The clinical burden of prostate cancer in Canada: forecasts from the Montreal Prostate Cancer Model

Research

Recherche

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This article has been peer reviewed.

CMAJ 2000;162(7):977-83

See related articles pages 987 and 1001

Abstract

Objectives: The incidence of prostate cancer is increasing, as is the number of diagnostic and therapeutic interventions to manage this disease. We developed a Markov state-transition model — the Montreal Prostate Cancer Model — for improved forecasting of the health care requirements and outcomes associated with prostate cancer. We then validated the model by comparing its forecasted outcomes with published observations for various cohorts of men.

Methods: We combined aggregate data on the age-specific incidence of prostate cancer, the distribution of diagnosed tumours according to patient age, clinical stage and tumour grade, initial treatment, treatment complications, and progression rates to metastatic disease and death. Five treatments were considered: prostatectomy, radiation therapy, hormonal therapies, combination therapies and watchful waiting. The resulting model was used to calculate age-, stage-, grade- and treatment-specific clinical outcomes such as expected age at prostate cancer diagnosis and death, and metastasis-free, disease-specific and overall survival.

Results: We compared the model's forecasts with available cohort data from the Surveillance, Epidemiology and End Results (SEER) Program, based on over 59 000 cases of localized prostate cancer. Among the SEER cases, the 10-year disease-specific survival rates following prostatectomy for tumour grades 1, 2 and 3 were 98%, 91% and 76% respectively, as compared with the model's estimates of 96%, 92% and 84%. We also compared the model's forecasts with the grade-specific survival among patients from the Connecticut Tumor Registry (CTR). The 10-year disease-specific survival among the CTR cases for grades 1, 2 and 3 were 91%, 76% and 54%, as compared with the model's estimates of 91%, 73% and 37%.

Interpretation: The Montreal Prostate Cancer Model can be used to support health policy decision-making for the management of prostate cancer. The model can also be used to forecast clinical outcomes for individual men who have prostate cancer or are at risk of the disease.

Prostate cancer develops slowly and affects primarily elderly men.[1] In recent years annual incidence rates have been increasing exponentially, yet mortality rates have been relatively stable.[2–4] Because the lag time between tumour diagnosis and death is often many years, the prevalence of prostate cancer is expected to rise as the proportion of elderly men increases in our society.[5] Several therapeutic options are available to prostate cancer patients. However, considerable controversy exists surrounding the appropriate choice of therapy.[6,7] This controversy stems from the lack of large randomized clinical trials comparing the benefits of therapeutic alternatives.

Given the increasing prevalence of prostate cancer and the uncertainty surrounding appropriate treatment, there is growing concern that the future burden of disease may be substantial.[8] To address these issues we have developed the

Montreal Prostate Cancer Model to estimate the probability of prostate cancer and the annual progression of the disease according to patient age, clinical stage and tumour grade, treatment modalities and competing causes of mortality. In this article we present the methodology underlying the model and demonstrate its validity by comparing the model's forecasts of the clinical burden of prostate cancer with observed outcomes from prospective cohort studies. In an accompanying article, we use the model to estimate the economic burden of prostate cancer in Canada (page 987).[9]

Methods

We developed a Markov state-transition model — the Montreal Prostate Cancer Model — to follow annually a hypothetical cohort of men with prostate cancer or men at risk of prostate cancer. Using this model, we estimated the annual probability of a diagnosis of prostate cancer, progression to metastatic disease, death from prostate cancer, and death from other causes with or without previously diagnosed prostate cancer (Fig. 1). A Markov model is a dynamic, multistate decision model that allows one to forecast prognosis for a particular disease over an extended period.[10,11] We estimated the annual and lifetime progression of prostate cancer according to patient age, clinical stage and tumour grade, and initial treatment.

The model uses the tumour–node–metastasis (TNM) classification for the staging of prostate cancer.[2] The model also considers 3 tumour histologic grades, as defined by the Gleason scoring system:[12] well-differentiated tumours (Gleason score of 2–4), moderately differentiated (Gleason score of 5–7) and poorly differentiated (Gleason score of 8–10). Data supporting the independent effect of tumour volume over tumour grade on prognosis is at present inconclusive,[13] but this potentially important factor has been incorporated into our model for future development.

