

RACE AND GENDER INFLUENCES ON THE SURVIVAL OF PATIENTS WITH MOUTH CANCER

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Abstract—Previous studies have shown that race and gender are important correlates of survival among patients with cancer of certain sites. Since race and gender influence the stage of disease at diagnosis and the choice of therapy it has been argued that survival differentials may not be real but instead, they represent secondary associations with clinical variables. Therefore, verification of the true prognostic effects of race and gender requires proper controlling for potential confounders, such as stage and treatment. We have studied the 15-year survival experience of a hospital-based cohort of 4527 patients diagnosed with cancer of the mouth over a 28-year period in Brazil. Race and gender were strong predictors of stage and treatment. The odds ratios for no treatment were 1.35 (95% confidence limits [CL]: 1.09, 1.66) for females and 1.63 (CL: 1.29, 2.06) for non-white patients even after adjustment by stage, presumably a key criterion to define treatment. Survival differentials were found for lip cancer, with respect to race, and for cancers of the gum, floor of mouth, and other oral subsites, with respect to gender. Non-whites experienced 2.1 times the risk of lip cancer recurrence (CL: 1.20, 3.61) and 2.3 times the risk of dying from it (CL: 1.29, 4.09) as compared to whites. However, controlling for stage and treatment modality variables by proportional hazards regression reduced the same risk ratios to 1.01 (CL: 0.57, 1.78) and 1.17 (CL: 0.65, 2.13), respectively. The survival advantage experienced by females (17% lower risk of recurrences and 29% lower risk of cancer deaths) regarding other oral sites was independent from the effect of clinical factors.

Survival Mouth cancer Cohort Race Gender

INTRODUCTION

Tertiary prevention as applied to cancer relies on the recognition of prognostic factors and other characteristics that may be predictive of the clinical outcome. Race and gender are two such factors. In the U.S., black-white and female-male differentials in survival have been well studied for a number of anatomic sites of cancer [1]. Racial and gender-related differences

in extension of disease at diagnosis, as well as in the access to the main cancer treatment modalities, i.e. surgery, radiotherapy, and chemotherapy, may account for such survival differentials. The poor survival experience for some sites among blacks has been ascribed to socioeconomic factors, rather than race *per se* [2]. Studies that examined the effect of socioeconomic factors after controlling for stage and treatment have ruled out a residual prognostic effect for income or education with respect to survival [3, 4]. However, differences in survival by race seem to persist for cancers of the breast,

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bladder, and uterus even after controlling for disease extension and other factors [5, 6].

Although it is plausible to expect that disease extension at diagnosis and treatment act as confounders of the race- and gender-survival associations, it is not clear how much of the confounding effect is exerted by each of these two clinical variables. Proper verification of the independence of prognostic effects for race and gender should also take into account the type of survival endpoint, i.e. whether censoring refers to all causes of death, to specific cancer-related deaths only, or even to first instances of tumor recurrence. Focus on the latter endpoint eliminates the time-dependent prognostic effects of clinical interventions occurring after disease recurrence. These interventions may themselves be correlated with gender or race, and thus, a secondary confounding effect may ensue, which cannot be adjusted away through stratification by the categories of initial treatment.

In the present report we attempt to shed light on possible mechanisms by which gender and race influence the survival of cancer patients. Unlike neoplastic lesions in most other anatomic sites, cancer of the mouth is generally perceived by the patient at relatively early stages. The patient's decision to seek medical care may reflect more closely his/her appraisal of the gravity of the oral lesions as compared to cancer in visceral sites, where symptoms rapidly escalate after the preclinical phase. Gender, race, and socioeconomic and cultural factors are important influences in this decision. In order to distinguish the confounding effects of disease extension and treatment we analyzed both crude and adjusted prognostic effects of gender and race using proportional hazards regression models based on the aforementioned three survival endpoints.

METHODS

Patient population

The patient cohort consisted of all cases of mouth cancer admitted to the A. C. Camargo Hospital in São Paulo, Brazil, between 1953 and 1980. The latter institution is one of the largest specialized cancer treatment centers in Latin America serving a metropolitan area with more than 12 million inhabitants. Approximately 30–50% of all incident cases of oral cancer in São Paulo are admitted for diagnosis and treat-

ment in this hospital, as judged by the accrual during the study period.

All cases of epithelial malignancies of the mouth were included, with the exception of salivary gland tumors. Eligible **International Classification of Disease** (9th revision) (ICD) codes were 140 (lip), 141 (tongue), 143 (gum), 144 (floor of mouth), and 145 (other parts of mouth: cheek mucosa, vestibule, palates, uvula, and retromolar area). All diagnoses were confirmed histopathologically.

