Association between age and survival in a cohort of Brazilian patients with operable breast cancer

Associação entre idade e sobrevida em uma coorte de pacientes brasileiras com câncer de mama operável

Asociación entre edad y supervivencia en una cohorte de pacientes brasileñas con cáncer de mama operable

Débora Balabram [1]
Cassio M. Turra [2]
Helenice Gobbi [1]

[1] Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil.
[2] Centro de Desenvolvimento e Planejamento Regional, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil.

Correspondence
D. Balabram
Faculdade de Medicina, Universidade Federal de Minas Gerais.
Av. Professor Alfredo Balena 190, Belo Horizonte, MG 30130-100, Brasil.
debalabra@gmail.com

Abstract

Whether age is an independent prognostic factor in breast cancer is a matter of debate. This is a retrospective cohort study of 767 breast cancer patients, stages I-III, treated at the Hospital das Clínicas, Minas Gerais Federal University, Belo Horizonte, Minas Gerais State, Brazil, from 2001 to 2008, aiming to study the relationship between age and survival. We included variables related to patients, tumors, and types of treatment. Different sets of Cox models were used for survival analysis. Hazard ratios (HR) and 95%CI were calculated. The relationship between age and breast cancer survival did not change substantially in any of them. In the model that accounted for all variables, women aged 70 and older (HR = 1.51, 95%CI: 1.04-2.18), and 35 or younger (HR = 1.78, 95%CI: 1.05-3.01) had shorter cancer specific survival than patients aged between 36 and 69. In addition, older age, having at least one comorbidity, and being white were associated with a higher risk of dying from other causes. In conclusion, shorter breast cancer survival is expected among the youngest and oldest patients.

Neoplasm Staging; Ethnicity and Health; Age Factors; Breast Neoplasms

Resumo

É discutível se idade é um fator prognóstico independente para câncer de mama. Conduzimos uma coorte retrospectiva de 767 pacientes com câncer de mama, estádios I-III, tratadas no Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil, de 2001 a 2008, para estudar a relação entre idade e sobrevida. Incluímos variáveis relacionadas às pacientes, aos tumores e ao tratamento. Diferentes conjuntos de modelos de Cox foram construídos. As razões de risco (RR) e IC95% foram calculados. A relação entre idade e sobrevida por câncer de mama não foi alterada substancialmente entre os modelos de Cox. No modelo com todas as variáveis explicativas, as mulheres de 70 anos ou mais (RR = 1,51; IC95%: 1,04-2,18) e até 35 anos (RR = 1,78; IC95%: 1,05-3,01) tiveram sobrevida causa-específica mais curta que as de 36-69 anos. Idades a partir de 70 anos, ter ao menos uma comorbidade e ser branca foram associadas a risco maior de óbito por outras causas. Em conclusão, as pacientes mais jovens e as mais idosas parecem ter sobrevida mais curta por câncer de mama.

Estadiamento de Neoplasias; Origem Étnica e Saúde; Fatores Etários; Neoplasias da Mama

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Introduction

Breast cancer is the most common malignant neoplasm among women in Brazil, with an expected incidence of 57,120 new cases for the year 2014 [1]. Age is the strongest risk factor for the disease [2] and thus, breast cancer incidence is increasing with population aging in Brazil [3,4].

Many studies have reported that older women (≥ 70 years of age) have less aggressive breast cancer, including a higher frequency of lower grade tumors and positivity for hormone receptors [5,6,7]. However, they may receive less than standard treatment, due to the presence of comorbidities or to a belief in a less aggressive disease in this age subgroup [6,8,9]. Compared to the elderly, young women (≤ 35 years of age) have more frequently higher grade breast cancer and negativity for hormone receptors [7,10]. Yet, it remains unclear whether age is an independent prognostic factor for the lower survival among younger and older patients [10,11] or if the increase in mortality risk is associated with different tumor features in these groups.