To forecast tumour management, the model uses aggregate data including the incidence rate of prostate cancer,[14] clinical stage and grade distribution at diagnosis,[15] distribution of initial therapies[15] and their complications,[16–21] choice of follow-up therapy,[19,22,23] progression rates to metastatic disease[21,24–27] and cancer-related mortality following the diagnosis of metastatic disease.[28] Initial clinical stages were based on reported distributions.[15] We assumed these distributions applied across all tumour grades and volume combinations.

For prostatectomy, annual probabilities of progression to metastatic disease were based on the actual number of events re-

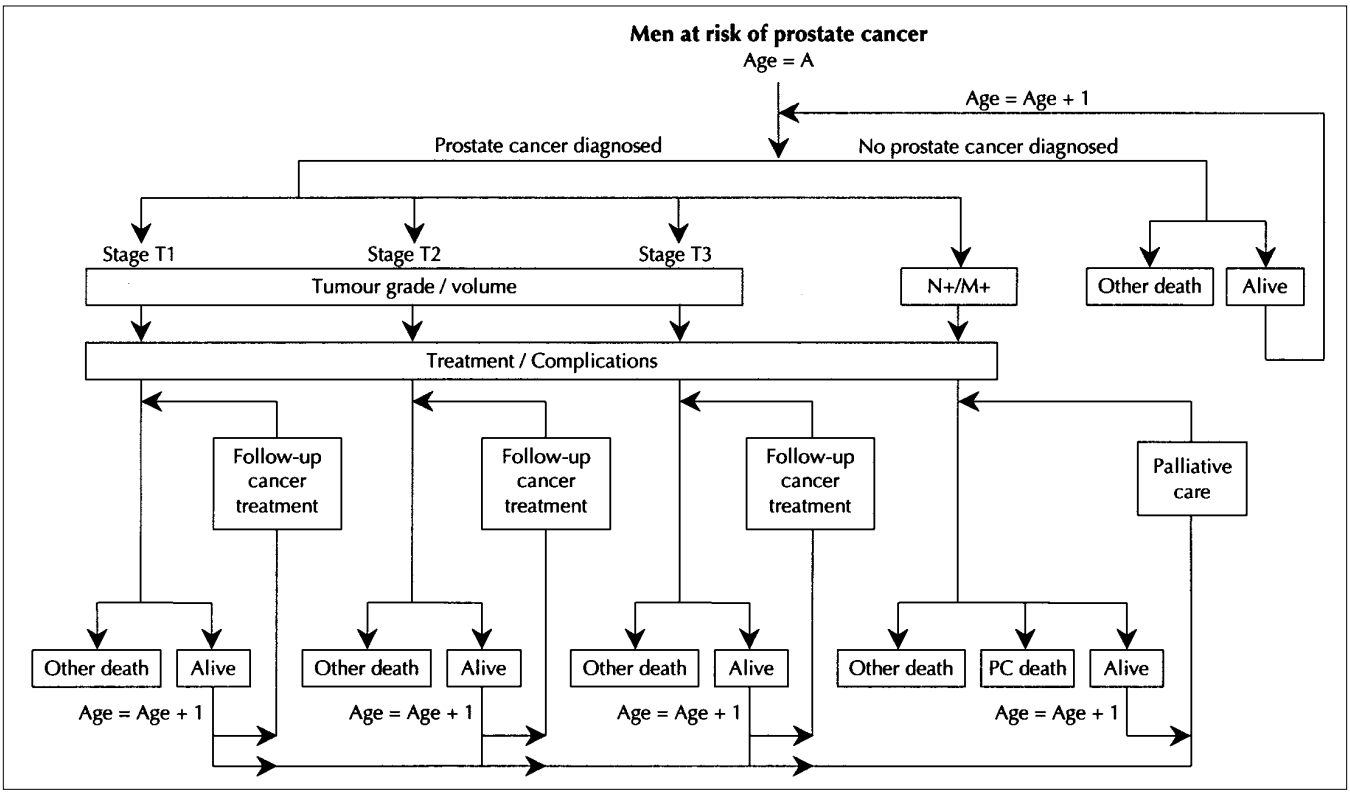

Fig. 1: Overview of the Montreal Prostate Cancer Model. Men at a specified age (A) who are free of prostate cancer are entered into the model, and their risk of cancer being diagnosed over the following year is estimated. Among those diagnosed with prostate cancer, the choice of initial therapy is determined by disease stage, tumour grade and tumour volume. Each therapeutic option is associated with morbidity and mortality risks. Those with prostate cancer who die of the disease or of other causes are removed from the model. All men without prostate cancer remain at risk of non-cancer-related death. After 1 year all survivors are re-entered into the model at age A+1. Those who had undergone initial treatments may receive follow-up therapies or palliative care, or both. N+ = nodal metastasis, M+ = distant metastasis, PC = prostate cancer.