Study variables

The above cohort was identified retrospectively through medical record review in the hospital's tumor registry. The abstracted data included: age, gender, race, places of birth and of residence, anatomic location, tumor size, lymph node involvement, and treatment history received both before and after the definitive diagnosis. All information was abstracted directly from the patients' main medical records containing the original hand-written notes by the attending head-and-neck surgeons, radiation therapists, and oncologists. The investigators who reviewed the charts (LLD and DSP) are dentists specialized in oral cancer diagnosis and management. Since staging practices varied considerably during the 28-year survey period, the stage index annotated in the charts would not have been a uniform indicator of disease extension for the entire cohort. Therefore, we restaged all patients according to the tumor-nodes-metastasis (TNM) system of the **Union Internationale Contre le Cancer** [7], using the detailed information on tumor size and cervical lymph node involvement contained in the charts.

Detailed follow-up information on dates and events since first admission was also abstracted to allow computation of the three survival time variables used in the analysis: (i) overall survival (OS) with any deaths as endpoints, (ii) disease-specific overall survival (DSOS) for mouth-cancer related deaths only, and (iii) disease-free interval (DFI) with first instances of tumor recurrence as endpoint. The OS and DSOS variables differed only with respect to censoring, i.e. patients dying of causes other than mouth cancer or its associated morbidity would be considered censored observations at the time of death for DSOS and uncensored for OS. Likewise, patients who had been free of disease and who died of causes unrelated to their original cancer were also considered as censored at

the time of death for the DFI variable. For the purpose of the present analysis only the first 15 years of follow-up were considered. Events occurring after this period did not alter the censorship status for the patients.

Both the clinical departments and the tumor registry maintained active follow-up of all patients. Patients who failed to return for their scheduled consultations were reminded by telephone or mail about the importance of the periodic clinical examinations and that they should contact their attending physician. Brief questionnaires probing for signs and symptoms of disease recurrence were periodically mailed to patients remaining asymptomatic for long periods. Lack of response by mail was followed by letters sent to relatives or other individuals originally designated by the patient as contact persons. At the study closing date (June 1988) 20.1% of the cases were considered lost to follow-up (cumulatively, 9.2% at 5 years and 15.9% at 10 years) but contributed survival time information up until the date they were last contacted.

Statistical analysis

The primary goal of the study was to demonstrate whether gender and race influence mouth cancer survival independently, or if any prognostic effects may be the result of confounding by secondary associations with clinical variables. As an initial verification of the potential for confounding we analyzed whether disease extension characteristics and treatment were associated with gender and race. To this end, frequency distributions according to the latter variables were compared by the chi-square test. In addition, since stage *per se* is typically related to treatment, we analyzed whether gender and race were associated with the likelihood of being treated for mouth cancer by computing odds ratios for no treatment within each stage category.

Actuarial survival rates were computed for categories of race, gender, and stage by the Kaplan-Meier product-limit method [8] using the three survival time variables and their respective censoring indicators. Survival distributions were compared by the Mantel-Cox test [9, 10].

Cox's proportional hazards regression method [10] was used to calculate hazard rate ratios (HRR) for gender and race based on the three outcomes of interest, i.e. deaths, mouth

cancer deaths, and mouth cancer recurrences. Multivariate control of confounding was performed in three steps by adding cumulatively to the univariate models containing only gender or race the following covariate sets (with respective numbers of dummy regressors): (i) age (3), place of residence (2), race (1) or gender (1); (ii) TNM stage grouping (4); and (iii) indicator variables for any previous treatment (1) and for surgery (1), radiotherapy (1), and chemotherapy (1). With the exception of surgery and radiotherapy, where an interaction term was also included, only main effect terms were fitted in the models. Models were fitted separately for each main topography group, i.e. lip (ICD 140), tongue (ICD 141) and other mouth subsites (ICD 143-5). Standard computer algorithms were used to calculate and compare survival distributions [11] and to build the proportional hazards models [12].