In a previous study [12], we found that women 70 years of age and older have a higher risk of dying from breast cancer, independent of tumor related factors, in comparison with patients 36 to 69 years of age. Other studies have also demonstrated a higher chance of dying from breast cancer for both older and younger age groups [2,8,10,13,14]. Furthermore, older age is related to a higher prevalence of comorbidities, which may reduce overall and disease-specific survival [15,16]. Here, we examine in more detail the relationship between age and mortality from breast cancer and other causes of death, by looking at the role played by several intervening variables, including skin color, comorbidities, tumor factors and use of systemic treatments. We use data from patients treated at a public Brazilian hospital between the years 2001 and 2008.

Methods

Study design and population

We obtained data from a retrospective cohort study of patients with breast cancer, stages I-III, who underwent surgery for breast cancer treatment at the Hospital das Clínicas of the Minas Gerais Federal University, Belo Horizonte, Minas Gerais State, Brazil (HC-UFMG), from the years 2001 to 2008. The UFMG Ethics Research Committee approved the study's protocol on March 7, 2012 (project CAAE number 0660.0.203.000-11).

Among the 1,004 patients who underwent surgery for treatment of invasive breast cancer at the HC-UFMG between 2001 and 2008, we excluded 75 women for whom treatment was not paid for by the public health system. Of the remaining 929 individuals, we excluded cases without medical records (n = 76), patients who underwent surgery only for palliative purposes (stage IV disease, n = 7), individuals with recurrent breast cancer (n = 14), patients who had incomplete information on tumor stage (n = 30), and 35 cases with missing data on the independent variables. After excluding these cases, our cohort analysis contained 767 patients.

Variables

We examined four sets of determinants of mortality: patient demographic characteristics, health status, tumor characteristics, and systemic treatments (hormone and chemotherapy).

Besides age, measured in three categories (up to 35, 36 to 69, and 70 years and older), we included tumor size and lymph node status according to the *American Joint Committee on Cancer Staging Manual* [17,18], as well as tumor type and grade [18]. From the patients' medical records we obtained information on skin color and comorbidities. Skin color was assigned by the attending physician as white, black and brown skin. We dichotomized the patients into white and non-white (black or brown skin). As for the comorbidities, we used the Charlson comorbidity index, which combines mortality risk levels associated with different chronic conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, and dementia [19]. Each condition receives a different score (1, 2, 3 or 6), depending on the risk of death associated with it. The scores are then added up to provide a total score for each individual [19]. In our study cohort, all patients had at least a score of 2 because of the presence of tumor without metastasis. Most of them (625 patients, 81.5%) had no other major comorbidities and thus, maintained a score of 2. 114 patients (14.9%) had a comorbidity that resulted in one extra point (final score of 3). The remaining patients (28, 3.7%) had scores of 4, 5 and 6. In order to reduce the small variability of counts in the index, we constructed a dichotomous variable, which is equal to one for patients who had at least a score of 3, and zero for those with a score that is equal to 2.

We added both the use of hormone and chemotherapy in our analysis. Some of the patients in our study underwent systemic therapies in other hospitals and therefore, have missing values for chemotherapy (36 patients, 4.7%) and hormone

therapy (41 patients, 5.5%). We used information on estrogen receptor status to impute the missing values of hormone therapy. We assumed that patients with estrogen receptor (ER) positive tumors (21 cases) received treatment, whereas patients with ER negative tumors (20 cases) did not. One may notice that we chose not to add ER as an independent variable in our models, since there were too many missing values for this measure (55 cases, 7.2%). For imputing missing data for chemotherapy we applied a relatively more complex algorithm, based on four variables: disease stage, age, use of hormone therapy, and presence of comorbidities. These variables are frequently used to predict the benefit of prescribing chemotherapy for patients with breast cancer [20,21]. We assumed that patients with stage I disease did not undergo chemotherapy. Also, we considered that stage II patients received chemotherapy, only if they were younger than 70 years of age, had no major comorbidities, and had not received endocrine therapy. We further assumed that stage II patients who were older than 70 years of age received chemotherapy if they did not receive hormone therapy and had no comorbidities. We considered all stage III patients who were younger than 70 years of age to have received chemotherapy. Stage III patients older than 70 years only received chemotherapy if they did not receive hormone therapy and had no major comorbidities. After the imputation procedure, we determined that 20 patients received chemotherapy, while the other 16 did not. Since the number of missing cases is somewhat small, alternative imputation procedures for both the hormone and chemotherapies proved to have only minor effects on our results.

