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TESE DE DOUTORADO

DÉBORA BALABRAM

SOBREVIDA DE PACIENTES COM CÂNCER DE MAMA TRATADAS NO HOSPITAL DAS CLÍNICAS DA UFMG ENTRE 2001 E 2008

BELO HORIZONTE

2014

Débora Balabram

SOBREVIDA DE PACIENTES COM CÂNCER DE MAMA TRATADAS NO HOSPITAL DAS CLÍNICAS DA UFMG ENTRE 2001 E 2008

Tese apresentada ao Programa de Pós-graduação em Patologia da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial para a obtenção do Título de Doutor em Patologia

Área de concentração: Patologia Médica

Orientadora: Prof[a]. Dra. Helenice Gobbi

Coorientador: Prof. Dr. Cássio Maldonado Turra

Belo Horizonte

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UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA

ATA DA DEFESA DE TESE DA ALUNA
DÉBORA BALABRAM

Realizou-se, no dia 24 de fevereiro de 2014, às 14:00 horas, Sala 340, Faculdade de Medicina da UFMG, Av. Alfredo Balena, 190, da Universidade Federal de Minas Gerais, a defesa de tese, intitulada *SOBREVIDA DE PACIENTES COM CÂNCER DE MAMA TRATADAS NO HOSPITAL DAS CLÍNICAS DA UFMG ENTRE 2001 E 2008*, apresentada por DÉBORA BALABRAM, número de registro 2010754586, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em PATOLOGIA, à seguinte Comissão Examinadora: Prof(a). Helenice Gobbi - Orientador (UFMG), Prof. Cassio Maldonado Turra- Coorientador (UFMG), Prof. Victor Hugo de Melo (UFMG), Prof. Alexandre de Almeida Barra (UFOP), Prof(a). Waleska Teixeira Caiaffa (UFMG), Prof. César Cabello dos Santos (UNICAMP).

A Comissão considerou a tese:

(X) Aprovada

( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 24 de fevereiro de 2014.

Prof(a). Helenice Gobbi (Doutora)

Prof(a). Cassio Maldonado Turra (Doutor)

Prof(a). Victor Hugo de Melo (Doutor)

Prof(a). Alexandre de Almeida Barra (Doutor)

Prof(a). Waleska Teixeira Caiaffa (Doutora)

Prof(a). César Cabello dos Santos (Doutor)

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA

UFMG

FOLHA DE APROVAÇÃO

SOBREVIDA DE PACIENTES COM CÂNCER DE MAMA TRATADAS NO HOSPITAL DAS CLÍNICAS DA UFMG ENTRE 2001 E 2008

DÉBORA BALABRAM

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em PATOLOGIA, como requisito para obtenção do grau de Doutor em PATOLOGIA, área de concentração PATOLOGIA MÉDICA.

Aprovada em 24 de fevereiro de 2014, pela banca constituída pelos membros:

Prof(a). Helenice Gobbi - Orientador
Universidade Federal de Minas Gerais

Prof. Cassio Maldonado Turra
Universidade Federal de Minas Gerais

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Prof. César Cabello dos Santos
Universidade Estadual de Campinas

Belo Horizonte, 24 de fevereiro de 2014.

Este trabalho foi realizado no Laboratório de Patologia Mamária da Faculdade de Medicina da Universidade Federal de Minas Gerais, com apoio financeiro do Conselho Nacional de Desenvolvimento da Pesquisa (CNPq), da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) e da Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG).

א באקאנטן טייוול איז בעסעסווי אן אומבאקאנטן.

“Melhor o diabo que você conhece do que o diabo desconhecido” (provérbio ídiche).

“Melhor, se arrepare: pois, num chão, e com igual formato de ramos e folhas, não dá a mandioca mansa, que se come comum, e a mandioca-brava, que mata? Agora, o senhor já viu uma estranhez? A mandioca-doce pode de repente virar azangada – motivos não sei; às vezes se diz que é por replantada no terreno sempre, com mudas seguidas, de manaíbas – vai em amargando, de tanto em tanto, de si mesma toma peçonhas. E, ora veja: a outra, a mandioca-brava, também é que às vezes pode ficar mansa, a esmo, de se comer sem nenhum mal. E que isso é?”

J. Guimarães Rosa, Grande Sertão: Veredas.

A Fany, Moysés e Elisa Balabram

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Às pacientes, que tanto enriquecem meu dia-a-dia. Que eu possa ajudá-las a enfrentar as dificuldades das doenças e tenha humildade para reconhecer os limites do tratamento cirúrgico.

A D-us, que me fez conforme a Sua Vontade: “alivia a minha alma, faze com que eu sinta que Tua mão está dada à minha (…), faze com que eu não Te indague demais, porque a resposta seria tão misteriosa quanto a pergunta (…), faze com que eu receba o mundo sem receio, pois para esse mundo incompreensível eu fui criada e eu mesma também incompreensível, então é que há uma conexão entre esse mistério do mundo e o nosso, mas essa conexão não é clara para nós enquanto quisermos entendê-la, abençoa-me para eu viva com alegria o pão que eu como, o sono que durmo, faze com que eu tenha caridade por mim mesma, pois senão não poderei sentir que D-us me amou, faze com que eu perca o pudor de desejar que na hora de minha morte haja uma mão humana amada para apertar a minha, amém.” Clarice Lispector, Uma aprendizagem ou o livro dos prazeres.

RESUMO

INTRODUÇÃO: Várias características estão associadas ao prognóstico do câncer de mama, como estadiamento, positividade de receptores hormonais, grau histológico, raça e fatores socioeconômicos. É discutível se idade é um fator prognóstico independente para a doença.

OBJETIVO: Neste estudo avaliamos a sobrevida de pacientes com câncer de mama tratadas cirurgicamente no Hospital das Clínicas (HC) da UFMG entre 2001 e 2008.

MATERIAL E MÉTODOS: Os casos de câncer de mama estádio I a III tratados no referido período foram identificados no Laboratório de Patologia Mamária da Faculdade de Medicina da UFMG. Foi feito um cruzamento probabilístico com o banco de dados do Sistema de Informações de Mortalidade (SIM) da Secretaria Estadual de Saúde de MG, no período de 01/01/2001 a 31/12/2011, com o programa RecLink, e consultaram-se os prontuários das pacientes. Foram construídas curvas de Kaplan-Meier e o modelo de Cox foi usado para análise uni e multivariada. Foram calculadas as Razões de Risco (RR) e o Intervalo de Confiança a 95% (IC). O nível de significância foi de 0,05. Inicialmente, foram analisadas 897 pacientes, tratadas pelo Sistema Único de Saúde (SUS) ou por financiamento privado. Em um segundo momento, foram analisadas apenas as pacientes tratadas pelo SUS, enfocando a idade como fator prognóstico da doença (n=783).

RESULTADOS: Na primeira análise, houve 282 óbitos, 228 deles por câncer de mama (81%). A sobrevida causa-específica em cinco anos foi de 95,5% para o estádio I, 85,1% para o estádio II e 62,1% para o estádio III. Pacientes tratadas pelo SUS tiveram estadiamento mais avançado ao diagnóstico e pior sobrevida em análise univariada. Em análise multivariada, maior estadiamento, maior grau histológico e idade acima de 70 anos foram associados a menor sobrevida. Na segunda análise, foram observadas mudanças na relação entre idade e sobrevida dependendo da inclusão de diferentes variáveis aos modelos de Cox. Na análise causa-específica, as pacientes com idade a partir de 70 anos e as com até 35 anos tiveram maior mortalidade em relação às com idade entre 36 e 69 anos (70 e mais, RR=1,42, IC=1,02-1,97; até 35, RR=1,77, IC=1,06-2,96). Quando características do tumor e das pacientes foram adicionadas ao modelo, a desvantagem de sobrevida se tornou não significativa para as até 35 anos mas se manteve para as com idade a partir de 70 anos (até 35, RR=1,58, IC=0,90-2,75; a partir de 70, RR=1,57, IC=1,07-2,31). Na análise de óbitos por outras causas, apenas ter idade

a partir de 70 anos, ser branca e ter ao menos uma comorbidade foram associados a maior risco de óbito.

CONCLUSÕES: Pacientes do SUS tiveram pior sobrevida, possivelmente devido a maior estádio da doença ao diagnóstico. Idade acima de 70 anos foi preditora independente de menor sobrevida causa-específica. A associação entre idade e sobrevida é mediada por fatores relacionadas às pacientes e aos tumores. Em pesquisas futuras, outros fatores devem ser levados em conta, como variáveis socioeconômicas e tratamentos empregados.

Palavras-chave: Neoplasias da mama, Análise de sobrevida, Estadiamento de neoplasias, Estudos de coorte, Brasil

ABSTRACT

INTRODUCTION: Several characteristics are associated with the prognosis of breast cancer, such as staging, positivity for hormone receptors, histological grade, race and socioeconomic factors. It is debatable whether age is an independent prognostic factor for the disease.

OBJECTIVE: This study evaluated the survival of patients with breast cancer surgically treated at the Hospital das Clínicas (HC)-UFMG between 2001 and 2008.

METHODS: Breast cancer cases stages I to III which underwent treatment in that period were identified in the Breast Pathology Laboratory of the Faculty of Medicine. A probabilistic record linkage with the database of the State Department of Health Mortality Information System (MIS) was performed in the period from 01/01/2001 to 31/12/2011, with the RecLink software. Then, medical records were consulted. Kaplan- Meier curves and Cox models were built for univariate and multivariate analysis. Hazard Ratios (HR) and 95% Confidence Intervals (CI) were calculated. The significance level was 0.05. Initially, 897 patients treated by the Unified Health System (SUS) or through private funding were analyzed. In a second step, we analyzed only the patients treated by the SUS, focusing on age as a prognostic factor for the disease (n=783).

RESULTS: In the first analysis, there were 282 deaths, 228 of them from breast cancer (81%). The cause-specific survival at five years was 95.5% for stage I, 85.1% for stage II and 62.1% for stage III disease. Patients treated by the SUS had more advanced tumors at diagnosis and poorer survival in univariate analysis. In multivariate analysis, higher stage, higher histological grade and age over 70 years were associated with poorer survival. In the second step, changes in the relationship between age and survival were observed depending on the inclusion of different variables to the Cox models. In cause-specific analysis, patients aged 70 years and older and up to 35 years had higher mortality compared with patients aged 36 to 69 years (70 and older, HR=1.42 , CI=1.02-1.97; up to 35 years, HR=1.77, CI=1.06- 2.96). When tumor and patients characteristics were added to the model, the disadvantage of survival became non-significant for those aged up to 35 years but remained significant for the patients 70 years old and older (up to 35, HR=1.58, CI=0.90-2.75; 70 and older, HR=1.57, CI=1.07-2.31). In other causes survival analysis, only being 70 years of age and older, being white, and having at least one comorbidity were associated with an increased risk of death.

CONCLUSIONS: Patients treated by the SUS had worse survival, possible due to higher stage of the disease at diagnoses. Being 70 years old and older was an independent predictor of shorter survival. The association between age and survival is mediated by factors related to the patient and to the tumor. In future research, other factors must be taken into account, such as socioeconomic variables and treatments employed.

Keywords: Breast neoplasms, Survival analysis, Neoplasia staging, Cohort studies, Brazil

LISTA DE ABREVIATURAS

AJCC – American Joint Committee on Cancer

BCS – Breast-conserving Surgery

CAM – Complexo Areolo-Mamilar

CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CNPq – Conselho Nacional de Desenvolvimento da Pesquisa

DCIS – Ductal carcinoma *in situ*

FAPEMIG – Fundação de Amparo à Pesquisa de Minas Gerais

HC-UFMG – Hospital das Clínicas da Universidade Federal de Minas Gerais

HR- Hazard Ratio

IDC – Invasive Ductal Carcinoma

ILC – Invasive Lobular Carcinoma

INCA – Instituto Nacional de Câncer

LCIS – Lobular carcinoma *in situ*

LPM – Laboratório de Patologia Mamária

pN – Status dos linfonodos regionais

pT – Tamanho patológico do tumor

RR- Razão de Riscos

SEER – Surveillance, Epidemiology and End Results Program

SES-MG – Secretaria de Estado da Saúde – MG

SIM – Sistema de Informações de Mortalidade

SISMAMA – Sistema de Informação do Controle do Câncer de Mama

SUS – Sistema Único de Saúde

UFMG – Universidade Federal de Minas Gerais

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1- INTRODUÇÃO

1.1- CÂNCER DE MAMA

Estima-se que, em 2014, o Brasil terá 57.120 novos casos de câncer de mama, a neoplasia maligna mais prevalente em mulheres no país e no mundo (BOYLE; LEVIN, 2008; BRASIL; INSTITUTO NACIONAL DE CÂNCER, 2014; COLEMAN et al., 2008; HARFORD, 2011; SAÚDE; INSTITUTO NACIONAL DO CÂNCER, 2013). A doença é também a principal causadora de óbitos por câncer na população feminina brasileira padronizada pela população mundial, com 11,8 óbitos para cada 100.000 mulheres em 2011 (BRASIL; INSTITUTO NACIONAL DE CÂNCER, 2014).

O câncer de mama é considerado um tumor de baixa letalidade. No entanto, a redução da mortalidade só ocorre quando o mesmo é diagnosticado e tratado em fase precoce e adequadamente. Segundo a Organização Mundial de Saúde, a sobrevida relativa em cinco anos (sobrevida de pacientes com câncer em relação à sobrevida esperada para a população de mesmo ano de nascimento e sexo) chega a 85% nos países desenvolvidos; nos países em desenvolvimento, estas taxas são menores, ficando em torno de 50 a 60% (BOYLE; LEVIN, 2008). No estudo CONCORD (COLEMAN et al., 2008), que comparou a sobrevida relativa com base em registros populacionais de diferentes tipos de câncer em vários países do mundo, a sobrevida mais baixa encontrada foi a de Sétif, na Algéria, com sobrevida relativa de 38,8% ao final de cinco anos de observação, para pacientes diagnosticadas entre os anos de 1990 e 1994, e acompanhadas até 1999.