RESULTS

Distribution of sites and sociodemographic characteristics

The cohort numbered 4527 patients whose cancer sites were distributed as follows: lip, 1847 (40.8%); tongue, 942 (20.8%); gum, 256 (5.7%); floor of mouth, 756 (16.7%); and other parts of mouth (cheek mucosa, vestibule, palates, uvula, retromolar area), 726 (16.0%). Most patients had ages at admission in the 50-69 year range, similarly divided between the 50-59 year (1213, 26.8%) and the 60-69 year (1216, 26.9%) categories. Approximately 5% of the patients were younger than 30 years (99, 2.2%) or older than 79 years of age (153, 3.4%). As expected, because of the known preponderance of the male gender in cancers of the upper aero-digestive tract, male patients outnumbered female patients at a 6:1 ratio. Three racial categories were enumerated: white (4129 patients, 91.2%), oriental (mostly of Japanese origin or descent, 36 patients, 0.8%), and black or mulatto (362 patients, 8.0%). Because of their small numbers frequencies of patients of oriental descent were included in the distributions for white patients in all subsequent analyses. The vast majority of the patients lived in the metropolitan area of São Paulo (3766, 83.2%), with the remainder originating from adjacent cities or states (466, 10.3%), or even from distant Brazilian states (295, 6.5%).

Associations between gender or race and clinical variables

Table 1 shows the distributions of disease extension indices and types of treatment received according to gender and racial categories. Less than 3% of the patients had been unstaged for the TNM T index and only 15 patients (0.3%) could not be assigned a stage grouping. Missing information on stage indices was not dependent on gender or race.

Male patients tended to harbor tumors of more advanced stages both locally (size as judged by the TNM T index) or regionally (cervical lymph node involvement as judged by the TNM N index). This also reflected in the stage grouping distributions by gender, where the excess of advanced stages (III-IV) was somewhat more pronounced among males. As for treatment, except for a slight deficit of chemotherapy among females, there were no marked imbalances by gender with respect to surgery, radiotherapy, or any cancer treatments received prior to hospital admission (Table 1).

Racial differences concerning stage and treatment were considerably more pronounced than those for gender. Blacks and mulattoes tended to have much more advanced tumors at diagnosis, both locally and regionally. It is noteworthy that only 9% of non-whites harbored tumors of stages I and II as opposed to 34% among white

patients. Highly significant differences between whites and non-whites were also seen for two (surgery and chemotherapy) modalities of standardized treatment after admission and for a history of any previous anti-neoplastic therapy (Table 1).

Since therapeutic choices are primarily based on disease extension, one could argue that any differences between genders or between races regarding treatment (as seen in Table 1) might have been a consequence of the different stages at presentation, rather than of additional gender- or racial-factors. If such a secondary relation were indeed operative any gender or racial differences in likelihood of being untreated for mouth cancer would disappear upon stratified analysis by stage. Table 2 presents the results from such an analysis. Females and non-whites were more likely to have their mouth tumors left untreated in all stage groupings. On average, females were 35% and non-whites were 63% more likely to be followed-up without surgery, radiotherapy, or chemotherapy as compared to males and whites, respectively.

Cumulative survival rates

As shown in Fig. 1, survival was markedly influenced by the anatomic site of the primary oral lesion and by disease stage. Lip cancers conferred the most favorable prognosis with a 5-year DSOS rate of 79%, all stages combined.

Table 1. Distribution* of disease extension characteristics and treatment modalities according to gender and race† among patients with cancer of the mouth

Clinical variable	Gender			Race			
	Male	Female	<i>p</i> Value‡	White	Non-white	<i>p</i> Value	
<i>Disease extension</i>							
Tumor size	T1-2	1410 (36)	259 (40)	0.0561	1616 (39)	53 (15)	<0.0001
	T3-4	2369 (61)	368 (57)		2430 (58)	307 (85)	
	NK§	107 (3)	14 (2)		119 (3)	2 (<1)	
Lymph node involvement	N0	1927 (50)	380 (59)	<0.0001	2213 (53)	94 (26)	<0.0001
	N1-2	969 (25)	121 (19)		973 (23)	117 (32)	
	N3	990 (25)	140 (22)		979 (24)	151 (42)	
Stage	I	547 (14)	113 (18)	0.0073	647 (16)	13 (4)	<0.0001
	II	630 (16)	120 (19)		730 (18)	20 (5)	
	III	710 (18)	120 (19)		776 (19)	54 (15)	
	IV	1988 (51)	284 (44)		1997 (48)	275 (76)	
	NK	11 (<1)	4 (<1)		15 (<1)	0 (0)	
<i>Treatment¶</i>							
Surgery	1682 (43)	266 (41)	0.3975	1861 (45)	87 (24)	<0.0001	
Radiotherapy	1687 (43)	270 (42)	0.5411	1807 (43)	150 (41)	0.4728	
Chemotherapy	323 (8)	38 (6)	0.0390	309 (7)	52 (14)	<0.0001	
Previous therapy	421 (11)	68 (11)	0.8648	468 (11)	21 (6)	0.0014	

*Numbers in parentheses refer to percentages by gender or race.