We retrieved data on cause and date of death as checked in the Mortality Information System (SIM) of the Brazilian Ministry of Health [3], from 2001 to 2011. When the cause of death was unknown or the patient died without assistance (7 cases, 2.8% of total of deaths), breast cancer was considered to be the cause [22,23]. We used a probabilistic record linkage strategy to identify patients in our database who had died up to December 31st, 2011 [24]. The program used was the RecLink version 3.0 [24]. Survival time was counted from the first day of treatment (surgery or chemotherapy) until the date of death or the end of the study period. The patient's first and last name, their mother's name and their date of birth were retrieved from both databases (the study's and the SIM database), and different linkage strategies were used to find patients who had died [12]. Patients not found in the MIS database were considered to be alive at the end of the observation period. We classified the causes of death according to the International Classification of Diseases, 10th revision (ICD-10) [25]. The linkage procedure was described in detail in an earlier study [12].

Statistical analysis

We used the exact two-sided linear-by-linear association statistic to compare the distribution of patient and tumor characteristics across age groups. The significance level was defined as 0.05. Mean and median survival times were calculated. We use Cox proportional hazards model for survival analysis. The hazard ratios (HR) and 95% confidence intervals (95%CI) for each independent variable were calculated.

We tested interaction terms between age and each one of the covariates in our final model, but none of them was significant. Further, adding interaction terms did not improve our model as indicated by the log-likelihood statistic. We confirmed the proportional hazard assumption for all variables in each of the models by verifying Schoenfeld residuals against survival time. All statistical analyses were performed with the IBM SPSS software, version 21.0 (IBM Corp., Armonk, USA).

In the first set of regression models, we examined cause-specific survival, by censoring patients who died from causes not related to breast cancer. We specified four Cox models to explore the effects of age on mortality. Model 1 includes only age. Model 2 adds other patient's characteristics (skin color and the Charlson comorbidity index). The tumor characteristics were added in Model 3, and in Model 4 the use of chemo and hormone therapy were included as well. In the second set of regression models, we followed the same sequence of Cox proportional hazard models as in the first set, but considered survival only from causes not related to the disease.

Results

The observation period ranged from 1 to 131 months, with a median of 62 months. Overall, there were 251 deaths (33.7%), 205 of them due to breast cancer (82% of the total of deaths, Table 1). Among deaths due to other causes, the most frequent causes were: cardiovascular diseases (13 cases, 5.2% of the total of deaths), respiratory diseases (9 deaths, 3.6%) and other cancers (9 deaths, 3.6%). There were no deaths related to external causes. Not surprisingly, deaths due to breast cancer were relatively more frequent in the youngest age group (94.1% of the total of deaths at this age), followed by women aged 36-69 years (89% of deaths), and the oldest age group (61.4%

Table 1

Age and covariates of Brazilian breast cancer patients treated from 2001 to 2008 (n = 767).