No mesmo estudo (COLEMAN et al., 2008), o único encontrado na literatura indexada baseado em registros populacionais brasileiros, a sobrevida relativa foi de 65,4% para Goiânia e 36,6% para Campinas (acredita-se que houve falha metodológica no segundo registro).

Nas coortes hospitalares brasileiras, a sobrevida causa-específica em cinco anos varia entre 90 e 97% para o estádio I, 87,8 e 96% para o estádio II e 51 a 73% para o estádio III (AYALA, 2012; BRITO; PORTELA; VASCONCELLOS, 2009; CINTRA; GUERRA; BUSTAMANTE-TEIXEIRA, 2008; GUERRA et al., 2009; SCHNEIDER; D'ORSI, 2009).

Até a realização deste trabalho, não haviam sido encontrados estudos baseados em coortes hospitalares de Belo Horizonte (MG) na literatura indexada (PubMed e LILACS).

1.2- FATORES PROGNÓSTICOS DO CÂNCER DE MAMA

Inúmeros fatores são associados direta ou indiretamente ao prognóstico do câncer de mama. O tamanho do tumor, o número de linfonodos axilares acometidos e a presença de metástase a distância são os principais determinantes da sobrevida global e livre de doença (EDGE et al., 2009). Outros fatores são tipo e grau histológico do tumor, positividade de receptores hormonais, nível socioeconômico, raça e idade (BOYLE; LEVIN, 2008; COLEMAN et al., 2008; EDGE et al., 2009; GREENE; AMERICAN JOINT COMMITTEE ON CANCER.; AMERICAN CANCER SOCIETY., 2002; MASKARINEC et al., 2011; SILBER et al., 2013; WOODS; RACHET; COLEMAN, 2006). As menores taxas de sobrevida observadas em países em desenvolvimento podem ser atribuídas a menores proporções de pacientes sendo submetidas a rastreamento e tratamento adequados, a atrasos entre a detecção e o tratamento, bem como a diferente distribuição de características biológicas da doença e estadiamento (BOYLE; LEVIN, 2008; BRITO; PORTELA; VASCONCELLOS, 2009; LIEDKE et al., 2014; RICHARDS et al., 1999; WOODS; RACHET; COLEMAN, 2006).

Alguns dos fatores prognósticos da doença serão abordados a seguir.

1.3- IDADE E CÂNCER DE MAMA

No Brasil, a expectativa de vida vem aumentando nas últimas décadas, juntamente com a diminuição das taxas de fecundidade (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2010). Portanto, a população de mulheres idosas vem crescendo. A idade é o principal fator de risco para o aparecimento do câncer de mama em mulheres (TURNER et al., 2013). O aumento da idade também está associado a maior incidência de outras doenças crônicas, como do aparelho cardiovascular, respiratório e demais neoplasias (TURNER et al., 2013).

Em geral, o câncer de mama em mulheres idosas tende a ser menos agressivo: há maior frequência de tumores de baixo grau e maiores taxas de positividade de receptores hormonais (DUTRA et al., 2009a; GENNARI et al., 2004; SCHONBERG et al., 2010, 2011; THOMAS;

LEONARD, 2009; TURNER et al., 2013; YOOD et al., 2008). No entanto, o subtratamento é descrito, estando associado tanto a comorbidades quanto à crença em uma doença mais indolente (SCHONBERG et al., 2010, 2011; YOOD et al., 2008). O rastreamento da doença não é preconizado para mulheres acima de 70 anos, o que pode resultar em diagnóstico de tumores em fases mais avançadas nesta faixa etária (BRASIL, 2004) (Item 1.5).

Por outro lado, em mulheres jovens, há maior frequência de tumores de alto grau e menor frequência de positividade de receptores hormonais (DUTRA et al., 2009a; THOMAS; LEONARD, 2009). É ainda discutível se a idade é fator prognóstico independente para sobrevida por câncer de mama (COLZANI et al., 2011; THOMAS; LEONARD, 2009).

1.4- RAÇA E CÂNCER DE MAMA

No Brasil, estudos enfocando a raça e o prognóstico das doenças são raros (RIBEIRO; FERREIRA, 2012) e os métodos de classificação dos indivíduos variam, incluindo autoclassificação e avaliação pelos pesquisadores (ALVES et al., 2010; CHOR; LIMA, 2005; CHOR, 2013). Embora estudos de ancestralidade genômica tenham demonstrado que a variabilidade genética entre os indivíduos brasileiros considerados de diferentes raças é muito pequena (PENA et al., 2011; SANTOS et al., 2009), do ponto de vista de saúde é interessante estudar as desigualdades entre elas, tanto em termos de incidência quanto de prognóstico das doenças (CHOR; LIMA, 2005; CHOR, 2013).

Nos Estados Unidos, o prognóstico do câncer de mama é pior em mulheres afro-americanas (MASKARINEC et al., 2011; SILBER et al., 2013). Os determinantes desta diferença são tanto fatores socioeconômicos quanto diferenças nas características biológicas da doença: é descrito que mulheres afro-americanas têm tumores mais agressivos, com maior grau histológico e menor positividade de receptores hormonais (MASKARINEC et al., 2011). Por outro lado, no Brasil, parte considerável da população de cor negra ou miscigenada se concentra na faixa socioeconômica mais carente, que, consequentemente, tem menor acesso a serviços de saúde, menores taxas de rastreamento e maior dificuldade de acesso ao tratamento do câncer de mama (BRITO; PORTELA; VASCONCELLOS, 2009; LIEDKE et al., 2014; MARCHI; GURGEL, 2010; NOVAES; MATTOS, 2009; OLIVEIRA et al., 2011; SMITH et al., 2008; WOODS; RACHET; COLEMAN, 2006; YU, 2009).

1.5- RASTREAMENTO DO CÂNCER DE MAMA

O método de escolha para detecção precoce do câncer de mama (rastreamento) é a mamografia, que vem sendo usada em alguns países desde a década de 80 (BASSETT; GOLD, 1988), quando estudos randomizados mostraram redução da mortalidade por câncer de mama nos grupos submetidos ao exame (GØTZSCHE; NIELSEN, 2011; TABÁR et al., 1999; ZORZI et al., 2006). No Brasil, até 2009 não havia programa público de saúde voltado para este rastreamento, apesar da recomendação do Instituto Nacional do Câncer (INCA) de exame mamográfico pelo menos a cada dois anos, para mulheres de 50 a 69 anos de idade, e a partir dos 35 anos para pacientes consideradas de risco elevado (BRASIL, 2004). Por outro lado, a recomendação da Sociedade Brasileira de Mastologia é de exame anual a partir dos 40 anos (SOCIEDADE BRASILEIRA DE MASTOLOGIA, 2008).

Até 2009, as taxas de pacientes efetivamente submetidas a rastreamento eram baixas. Lima-Costa (LIMA-COSTA; MATOS, 2007) mostrou que, em 2003, apenas 43% das mulheres com idade entre 50 e 69 anos haviam sido submetidas a exame mamográfico nos dois anos anteriores no Brasil (34,9% para pacientes do Sistema Único de Saúde e 71% para o sistema privado). Marchi & Gurgel (MARCHI; GURGEL, 2010) mostraram maior porcentagem de exame mamográfico inicial (68%), porém menos de 50% das pacientes aderiram ao rastreamento bianual (24,5% para pacientes do SUS e 42,9% para pacientes do sistema privado). Outro estudo mostrou crescimento do uso do exame ao longo da última década: em 2003, 54,6% das mulheres entre 50 e 69 já haviam feito ao menos uma mamografia, enquanto em 2008 esta proporção mudou para 71,5% (DE OLIVEIRA et al., 2011). Para mulheres com idade acima de 70 anos, menores taxas de rastreamento foram relatadas no mesmo estudo (37,1% até 2003 e 54,5% até 2008).

Em 2009, foi implantado o SISMAMA – Sistema de Informação do Câncer de Mama, que visa não apenas unificar as informações a respeito das pacientes acometidas pela doença (como achados em exames de imagem e cito e histopatológicos) como também direcionar as verbas de saúde para as pacientes que são o alvo do rastreamento (PASSMAN et al., 2011). É esperada uma cobertura de 60% das mulheres alvo do rastreamento (ou seja, aquelas entre 50 e 69 anos) (BRASIL; INSTITUTO NACIONAL DE CÂNCER, 2004). Com isso, deseja-se que o câncer de mama seja diagnosticado em fases mais precoces, como ocorre em países que adotam o rastreamento mamográfico. Nos Estados Unidos, por exemplo (que emprega

rastreamento mamográfico anual a partir dos 40 anos), 60% dos diagnósticos de câncer de mama feitos entre 2002 e 2008 correspondiam a doença localizada (U.S., 2012).

Não há consenso em relação ao rastreamento do câncer de mama em mulheres a partir dos 70 anos. A Sociedade Internacional de Oncologia Geriátrica recomenda que o rastreamento acima desta idade seja baseado nos riscos e benefícios, nas preferências da paciente, na idade fisiológica e na expectativa de vida (BIGANZOLI et al., 2012).

1.7- LABORATÓRIO DE PATOLOGIA MAMÁRIA DA FACULDADE DE MEDICINA DA UFMG

O Laboratório de Patologia Mamária da Faculdade de Medicina da Universidade Federal de Minas Gerais (LPM) foi estruturado em 1989, como parte do Serviço de Anatomia Patológica da mesma instituição. A partir deste ano, todos os exames histopatológicos de mama de materiais provenientes do Hospital das Clínicas da UFMG passaram a ser realizados pela mesma patologista ou sob sua orientação. Protocolos para estudo citológico e histopatológico foram desenvolvidos e implantados para normatizar os exames e ainda formar as bases de um laboratório de pesquisa especializado (GOBBI et al., 1993; XAVIER et al, 2005). Além de atender à demanda de exames provenientes do Hospital das Clínicas da UFMG (HC-UFMG), o LPM cresceu também como centro de referência e realização de exames em consultoria aberto à comunidade em geral. Além disto, a técnica imunohistoquímica foi implantada no LPM com finalidade de pesquisa e avaliação de fatores preditivos e prognósticos no câncer de mama e no diagnóstico diferencial de lesões mamárias.

1.8– HOSPITAL DAS CLÍNICAS DA UFMG

O HC-UFMG é um hospital universitário de referência para tratamento de doenças de média e alta complexidade. Até 2008, ele tratava pacientes procedentes tanto do sistema público (Sistema Único de Saúde, SUS) quanto do sistema privado de saúde (particulares e convênios) (BALABRAM et al., 2012; UFMG; COMUNICAÇÃO, 2013).

No Brasil, em 2008, apenas 26% da população tinha seguro privado de saúde, sendo que, atualmente, a maior parte da população depende do Sistema Único de Saúde (SUS) para acesso ao diagnóstico e tratamento do câncer de mama (PAIM et al., 2011).

2- OBJETIVOS

2. 1- OBJETIVO GERAL

- Avaliar a sobrevida global e causa-específica das pacientes com câncer de mama submetidas a tratamento cirúrgico no Hospital das Clínicas da UFMG entre 2001 e 2008.

2.2- OBJETIVOS ESPECÍFICOS

a) Avaliar os fatores determinantes do prognóstico da doença no mesmo período (estadiamento, ter sido tratada pelo SUS, idade, tipo e grau histológico) – Artigo 1
b) Avaliar especificamente a idade enquanto fator prognóstico do câncer de mama na presença de covariáveis relacionadas ao tumor (estadiamento, tipo e grau histológico) e às pacientes (cor e comorbidades) – Artigo 2

3- MATERIAIS E MÉTODOS

3.1- APROVAÇÃO PELO COMITÊ DE ÉTICA

O presente projeto foi aprovado pelo Comitê de Ética em Pesquisa da UFMG (COEP), protocolo número 0660.0.203.000-11, em março de 2012 (Anexo I), pela Diretoria de Ensino, Pesquisa e Extensão do HC-UFMG (Anexo II) e pela Secretaria de Estado de Saúde de Minas Gerais (Anexo III).

3.2- DESENHO DO ESTUDO

Trata-se de estudo de coorte histórica, de base hospitalar.

3.3- OBTENÇÃO DE DADOS DE EXAMES DIAGNÓSTICOS DO LABORATÓRIO E DESCRIÇÃO DA AMOSTRA

Um banco de dados de espécimes histológicos correspondentes a tratamento cirúrgico de câncer de mama recebidos no LPM entre os anos de 1989 e 2008 foi montado para o Mestrado da aluna. Ele contém informações relativas a 2061 pacientes cujo tratamento cirúrgico foi realizado no Hospital das Clínicas da UFMG (BALABRAM, 2010; BALABRAM et al., 2012), e foi complementado durante este trabalho. Um protocolo específico foi utilizado na coleta dos dados (vide Anexo IV), tendo como base as orientações do Instituto Nacional do Câncer (BRASIL, 2002), Xavier *et al.* (XAVIER et al, 2005) e Gobbi *et al.* (GOBBI; RIBEIRO; LOUREIRO, 1993).

As variáveis coletadas nesta etapa foram: nome, registro hospitalar, data de nascimento, nome do pai e da mãe, endereço, categoria sócio-previdenciária (tratamento pelo SUS ou por convênio/particular), data do primeiro tratamento cirúrgico (ou da *core biopsy* nos casos de quimioterapia neoadjuvante), tipo de tratamento cirúrgico empregado (mastectomia ou cirurgia conservadora, esvaziamento axilar ou biopsia de linfonodo sentinela), ano, lateralidade (direita ou esquerda), ter ou não câncer bilateral, sexo, idade, diagnóstico

anatomo-patológico, grau histológico, estadiamento clínico e anatomo-patológico (conforme TNM), e *status* dos receptores hormonais. Para pacientes não submetidas a terapia neoadjuvante, o estadiamento anatomo-patológico foi utilizado; para as submetidas a quimio ou hormonioterapia, o estadiamento clínico na data da *core biopsy* foi usado.