†Patients of oriental origin or descent were included among whites.

‡Chi-square test for differences in frequency distributions.

§Not known or unstaged.

¶Categories are non-exclusive. Frequencies refer to those receiving the stated therapy.

Table 2. Stage-specific and overall odds ratios for no treatment according to gender and race of mouth cancer patients

Variable	Stage*	Categories	Untreated	Treated	Odds ratios	
					Crude	Adjusted†
Gender	I	Male	29	518		
		Female	8	105	1.36	
	II	Male	43	587		
		Female	13	107	1.66	
	III	Male	75	635		
		Female	21	99	1.80	
	IV	Male	694	1294		
		Female	113	171	1.23	
All stages	Male	841	3034			
	Female	155	482	1.16	1.35 (1.09, 1.66)	
Race	I	White	33	614		
		Non-white	4	9	8.27	
	II	White	53	677		
		Non-white	3	17	2.25	
	III	White	86	690		
		Non-white	10	44	1.82	
	IV	White	685	1312		
		Non-white	122	153	1.53	
	All stages	White	857	3293		
		Non-white	139	223	2.40	1.63 (1.29, 2.06)

*15 unstaged patients excluded.

†By stage (95% confidence limits in parentheses).

On the other hand, patients with tongue cancers fared poorly on average, with a 5-year DSOS

rate of only 15%. Lesions in other oral subsites (ICD 143-5) were also associated with a poor prognosis (28% 5-year DSOS rate) but to a lesser extent than those in the tongue. Disease stage was uniformly predictive of survival across all site categories with little or no overlapping of the actuarial distributions (Fig. 1).

Table 3 displays the cumulative rates at 2, 5, 10, and 15 years for males and females separately and for each of the three survival time variables. Important differences in actuarial distributions can be seen only for other oral subsites (ICD 143-5), where women had significant survival advantages with all three endpoints. Survival rates seemed to be slightly higher also among females with tongue cancer, but the differences did not reach the 10% significance level.

Table 4 shows the same information on survival rates for the two racial categories as defined above. Non-whites with cancer of the lip fared poorly as compared to whites (and orientals), regardless of the outcome analyzed. However, the most dramatic difference in actuarial distributions was seen with the OS time variable, with long-term cumulative rates for non-whites approaching 0%. A somewhat less pronounced prognostic disadvantage among non-whites was seen also for cancer of other parts of mouth, but the differences in distributions were not significant.

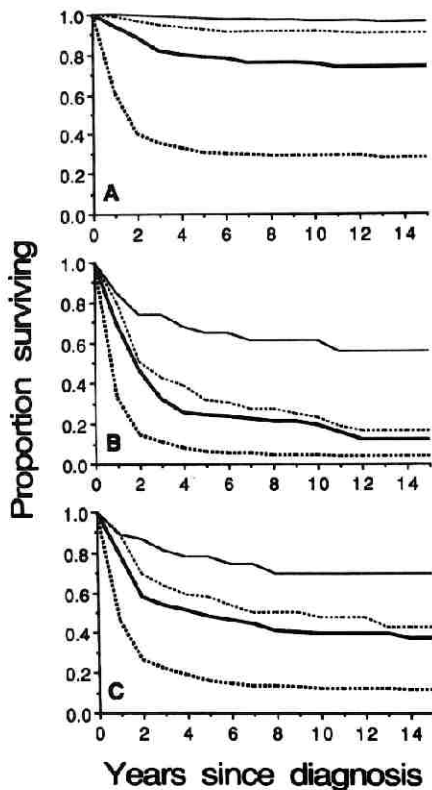


Fig. 1. Actuarial survival curves for mouth cancer patients according to anatomic site (A, lip; B, tongue; C, gum, floor of mouth, and other oral subsites) and stage grouping (I, —; II, - - -; III, ····; IV, - · - ·). Mouth cancer deaths were used as endpoints.

Table 3. Overall and disease-free survival rates according to gender for patients with cancer of the mouth

Anatomic site	Type of outcome	Gender	Rates (%) by time in years since diagnosis				p Value*
			2	5	10	15	
Lip (ICD 140)	All deaths	Male	80	70	59	48	0.3886
		Female	80	71	55	43	
	Mouth cancer deaths	Male	84	78	76	75	0.5570
		Female	86	81	78	75	
	Mouth cancer recurrences	Male	78	73	71	70	0.2890
		Female	82	79	74	69	
Tongue (ICD 141)	All deaths	Male	26	14	9	6	0.2258
		Female	31	17	13	11	
	Mouth cancer deaths	Male	27	15	11	9	0.2847
		Female	32	17	14	12	
	Mouth cancer recurrences	Male	19	11	7	5	0.1188
		Female	26	15	12	5	
Other mouth subsites (ICD 143-5)	All deaths	Male	34	22	15	11	<0.0001
		Female	50	38	30	26	
	Mouth cancer deaths	Male	36	26	21	19	0.0001
		Female	50	40	33	32	
	Mouth cancer recurrences	Male	30	22	16	15	0.0078
		Female	38	29	24	24	

*Testing the equality of actuarial distributions.