	Up to 35 years (%)	36-69 years (%)	70 and older (%)	Total (%)	p-value
Age	41 (100.0)	584 (100.0)	142 (100.0)	767 (100.0)	
Life status					
Alive at the end of the study	24 (58.5)	420 (71.9)	72 (50.7)	516 (67.3)	< 0.001
Death due to breast cancer	16 (39.0)	146 (25.0)	43 (30.3)	205 (26.7)	
Death due to other causes	1 (2.4)	18 (3.1)	27 (19.0)	46 (6.0)	
Skin color					
White	9 (22.0)	201 (34.4)	67 (47.2)	277 (36.1)	0.001
Non-white	32 (78.0)	383 (65.6)	75 (52.8)	490 (63.9)	
Charlson comorbidity index					
No comorbidities	41 (100.0)	498 (85.3)	86 (60.6)	625 (81.5)	*
At least one comorbidity	0 (0.0)	86 (14.7)	56 (39.4)	142 (18.5)	
Tumor type					
Ductal	35 (85.4)	502 (86.0)	119 (83.8)	656 (85.5)	0.838
Lobular	4 (9.8)	45 (7.7)	15 (10.6)	64 (8.3)	
Other	2 (4.9)	37 (6.3)	8 (5.6)	47 (6.1)	
Tumor size					
T1	11 (26.8)	192 (32.9)	52 (36.6)	255 (33.2)	0.736
T2	18 (43.9)	232 (39.7)	53 (37.3)	303 (39.5)	
T3	6 (14.6)	78 (13.4)	11 (7.7)	95 (12.4)	
T4	6 (14.6)	82 (14.0)	26 (18.3)	114 (14.9)	
Lymph node status					
N0	13 (31.7)	232 (39.7)	68 (47.9)	313 (40.8)	0.335
N1	15 (36.6)	174 (29.8)	33 (23.2)	222 (28.9)	
N2	8 (19.5)	111 (19.0)	21 (14.8)	140 (18.3)	
N3	5 (12.2)	67 (11.5)	20 (14.1)	92 (11.0)	
Histologic grade					
Low grade	6 (14.6)	107 (18.3)	32 (22.5)	145 (18.9)	0.034
Intermediate grade	13 (31.7)	261 (44.7)	64 (45.1)	338 (44.1)	
High grade	22 (53.7)	216 (37.0)	46 (32.4)	284 (37.0)	
Use of chemotherapy					
Yes	35 (85.4)	507 (86.8)	68 (47.9)	610 (79.5)	< 0.001
No	6 (14.6)	77 (13.2)	74 (52.1)	157 (20.5)	
Use of hormone therapy					
Yes	28 (68.3)	404 (69.2)	92 (64.8)	524 (68.3)	0.411
No	13 (31.7)	180 (30.8)	50 (35.2)	243 (31.7)	

* Fisher's exact text was not performed because one of the values is equal to 0.

of deaths). The prevalence of comorbidities increased with age (39.4% of patients 70 years and older had at least one comorbidity).

Table 1 shows the distribution of the explanatory variables by age. Younger patients were more frequently non-white (78% non-white versus 22% white) than the oldest age group (52.8% non-white versus 47.2% white). The distributions of tumor type, tumor size, and lymph node status were not different across age groups. However, when lymph node status was dichotomized in negative and positive, younger patients were more likely to have positive axillary lymph nodes than the older patients: 28 patients younger than 35 years of age (68.3%) had at least one positive lymph node compared to 74 patients (52.1%) at the age of 70 years old and older. High-grade tumors were also more frequent among the youngest patients. Regarding the use of systemic therapies, chemotherapy was more frequently used by younger women (35 women in the youngest age group, 85.4%, versus 68 women, 47.9%, in the

oldest cohort). The use of hormone therapy did not change across age categories. Table 2 shows crude hazard ratios for each of the covariates, in models of disease-specific and mortality associated with other causes.

Table 3 shows the results for cause-specific Cox regression models. According to model 1, both patients aged 35 years old and younger (HR = 1.81; 95%CI: 1.08-3.03), and 70 years old and older (HR = 1.42; 95%CI: 1.01-2.00), had lower disease-specific survival than women 36 to 69 years old. The coefficients for age changed little in Model 2, indicating that most of the effect of age is not captured by the presence of at least one comorbidity and patients' skin color. Model 2 also shows that non-white women have a higher risk of dying than white women (HR = 0.71; 95%CI: 0.53-0.96). Having at least one comorbidity was not associated with lower disease-specific survival (HR = 1.06; 95%CI: 0.73-1.54).

Model 3 (Table 3) shows that multiple tumor characteristics are significantly associated with the risk of dying during the observation period. Higher tumor grade, larger tumor size, and higher number of positive nodes were all associated with higher mortality risks. The effect of the youngest age group, however, became no longer statistically significant (HR = 1.64; 95%CI:

Table 2

Factors related to breast cancer-specific survival (n = 767) and death due to other causes (n = 726) in Brazilian breast cancer patients stages I-III, treated from 2001 to 2008, univariate analysis.