Deste banco de dados, foram selecionadas todas as pacientes com carcinoma de mama operadas a partir de 2001 (1119 pacientes). Para o Artigo 1, foram excluídos os casos de carcinoma ductal e lobular *in situ* (166), pacientes com metástase axilar apenas (primário oculto, dois casos), estádio desconhecido (um caso), casos sem amostra tumoral em nossa instituição (primeira cirurgia em outro hospital, sem tumor residual na ampliação de margens, 27 casos), pacientes com câncer de mama metastático, submetidas a cirurgia paliativa apenas (sete casos), câncer de mama recidivado (14 casos), uma paciente que mudou para outro estado durante o tratamento e quatro pacientes cuja data de nascimento e nome da mãe não foram encontrados. O total de casos disponível para análise foi de 897.

Numa segunda etapa (para o artigo 2), foram excluídas adicionalmente as pacientes cujo tratamento não foi custeado pelo SUS (75 casos) e aquelas cujo prontuário não foi localizado no SAME (20 casos). O total de casos disponível para análise foi de 783.

3.4- BANCO DE DADOS DO SISTEMA DE INFORMAÇÕES DE MORTALIDADE (SIM)

O banco de dados relativo aos óbitos de mulheres acima de 15 anos residentes em Minas Gerais no período de 01/01/2000 a 31/12/2011 foi obtido na Secretaria Estadual de Vigilância e Proteção à Saúde, Sistema de Informação sobre Mortalidade (SES-MG), a partir do ano 2000. Ele contém informações provenientes da Declaração de Óbito das referidas mulheres. No entanto, para o ano 2000, os nomes das pacientes e a data do óbito não foram registrados, e optou-se por limitar a análise a pacientes tratadas cirurgicamente a partir de 2001 (n=488490).

O SIM é um sistema nacional computadorizado que engloba informações relativas a óbitos, e foi implementado em 1975 ("SISTEMA NACIONAL DE VIGILÂNCIA EM SAÚDE - RELATÓRIO DE SITUAÇÃO - MINAS GERAIS," 2013). Ao longo dos anos, sua

completude vem aumentando, chegando a 93.5% em 2007 em Minas Gerais. Como as pacientes tratadas no HC-UFMG eram todas residentes no estado de Minas Gerais, a busca foi restrita às mulheres residentes no referido estado.

No SIM, as causas de óbito são reportadas de acordo com a Classificação Internacional de Doenças versão 10.0, codificação da Organização Mundial de Saúde ("WHO | International Classification of Diseases (ICD)," 2007).

Optou-se por utilizar o banco de dados do SIM para minimizar as possíveis perdas de seguimento das pacientes, e também pela dificuldade de obter os prontuários das mesmas no Serviço de Arquivo Médico e Estatística (SAME) do HC-UFMG.

3.5- CRUZAMENTO DE DADOS

Foi feito cruzamento do banco de dados do presente trabalho com o banco de dados do SIM para identificar as pacientes que vieram a óbito e qual a data do mesmo.

O método utilizado foi o relacionamento probabilístico, que é considerado o de escolha quando não há uma variável única comum a ambos os bancos de dados (número de seguridade social, por exemplo). Inicialmente, ambos os bancos de dados (do presente trabalho e do SIM) foram padronizados. O primeiro e último nome das pacientes e suas mães foram transformados no código Soundex, o qual é um sistema fonético que considera apenas as consoantes dos nomes (CAMARGO; COELI, 2000).

O relacionamento probabilístico é baseado em escores, que definem a probabilidade de tratar-se ou não de par verdadeiro. Quanto maior o escore, maior é esta probabilidade (CAMARGO; COELI, 2000; COUTINHO; COELI, 2006; NEWCOMBE, 1967). Com o objetivo de minimizar as chances de pacientes com erros em algum dos campos de preenchimento no atestado de óbito não serem encontradas no banco de dados do SIM, cinco chaves sequenciais de pareamento foram utilizadas (Tabela 1). Foram conferidos os pares com escore acima de um em cada chave do cruzamento. Em todos os casos, inclusive quando o cruzamento era perfeito (ou seja, quando o escore atingia o máximo), as demais variáveis disponíveis no banco de dados do trabalho e do SIM, como nome do pai e endereço, eram usadas para confirmação de tratar-se ou não de par verdadeiro.

Para permitir a utilização de casos posteriormente excluídos (por exemplo, a sobrevida de pacientes com carcinoma *in situ*), o cruzamento foi realizado antes da exclusão.

Com o objetivo de otimizar o pareamento e diminuir a proporção de pares falsamente verdadeiros (falso-positivos), o banco de dados do trabalho e o do SIM foram divididos. Por exemplo, pacientes operadas em 2004 foram buscadas num sub-banco de óbitos abrangendo o intervalo de 01/01/2004 a 31/12/2011.

O programa utilizado para este cruzamento foi o RecLink versão III (disponível online: http://www.iesc.ufrj.br/reclink/RecLink_arquivos/RecLinkdl.html).

Os casos foram censurados quando a paciente não foi encontrada na base de dados do SIM até a data de 31/12/2011.

Tabela 1. Chaves de blocagem realizadas para o cruzamento de banco de dados

Passo	Blocagem	Pareamento	Escore máximo	Número de pares encontrados
1	PBLOCO* + UBLOCO** + Ano de nascimento	Nome + Data de nascimento	10,69	278
2	PBLOCO* (MÃE) + UBLOCO** (MÃE) + Ano de nascimento	Nome + Nome da mãe + Data de nascimento	10,69	28
3	PBLOCO* + PBLOCO* (MÃE) + Ano de nascimento	Nome + Nome da mãe + Data de nascimento	7,08	1
4	PBLOCO* + Ano de nascimento	Nome + Nome da mãe	2,68	1
5	UBLOCO** + Ano de nascimento	Nome	6,2	3

*Código Soundex do primeiro nome

**Código Soundex do último nome

3.6- DETERMINAÇÃO DAS CAUSAS DE ÓBITO

Quando a paciente foi encontrada na base de dados do SIM, foi feita a leitura e classificação da causa de óbito. Inicialmente, foi utilizada a metodologia proposta pelo Surveillance, Epidemiology and End Results (SEER), do Instituto Nacional de Saúde Americano. Quando a causa de óbito era desconhecida ou a paciente faleceu sem assistência médica, o câncer de mama foi considerado como causador do óbito (DIGNAM et al., 2009; HOWLADER et al., 2010). O mesmo foi feito quando a doença foi citada como contribuinte para o óbito.

Uma análise alternativa foi realizada, considerando apenas a causa básica de óbito, conforme classificada pelo técnico da SES-MG.

3.7- REVISÃO DE PRONTUÁRIOS

Para o primeiro artigo, setenta prontuários de pacientes foram revistos no Serviço de Arquivo Médico e Estatística (SAME) do Hospital das Clínicas da UFMG com o objetivo de encontrar a data da *core biopsy* quando o material obtido na mesma não foi encaminhado ao LPM ou em casos de pacientes submetidas a quimioterapia neoadjuvante e em que não havia dados relativos ao estadiamento clínico no pedido do exame anatomopatológico.

Em uma nova etapa, para o segundo artigo, no intuito de obter novas informações a respeito das pacientes, foram buscados os demais prontuários. As variáveis coletadas foram: uso de tratamentos adjuvantes (quimio, hormônio e radioterapia), cor da pele (melanoderma, faioderma e leucoderma) e presença de comorbidades.

As comorbidades foram classificadas segundo o índice de Charlson (CHARLSON et al., 1987), o qual dá um peso a doenças da paciente que potencialmente poderiam diminuir a sobrevida. Devido ao número restrito de pacientes, elas foram classificadas como tendo ou não alguma das comorbidades descritas no índice.

3.8- ANÁLISE DOS DADOS

A sobrevida foi calculada em meses, a partir da data do primeiro tratamento cirúrgico nos casos de pacientes não submetidas a tratamento neoadjuvante (quimio ou hormonioterapia) ou a partir da data da *core biopsy*, para as pacientes submetidas a tal tratamento.

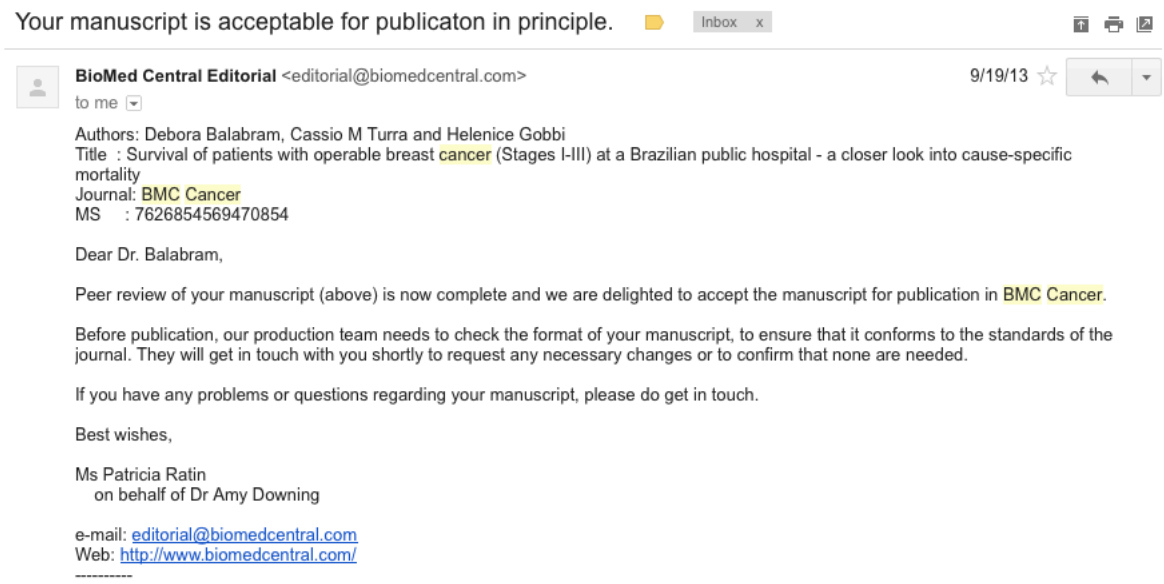
Inicialmente, foi realizada análise descritiva dos dados. Em seguida, o teste qui-quadrado foi utilizado para comparação da proporção de variáveis categóricas. A média, mediana e o desvio-padrão da idade das pacientes foram também calculados. Então, foram calculados o tempo médio e mediano de seguimento, a sobrevida mediana e a sobrevida em cinco anos. Foram feitas curvas de Kaplan-Meyer para as variáveis categóricas, as quais foram comparadas através do teste Log-rank. Análise uni e multivariada foi feita através do modelo de riscos proporcionais de Cox, com obtenção das razões de risco (RR) e seus respectivos intervalos de confiança a 95% (IC 95%). O nível de significância considerado foi de 5%.

O software SPSS versões 17.0 e 21.0 (SPSS Inc, Chicago, IL) foi utilizado para análise dos dados.

4 – RESULTADOS E DISCUSSÃO

Os resultados e a discussão serão apresentados no formato de artigos científicos. O primeiro deles foi publicado no periódico *BMC Cancer*, e o segundo foi submetido a publicação no periódico *Cancer Epidemiology*.

4.1- ARTIGO PUBLICADO NO PERIÓDICO BMC CANCER



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Journal: BMC Cancer
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RESEARCH ARTICLE Open Access

Survival of patients with operable breast cancer (Stages I-III) at a Brazilian public hospital - a closer look into cause-specific mortality

Débora Balabram[1], Cassio M Turra[2] and Helenice Gobbi[1*]

Abstract

Background: Breast cancer incidence is increasing. The survival rate varies and is longer in high-income countries. In Brazil, lower-income populations rely on the Unified Public Health System (Sistema Único de Saude, SUS) for breast cancer care. The goal of our study is to evaluate the survival of patients with operable breast cancer stages I-III at a Brazilian public hospital that treats mostly patients from the SUS.

Methods: A cohort study of patients who underwent surgery for breast cancer treatment at the Clinical Hospital of the Federal University of Minas Gerais from 2001 to 2008 was performed, with a population of 897 cases. Information on tumor pathology and staging, as well as patients' age and type of health coverage (SUS or private system) was collected. A probabilistic record linkage was performed with the database of the Mortality Information System to identify patients who died by December 31th, 2011. The basic cause of death was retrieved, and breast cancer-specific survival rates were estimated with the Kaplan-Meier method. The Cox proportional hazards model was used for univariate and multivariate analysis of factors related to survival.

Results: A total of 282 deaths occurred during the study's period, 228 of them due to breast cancer. Five-year breast cancer-specific survival rates were 95.5% for stage I, 85.1% for stage II and 62.1% for stage III disease. Patients from the SUS had higher stages at diagnosis (42% was in stage III, and from the private system only 17.6% was in this stage), and in the univariate but not multivariate analysis, being treated by the SUS was associated with shorter survival (hazard ratio, HR = 2.22, 95% CI 1.24-3.98). In the multivariate analysis, larger tumor size, higher histologic grade, higher number of positive nodes and age older than 70 years were associated with a shorter breast cancer-specific survival.

Conclusions: Five-year breast cancer survival was comparable to other Brazilian cohorts. Patients treated by the SUS, rather than by the private system, had shorter survival times, mostly due to higher initial stage of the disease.

Keywords: Breast neoplasms, Survival analysis, Neoplasm staging, Brazil, Cohort study

Background

Breast cancer is the most common malignant neoplasm among women in the world. The incidence is increasing, especially in low and middle-income countries [1]. In 2012, the incidence of breast cancer was expected to be 52.5 per 100,000 women in Brazil [2], whereas the age-adjusted mortality was 11.5 deaths per 100,000 women in 2009 [3]. In high-income regions, population-based studies show higher survival rates [4]: for patients diagnosed between 1990 and 1994, 5-year relative survival was 83.9% in the United States (US) and 73.1% in Europe [4]. In low-income countries, shorter overall survival has been documented, being as low as 38.8% in Sétif, Algeria, for patients diagnosed in the same period [4]. In Goiania, located in the central-west region of Brazil, the survival rate was 65.4% [4].

A patient's survival is related to several prognostic factors, including number of positive lymph nodes, tumor size, hormone receptor status, histological type and grade, and patient's age [5]. Socioeconomic status is

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known to be an intervening factor, mostly because of lower frequencies of patients undergoing interval screening, treatment's delay and smaller availability of modalities of treatment, such as chemo, hormone, and radiotherapy, among the less affluent populations [6-9].