Confounding effects of clinical variables

Using proportional hazards regression we computed HRRs for gender and race while controlling for confounders of interest. Table 5

summarizes the crude and adjusted estimates for all deaths, mouth cancer deaths, and mouth cancer recurrences of the risk among female patients with respect to that of male patients. There was no indication that gender influenced

Table 4. Overall and disease-free survival rates according to race for patients with cancer of the mouth

Anatomic site	Type of outcome	Race	Rates (%) by time in years since diagnosis				p Value*
			2	5	10	15	
Lip (ICD 140)	All deaths	White†	81	70	59	48	<0.0001
		Non-white	63	45	31	0	
	Mouth cancer deaths	White	84	79	77	76	0.0036
		Non-white	66	62	49	49	
	Mouth cancer recurrences	White	79	74	72	70	0.0079
		Non-white	63	58	50	50	
Tongue (ICD 141)	All deaths	White	27	14	9	8	0.4374
		Non-white	28	15	7	5	
	Mouth cancer deaths	White	27	15	12	9	0.4256
		Non-white	28	15	12	8	
	Mouth cancer recurrences	White	20	11	8	5	0.9942
		Non-white	24	12	9	4	
Other mouth subsites (ICD 143-5)	All deaths	White	37	25	17	13	0.5072
		Non-white	35	22	15	12	
	Mouth cancer deaths	White	38	29	23	22	0.4845
		Non-white	37	25	19	19	
	Mouth cancer recurrences	White	32	23	18	16	0.5357
		Non-white	29	19	16	16	

*Testing the equality of actuarial distributions.

†Includes patients of oriental origin or descent.

Table 5. Crude and adjusted gender-specific (female vs male) hazard rate ratios according to main outcomes and subsites of mouth cancer

Variables adjusted* for in the analysis	Hazard ratio (95% confidence limits) by outcome		
	All deaths	Deaths due to mouth cancer	Mouth cancer recurrence
<i>Lip (ICD 140)</i>			
None	1.10 (0.89, 1.36)	0.91 (0.67, 1.24)	0.86 (0.65, 1.14)
Race, age, origin	0.91 (0.73, 1.13)	0.79 (0.56, 1.09)	0.77 (0.57, 1.02)
Above plus stage	0.96 (0.77, 1.20)	0.92 (0.66, 1.26)	0.88 (0.66, 1.17)
Above plus treatment	0.98 (0.79, 1.22)	0.95 (0.69, 1.30)	0.89 (0.67, 1.20)
<i>Tongue (ICD 141)</i>			
None	0.87 (0.69, 1.09)	0.88 (0.70, 1.11)	0.83 (0.66, 1.05)
Race, age, origin	0.86 (0.68, 1.08)	0.88 (0.69, 1.11)	0.84 (0.67, 1.06)
Above plus stage	0.95 (0.75, 1.20)	0.98 (0.77, 1.24)	0.90 (0.71, 1.14)
Above plus treatment	0.88 (0.69, 1.11)	0.91 (0.72, 1.16)	0.86 (0.68, 1.09)
<i>Other mouth subsites (ICD 143-145)</i>			
None	0.65 (0.55, 0.77)	0.70 (0.59, 0.84)	0.80 (0.68, 0.94)
Race, age, origin	0.63 (0.53, 0.75)	0.69 (0.57, 0.82)	0.79 (0.67, 0.93)
Above plus stage	0.66 (0.56, 0.79)	0.73 (0.61, 0.87)	0.84 (0.71, 0.99)
Above plus treatment	0.65 (0.55, 0.77)	0.71 (0.60, 0.86)	0.83 (0.71, 0.99)

*Using Cox's proportional hazards regression.

the risk of any one of the three outcomes of interest among lip and tongue cancer patients, as judged by the 95% confidence intervals around the crude and adjusted HRRs. On the other hand, gender had a significant prognostic effect for cancers of other mouth subsites. Female patients experienced approximately 35, 30, and 20% less risk of all deaths, mouth cancer deaths, and mouth cancer recurrences, respectively, as compared to male patients. The association of gender with survival seemed to be independent, as crude HRR estimates were not materially different than the adjusted ones.

