group. For this reason, we excluded the U group from our analysis, as it could skew the study's findings. We also noted that the percentage of U status for all Singaporeans was decreasing, from 52% in 1983 to 1987, to 36% in 1998 to 2002. This reduction of percentage is probably a reflection of the better awareness among doctors, and thus the increase in notifications to the cancer registry.

The interpretation of survival trends of prostate cancer could also be complicated by bias created by the screening of prostate cancer. If screening is effective, it should detect cancer at an earlier stage in the natural history among asymptomatic persons. As these early stages of cancer would take a longer time to progress and cause fewer deaths than more advanced tumours, an improvement in the survival of prostate cancer cases could be expected in the coming years. However, the improvement in RSRs for Chinese N cases could also be attributed to lead-time bias arising from PSA testing.

In conclusion, this study shows that there has been an increase in the RSR for N cases but not for the M cases among the Chinese. Possible explanations are lifestyle and dietary factors, changes in treatment modalities for prostate cancer, or early detection as a consequence of PSA testing.

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