	Cause-specific		Other causes	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)				
36-69 (reference)	1.00		1.00	
Up to 35	1.81 (1.08-3.03)	0.025	1.00 (0.13-7.47)	1.000
70 and older	1.42 (1.01-2.00)	0.042	7.39 (4.06-13.44)	< 0.001
Comorbidities				
No (reference)	1.00		1.00	
Yes	1.10 (0.77-1.57)	0.609	6.06 (3.36-10.92)	< 0.001
Skin color				
Non-white (reference)	1.00		1.00	
White	0.73 (0.54-0.98)	0.034	2.40 (1.32-4.35)	0.004
Tumor size				
T1 (reference)	1.00		1.00	
T2	2.04 (1.35-3.08)	0.001	1.12 (0.57-2.21)	0.741
T3	3.11 (1.90-5.08)	< 0.001	1.10 (0.40-3.02)	0.858
T4	6.50 (4.25-9.93)	< 0.001	1.42 (0.55-3.67)	0.471
Lymph node status				
N0 (reference)	1.00		1.00	
N1	2.58 (1.71-3.88)	< 0.001	0.78 (0.37-1.65)	0.513
N2	4.90 (3.26-7.35)	< 0.001	1.10 (0.49-2.47)	0.818
N3	5.21 (3.37-8.06)	< 0.001	0.99 (0.38-2.63)	0.989
Tumor grade				
Low grade (reference)	1.00		1.00	
Intermediate grade	1.78 (1.08-2.95)	0.025	1.61 (0.69-3.73)	0.271
High grade	3.59 (2.21-5.84)	< 0.001	1.30 (0.52-3.22)	0.574
Use of chemotherapy				
No (reference)	1.00		1.00	
Yes	2.92 (1.80-4.74)	< 0.001	0.28 (0.16-0.50)	< 0.001
Use of hormone therapy				
No (reference)	1.00		1.00	
Yes	0.45 (0.34-0.59)	< 0.001	0.95 (0.50-1.82)	0.886

95%CI: 95% confidence interval; HR: hazard ratio.

Table 3

Cox regression models of factors related to breast cancer-specific survival in Brazilian breast cancer patients stages I-III, treated from 2001 to 2008 (n = 767).

	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)								
36-69 (reference)	1.00		1.00		1.00		1.00	
Up to 35	1.81 (1.08-3.03)	0.025	1.77 (1.05-2.97)	0.032	1.64 (0.97-2.76)	0.065	1.78 (1.05-3.01)	0.031
70 and older	1.42 (1.01-2.00)	0.042	1.46 (1.03-2.08)	0.034	1.44 (1.01-2.06)	0.043	1.51 (1.04-2.18)	0.028
Comorbidities								
No (reference)			1.00		1.00		1.00	
Yes			1.06 (0.73-1.54)	0.753	1.19 (0.82-1.72)	0.37	1.28 (0.87-1.86)	0.209
Skin color								
Non-white (reference)			1.00		1.00		1.00	
White			0.71 (0.53-0.96)	0.027	0.79 (0.58-1.07)	0.127	0.83 (0.61-1.13)	0.242
Tumor size								
T1 (reference)					1.00		1.00	
T2					1.19 (0.77-1.83)	0.437	1.15 (0.74-1.77)	0.542
T3					1.75 (1.05-2.93)	0.033	1.60 (0.95-2.69)	0.076
T4					3.69 (2.34-5.82)	< 0.001	3.31 (2.08-5.26)	< 0.001
Lymph node status								
N0 (reference)					1.00		1.00	
N1					1.94 (1.26-2.97)	0.005	1.87 (1.21-2.89)	0.003
N2					2.93 (1.90-4.52)	< 0.001	2.90 (1.87-4.50)	< 0.001
N3					3.92 (2.48-6.20)	< 0.001	4.02 (2.52-6.43)	< 0.001
Tumor grade								
Low grade (reference)					1.00		1.00	
Intermediate grade					1.46 (0.88-2.42)	0.145	1.40 (0.84-2.33)	0.191
High grade					2.71 (1.65-4.44)	< 0.001	2.12 (1.27-3.54)	0.004
Use of chemotherapy								
No (reference)							1.00	
Yes							1.31 (0.74-2.29)	0.354
Use of hormone therapy								
No (reference)							1.00	
Yes							0.59 (0.44-0.80)	0.001

95%CI: 95% confidence interval; HR: hazard ratio.