Crude and cumulatively adjusted HRRs for race are shown in Table 6. As above, in the analysis of survival distributions, the unadjusted HRRs for lip cancer seem to indicate a strong prognostic effect for race as non-whites experienced more than twice the risk of any one of the three outcomes as compared to whites. Adjustment by gender, age, and origin (place of residence) caused no material changes in the HRRs for race. It was only when regressors for stage and, subsequently for treatment, were added to the models that the estimates for race tended to approach unity. This indicates that most of the

Table 6. Crude and adjusted race-specific (non-white vs white*) hazard rate ratios according to main outcomes and subsites of mouth cancer

Variables adjusted† for in the analysis	Hazard ratio (95% confidence limits) by outcome		
	All deaths	Deaths due to mouth cancer	Mouth cancer recurrence
<i>Lip (ICD 140)</i>			
None	2.46 (1.58, 3.85)	2.30 (1.29, 4.09)	2.08 (1.20, 3.61)
Gender, age, origin	2.32 (1.47, 3.67)	2.29 (1.28, 4.13)	2.11 (1.20, 3.69)
Above plus stage	1.57 (0.99, 2.49)	1.39 (0.77, 2.53)	1.28 (0.73, 2.26)
Above plus treatment	1.44 (0.91, 2.28)	1.17 (0.65, 2.13)	1.01 (0.57, 1.78)
<i>Tongue (ICD 141)</i>			
None	1.09 (0.88, 1.35)	1.09 (0.88, 1.36)	1.00 (0.81, 1.24)
Gender, age, origin	1.10 (0.89, 1.37)	1.11 (0.89, 1.38)	1.03 (0.83, 1.27)
Above plus stage	1.00 (0.80, 1.25)	0.99 (0.79, 1.24)	0.97 (0.78, 1.21)
Above plus treatment	0.92 (0.74, 1.15)	0.91 (0.72, 1.14)	0.89 (0.71, 1.11)
<i>Other mouth subsites (ICD 143-145)</i>			
None	1.07 (0.88, 1.28)	1.07 (0.88, 1.30)	1.06 (0.88, 1.28)
Gender, age, origin	1.15 (0.95, 1.39)	1.13 (0.93, 1.38)	1.10 (0.91, 1.32)
Above plus stage	1.03 (0.85, 1.25)	1.00 (0.82, 1.22)	0.98 (0.81, 1.19)
Above plus treatment	0.85 (0.70, 1.03)	0.82 (0.67, 1.00)	0.83 (0.69, 1.01)

*Includes patients of oriental origin or descent.

†Using Cox's proportional hazards regression.

prognostic effects seen for race were, in fact, due to secondary associations with stage and treatment. Interestingly, some indication of a "switchover" bias was seen in the contrast of crude and adjusted HRRs for race obtained with tongue and other mouth cancers. Particularly in the case of the latter site, what seemed to be excess risks around 10% among non-whites, as judged by the naive estimates, changed upon adjustment indicating an approximate 15% reduction in risk. Such reductions were significant at the 10% level for all deaths and mouth cancer recurrences and at the 5% level for mouth cancer deaths.

DISCUSSION

In the present set of analyses we have shown that gender, to some extent, and race, to a considerable extent, can be associated with measures of disease extension and treatment modalities for mouth cancer. The effects of gender or race on the choice of treatment seems to go beyond a secondary relation with how advanced the disease may be at diagnosis. Receiving any therapy for mouth cancer was influenced by gender and race even within the homogeneous prognostic strata formed by disease stage groupings. Since disease extension and treatment represent primary prognostic factors with respect to patient survival, the unadjusted analysis of the gender-survival and race-survival relations is liable to produce biased results due to confounding by those clinical factors. Our study has shown that such biases are indeed operative for race but that the prognostic effect of gender may be genuine since it persisted after adjustment by stage and treatment.

Before considering the implications of the above findings it is necessary to understand possible limitations of our study. The survival experience and clinical data on the patient cohort was obtained through a retrospective survey of tumor registry records of a single large cancer treatment hospital. The patient population admitted to this hospital is not a random sample of all mouth cancer cases occurring in the general population of São Paulo and thus, some imbalances in distribution of prognostic factors may have occurred. For instance, if we assume that low clinical risk female patients with cancer of the mouth may have been preferentially referred to our hospital then the survival advantage seen in our study would have merely

reflected this fact and could not be generalized to other clinical settings. The same rationale applies to our findings regarding race. However, the latter hypothetical distortions in referral patterns according to gender and race are unlikely to have occurred. Cancer diagnosis and treatment referral practices in effect during the 28-year period covered by the study were largely unrelated to sociocultural factors and ability to pay and were mainly linked to the proximity of a patient's residence to the hospital.