ported by Gerber and associates[24] (Table 1). We assumed that, for prostatectomy, the annual grade-specific progression rates would be the same for stages T2 and T3, since only 49% of patients with clinically localized prostate cancer are found postoperatively to have documented organ-confined tumours (T1 or T2) as opposed to extracapsular (T3) or metastatic (M+) tumours.[24]

Similar estimates were derived from the study by Chodak and colleagues[25] for conservatively managed localized prostate cancer. Because of a lack of comprehensive grade-specific data for T3 tumours, we assumed that the progression rates for T3 would be the same as those for T2.

Stage- and grade-specific progression rates to distant metastatic disease following external-beam radiation therapy were derived from the study by Perez and colleagues.[26] Because grade-specific estimates for T1 tumours were not available, owing to a small number of observations, we assumed that the progression rates for T2 tumours would be the same as those for T1 tumours.

Table 1: Parameters selected for the Montreal Prostate Cancer Model to estimate the clinical outcomes of prostate cancer

Variable (and data source); disease stage/tumour grade	Annual rate, %
Progression to distant metastasis	
After prostatectomy (Gerber et al[24])	
Stage T1	
Grade 1	0.48
Grade 2	1.04
Grade 3	2.32
Stages T2 and T3	
Grade 1	0.47
Grade 2	1.05
Grade 3	2.21
After radiation therapy (Perez et al[26])	
Stages T1 and T2	
Grade 1	1.84
Grade 2	3.32
Grade 3	4.80
Stage T3	
Grade 1	4.40
Grade 2	7.93
Grade 3	11.45
*After conservative management** (Chodak et al[25])	
Stage T1	
Grade 1	0.54
Grade 2	1.41
Grade 3	3.82
Stages T2 and T3	
Grade 1	1.82
Grade 2	4.73
Grade 3	12.80
In patients with regional metastasis† (Lee and Sause[27])	11.18
Progression from distant metastasis to death† (Johansson et al[28])	24.42

*Watchful waiting and hormonal therapies.
†Across all grades and procedures.

For combination therapies we used a weighted sum of the probabilities of progression from prostatectomy, radiation therapy and hormonal therapies derived from the study by Mettlin and colleagues.[21] The annual progression rate to distant metastasis from nodal metastasis was derived from the study by Lee and colleagues.[27]

Three types of death were considered in the model: death without prostate cancer, death with but not resulting from prostate cancer, and death from prostate cancer. Adjusted Canadian life tables[29] were used to estimate the background mortality of all subjects without distant metastatic disease in the following way:

$$\Pr\{\text{death}\} = 1 - \exp\{-[\mu(\text{death}) - \mu(\text{prostate cancer death})]\}$$

where

$$\mu(\text{death}) = -\text{Ln}(1 - \Pr\{\text{death given by the CLT}\})$$

CLT represents the Canadian life tables, and μ(prostate cancer death) is taken from the National Cancer Incidence Reporting System.[14]

Deaths from prostate cancer were assumed to occur only following progression to metastatic disease. The annual risk of death from prostate cancer among subjects with metastatic disease was derived from the 15-year follow-up data reported by Johansson and colleagues.[28] We assumed that all patients with metastatic cancer died as a consequence of their cancer.

Survival rates were transformed to yearly rates using the formula

$$\mu = -\frac{1}{t}\ln(S)$$

where μ is the annual rate, t represents time horizon, and S is the t-year survival probability. This rate is then transformed into a yearly probability (m) using

$$m = 1 - \exp\{-\mu\}$$

The model computes life expectancy, the expected age at which prostate cancer will be diagnosed and the expected age at which prostate cancer will metastasize. It also computes 5-, 10- and 15-year overall, metastasis-free and disease-specific survival rates, the number of person-years of life spent with and without prostate cancer, and the number of person-years spent with metastatic disease. The number and type of initial treatments and their associated complications are also estimated.