In Brazil, most of the population does not have private health insurance, and relies on the Unified Public Health System (Sistema Único de Saúde, SUS) for care, which provides patients with screening, diagnosis, and breast cancer treatment [10,11]. In 2008, only 26% of the Brazilian population had private health insurance [11].

Studies from Brazil and other countries were retrieved from the PubMed and LILACS databases in February 14, 2013, using the search terms breast cancer, survival, and Brazil. Seven hospital cohort studies that separated patients by stage and were not aiming to evaluate specific prognostic markers or new treatments were selected. For PubMed, English language was used, and for LILACS, both the English and Portuguese languages were used. Findings from these observational cohorts in different Brazilian hospitals suggested that 5-year breast cancer-specific survival rates have ranged from 90% to 97% for stage I, 87.8% to 89% for stage II and 51% to 73% for stage III breast cancer diagnosed since the 1990s [6,12-16]. In these studies, the methods used to classify a death as due to breast cancer or its treatment vary, and they are sometimes poorly reported or derived only from the basic cause of death, as reported in patients' death certificates.

In this article, we present new estimates of survival for Brazilian female patients with operable breast carcinoma (stages I-III). We provide estimates for both overall survival rates and breast cancer-specific survival rates, calculated as the probability of surviving breast cancer in the absence of other causes of death [17]. We also look at the association between several prognostic markers and survival rates. Our data come from patients treated from 2001 to 2008 at the Clinical Hospital of the Federal University of Minas Gerais (Hospital das Clínicas, Universidade Federal de Minas Gerais, HC-UFMG), Belo Horizonte, Brazil. The HC-UFMG is a general teaching hospital that treats mostly patients from the SUS coming from Belo Horizonte (the state's capital) or from smaller cities without a tertiary health care center [18]. It provides patients with surgery as well as chemo- and endocrine therapies. Radiotherapy is performed at other cancer centers in the city. The Breast Pathology Laboratory of the UFMG School of Medicine is responsible for all breast pathology exams from the HC-UFMG and it has kept records of diagnostic and surgical specimens from it since 1989 [18].

Methods

Study's design

We designed a cohort study of patients with invasive operable breast carcinoma in stages I-III surgically treated at HC-UFMG from 2001 to 2008. The study protocol was approved by the UFMG Ethics Committee on March 7, 2012 (project CAAE number 0660.0.203.000-11).

Study's population

The cases were retrieved from files of the Breast Pathology Laboratory of the UFMG School of Medicine. We selected all specimens related to surgical treatment of breast cancer.

Among the 1119 patients who underwent surgery for breast cancer treatment at HC-UFMG from 2001 to 2008, we excluded 166 cases of ductal and lobular carcinoma *in situ*, as well as 2 patients with axillary metastasis only (unknown primary site), 1 patient with unknown tumor stage, 27 patients with unavailable primary tumor sample at our institution (first surgery at another institution, no remaining tumor in re-excision for clear margins), 7 patients with metastatic breast cancer who underwent palliative surgery only, 14 patients who underwent surgery for recurrent breast cancer, 1 patient who moved to a different state while on treatment and 4 patients with missing date of birth and mother's name. Eight hundred ninety-seven cases were available for the final analysis.

Variables

In addition to date of birth and type of health plan (private insurance or SUS), we recorded twelve variables related to breast cancer diagnosis and treatment: patient's age, tumor size (T), regional lymph node status (N), age, laterality (right or left), having bilateral cancer, histopathological type (invasive ductal carcinoma not otherwise specified; invasive lobular carcinoma; and special-type carcinomas), histologic tumor grade (according to the Nottingham grading system) [5], type of surgery performed (mastectomy or breast-conserving surgery), undergoing axillary node dissection, use of neoadjuvant chemo- or hormone therapy, and type of health plan (SUS or private system) [11]. Tumor staging was performed in accordance with the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [5]. For patients who did not undergo neoadjuvant systemic therapies, pathologic tumor stage (which is the gold standard for cancer staging) was used [5]; in the other cases, clinical tumor stage prior to therapy was used as a surrogate.

Information on survival status and death causes

We retrieved information on survival status, and date and cause of death from the Mortality Information System (MIS) of the Ministry of Health in Brazil for the years 2001 through 2011. The MIS is a national, computerized index of death record information that was implemented in 1975. Over the years, the completeness

of death registration in the MIS has improved substantially, reaching 93.5% as of 2007 in Minas Gerais [19]. Because patients from the HC-UFMG were all residents of the state of Minas Gerais, we restricted the MIS database to the cases who were residing in Minas Gerais at the date of their death. To identify patients from the study cohort who died from January 1, 2001 to December 31, 2011, we linked the MIS death records to the HC-UFMG data. A probabilistic record linkage was conducted using the software RecLink, version 3.0 (http://www.iesc.ufrj.br/reclink/) [20]. The probabilistic method is used when a unique identifier, such as social security number, is unavailable. To reduce the number of possible pairs, after standardizing both databases, we applied a four-step blocking strategy: first, using the soundex code of patients' first and last names and years of birth; second, using the soundex code of the mothers' first and last names and years of birth; third, based on soundex code of patients' and mothers' first name and years of birth; and fourth with only patients' first names and years of birth. We then paired the cases within each block, and estimated a linkage score for each pair based on the name and date of birth. All pairs with scores higher than 1 were reviewed in order to confirm them as true or false by using the fathers' names and addresses. Patients who were not found in the MIS database were presumed to be alive as of December 31, 2011 and therefore censored at this date.

In the Mortality Information System, causes of death are classified according to the International Classification of Diseases, version 10 (ICD 10) [21], by a technician [22].

After reading all causes of death described in each death certificate, we applied the coding by the Surveillance, Epidemiology, and End Results (SEER), of the U.S. National Cancer Institute to estimate breast cancer-specific survival. Cases with unknown death causes were not excluded [17]. When the cause of death was unknown or the patient died without assistance (8 cases, 2.8%), breast cancer was considered to be the cause [23]. When breast cancer was considered to have contributed to death, the patient was classified as having died from the disease (12 cases, 4.3%) [9].

An alternative analysis was performed, considering only the basic cause of death, as selected by technicians from the State's Secretaries in Health, which is used for national mortality statistics. The methods reported by SEER were also used in this situation.

Statistical analysis

We estimated Kaplan-Meier curves to describe the survival of this cohort over 5- and 10-year periods. We used the log-rank test to compare the survival distributions of different subgroups in our data. Since the date of the first biopsy was not available for all patients who had surgery as the primary treatment, survival interval was calculated in months from date of surgery in patients who did not undergo neoadjuvant chemo- or hormone therapy and from biopsy date in patients who underwent such therapies. Also, we tried to keep the staging as accurate as possible by using the clinical stage at the date of biopsy or the pathological stage at the date of surgery.

Age was categorized in three subgroups: up to 35 years, 36–69 years, and 70 years and older.

Mean age and standard deviation (SD) were calculated. The chi-square test was used to compare categorical variables. The chi-square test for a linear trend was used to compare the frequencies of tumor stage over the years of the study, as well as tumor stage in each age category. The significance level was defined as 0.05. The Cox proportional hazards model was used for hazard ratio (HR) and 95% confidence interval (CI) estimation in the univariate analysis and for multivariate survival analysis with a stepwise backward conditional strategy. Variables with statistical significance ($p < 0.05$) in the univariate analysis were initially used for the multivariate model, except for type of surgery, performing axillary node dissection, and use of neoadjuvant therapy, since we had incomplete data on treatment, to avoid biasing the results. For instance, patients diagnosed at higher stages probably underwent adjuvant systemic therapies later on. However, we did not have the data to confirm this information. Only variables with a p value bellow 0.05 were kept in the final multivariate model. All statistical analyses were performed with the SPSS software, version 17.0 (SPSS Inc, Chicago, IL).

Results

Five-year breast cancer-specific survival for the entire cohort was 78.5%, and 10-year survival was 64.5%. The cause-specific survival was 95.5% at 5 years for stage I, 85.1% for stage II, and 62.1% for stage III disease. Overall survival was 92.1% for stage I, 81.8% for stage II, and 58% for stage III disease. Only a small proportion of our patients were followed over a 10-year period (45 patients, 5%); among those in stage I, 10-year survival rate was 91.2%, 69.8% for stage II, and 43% for stage III patients.

The median period of follow-up was 64 months (range 1–131 months). Among the 897 patients, 282 (31.44%) died during follow-up, out of whom 228 (80.9%) died from breast cancer and 54 (19.1%) from other causes. Cardiovascular diseases (ICD 10 chapter IX) was a frequent cause of death unrelated to breast cancer, with 16 cases (29.6% of other death causes, data not shown). Four patients had unattended deaths (1.42% of total of deaths), and 3 patients (1.06% of total of deaths) had deaths from unknown causes.

Table 1 Patients' characteristics and univariate analysis of factors related to survival

Factor	Cases	%	Events	%	p value*	HR	95% CI**
Age					.012		
Up to 35 years old	47	5.24	16	34.04		1.63	0.98–2.73
36-69 years old	677	75.47	159	23.49		1.00	
70 and older	173	19.29	53	30.64		1.50	1.10–2.04
Tumor size					< 0.001		
T1 (up to 2 cm)	319	35.56	33	10.34		1.00	
T2 (2–5 cm)	348	38.80	88	25.29		2.59	1.73–3.86
T3	105	11.71	37	35.24		4.03	2.52–6.45
T4	125	13.94	70	56.00		8.02	5.29–12.16
Lymph node status					< 0.001		
N0	387	43.14	45	11.63		1.00	
N1	255	28.43	67	26.27		2.56	1.76–3.74
N2	155	17.28	68	43.87		4.83	3.31–7.04
N3	100	11.15	48	48.00		5.25	3.50–7.90
Stage					< 0.001		
I	223	24.86	13	5.83		1.00	
II	315	35.12	58	18.41		3.34	1.83–6.10
III	359	40.02	157	43.73		9.84	5.58–17.33
Bilateral breast cancer					0.380		
Yes	29	3.23	10	34.48		1.33	0.70–2.50
No	868	96.77	218	25.12		1.00	
Histologic grade					< 0.001		
Grade 1	181	20.18	23	12.71		1.00	
Grade 2	385	42.92	77	20.00		1.71	1.07–2.72
Grade 3	320	35.67	124	38.75		3.72	2.38–5.80
Unknown	11	1.23	4	36.36			
Pathology		0.00			.449		
Invasive ductal carcinoma	760	84.73	199	26.18		1.00	
Invasive lobular carcinoma	79	8.81	15	18.99		0.73	0.43–1.23
Other	58	6.47	14	24.14		0.86	0.50–1.48
Public health system					0.006		
Yes	823	91.75	216	26.25		2.22	1.24–3.98
No	74	8.25	12	16.22		1.00	
Neoadjuvant therapy					<0.001		
Yes	166	18.51	77	46.39		2.87	2.18–3.78
No	731	81.49	151	20.66		1.00	
Axillary node dissection					<0.001		
Yes	684	76.25	211	30.85		3.82	2.33–6.27
No	213	23.75	17	7.98		1.00	
Type of surgery					<0.001		
Mastectomy	537	59.87	182	33.89		2.89	2.09–4.00
Breast-conserving surgery	360	40.13	46	12.78		1.00	

*Log-rank test.
**95% Confidence interval.

Table 1 shows the distribution of patient characteristics, life status at the end of the study period, and HR for the different factors examined in the univariate analyses. The mean age of patients was 55.32 years (SD = 13.97, range 20–97 years), and the median age was 53 years. Only 47 patients (5.24%) were 35 years old or younger; 677 patients (75.47%) were between 36 and 69 years, and 173 patients (19.29%) were 70 and older. Most individuals (823, 91.75%) were treated in the SUS; only 74 (8.25%) were treated in the private health system. Of those, 65 had private insurance and 9 paid for their treatment. Three hundred forty-eight patients had T2 tumors (2 to 5 cm, 38.8%). As for the axilla, 387 patients (43.14%) had negative lymph nodes, while 510 patients (56.86%) had at least one positive node. A great number of patients were in stage III at diagnosis (359 cases, 40.02%). Twenty-nine patients had bilateral breast cancer either concomitantly or at follow-up, that was treated at our institution (3.23%). Left breast tumors were more common (472 patients, 52.6%). Regarding pathologic type, most patients had invasive ductal carcinoma not otherwise specified (760, 84.73%). Seventy-nine patients had invasive lobular carcinoma (8.81%), and 58 patients (6.47%) had other pathologic subtypes. One hundred eighty-one patients had low-grade tumors (20.18%), 385 had intermediate-grade tumors (42.92%) and 320 had high-grade tumors (35.67% of patients). The most common surgery was mastectomy, performed in 59.87% of patients (537 cases). Axillary node dissection was performed in 684 (78.25%) patients. One hundred sixty-six patients (18.51%) underwent neoadjuvant therapies (3 had combined neoadjuvant chemo- and hormone therapy, 4 had hormone therapy exclusively and the other patients had neoadjuvant chemotherapy only).

The stage at diagnosis was higher among patients from the SUS (23.1% was stage I, 34.9 stage II and 42% stage III in the public health system, while 44.6% was stage I, 37.8 was stage II, and 17.6% was stage III in the private health system, $p < 0.001$). The frequencies of stages did not change over the years ($p = 0.11$, data not shown).