A study conducted in a single specialized center has the advantage that diagnostic and treatment practices are relatively uniform, leading to more homogeneous prognostic categories for the purpose of controlling confounding. Staging and treatment information gathered in population-based studies come from different hospitals with potentially diverse oncological practices. This would lead to misclassification, in the case of staging, and to heterogeneous prognostic effects, in the case of treatment. The end result would be inadequate control of confounding in examining the effects of gender and race.

Although the proportion of losses to follow-up (20%) may seem high by prospectively approached, clinical trial standards, it represents a reasonable expectation, in terms of retrospectively reconstructed cohorts spanning long accrual periods. Important distortions would have occurred if gender and race were found to be direct, independent determinants of losses to follow-up. In general, we found that those lost to follow-up tended to be patients with good prognosis. Therefore, the probability of being lost to follow up was related to stage and anatomic site. Gender and race were only weakly predictive of losses to follow-up because of their associations with stage and site. Any imbalances in frequencies of losses to follow-up by gender and race disappeared completely once stage and site were controlled for by stratification (data not shown).

Cancer diagnosis and management practices have evolved substantially in our institution during the almost three decades spanned by the study. To improve the homogeneity of the prognostic categories we took the precaution to re-stage all patients using the same set of TNM criteria. On the other hand, with treatment variables it would not have been practical to abstract complex information on radiotherapy protocols, surgical procedures, and chemotherapy regimens for every patient. Our goal was

not to examine cancer survival statistics according to clinical factors, but rather, to use them as covariates to be controlled for in the analysis of gender and race.

Proper classification of disease extension measures and of individual treatment variables for the purpose of controlling confounding by stratification cannot be overemphasized. Some studies have used dichotomous indicators of regional or distant disease to control for stage. Use of such indicators instead of the complete stage grouping categories in our study afforded only partial control of confounding, as judged by preliminary analyses of the effects of race on lip cancer survival (data not shown). Likewise, it was only with a relatively complex covariate set for treatment that we obtained improved control of confounding for both gender and race. This set contained indicators for surgery, radiotherapy, and their cross-product terms, for chemotherapy, and for any previous treatment. Since treatment and stage variables are heavily interrelated occasional convergence problems occur during the computation of maximum likelihood estimates of HRRs. This problem can be easily circumvented by combining categories of stage or by eliminating cross-product terms without affecting the ability to control confounding by stage and treatment.

Racial differences with respect to disease severity or patient survival have been extensively studied in breast cancer [5, 6, 13–15]. Some authors contend that the survival differentials by race reflect mostly the imbalances in socioeconomic status [14], whereas others have found independent prognostic effects for race even after accounting for socioeconomic indicators [5]. Other sites of cancer, such as bladder, rectum, and uterus, seem also to exhibit race-specific differences in survival that are more or less independent from the stage at diagnosis [6]. Any such imbalances in cultural characteristics and socioeconomic factors underlying the effects of race and/or gender on survival are likely to emerge in a study of mouth cancer patients. Oral cancer lesions become noticeable by the patient or his/her relatives at comparatively earlier phases as compared to neoplasms in visceral sites, which tend to produce symptoms that rapidly escalate after a preclinical phase. Therefore, the oral cancer patients decision to seek medical attention is largely influenced by his knowledge, preventive behavior, and by the pressure exerted by family members and other close individuals. In consequence,

stage at diagnosis among oral cancer patients may be more closely influenced by sociocultural characteristics related to gender and race, in contrast to many other cancer sites where disease burden may be more influenced by the biologic behavior of the tumor, e.g. histologic type.

The difficulty in unveiling whether the prognostic effect of race is genuine or confounded by other factors is related to the complexity with which race or gender may influence cancer survival. In addition to possible *de facto* mechanisms, e.g. genetic, hormonal, immunologic, or nutritional, that may affect the natural history of the disease, one must entertain the following non-exclusive, indirect influences. First, gender and race influence the overall delay in seeking medical attention and, hence, the disease stage, a very important prognostic factor regardless of the anatomic site. Second, the choice of initial course of curative or palliative therapy may also be influenced by gender and race in addition to other clinical criteria—albeit obliviously to the oncological team. Third, compliance to scheduled treatment, e.g. courses of chemotherapy and radiotherapy sessions, may vary by gender and race, with a subsequent impact on the therapeutic dose effectively delivered. Fourth, in analogy with the first mechanism, gender and race may play a role in whether any recurrences of the disease are promptly diagnosed and arrested (or at least controlled) by curative treatment during follow-up. Fifth, and also in analogy with the second mechanism above, gender and race may also affect the choice of treatment after disease recurrence, which in turn may affect the length of the post-recurrence survival period. Sixth, the likelihood of deaths from other causes while under clinical surveillance for cancer relapse is also influenced by gender and race. While adjustment by stage and initial therapy may suitably control for the first and second mechanisms discussed above, there may be residual influences of gender and race on the overall survival depending on how end-points are defined, i.e. recurrences, cancer-related deaths, or all deaths.