Results

Validity of the model

The model was validated by comparing specific forecasts with observed outcomes of prospectively followed cohorts. We compared the model's forecasts with the results from the Surveillance, Epidemiology and End Results (SEER) Program data for localized prostate cancer (stages T1 and T2).[30] Table 2 shows the model's estimates compared with the 10-year disease-specific and overall survival data ac-

cording to age, initial treatment and tumour grade. For prostatectomy, the 10-year disease-specific survival rates for grades 1, 2 and 3 were 98%, 91% and 76%, as compared with the model estimates of 96%, 92% and 84%. The overall 10-year survival rates for the SEER cohort were 77%, 71% and 54% for grade 1, 2 and 3 tumours, as compared with the model's estimates of 70%, 65% and 59%. Disease-specific and overall survival rates across all tumour grades were 89% and 68%, respectively, as compared with the model's estimates of 92% and 65%. Similar comparisons were made for radiation therapy and conservative management. The model tended to overestimate survival for grade 3 tumours compared with lower grade tumours.

We also compared our forecasts with the population-based Connecticut Tumor Registry data for localized prostate cancer.[31] The 10-year disease-specific survival rates for tumour grades 1, 2 and 3 were 91%, 76% and 54% respectively (Table 3), as compared with the model's estimates of 91%, 73% and 37%. The reported cumulative rates of death from causes other than prostate cancer at 10 and 15 years were 35% and 43% respectively, as compared with the model's estimates of 36% and 50%.

We also compared the model's estimated life expectancies with the estimates of the Connecticut Tumor Registry (Table 4). For example, the registry estimated that 65-year-old men with conservatively treated, localized grade 1, 2 and 3 prostate cancer would have 16.1, 11.3 and 7.9 remaining years of life. The model's estimates were 14.2, 11.5 and 7.4 years.

Finally, we tested the model's validity against the results reported by Zagars and colleagues.[32] They reviewed the medical records of patients with stage T3 prostate cancer treated with external-beam radiation therapy and reported 5-, 10- and 15-year overall survival rates of 72%, 47% and 27%; the model's estimates were 70%, 40% and 20% respectively.

Estimated clinical outcomes of prostate cancer

We used the model to estimate the probabilities of various clinical outcomes for men at risk of prostate cancer and for those in whom the disease had already been diagnosed. For example, among 60-year-old men at risk of prostate cancer, the lifetime probability of the disease developing was 12.5% (Table 5). The overall 10-, 15- and 20-year survival rates were estimated to be 81.7%, 66.8% and 48.7% respectively. At age 60 the remaining life expectancy was estimated to be 18.8 years. On average, for a 60-year-old man, the age at which prostate cancer would be diagnosed was estimated to be 74.1 and the age at which death from prostate cancer would occur was estimated to be 79.0 years. Among those in whom cancer develops, the probability of clinical stage T1 cancer being diagnosed was 30.8% and the probability of radical prostatectomy being the initial treatment was 21.9%.

We also used the model to forecast the lifetime clinical outcomes of men in whom prostate cancer is diagnosed, according to patient age, clinical stage, tumour grade and initial treatment at the time of diagnosis. For example, the model forecasted the expected outcomes for 60-, 70- and

Table 2: Disease-specific and overall 10-year survival rates among men with localized prostate cancer: observations from the SEER Program[30] and estimates from the Montreal Prostate Cancer Model

Initial therapy; tumour grade	Mean age at diagnosis, yr	Disease-specific survival rate, % (and 95% CI*)		Overall survival rate, % (and 95% CI*)	
		SEER	Model	SEER	Model
Prostatectomy					
Grade 1	65	98 (97–99)	96	77 (73–80)	70
Grade 2	66	91 (89–93)	92	71 (68–74)	65
Grade 3	66	76 (71–80)	84	54 (50–58)	59
All grades	66	89 (87–91)	92	68 (NA)	65
Radiation therapy					
Grade 1	70	89 (87–92)	86	63 (60–66)	53
Grade 2	71	74 (71–77)	77	48 (45–51)	45
Grade 3	71	52 (46–57)	68	33 (28–38)	40
All grades	70	74 (72–76)	78	50 (NA)	48
Conservative management					
Grade 1	70	92 (90–93)	88	54 (52–56)	54
Grade 2	71	76 (73–78)	73	38 (36–41)	43
Grade 3	72	43 (38–48)	42	17 (14–20)	24
All grades	71	80 (79–81)	74	44 (NA)	44

Note: SEER = Surveillance, Epidemiology and End Results, CI = confidence interval, NA = not available.
*Confidence intervals were provided in the SEER Program report.[30] Because of the model's complexity, confidence intervals for the model estimates could not be given.