In the univariate analysis, breast cancer in patients older than 70 years of age was associated with significantly lower chances of survival compared to patients 35 to 69 years old. Also, higher histologic tumor grade, larger tumor size, and higher number of involved lymph nodes were associated with lower survival (Figure 1, Table 1). Being treated by the SUS was associated with a shorter survival, with an HR of 2.22 ($p = 0.005$, CI 1.24-3.98). Older age was not associated with a different stage of disease (p value of X^2 for a linear trend = 0.22) but was associated with a smaller proportion of patients undergoing neoadjuvant systemic therapies (only 8.7% of

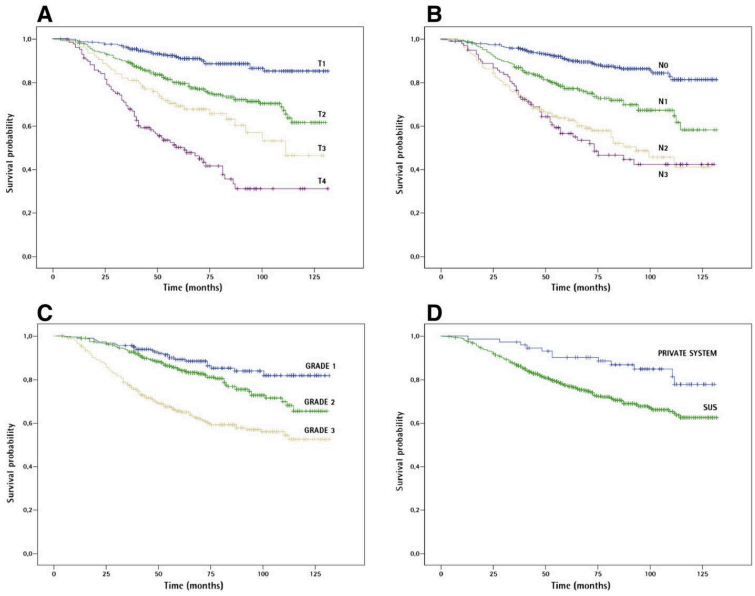

Figure 1 Kaplan-Meier curves of factors associated with breast cancer survival. A, breast cancer-specific survival in relation to tumor size ($p < 0.001$). **B**, survival in relation to lymph node status ($p < 0.001$). **C**, survival in relation to histologic grade ($p < 0.001$). **D**, survival in relation to health care system ($p = 0.006$).

patients older than 70 years underwent such therapies, whereas 20.8% of patients 36–69 years and 21.3% of patients up to 35 years of age underwent such treatments, p = 0.001, data not shown).

Having bilateral breast cancer and having lobular or special-type carcinomas was not associated with a shorter survival time. In terms of therapy, undergoing neoadjuvant systemic therapy, undergoing mastectomy and undergoing axillary node dissection were associated with shorter survival time, but these variables are highly correlated to tumor stage (Table 1).

In the multivariate analysis, tumor size remained an important prognostic factor. Patients with tumors larger than 5 cm (T3) had an HR of dying due to breast cancer of 2.31 (CI 1.41-3.80) compared to patients with tumors measuring up to 2 cm (T1, Table 2). In addition, patients with tumors infiltrating the skin or chest wall had an HR of 4.34 (CI 2.77-6.79) in relation to T1 patients. Patients with 9 or more positive axillary lymph nodes had an HR of 3.59 (CI 2.35-5.48) in relation to patients with negative nodes. Also, patients aged 70 years and older had a shorter survival (HR in relation to women 36–69 years old, 1.64; CI 1.19-2.26). Patients with high-grade tumors had an HR of 2.54 (CI 1.62-3.96) in relation to patients with low-grade tumors. Being treated by the SUS was not associated with a shorter survival in multivariate analysis.

When the basic cause of death, as classified by the state's technician, was used alone, 25 patients (9.22% of the total of deaths) would have been censored and not considered to have died from breast cancer. In such cases, information contained in the death certificate suggested breast cancer as a contributing cause of death, and we decided to be conservative and, as done by other authors, consider the patient as having died from breast cancer [12]. These patients' basic causes of death were: diseases of the circulatory system (7 cases, ICD chapter IX); endocrine, nutritional and metabolic diseases (3 cases, ICD chapter IV); diseases of the respiratory system (2 cases, ICD chapter X); diseases of the blood and blood-forming organs (1 case, ICD chapter III), and other neoplasms: unspecified malignant neoplasm of the liver (3 patients), unspecified malignant neoplasm of the bronchus and lung (3 cases), malignant neoplasm of the cerebellum (1 case, C71.6), malignant neoplasm of the cervix uteri (1 case, C53.9), malignant neoplasm of bone and articular cartilage of other and unspecified sites (1 case, C41.9), Letterer-Siwe disease (C96.0, 1 case), malignant neoplasm of the brain (1 case, C71.9), and malignant neoplasm of the mandible (1 case, C41.4). In those latter cases, the other cancer could have been the primary cause of death, but it seems more plausible, except for the patient who had a cervical cancer, that they were secondary malignancies.

When patients with deaths that were correctly classified as due to breast cancer were excluded (203 cases, 72% of total of deaths), higher stage (stage III versus stages I and II) remained associated with a higher HR of dying from other causes (HR = 2.02, CI 1.30-3.14, p = 0.002). After reading other death causes present in the death certificate and reassigning the basic death cause, this effect disappeared (p = 0.16).

Table 2 Multivariate survival analysis – final model

Factor	p value	HR	95% CI
Age			
Up to 35	0.125	1.50	0.89–2.51
36-69	0.005	1.00	
70 and above	0.002	1.64	1.19–2.26
Tumor size			
T1	<0.001	1.00	
T2	0,027	1.60	1.05–2.43
T3	<0.001	2.31	1.41–3.80
T4	<0.001	4.34	2.77–6.79
Lymph node status			
N0	<0.001	1.00	
N1	0.005	1.75	1.18–2.60
N2	<0.001	2.73	1.82–4.09
N3	<0.001	3.59	2.35–5.48
Histologic grade			
Grade 1	<0.001	1.00	
Grade 2	0.313	1.27	0.80–2.01
Grade 3	<0.001	2.54	1.62–3.96

HR hazard ratio, *95% CI* 95%, Confidence interval.

Discussion

Five-year breast cancer-specific survival for the entire cohort was 78.5%. Our survival findings are in accordance with earlier studies that were based on different Brazilian cohorts. The study by Ayala [13] described 5-year survival rates of 97% for stage I, 88% for stage II, and 51% for stage III in patients treated in the SUS, considering patients diagnosed at a similar period to the one of our study (2000–2009). Cintra *et al.* [14] showed a 5-year breast cancer-specific survival of 90% for stage I, 89% for stage II, and 68.7% for stage III patients from a mixed sample of the SUS and private systems treated from 1998 to 2000. Schneider & d'Orsi [12] showed survival proportions of 93.6% for stage I, 87.8% for stage II, and 62.5% for stage III patients, also from a mixed sample, diagnosed between 2000 and 2002. Menke *et al.* [24] showed an overall survival (all causes of death) above 80% in Porto Alegre, Rio Grande do Sul, in a study with patients treated from 1972 to 2002. In this study, the origin of the sample (SUS or private system) was not specified. Variations in survival could be due to different

methodologies applied in each of the studies but also to different sample compositions regarding stage, age, and other biologic tumor factors, as well as differences in local cancer care.

For patients diagnosed in the United States in the years 2001 and 2002 (National Cancer Data Base), 5-year overall survival was 87.8% for stage I, ranged from 74% to 81.4% for stage II (IIB and IIA, respectively) and from 41% to 66.7% for stage III disease (IIIB and IIIA, respectively) [5]. In a public hospital in Barcelona, Spain, 5-year breast cancer-specific survival of patients diagnosed from 1992 to 2005 was 97.1% for stage I, 88% for stage II, and 70.1% for stage III patients [25].

Studying breast cancer survival and prognostic factors gives us insight into the natural history of the disease. Many prognostic factors have been studied over the years. The factor with the highest impact on survival is lymph node invasion (N). Tumor size (T) and distant metastasis (M) also play an important role, as well as lymph vascular invasion, positivity for hormone receptors, and over-expression of the HER2 protein [5]. Many other markers are linked to breast cancer survival [5]. In spite of the growing number of markers being discovered recently, the TNM remains the most important predictor of breast cancer survival [5]. In our study, tumor size and lymph node status were the strongest predictors of survival.

Socioeconomic status is also an intervening factor [6-8]. Most patients from our study were treated in the Brazilian public health system (SUS). Since lower income patients do not have private health insurance and usually cannot afford breast cancer treatment, they rely on the SUS for it. Not having private insurance and thus using the SUS was considered a surrogate for socio-economic information. The SUS provides multiple modalities of treatment for breast cancer patients, such as surgery and radio- and systemic therapy [10,11]. Our findings suggest that the survival of patients from the SUS is shorter than from the ones of the private system. Most of this difference is likely due to the different distribution of stages at diagnosis. Other contributing factors that were not analyzed in the present study could also explain this finding, such as larger interval between diagnosis and treatment in SUS' patients [6,14], more difficult access to health care facilities, different comorbidities, smaller proportion of women undergoing screening, and a different lifestyle with other risk factors for death [8,9,26,27]. To minimize treatment delay, a federal law that was approved in 2012 stated that after diagnosis, cancer patients should be treated at an interval no longer than 60 days in the SUS [28].

The Brazilian SUS also provides breast cancer screening with mammography according to national guidelines [29]: since 2004, women aged 50–69 years have been encouraged to undergo mammography every 2 years, and also to have their breasts examined by a physician since 40 years of age. In private practice, guidelines from the Brazilian Society of Breast Surgery (Sociedade Brasileira de Mastologia) are followed, with a recommendation to use mammography screening yearly since 40 years of age [30]. In spite of these recommendations, Marchi and Gurgel [31] showed that women's adherence to screening is low, with less than 50% performing biannual exams (24.5% for SUS patients and 42.9% for patients from the private system from 2003 to 2008). Another study showed similar results (34.9% adherence for women aged 50–59 years of the SUS and 71% for women of the private health system) [32]. Nevertheless, the use of mammograms is growing, with 54.6% of women 50 to 69 years of age having undergone at least one mammogram in their lifetime up to 2003 and 71.5% up to 2008 [33]. The proportion of women older than 70 years old undergoing mammography is smaller (37.1% up to 2003 and 54.5% up to 2008) [33]. Lower screening rates are consistently associated with not having private insurance and smaller income in many studies [31-34]. With the Brazilian Information System for Breast Cancer (Sistema de Informação do Câncer de mama - SISMAMA), implemented by the Brazilian National Cancer Institute in 2009, the number of women undergoing screening in the SUS is expected to rise. It will possibly result in more patients being diagnosed at earlier stages [29] and better overall survival. In our study, the frequencies of stages did not change over the years ($P = 0.114$, data not shown). It is possible that in the later years of the study, more patients were diagnosed with *in situ* tumors, which has been shown in a previous publication [18], but these tumors were not the scope of the present study. Also, our time span was too small to show any differences.

In our study, patients 70 years old and older had shorter breast cancer-specific survival. Schonberg *et al.* [35] showed a higher mortality for women older than 80 years in the US, and they argue that these women could have undergone less-than-standard treatment. This explanation has been presented by other authors and could have been the case for our patients [25,36]. Comorbidities can play a role, as well as smaller proportions of patients undergoing screening in this population [25,33]. Thus, our results differ from the findings of Brito *et al.* [6], which show better breast-cancer specific survival for patients older than 70 years treated in the SUS between 1999 and 2002 and shorter for younger patients (at the end of their study, 81.5% of patients older than 70 years were alive, versus only 45.4% of patients less than 35 and 72% for patients 35 or more and less than 70 years of age) [6]. On the other hand, older women are more likely to die of a variety of other causes, mainly cardiovascular diseases [26,37].

Patients up to 35 years of age were not more likely to die from breast cancer than patients 36–69 years of age. This could be due to our small number of cases at this age (only 47 women were younger than 35 years of age). These patients are unlikely to die from other causes when diagnosed with breast cancer [37,38]. Women with more advanced stages at diagnosis or recurrent disease are also more likely to die of breast cancer [23,37,38]. It is still debated whether younger age at diagnosis is an independent prognostic factor for shorter survival or if younger patients have tumors with worse biological features [37,39].

Our study has some limitations. First, the possibility of having wrongly classified a woman as being dead or alive exists, due to possible errors in the Mortality Information System. Three variables (patients' names, mothers' names and date of birth) were used in the record linkage to minimize this bias. Also, fathers' names and patients' addresses were used to confirm the pair as a true one. The medical records for a small sample of patients (70 cases, 0.08%) were checked. Only one patient was identified as having moved to another state, and since information on life status could be wrong, she was excluded from the study. Second, since high-quality data were only available in surgical treatment and neoadjuvant therapies, we chose not to include these variables in the multivariate Cox model, to avoid bias. The inclusion of patients who underwent neoadjuvant systemic therapies is unlikely to have affected our results; those patients had more advanced tumors at diagnosis and thus would very likely have undergone chemotherapy after surgery. Also, information on socioeconomic status, such as family income and educational level, were not available. Paim *et al.* [11] reported that having a private insurance is correlated with family income; thus, in our study, not having a private insurance was considered a surrogate for lower socioeconomic status.

On the other hand, our study also has strengths. Selecting patients from pathology reports has the advantage of providing good-quality data regarding stage, histologic tumor grade, and type. The information on histologic grade was missing in only 11 patients, either because the invasive component was too small (microinvasive tumor) or because the patient underwent neoadjuvant systemic therapy and the tumor sample prior to the systemic treatment was insufficient to assess histological grade. Even though we have limited information on treatment due to the origin of our data, this study brings insight into recent survival of women with operable breast cancer at a tertiary health facility that treats mostly low-income patients.

Different methods are used for survival analysis. Overall mortality, cause-specific mortality, and relative survival have all been used as endpoints [23,37,40]. The problem with the use of cause-specific mortality is the difficulty, in some cases, in attributing a death to breast cancer or its treatment [23,41]. For instance, some common sites for metastases of breast tumors can be reported as the primary site in death certificates, such as lung, bone, liver, and brain [41].

Cancer-specific survival depends on the data quality of death certificates, as well as in appropriate coding of reported causes of death. In Brazil, data quality has improved over the years [22], but still there are deaths of unknown causes or without medical assistance (2.8% of our cases). Moreover, even when death causes are cited in the death certificate, sometimes it is difficult to attribute a death to breast cancer or its treatment [17,23]. In our study, 25 deaths (9.22% of total of deaths) were not initially considered to be from breast cancer in the Mortality Information System. The cause reported by this system is the one considered in national mortality statistics; thus, wrongly assigning a cause could influence these indexes. On the contrary, all-cause mortality could result in underestimation of breast cancer survival [23,40]. Since we needed comparability with Brazilian cohorts, breast-cancer specific survival was used.