Although our study identified gender and race associations with survival that are apparently independent (e.g. gender and other oral subsites), we know nothing about the actual mechanism for this relation. Likewise, our characterization of the confounded (by stage and treatment) association between race and lip cancer does not shed light on the nature of the

relation between race and patient management practices. Future studies should extend our observations by collecting information also on correlates of race and gender, such as income and education. It would be useful also to obtain additional measures pertaining to the disease's natural history (e.g. duration of symptoms as a measure of the delay in seeking medical attention) and the patient's response and compliance to treatment. This would allow one to disentangle the multiple mechanisms by which gender and race may affect the clinical outcome of oral cancer.

Our findings indicate that, whenever present, the prognostic effects of gender or race on the survival of mouth cancer patients are more pronounced with all deaths as endpoints and least evident when key intermediate outcomes are considered, i.e. recurrences. In this regard, it is noteworthy that elimination of the confounding effect of stage and treatment on the survival differentials by race among lip cancer patients was only achieved with cancer recurrences as endpoint. This suggests that, particularly for race, residual prognostic effects may result from one or more of the mechanisms underlying clinical events occurring after the initial treatment is completed and during follow-up. If confirmed by further studies, this finding may indicate that proper elimination of racial influences on cancer survival should be targeted not only on the reasons for delayed diagnosis and differential initial therapy but also on any further opportunities for clinical intervention during follow-up of the patient.

It could be argued that cancer recurrences represent a more sensitive and scientifically sound endpoint to measure the impact of therapy and the prognostic value of selected variables. However, it is the overall mortality resulting directly or indirectly from the original cancer that will be the ultimate endpoint in public health terms. On that basis, it is important to characterize well any further influences of race or gender on survival that do not occur

merely via associations with stage at diagnosis and initial treatment.

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REFERENCES

1. Ries LAG, Hankey BF, Edwards BK. **Cancer Statistics Review 1973-87**. Bethesda, MD: National Cancer Institute; 1990: 4-18.
2. Axtell LM, Asire AJ, Myers MH. **Cancer Patient Survival Report No. 5**. Bethesda, MD: National Cancer Institute; 1976: 5.
3. Chirikos TN, Reiches NA, Moeschberger ML. Economic differentials in cancer survival: A multivariate analysis. *J Chron Dis* 1984; 37: 183-193.
4. Stavray KM, Kincade JE, Stewart MA *et al.* The effect of socioeconomic factors on the early prognosis of cancer. *J Chron Dis* 1987; 40: 237-244.
5. Bain RP, Greenberg RS, Whitaker JP. Racial differences in survival of women with breast cancer. *J Chron Dis* 1986; 39: 631-642.
6. Ragland KE, Selvin S, Merrill DW. Black-white differences in stage-specific cancer survival: Analysis of seven selected sites. *Am J Epidemiol* 1991; 133: 672-682.
7. **Union Internationale Contre le Cancer**. TNM classification. Geneva: UICC; 1978.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc J* 1958; 53: 457-481.
9. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; 50: 163-170.
10. Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972; 34: 187-220.
11. Campos-Filho N, Franco EL. Microcomputer-assisted univariate survival data analysis using Kaplan-Meier life table estimators. *Comput Methods Programs Biomed* 1988; 27: 223-228.
12. Campos-Filho N, Franco EL. Microcomputer-assisted multivariate survival data analysis using Cox's proportional hazards regression model. *Comput Methods Programs Biomed* 1990; 31: 81-87.
13. Satariano WA, Belle SH, Swanson GM. The severity of breast cancer at diagnosis: A comparison of age and extent of disease in black and white women. *Am J Publ Health* 1986; 76: 779-782.
14. Bassett MT, Krieger N. Social class and black-white differences in breast cancer survival. *Am J Publ Health* 1986; 76: 1400-1403.
15. McWhorter WP, Mayer WJ. Black/white differences in type of initial cancer treatment and implications for survival. *Am J Publ Health* 1987; 77: 1515-1517.