0.97-2.76). On the other hand, the coefficient for the oldest age group remained virtually unchanged and statistically significant in Model 3 (HR = 1.44; 95%CI: 1.01-2.06). The patient's skin color (HR = 0.79; 95%CI: 0.58-1.07), and the presence of at least one comorbidity (HR = 1.19; 95%CI: 0.82-1.72), were not statistically associated with death due to breast cancer.

When adding chemo and hormone therapies (Model 4, Table 3), the youngest age group became again associated with a higher risk of dying due to breast cancer (HR = 1.78; 95%CI: 1.05-3.01), while the effect for the oldest age group became slightly greater (HR = 1.51; 95%CI: 1.04-2.18). Tumor related factors remained significantly associated with survival. Chemotherapy was not statistically associated with longer survival among the patients, although the use of hormone therapy seemed to have a statistically significant protective effect (HR = 0.59; 95%CI: 0.44-0.80).

In Table 4, we compare the regression models for mortality risk due to causes other than breast cancer, excluding patients up to 35 years of age, since there was only one death not associated with breast cancer in this age group. Thus, we had a total of 726 cases in this analysis. The oldest age category was significantly associated with a higher risk of dying in every model than the age group 36 to 69 years old. Also, the mortality

Table 4

Cox regression models of factors related to death due to causes other than breast cancer in Brazilian patients with breast cancer stages I-III, treated from 2001 to 2008 (n = 726).

	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)								
36-69 (refence)	1.00		1.00		1.00		1.00	
70 and older	7.42 (4.08-13.49)	< 0.001	4.73 (2.52-8.89)	< 0.001	5.23 (2.74-9.97)	< 0.001	4.24 (2.06-8.73)	< 0.001
Comorbidities								
No (reference)			1.00		1.00		1.00	
Yes			3.90 (2.10-7.23)	< 0.001	4.09 (2.16-7.75)	< 0.001	3.72 (1.92-7.24)	0.001
Skin color								
Non-white (reference)			1.00		1.00		1.00	
White			2.05 (1.12-3.75)	0.02	2.22 (1.19-4.14)	0.012	2.08 (1.11-3.89)	0.023
Tumor size								
T1 (reference)					1.00		1.00	
T2					0.91 (0.43-1.94)	0.815	0.99 (0.46-2.13)	0.975
T3					1.44 (0.50-4.19)	0.501	1.77 (0.57-5.52)	0.324
T4					0.82 (0.29-2.33)	0.706	1.03 (0.33-3.16)	0.964
Lymph node status								
N0 (reference)					1.00		1.00	
N1					0.98 (0.45-2.16)	0.967	1.10 (0.49-2.48)	0.819
N2					1.12 (0.45-2.79)	0.803	1.22 (0.48-3.11)	0.683
N3					1.59 (0.57-4.42)	0.371	1.98 (0.67-5.88)	0.217
Tumor grade								
Low grade (reference)					1.00		1.00	
Intermediate grade					2.00 (0.83-4.86)	0.124	2.05 (0.84-5.04)	0.117
High grade					1.97 (0.74-5.25)	0.175	2.08 (0.73-5.94)	0.172
Use of chemotherapy								
No (reference)							1.00	
Yes							0.57 (0.25-1.33)	0.195
Use of hormone therapy								
No (reference)							1.00	
Yes							0.88 (0.43-1.82)	0.738

95%CI: 95% confidence interval; HR: hazard ratio.

risk from other causes of death was significantly increased for white women and for those who had at least one comorbidity. The variables associated with tumor characteristics and systemic treatments were not predictors of mortality from other causes of death in any of the models.