Different populations are subject to innumerous differences in life expectancy, life styles, and access to health care that could affect their survival, both from breast cancer and from other causes [4,6,9,23,27]. Trying to make comparisons among populations can help highlight these differences and guide local policies towards a more effective approach to breast cancer care, especially through earlier diagnosis and treatment of the disease [1,8,10,33]. For instance, in spite of not having addressed patients' comorbidities, this study suggests that policymakers should pay attention to women older than 70 years; with screening, it is possible that they will be diagnosed with earlier tumors. Since age is the most important risk factor for breast cancer, and the Brazilian population is aging [11], this should be taken into account.

Conclusions

In our study, 5-year breast cancer-specific survival was comparable to the one estimated for other Brazilian cohorts. Comparisons with estimates for high-income countries showed mixed results, which may be due to differences in the socioeconomic, demographic and health characteristics of the population subgroups analysed in each study. Also, patients treated by the SUS had a shorter survival rate than those treated through the private system, mostly due to higher initial stage of the disease. Patients older than 70 years had shorter survival time in comparison with patients 36–69 years of age. After reassigning the cause of death reported in the death certificate, more patients were considered to have died from breast cancer than when using only the basic

cause of death, suggesting that one should be aware of the possible pitfalls of national cancer mortality statistics.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
DB planned the study, gathered the sample, performed the record linkage, statistical analysis and wrote the manuscript. CMT planned the study, aided in the record linkage and statistical analysis and critically revised the manuscript. HG planned the study, analyzed all pathology samples and critically revised the manuscript. All authors approved the final version of the manuscript.

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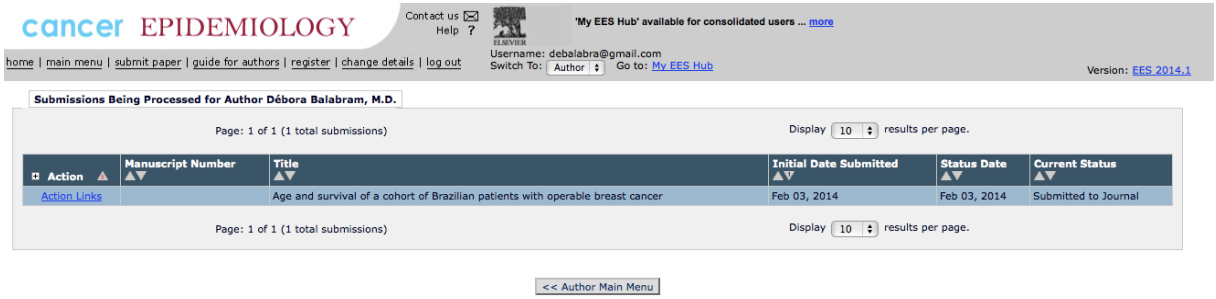

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Age and survival of a cohort of Brazilian patients with operable breast cancer

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ABSTRACT

OBJECTIVES: To study the relationship between age, cause-specific survival and deaths due to other causes in patients with breast cancer, controlling for several variables, including patients and tumor factors.

METHODS: A retrospective cohort study including 783 breast cancer patients, stages I-III, who underwent surgery at the Hospital das Clínicas of the Federal University of Minas Gerais (HC-UFMG), from the years 2001 to 2008. Different sets of Cox proportional hazards models were used for survival analysis. The hazard ratios (HR) and 95% confidence intervals (CI) for each variable were calculated.

RESULTS: The relationship between age and breast cancer survival changed depending on the inclusion of different sets of variables to Cox models. In cause-specific survival, when age was considered alone, we found that the oldest age group (70 and older, HR=1.42, CI=1.02-1.97) and the youngest one (up to 35 years old, HR=1.77, CI=1.06-2.96) had higher risk of dying due to breast cancer than patients 36 to 69 years old. When tumor and patient characteristics were added to the model, the survival disadvantage became non-significant for the youngest age group (HR=1.58, CI=0.90-2.75), but remained significant for the oldest patients (HR=1.57, CI=1.07-2.31). In other-cause survival analysis, only older age HR=6.23, CI=3.33-11.67), being white (HR=2.34, CI=1.29-4.23), and having at least one comorbidity (HR=2.92, CI=1.62-5.26) were associated with a higher risk of dying.

CONCLUSIONS: Multiple factors are involved in survival from breast cancer in Brazil. Age is not an independent predictor of cause-specific mortality. The association between age and breast cancer survival is mediated by patients and tumor characteristics. In future research, other factors should be accounted for, including measures of socioeconomic status and the types of treatment used.

1. 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]. Age is also related to higher frequency of a number of chronic diseases, including cardiovascular and pulmonary conditions, as well as other types of cancer [2].

Many studies have reported that older women (≥ 70 years of age) have less aggressive breast cancer, including a higher frequency of low grade tumors and positivity for hormone receptors [5–7]. 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 lower age is an independent prognostic factor for the lower survival among younger patients [10,11] or if the increase in mortality risk is associated with different tumor features in this group. In addition to age, race is also a known prognostic factor for breast cancer in the United States, with lower survival prospects among African American women [12].

In a previous study [13], we have found that women 70 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. Here, we examine in more detail the relation between age and mortality from breast cancer and other causes of death, by looking at the role played by several intervening variables, including color, comorbidities and tumor factors. We use data from patients treated at a public Brazilian hospital between the years 2001 and 2008.

2. Methods

2.1 Study's design and population

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

Among the 953 patients who underwent surgery for invasive breast cancer at the HC-UFMG between 2001 and 2008, we excluded seventy-five cases for whom treatment was not paid by the public health system. Of the remaining 878 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 cases with missing information on the identification variables, which could lead to a bias in the mortality record linkage. We also excluded 19 cases with missing data on the independent variables. The number of missing cases for each variable is presented on Table 1. After excluding all these cases, our analysis sample contained 783 patients: 522 (66.7%) survivors and 261 (33.3%) deceased. The results from a chi-square test (available upon request) reveal that individuals for whom the independent

variables were missing are similar to the individuals included in the analysis with regard to all variables.

2.2- Variables

We examine three sets of determinants of mortality: patients demographic characteristics, health status, and tumor characteristics.

Besides age, measured in three categories (up to 35, 36 to 69, and 70 years and older), we include tumor size and lymph node status according to the American Joint Committee on Cancer Staging Manual [14], as well as tumor type and grade [15]. From the patients' medical records we obtained information on skin color (white versus non-white), and comorbidities, which we measured according to Charlson's comorbidity index [16]. Because of the small sample size, we constructed a dichotomous variable from the Charlson's index equal to one for patients who had at least one comorbidity. Type of surgical treatment was omitted from our analyses, since it has a weaker association with overall survival than the other measures [17,18].

We retrieved data on cause and date of death or date of last follow-up as checked in the Mortality Information System (MIS) of the Ministry of Health of Brazil [3]. We used a probabilistic record linkage strategy to identify patients in our database who had died up to December 31th, 2011 [19]. The linkage method was described in detail in an earlier article [13]. Patients not found in the MIS database were considered to be alive at end of the observation period. We classified causes of death according to the International Classification of Diseases, version 10 (ICD 10) [20].

2.2 Statistical analysis

We use the chi-square test for a linear trend 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 (CI) for each independent variable were calculated. All statistical analyses were performed with the SPSS software, version 21.0 (SPSS Inc, Chicago, IL).

In the first set of regression models, we examine cause-specific survival, by censoring patients who died from causes not related to breast cancer. We specify three Cox models to explore the net effects of age on mortality. Model 1 includes only age. Model 2 adds other patient's characteristics (color and the Charlson comorbidity index). The tumor characteristics are added in Model 3. In the second set of regression models, we follow the same sequence of Cox proportional hazard models as in the first set, but considering survival only from causes not related to the disease.

3. Results

The observation period ranged from 1 to 131 months, with a median of 62 months. Overall, there were 261 deaths (33.3%), 211 of them due to breast cancer (81% of the total of deaths). Not surprisingly, deaths due to breast were relatively more frequent in the youngest age group (94.1%), followed by the age group 36-69 (89.3%), and the oldest age group (59.2%) ($p<0.001$).

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 (52.7% non white versus 47.3% white, $p<0.001$). The distributions of tumor type ($p=0.836$), tumor size ($p=0.533$), and lymph node status ($p=0.324$) 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 78 patients (52%) at the ages 70 and above ($p=0.025$). High grade tumors were also more frequent among the youngest patients ($p=0.030$). Not surprisingly, the prevalence of comorbidities increased with age ($p<0.001$, 40.0% of patients 70 years and older had at least one comorbidity).

Table 2 shows the results for cause-specific Cox regression models. According to model 1, both patients aged 35 years old and younger (HR=1.78, CI=1.06-2.97), and 70 years and older (HR=1.42, CI=1.02-1.98), 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 higher risk of dying than whites (HR=0.73, CI=0.55-0.99). Having at least one comorbidity was not associated with lower cause-specific survival (HR=1.09, CI=0.76-1.56).

Model 3 (Table 2) shows that numerous tumor characteristics are significantly associated with the risk of dying over the observation period. Higher tumor grade ($p<0.001$), larger tumor size ($p<0.001$), and higher number of positive nodes ($p<0.001$) were all associated with higher mortality risks. The effect of the youngest age group, however, was reduced and became no longer statistically significant (HR=1.62, CI=0.96-2.73). On the other hand, the coefficient for the oldest age group remained virtually unchanged and statistically significant in Model 3. Patients skin color (HR=0.81, CI=0.60-1.09), and the presence of at least one comorbidity (HR=1.22, CI=0.85-1.75), were not statistically associated with death due to breast cancer.

In Table 3, we compare the same regression models for mortality risk due to other causes rather than breast cancer. Contrary to what we found in the previous analysis, the oldest age category was significantly associated with a higher risk of dying in every model ($p<0.001$), while it was not the case for the youngest age group. Also, the mortality risk from other causes of death was significantly increased for white women and those who had at least one comorbidity. Not surprisingly, the variables associated with tumor characteristics were not statistically significant predictors of mortality from other causes of death in any of the models.

4. Discussion

In the current study, we show that the relationship between age and breast cancer survival depends on the effects of different intervening variables. When age was considered alone, we found that the oldest age group (70 and older, HR=1.42, CI=1.02-1.97) and the youngest one (up to 35 years old, HR=1.77, CI=1.06-2.96) had higher risk of dying due to breast cancer than patients 36 to 69 years old. When tumor and patient characteristics were added to the model, the survival disadvantage became non-significant for the youngest age group (HR=1.58, CI=0.90-2.75), but remained significant for the oldest patients (HR=1.57, CI=1.07-2.31).

Our results reveal the importance of comorbidities and tumor characteristics in explaining age differences in mortality risk due to breast cancer. They are in accordance with previous research that have showed that younger patients have more aggressive tumors, whereas older patients have lower grade disease, but higher frequency of comorbidities, and more advanced stages at diagnosis [2,7,10,18,21,22].

One of the limitations of our study is that we draw 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 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.

The appropriate treatment for elderly women with breast cancer remains a matter of debate. Because older women are usually not included in treatment trials, the benefits of therapy for them are more difficult to evaluate [2,18]. Also, the incidence of toxicity after adjuvant treatments is higher among the elderly [2], 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. Although we collected data on both estrogen receptor and adjuvant therapies (chemotherapy, hormone therapy and radiation therapy), there were too many missing cases for these variables (n=123) and missing were not at random, which precluded us from publishing the results on the intervening effects of the use of adjuvant therapies. However, for the sake of speculation, in models not presented here, we added adjuvant therapies to our analysis and the coefficient for the oldest age group was no longer statistically significant, suggesting that the omission of systemic therapies in older patients may explain part of the excess of mortality associate with old age. In future analysis, we plan to input the missing information to explore on a more firm basis the question on the use of appropriate breast cancer treatment for elderly women in Brazil.

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 [23]. 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" [18]. 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 there are more advanced cases in Brazil, particularly among the elderly [24,25].

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 [26], and thus we used information on patients color instead of race. The prevalence of non-white women was higher in the youngest age group (78%) than among older individuals (for example, 52.7% of women 70 and above 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 non significant, 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 [27], more difficult access to health care, or both. In the analysis of mortality due to other causes of death,

we found an inverted relation between color and mortality: white patients had a higher risk of dying than non-white patients. This finding may reflect the larger proportion of non-white women who die sooner from breast cancer (and thus are censored from the sample) than white women.

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 [28,29], especially after ten years. Since the median follow-up time in our study was much shorter, we already expected a larger proportion of deaths (81% of total of deaths) due to breast cancer compared to other studies. Although, in at least one study for the U.S., 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%). [30]

Multiple factors are involved in survival from breast cancer. This study has extended previous research for Brazil in showing that age is not an independent predictor of cause-specific mortality. The association between age and breast cancer survival depends on other demographic characteristics, the presence of comorbidities, and tumor characteristics. But it also probably depends on a variety of other key factors not included in our Models such as the socioeconomic status of patients [26], access to health care [27,28] and types of treatment employed [12–14,31]. 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 surviving for women of different age groups, particularly in a context of profound changes in the population age structure.

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Footnotes

The authors declare they have no conflicts of interest.