80-year-old men with clinical stage T2 cancer managed conservatively with watchful waiting for tumour grades 1, 2 and 3 (Table 6). Among 60-year-old men, the 10-year overall survival was estimated to be 72% for those with a grade 1 tumour and 33% for those with a grade 3 tumour. The remaining life expectancy was estimated to be 16.1 years for those with a grade 1 tumour, as compared with 7.9 years for those with a grade 3 tumour. In other words, relative to a grade 1 tumour, a diagnosis of a grade 3 tumour would reduce life expectancy by 8.2 years. Those with a grade 1 tumour would spend 1.1 years on average with metastatic disease, as compared with 3.1 years for men with a grade 3 tumour; this difference is consistent with the higher incidence of metastases among patients with higher grade tumours.

Relative to the general population, the life expectancy of 60-year-old men with a grade 1 tumour was reduced by 3.3 years; for those with a grade 3 tumour it was reduced by 11.5 years.

Among 60-, 70- and 80-year-old men with prostate cancer, the effect of higher tumour grades on life expectancy decreased with increasing age at diagnosis. For 60-year-old men, the difference in life expectancy between those with a grade 1 tumour and those with a grade 3 tumour was 8.2 years (Table 6); this difference decreased to 4.5 and 2.1 years among 70- and 80-year-old men, respectively. Moreover, the premature loss of life across all tumour grades decreased with increasing age at diagnosis.

Interpretation

We have developed a detailed clinical model of prostate cancer management from diagnosis to death. The Montreal Prostate Cancer Model can follow a cohort of men at risk of cancer, or men with diagnosed prostate cancer, and forecast the annual clinical outcomes according to the patient's age, clinical stage and tumour grade, treatment modalities and competing causes of mortality. Similar models have been previously published, including those that estimated disease progression and survival alone,[18,33,34] and others that were primarily designed to evaluate screening programs for prostate cancer.[35–37]

In 1994 Cowen and colleagues[33] built a Markov model of the natural history of prostate cancer that provided an excellent summary of existing data on disease progression and survival. However, disease progression rates were not reported according to treatment modalities and tumour grade. In a detailed decision analysis, Fleming and colleages[34] provided a structured model of grade-specific disease progression and management with explicit comparisons between treatment modalities. However, the estimated efficacy of radical prostatectomy was based on data from studies with small samples available at the time, as was the rate of progression to metastatic disease among untreated patients. The Office of Technology Assessment of the US Congress[37] prepared an extensive cost-effectiveness analysis of prostate

Table 3: Disease-specific survival rates among men with conservatively treated localized prostate cancer: observations from the Connecticut Tumor Registry (CTR)[31] and model estimates*

Tumour grade	10-year survival rate, %		15-year survival rate, %	
	CTR	Model	CTR	Model
1	91	91	91	87
2	76	73	72	60
3	54	37	49	20

*Model estimates are based on CTR cohort's mean age of 71 years.

Table 4: Life expectancy for men with conservatively treated localized prostate cancer estimated by the CTR and the model, by patient age at diagnosis

Tumour grade	Age at diagnosis; life expectancy, yr					
	65 years		70 years		75 years	
	CTR	Model	CTR	Model	CTR	Model
1	16.1	14.2	13.0	11.3	10.2	8.8
2	11.3	11.5	8.8	9.5	6.7	7.6
3	7.9	7.4	5.9	6.4	4.4	5.5

Table 5: Model estimates of clinical outcomes among men at risk of prostate cancer