Discussion

In the current study, we showed that the relationship between age and breast cancer survival remained statistically significant after including all the control variables available for our analysis. When age was considered alone, we found that the oldest age group (70 years old and older, HR = 1.42; 95%CI: 1.01-2.00) and the youngest one (up to 35 years old, HR = 1.81; 95%CI: 1.08-3.03) had higher risk of dying due to breast cancer than patients 36 to 69 years old. When tumor and patient characteristics, as well as use of systemic therapies were added to the model, the survival disadvantage of the youngest (up to 35 years old, HR = 1.78; 95%CI: 1.05-3.01) and the oldest groups (70 years old and older, HR = 1.51; 95%CI: 1.04-2.18) remained statistically significant.

Nevertheless, our results also revealed that the magnitude and significance of some of the age effects varied depending on the different sets of variables included in the models. We found

that tumor characteristics explain to some extent the survival disadvantage among the youngest patients. These results are in accordance with previous research that has shown that younger patients have more aggressive tumors, whereas older patients have lower grade diseases, but a higher frequency of comorbidities, and more advanced stages at diagnosis [2,7,10,13,14,26,27]. In our study, the presence of comorbidities was not associated with a higher hazard of dying from breast cancer, as shown in the study by Berglund et al. [15].

Some of the crude hazard ratios for tumor related factors (tumor size and grade, and lymph node status) in the univariate analysis (Table 2) were substantially larger than the adjusted effects in the multivariate models shown in Table 3. One possible explanation for this pattern is the existence of high correlation among the predictor variables. Yet, in tests that we performed using the variance inflation factor, we found multicollinearity to be within the limits of tolerance. Keeping the predictor variables together in our final model is also in accordance with the literature that has shown they are independent prognostic factors in cancer survival.

The appropriate treatment for elderly women with breast cancer remains a matter of debate. Since older women are usually not included in treatment trials, the benefits of therapy for them are more difficult to evaluate [2,26]. Also, the incidence of toxicity after adjuvant treatments [2] and the presence of comorbidities [15,16] is higher among the elderly, thus reducing the use of these types of therapies. On the other hand, some studies have shown that less than standard treatment can be harmful for older patients [6,8,9], and thus, the individualization of treatment strategies is recommended. Chemotherapy was less frequently used among older patients (p-value < 0.001) in our cohort and it did not seem to offer mortality protection among patients of any age group. The benefits of chemotherapy are known to be more important among hormone receptor-negative patients [20,21], and since around 70% of our study comprises patients with hormone receptor-positive tumors, the cohort size may be too small to show the protective effects of this type of treatment. Other treatment modalities, like type of surgical treatment and use of radiation therapy, were omitted from our analysis, since they have a weaker association with overall survival than the other measures [20,21,26].

A similar debate exists surrounding the ideal age to interrupt breast cancer screening. In Brazil, the recommended age span for screening by the Public Health System is from 50 to 69 years of age [28]. According to the International Society of Geriatric Oncology (SIOG), the decision to maintain screening over the age of 70 should be "*based on risks and benefits, patient preference, physiological age, and life expectancy*" [26] (p. e152). Unfortunately we cannot test directly for delayed diagnosis, although in our sample the distribution of patients by tumor size and lymph node status, compared to countries where screening is available, suggests that there are more advanced cases in Brazil, particularly among the elderly [29,30].

One of the limitations of our study is that we drew our data from pathology records, which means we have selected a sample of patients which were at least fit enough to undergo surgical treatment. Patients with a lower health status who could not have undergone surgery were excluded from our cohort study from the start, which precludes us from generalizing our conclusions to all breast cancer patients. In addition, we obtained data on comorbidities and adjuvant therapies from medical records. Therefore, we were not able to identify which chemo and hormone therapy regimens were applied to each patient, although we recognize that they vary depending on disease characteristics and comorbidities.