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Table 1

Table 1. Baseline distribution of patients' and tumor characteristics by age

	Up to 35 years (%)	36-69 years (%)	70 and older (%)	Total (%)	p value
Age	41 (100.0)	592 (100.0)	150 (100.0)	783 (100.0)	
Color					
White	9 (22.0)	205 (34.6)	71 (47.3)	285 (36.4)	<0.001
Non-white	32 (78.0)	387 (65.4)	79 (52.7)	498 (63.6)	
Total	41 (100.0)	592 (100.0)	150 (100.0)	783 (100.0)	
Charlson comorbidity index					
No comorbidities	41 (100.0)	503 (85.0)	90 (60.0)	634 (81.0)	<0.001
At least one comorbidity	0 (0.0)	89 (15.0)	60 (40.0)	149 (19.0)	
Total	41 (100.0)	592 (100.0)	150 (100.0)	783 (100.0)	
Tumor type					
Ductal	35 (85.4)	509 (86.0)	125 (83.3)	669 (85.4)	0.836
Lobular	4 (9.8)	46 (7.8)	17 (11.3)	67 (8.6)	
Other	2 (4.9)	37 (6.3)	8 (5.3)	47 (6.0)	
Total	41 (100.0)	592 (100.0)	150 (100.0)	783 (100.0)	
Tumor size					
T1	11 (26.8)	194 (32.8)	57 (38.0)	262 (33.5)	0.533
T2	18 (43.9)	235 (39.7)	55 (36.7)	308 (39.3)	
T3	6 (14.6)	79 (13.3)	11 (7.3)	96 (12.3)	
T4	6 (14.6)	84 (14.2)	27 (18.0)	117 (14.9)	
Total	41 (100.0)	592 (100)	150 (100)	783 (100.0)	
Lymph node status					
N0	13 (31.7)	234 (39.5)	72 (48.0)	319 (40.7)	0.324
N1	15 (36.6)	178 (30.1)	35 (23.3)	228 (29.1)	
N2	8 (19.5)	113 (19.1)	21 (14.0)	142 (18.1)	
N3	5 (12.2)	67 (11.3)	22 (14.7)	94 (12.0)	
Total	41 (100.0)	592 (100)	150 (100)	783 (100.0)	
Histologic grade					
Low grade	6 (14.6)	108 (18.2)	34 (22.7)	148 (18.9)	0.030
Intermediate grade	13 (31.7)	264 (44.6)	67 (44.7)	344 (43.9)	
High grade	22 (53.7)	220 (37.2)	49 (32.7)	291 (37.2)	
Total	41 (100.0)	592 (100.0)	150 (100.0)	783 (100.0)	

Table 2

Table 2. Cox regression models of factors related to cause-specific survival

	Model 1 HR (95% CI)[b]	p value	Model 2 HR (95% CI)[b]	p value	Model 3 HR (95% CI)[b]	p value
Age						
36-69 years (ref)[a]		0.020		0.020		0.033
Up to 35 years	1.78 (1.06-2.97)	0.029	1.75 (1.04-2.94)	0.035	1.62 (0.96-2.73)	0.070
70 and up	1.42 (1.02-1.98)	0.041	1.44 (1.02-2.03)	0.039	1.44 (1.02-2.04)	0.039
Comorbidities						
Yes			1.09 (0.76-1.56)	0.643	1.22 (0.85-1.75)	0.285
Color						
Being white			0.73 (0.55-0.99)	0.039	0.81 (0.60-1.09)	0.167
Tumor size						
T1 (ref)[a]						<0.001
T2					1.26 (0.82-1.94)	0.290
T3					1.89 (1.13-3.15)	0.015
T4					3.95 (2.52-6.20)	<0.001
Lymph node status						
N0 (ref)[a]						<0.001
N1					1.93 (1.27-2.93)	0.002
N2					2.88 (1.88-4.42)	<0.001
N3					3.72 (2.37-5.85)	<0.001
Tumor grade						
Low grade (ref)[a]						<0.001
Intermediate grade					1.41 (0.86-2.32)	0.171
High grade					2.71 (1.67-4.39)	<0.001

a Reference category

b Hazard ratio and 95% Confidence Interval

Table 3

Table 3. Cox regression models of factors related to death due to causes other than breast cancer

	Model 1		Model 2		Model 3	
	HR (95% CI)[b]	p value	HR (95% CI)[b]	p value	HR (95% CI)[b]	p value
Age						
36-69 years (ref)[a]		<0.001		<0.001		<0.001
Up to 35 years	0.99 (0.13-7.45)	0.994	1.35 (0.18-10.23)	0.771	1.33 (0.17-10.20)	0.784
70 and up	8.20 (4.58-14.68)	<0.001	5.68 (3.08-10.48)	<0.001	6.23 (3.33-11.67)	<0.001
Comorbidities						
Yes			2.92 (1.62-5.26)	<0.001	2.91 (1.59-5.31)	0.001
Color						
Being white			2.13 (1.20-3.77)	0.010	2.34 (1.29-4.23)	0.005
Tumor size						
T1 (ref)[a]						0.836
T2					0.71 (0.26-1.95)	0.509
T3					0.96 (0.48-1.93)	0.914
T4					1.26 (0.45-3.54)	0.666
Lymph node status						
N0 (ref)[a]						0.943
N1					1.34 (0.53-3.39)	0.541
N2					1.09 (0.53-2.26)	0.817
N3					1.13 (0.47-2.75)	0.783
Tumor grade						
Low grade (ref)[a]						0.280
Intermediate grade					1.77 (0.70-4.48)	0.225
High grade					1.95 (0.86-4.45)	0.111

a Reference category

b Hazard ratio and 95% Confidence Interval

5- CONSIDERAÇÕES FINAIS

O câncer de mama é a neoplasia maligna mais frequente em mulheres no Brasil e no mundo (BOYLE; LEVIN, 2008; INSTITUTO NACIONAL DO CÂNCER, 2013). Vários fatores são associados à sobrevida das pacientes, como estadiamento, grau histológico, positividade de receptores hormonais, nível socioeconômico, raça e idade (COLEMAN et al., 2008; EDGE et al., 2009; MASKARINEC et al., 2011).

Neste estudo, os fatores prognósticos referidos foram estudados em uma população de 897 mulheres brasileiras, sendo que a grande maioria delas (91,8%) recebeu tratamento pelo Sistema Único de Saúde (SUS). Ter maior tamanho tumoral, maior número de linfonodos axilares acometidos, maior grau histológico, idade a partir de 70 anos e ter sido tratada pelo SUS foram associados a menor tempo de sobrevida global (causa-específica). Chama atenção o fato de que pacientes acima de 70 anos tiveram pior sobrevida. Embora elas tenham em geral tumores menos agressivos (DUTRA et al., 2009b; THOMAS; LEONARD, 2009; TURNER et al., 2013), o SUS recomenda mamografia de rastreamento apenas até os 69 anos de idade (INSTITUTO NACIONAL DE CÂNCER, 2004), o que poderia levar a diagnóstico em estádios mais avançados. No entanto, em nosso estudo não houve diferença quanto ao tamanho tumoral e número de linfonodos axilares acometidos em relação à idade. Por outro lado, alguns trabalhos sugerem que estas pacientes são sub-tratadas, ou devido a comorbidades ou pela crença em uma doença menos agressiva nesta faixa etária (SCHONBERG et al., 2010, 2011). Como para muitas pacientes não foram encontradas informações em relação a tratamentos adjuvantes, e os casos faltantes não eram aleatórios, não utilizamos estas variáveis na análise principal. Quando incluímos os tratamentos adjuvantes (quimio, radio e hormonioterapia) no modelo de Cox, notamos que as idosas deixaram de ter menor sobrevida em relação às pacientes com idade entre 36 e 59 anos. Quanto às pacientes com idade até 35 anos, em nosso estudo não observamos menor sobrevida em análise multivariada, sugerindo que idade não é fator prognóstico independente neste grupo, o que vai de encontro ao descrito por alguns autores (COLZANI et al., 2011; DU; FOX; LAI, 2008; DUTRA et al., 2009b).

Também chama atenção a pior sobrevida em pacientes tratadas pelo SUS. Foi observado que estas pacientes tinham maior estadiamento ao diagnóstico. Embora não tenhamos analisado com detalhes as causas desta diferença, é provável que elas tenham tido maior dificuldade de acesso a rastreamento e tratamento adequados. Em um estudo retrospectivo observacional incluindo pacientes de diversas instituições brasileiras, observou-se também pior sobrevida em pacientes tratadas pelo SUS cujos estádios iniciais eram III e IV (LIEDKE et al., 2014). Os autores apontam as mesmas hipóteses referidas acima para esta diferença.

Em termos de sobrevida, a porcentagem de pacientes vivas após cinco anos foi de 95,5% para o estádio I, 85,1% para o estádio II e 62,1% para o estádio III, o que é semelhante ao descrito em outras coortes hospitalares brasileiras (AYALA, 2012; BRITO; PORTELA; VASCONCELLOS, 2009; CINTRA; GUERRA; BUSTAMANTE-TEIXEIRA, 2008; GUERRA et al., 2009; SCHNEIDER; D'ORSI, 2009).

Quanto à cor da pele, foi observada maior frequência de pacientes não brancas entre as jovens, bem como pior sobrevida causa-específica em não brancas quando variáveis relacionadas ao tumor não foram incluídas no modelo de Cox, o que sugere que a cor não é um fator prognóstico independente de sobrevida por câncer de mama. Já em relação a óbitos por outras causas, pacientes brancas tiveram menor sobrevida em relação às não brancas (pardas e negras). Sabe-se que nos Estados Unidos a sobrevida de pacientes afro-americanas com câncer de mama é pior em relação às brancas; acredita-se que haja tumores mais agressivos e possivelmente maior dificuldade de acesso a tratamento neste grupo (BRITO; PORTELA; VASCONCELLOS, 2009; MASKARINEC et al., 2011; OLIVEIRA et al., 2011; SILBER et al., 2013; WOODS; RACHET; COLEMAN, 2006). No entanto, no Brasil, há grande miscigenação, bem como maior proporção de pacientes não brancas nas faixas socioeconômicas mais carentes, o que dificulta a análise da cor enquanto fator prognóstico da doença (CHOR; LIMA, 2005; CHOR, 2013; SANTOS et al., 2009).

Concluímos, portanto, que os fatores tamanho tumoral, número de linfonodos axilares acometidos, grau histológico, idade acima de 70 anos e fonte de financiamento do tratamento foram fatores prognósticos associados ao câncer de mama, em nossa amostra. Em pesquisas futuras, pretendemos estudar o impacto de fatores socioeconômicos na sobrevida das pacientes.

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7- ANEXO I – APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Projeto: CAAE – 0660.0.203.000-11

Interessado(a): Profa. Helenice Gobbi
Departamento de Anatomia Patológica e Medicina Legal
Faculdade de Medicina - UFMG

DECISÃO

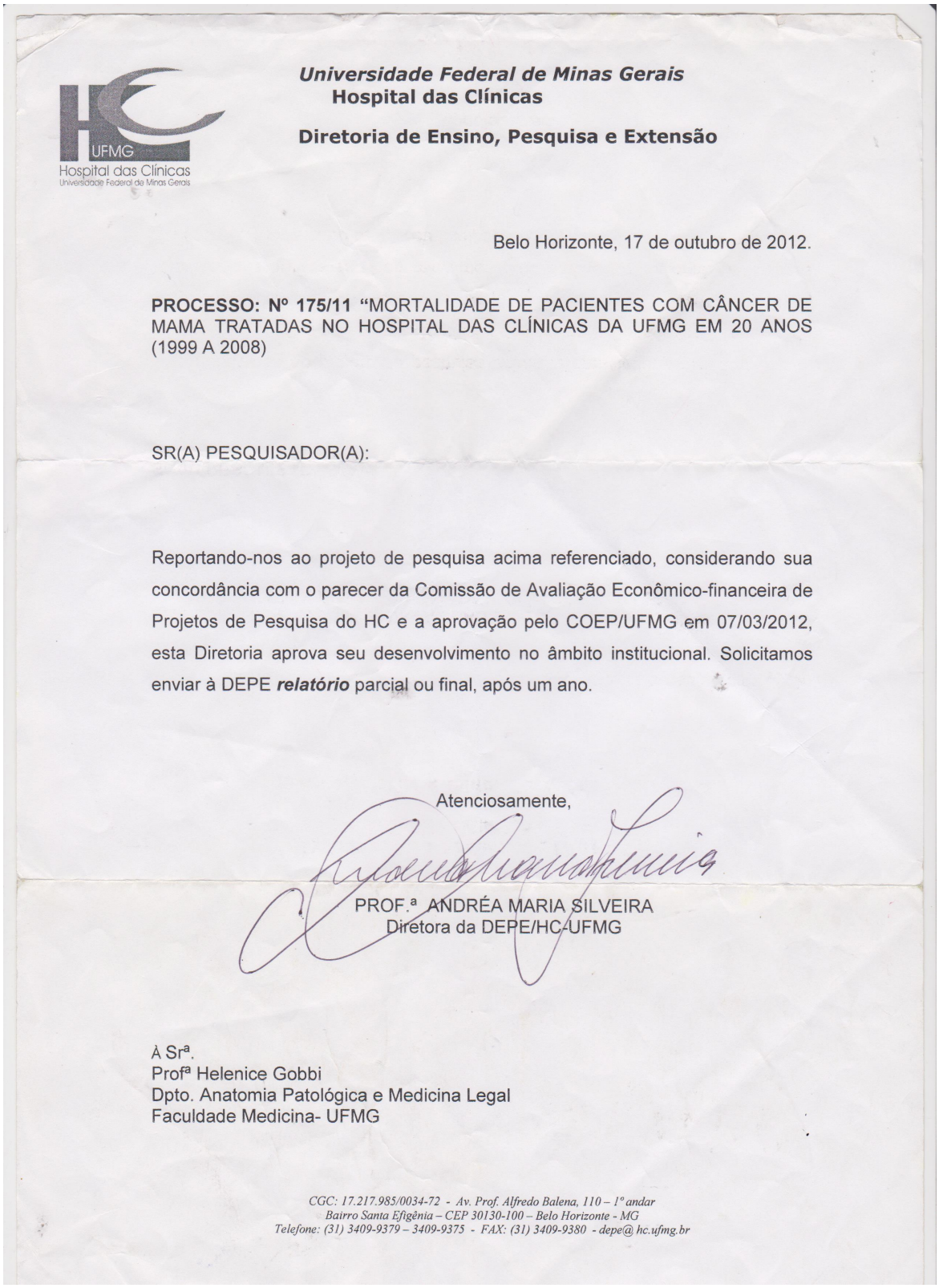
O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 07 de março de 2012, o projeto de pesquisa intitulado **"Mortalidade de pacientes com câncer de mama tratadas no Hospital das Clínicas da UFMG em 20 anos (1989 a 2008)"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Maria Teresa Marques Amaral
Coordenadora do COEP-UFMG

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2º andar – Sala 2005 – Cep:31270-901 – BH-MG
Telefax: (031) 3409-4592 - e-mail: coep@prpq.ufmg.br

8- ANEXO II – APROVAÇÃO DA DIRETORIA DE ENSINO, PESQUISA E EXTENSÃO DO HC-UFMG



UFMG
Hospital das Clínicas
Universidade Federal de Minas Gerais

Universidade Federal de Minas Gerais
Hospital das Clínicas

Diretoria de Ensino, Pesquisa e Extensão

Belo Horizonte, 17 de outubro de 2012.