Outcome	Men at risk of prostate cancer		
	Age 60 yr	Age 70 yr	Age 80 yr
Probability of prostate cancer developing over remaining lifetime, %	12.5	11.3	8.3
Overall survival rate, %			
10 year	81.7	60.1	28.0
15 year	66.8	36.1	8.5
20 year	48.7	16.5	1.4
Mean no. of years of life remaining	18.8	12.0	6.8
Mean age at diagnosis of prostate cancer, yr	74.1	78.0	84.1
Mean age at death from prostate cancer, yr	79.0	82.3	87.1
Probability of clinical stage at diagnosis, %			
T1	30.8	33.2	35.8
T2	39.5	39.0	35.6
T3	16.0	13.3	9.4
M+	13.7	14.6	19.2
Probability of treatment chosen as initial therapy, %			
Prostatectomy	21.9	12.6	2.2
Radiation therapy	32.1	35.4	25.2
Hormonal therapies	14.4	17.5	27.4
Combination therapies	6.5	5.1	3.2
Watchful waiting	25.0	29.4	42.0

Note: M+ = metastatic disease.

cancer screening among elderly men. The analysis included the most recent literature on prostate management and provided grade-specific disease progression rates.

Our objective was to build a model that would capture the most important clinical outcomes over the course of prostate cancer. The model was based on the latest pooled analyses and population-based data for prostate cancer and emphasizes grade-specific outcomes, since tumour grade has been documented to be one of the strongest predictors of survival.[24,25,30,31] Unlike models used in other studies, our model has been independently validated against results from long-term, population-based studies in which data were reported according to patient age, clinical stage, tumour grade and initial treatment modalities.

The main limitation of our model is that patient selection bias may have been present in the estimation of treatment-specific survival rates (i.e. prostatectomy v. radiation therapy). Disease progression rates across treatment alternatives cannot be compared directly because they were not based on the results of randomized clinical trials. Nonetheless, as results from long-term randomized clinical trials become available, we will be able to incorporate them into our model. Moreover, because of our assumptions regarding grade-specific data for stage T1 following radiation therapy, and stage T3 following watchful waiting, we may have overestimated the progression rates after radiation therapy in T1 and underestimated the rates following watchful waiting in T3. In addition, because of the model's complexity, we were unable to provide confidence intervals around our estimates using techniques such as Monte Carlo simulations.

Despite these limitations, the model has been built to retain a great amount of flexibility because the baseline parameters can be easily modified to evaluate specific clinical outcomes. The overall potential effect of changes in disease management on disease progression, life expectancy and future health care utilization can be forecasted.

Despite the paucity of data from long-term randomized clinical trials, decision-making at many levels must be supported as patients must be treated without perfect scientific data. Computer simulation models offer one alternative to health care decision-makers who must appropriate health care resources as efficiently as possible despite the absence of head-to-head data comparing treatment alternatives. Clinical decisions between patients and physicians are even more problematic when data from clinical trials are lacking. Computer modeling can play an important role in identifying critical gaps in our current knowledge and thereby providing the foundations for future clinical research. Finally, these simulations can be used to encourage a reconsideration of current clinical practice such that anticipated benefits of therapy are consistent with the objectively forecasted outcomes. The Montreal Prostate Cancer Model can be used to provide these objective forecasts based on the best scientific data currently available.

We thank Ms. Nadine Bouchard for preparing the manuscript.

Dr. Grover is a senior research scholar (Chercheur-boursier) supported by the Fonds de la recherche en santé du Québec. Financial support for this study was provided by an investigator-initiated research project supported by an unrestricted grant from Abbott Laboratories, Limited. At no time did Abbott Laboratories staff provide any input into the study analysis, results or conclusions.

Competing interests: None declared.

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Table 6: Model estimates of clinical outcomes among men with stage T2 prostate cancer managed conservatively with watchful waiting

	Age at diagnosis; tumour grade								
	60 years			70 years			80 years		
Outcome	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Overall survival, %									
10 year	72	58	33	53	42	23	25	19	10
15 year	54	38	14	30	20	7	7	5	1
20 year	36	22	5	13	7	2	1	1	0
Life expectancy, no. of yr									
Metastasis free	15.0	10.6	4.8	10.2	7.7	3.9	6.0	4.9	2.8
Overall	16.1	12.6	7.9	10.8	9.1	6.3	6.4	5.7	4.3
Premature loss of life*	3.3	6.8	11.5	1.7	3.4	6.2	0.8	1.5	2.9

*Difference between overall life expectancy of cancer patients and that of an age-matched general population.

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