One interesting finding from our study is the association between skin color and mortality. In Brazil, classifying patients by race is not trivial due to the high miscegenation rate [31,32,33], and thus, we used information on patient's skin color collected by the attending physicians. The prevalence of non-white women was higher in the youngest age group (78%) compared with older individuals (52.8% of women 70 years old and older were non-white). Also, non-white women had shorter breast-cancer specific survival, when controlling for age and the presence of comorbidities. The mortality disadvantage, however, became insignificant when the variables associated with tumor characteristics were accounted for in our regression models. These results suggest that non-white patients may have more aggressive tumors [34], more difficult access to health care [35,36], or both. In the analysis of mortality due to other causes of death, we found an inverted relation between skin color and mortality: white patients had a higher risk of dying than non-white patients. To interpret these results, one should note that when implementing the cause-specific Cox regression models we treated deaths from cause of interest as events and the other group of deaths as right censored observations. In the presence of right censored event times, the regression coefficients give us only the effect of skin color on the instantaneous hazard of dying. Therefore, we cannot directly link our results to the cumulative incidence function [37] and con-

clude, based on the lower instantaneous hazard from other causes of deaths among non-whites, that this group truly experiences lower incidence of this types of deaths.

Our finding that tumor related characteristics were not significantly associated with mortality due to other causes of death is not surprising and indicates the quality of our data, particularly the accuracy of the classification of causes of death. One should note that the risk of dying from diseases other than breast cancer increases with time since diagnosis [38,39], especially after ten years. Since the median follow-up time in our study was much shorter, we already expected a larger proportion of deaths (82% of total of deaths) due to breast cancer compared to other studies. However, in at least one study of American women, which followed patients for a period of time (2000 to 2007) shorter than the observation period in our study, the proportion of breast cancer deaths was relatively lower (only 56%) [40].

Multiple factors are involved in mortality from breast cancer and there is still much to be learned about the biological, medical and socioeconomic mechanisms responsible for improving survival. The current study has extended previous research for Brazil in showing that age is an independent predictor of cause-specific mortality, at least in the presence of the numerous control variables available for our analysis. Of course, survival differentials by age may depend on a variety of other key factors not included in our models such as the socioeconomic status of patients [30], access to health care [31,32], and more detailed data on types of treatment employed [12,17,41,42], which reinforces the need for further analysis. Understanding the pathways linking age to mortality due to breast cancer should help doctors, epidemiologists and policy makers to propose specific measures to improve the chances of survival for women of different age groups, particularly in a context of profound changes in the population age structure.

Resumen

Es discutible si la edad es un factor pronóstico independiente para el cáncer de mama. Se realizó sobre una cohorte retrospectiva de 767 pacientes con cáncer de mama, etapas I-III, atendidas en el Hospital de Clínicas, Universidad Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil, entre 2001 y 2008, para estudiar la relación entre edad y supervivencia. Incluimos variables relacionadas con las pacientes, los tumores y el tratamiento. Se construyeron diferentes conjuntos de modelos de Cox. Se calcularon los cocientes de riesgo (CR) e IC95%. La relación entre edad y supervivencia del cáncer de mama no ha cambiado substancialmente en los modelos. En el modelo con todas las variables, las mujeres de 70 años o más (CR = 1,51; IC95%: 1,04-2,18) y 35 años o menos (CR = 1,78; IC95%: 1,05-3,01) tuvieron menor supervivencia por cáncer de mama que las de 36 a 69 años. Tener edad avanzada, al menos una comorbilidad, y ser de piel blanca se asociaron a un mayor riesgo de morir por otras causas. En conclusión, las mujeres más jóvenes y las mayores parecen tener menor supervivencia de cáncer de mama.

Estadificacíon de Neoplasias; Origem Étnico y Salud; Factores de Edad; Neoplasias de la Mama

Contributors

D. Balabram was responsible for the study design, data collection and analysis, and for writing the paper. C. M. Turra was responsible for the study design, analysis of data and aided in paper writing. H. Gobbi aided in the study design, reviewed specimen slides and aided in paper writing. All authors have read and approved the submitted version of the manuscript.

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