PROCESSO: Nº 175/11 "MORTALIDADE DE PACIENTES COM CÂNCER DE MAMA TRATADAS NO HOSPITAL DAS CLÍNICAS DA UFMG EM 20 ANOS (1999 A 2008)

SR(A) PESQUISADOR(A):

Reportando-nos ao projeto de pesquisa acima referenciado, considerando sua concordância com o parecer da Comissão de Avaliação Econômico-financeira de Projetos de Pesquisa do HC e a aprovação pelo COEP/UFMG em 07/03/2012, esta Diretoria aprova seu desenvolvimento no âmbito institucional. Solicitamos enviar à DEPE ***relatório*** parcial ou final, após um ano.

Atenciosamente,

PROF.ª ANDRÉA MARIA SILVEIRA
Diretora da DEPE/HC-UFMG

À Srª.
Profª Helenice Gobbi
Dpto. Anatomia Patológica e Medicina Legal
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9- ANEXO III- TERMO DE COMPROMISSO ENTREGUE À SECRETARIA DE ESTADO EM SAÚDE

GOVERNO DO ESTADO DE MINAS GERAIS
SECRETARIA DE ESTADO DE SAÚDE
SUPERINTENDÊNCIA DE VIGILÂNCIA EPIDEMIOLÓGICA, AMBIENTAL E SAÚDE DO TRABALHADOR
Diretoria de Análise e Situação da Saúde

Termo de Compromisso para uso de bancos de dados nominais do Sistema de Informação de Mortalidade (SIM)

Declaro ciência das disposições referentes à segurança quanto ao uso do banco de dados dos Sistemas de Informação da Secretaria de Estado de Saúde de Minas Gerais (SES/MG), conforme Resolução nº 2653 de 21 de janeiro de 2010, que institui a Política e define Diretrizes de Segurança da Informação no âmbito da SES/MG.

Declaro ainda que os referidos registros serão utilizados exclusivamente na pesquisa ***"Mortalidade por câncer de mama em pacientes tratadas no Hospital das Clínicas da UFMG em 20 anos (1989 a 2008)"***, será desenvolvida no Departamento de Anatomia Patológica e Medicina Legal, Faculdade de Medicina da Universidade Federal de Minas Gerais e os resultados serão apresentados, no segundo semestre de 2014, como requisito obrigatório para a conclusão do Doutorado em Patologia.

Informo que o Projeto de Pesquisa foi submetido ao Comitê de Ética em Pesquisa desta Universidade (CONEP/UFMG) conforme Parecer CAAE-0600.0.203.000-11.

Informo ainda que assumo integral responsabilidade quanto ao uso dos bancos de dados do Sistema de Informação de Mortalidade – SIM, comprometendo-me a garantir o direito individual e coletivo das pessoas, a inviolabilidade de sua intimidade e o sigilo de suas informações, nos termos previstos em Lei, bem como disponibilizar as recomendações que se fizerem necessárias referentes ao Sistema de Informação de Mortalidade.

Atenciosamente,

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ASSINATURA DO DECLARANTE

10- ANEXO IV- MANUAL PARA PREENCHIMENTO DE BANCO DE DADOS DE ESPÉCIMES MAMÁRIOS

Estudo: "Sobrevida de pacientes com câncer de mama tratadas no Hospital das Clínicas da UFMG entre 2001 e 2008"

Autora: Débora Balabram

Orientadora: Profa. Helenice Gobbi

Coorientador: Prof. Cassio M. Turra

Nome: digitar por extenso, sem abreviações

Nome da mãe: digitar por extenso, sem abreviações

Nome do pai: digitar por extenso, sem abreviações

Data de nascimento: dd/mm/aaaa

Endereço: por extenso

Sexo:

1- feminino
2- masculino

Idade: número inteiro - nos casos de peças de revisão, há grande número de entradas com a idade faltante. Porém, pude perceber que os dados estão nos laudos do laboratório de origem, e devem ser completados.

Categoria sócio-previdenciária:

1- SUS
2- Sistema privado (particular ou convênio)

Biópsia: número

Ano: número de 4 dígitos (por exemplo, 2000, e não 00). Notar que, no início das pastas, temos na verdade exames de procedimentos realizados no ano anterior, mas que só foram analisados no início do ano seguinte. Devemos respeitar o ano em que o procedimento foi realizado e não o da pasta correspondente.

RG: Cada paciente que vem consultar no Hospital das Clínicas recebe um número de registro; geralmente, o mesmo tem 6 dígitos, porém podem haver casos de registros contendo até 8 dígitos. Isto ocorre quando a paciente vem realizar somente um procedimento no Hospital, ou quando seu material vem para revisão. Mas pode ocorrer também nas primeiras consultas das pacientes, caso no qual em seguida a paciente receberá novo número de protocolo. Esta é a principal forma de identificação da paciente, e não deve faltar em nenhum caso. Associado a este número, as pacientes apresentam também um número de biópsia, que deve ser anotado, já que a quantificação das biópsias também é um objetivo do estudo.

Cirurgia

0- Conservadora
1- Mastectomia

Cor

1- Leucoderma
2- Faioderma/melanoderma

Esvaziamento axilar:

0- Não
1- Sim

Grau histológico:

1- Bem diferenciado
2- Moderadamente diferenciado
3- Pouco diferenciado

Diagnóstico

1- Ductal

2- Lobular

3- Outros

Lateralidade:

1- Unilateral

2- Bilateral

LatBIO:

1- Direita

2- Esquerda

Estadiamento:

O T, N e M correspondem ao estadiamento clínico da paciente com carcinoma de mama (neoplasia epitelial maligna mamária), e devem ser copiados do prontuário quando presentes no mesmo. Nos casos de nódulo mamário que por fim tratar-se de doença benigna (fibroadenoma, por exemplo), o estadiamento não deverá ser anotado. Já o estadiamento patológico (pT e pN) deverá ser estimado por vocês de acordo com o que for encontrado nas peças. O laudo não especifica o estadiamento. O estadiamento deve ser feito conforme as orientações do AJCC de 2009.

Receptor de estrógeno

0- Negativo

1- Positivo

Receptor de Progesterona

2- Negativo

3- Positivo

Proteína HER2

4- Negativa

5- Positiva

Radioterapia

0- Não

1- Sim

Quimioterapia

0- Não

1- Sim

Hormonioterapia

0- Não

1- Sim

Índice de comorbidades de Charlson

0- Nenhuma comorbidade do índice

1- Ao menos uma comorbidade

Cor da pele

0- Não branca
1- Branca

11- PRODUÇÃO CIENTÍFICA

11.1- ARTIGO RELACIONADO À TESE

BALABRAM, D., TURRA, C. M., GOBBI, H.

Survival of patients with operable breast cancer (Stages I-III) at a Brazilian public hospital - a closer look into cause-specific mortality. BMC Cancer (Online)., v.13, p.434 - , 2013.

11.2- OUTRAS PUBLICAÇÕES CIENTÍFICAS

1. **BALABRAM, D.**, CABRAL, C.C.S.R., FILHO, OPR, BARROS, C.P.

Intramuscular lipoma of the subscapularis muscle. São Paulo Medical Journal (Impresso)., v.132, p.65 - 67, 2014.

2. NUNES, C. B., ROCHA, R. M., BUZELIN, M. A., **BALABRAM, D.**, FOUREAUX, F. S., PORTO, S. S., GOBBI, H.

False positivity in HER2 testing of breast cancer: novel paths for approaching an old dilemma. Journal of Clinical Pathology., p.1 - 5, 2013.

3. PEREZ, A. A., **BALABRAM, D.**, SOUZA, A. S., GOBBI, H.

Immunohistochemical profile of high-grade ductal carcinoma in situ of the breast. Clinics (USP. Impresso)., v.68, p.674 - 678, 2013.

4. PEREZ, A. A., **BALABRAM, D.**, SALLES, M. A., GOBBI, H.

Consultoria em patologia cirúrgica mamária: variabilidade interobservador no diagnóstico de lesões proliferativas intraductais atípicas. Revista Brasileira de Ginecologia e Obstetrícia (Impresso)., v.35, p.164 - 170, 2013.

5. BARRA, A.A., SANTOS, A.M.R., BARROS, C.P., SILVEIRA, D.S., **BALABRAM, D.**, SOARES, K. F., TROTA, S. T. A.

Avaliação endometrial em pacientes usuárias de tamoxifeno. Femina (Rio de Janeiro)., v.41, p.5 - 8, 2013.

6. **BALABRAM, D.**, ARAUJO, F. B., PORTO, S. S., RODRIGUES, J.S., SOUZA, A. S., SIQUEIRA, A.L., GOBBI, H.

Changes in mastectomy rates at a Brazilian public hospital over 20 years (1989 to 2008). São Paulo Medical Journal (Impresso)., v.130, p.360 - 366, 2012.

7. SILVA, R. A., BARRA, A. A., GOMES, D. S., **BALABRAM, D.**, GOBBI, H., VELOSO, G. G. V., PIRES, J. C.

Acuidade da mamografia na predição de malignidade em lesões não palpáveis da mama. Revista Multidisciplinar das Faculdades Integradas Pitágoras., v.Suplemento, p.76 - 87, 2012.

8. GOMES, D. S., **BALABRAM, D** , PORTO, S S, GOBBI, H

Lobular neoplasia: frequency and association with other breast lesions. Diagnostic Pathology., v.6, p.74 - , 2011.

11.3- RESUMOS PUBLICADOS EM ANAIS DE CONGRESSOS

1. **BALABRAM, D.**, TURRA, C. M., GOBBI, H.

Sobrevida e uso de tratamentos adjuvantes em pacientes idosas operadas por câncer de mama em uma instituição pública brasileira entre 2001 e 2008.

Apresentação oral e Poster / Painel no(a) **XVII Congresso Brasileiro de Mastologia**, 2013.

2. NUNES, C. B., ROCHA, R M, BUZELIN, M. A., **BALABRAM, D.**, FOUREAUX, F. S., PORTO, S. S., GOBBI, H.

Análise comparativa da expressão proteica de anticorpos anti-HER-2 através da imagem da lâmina escaneada no computador e da microscopia de luz usual In: XXIX Congresso Brasileiro de Patologia, 2013, Florianópolis.

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3. NUNES, C. B., ROCHA, R M, BUZELIN, M. A., **BALABRAM, D.**, FOUREAUX, F. S., PORTO, S. S., GOBBI, H.

High sensitivity and specificity of five different antibodies to detect HER2 amplification as defined by the new dual colour brightfield in situ hybridisation in breast carcinomas In: XXIX Congresso Brasileiro de Patologia, 2013, Florianópolis.

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4. **BALABRAM, D.**, ARAUJO, F. B., PORTO, S. S., SOUZA, A. S., SIQUEIRA, A.L., GOBBI, H.

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5. ARAUJO, F. B., **BALABRAM, D.**, SOUZA, A. S., GOBBI, H.

Análise do acometimento de margens cirúrgicas em espécimes de cirurgias conservadoras da mama de pacientes operadas na mesma instituição no período de cinco anos (2006-2010) In: XXVIII Congresso Brasileiro de Patologia - Congreso de la Sociedad Latinoamericana de Patologia, 2011, Maceió.

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6. PORTO, S. S., GOMES, D. S., **BALABRAM, D.**, GOBBI, H.

Carcinoma in situ da mama com características indeterminadas (CIS-I): frequência e associação com outras lesões mamárias. In: XXVIII Congresso Brasileiro de Patologia - Congreso de la Sociedad Latinoamericana de Patologia, 2011, M.

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7. PEREZ, A. A., ROCHA, R. M., **BALABRAM, D.**, SOUZA, A. S., GOBBI, H.

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Revista Brasileira de Mastologia. São Paulo: Sociedade Brasileira de Mastologia, 2011. v.21. p.59 - 60

8. SOUZA, A. S., ARAUJO, F. B., **BALABRAM, D.**, PORTO, S. S., GOBBI, H.

Concordância entre o diagnóstico histopatológico de lesões mamárias em core biopsy e espécime excisional subsequente In: XXVIII Congresso Brasileiro de Patologia - Congreso de la Sociedad Latinoamericana de Patologia, 2011, Maceió.

Jornal Brasileiro de Patologia e Medicina Laboratorial., 2011. v.47.

9. PORTO, S. S., GOMES, D. S., **BALABRAM, D.**, GOBBI, H.

Diagnósticos histopatológicos de lesões mamárias feitos por patologistas gerais e revisão especializada: implicações terapêuticas. In: XXVIII Congresso Brasileiro de Patologia - Congreso de la Sociedad Latinoamericana de Patologia, 2011, Maceió.

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10. GOMES, D. S., PORTO, S. S., **BALABRAM, D.**, GOBBI, H.

Diagnósticos histopatológicos de lesões mamárias feitos por patologistas gerais e revisão especializada: implicações terapêuticas. In: XVI Congresso Brasileiro de Mastologia, 2011, Goiânia.

Revista Brasileira de Mastologia., 2011. v.21. p.62 - 62

11. **BALABRAM, D.**, ARAUJO, F. B., PORTO, S. S., RODRIGUES, J.S., SOUZA, A. S., SIQUEIRA, A.L., GOBBI, H.

Mudanças nas taxas de mastectomia em um hospital público de Belo Horizonte ao longo de 20 anos (1989 a 2008) In: XVI Congresso Brasileiro de Mastologia, 2011, Goiânia.

Revista Brasileira de Mastologia., 2011. v.21. p.47 - 48