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Cardiovascular risk in middle-aged breast cancer survivors: a comparison between two risk models

Risco cardiovascular em mulheres de meia-idade com câncer de mama: uma comparação entre dois modelos de risco

Original Article

Abstract

PURPOSE: It was to assess the risk of cardiovascular disease (CVD) in breast cancer survivors (BCS). **METHODS:** This cross-sectional study analyzed 67 BCS, aged 45–65 years, who underwent complete oncological treatment, but had not received hormone therapy, tamoxifen or aromatase inhibitors during the previous 6 months. Lipid profile and CVD risk were evaluated, the latter using the Framingham and Systematic COronary Risk Evaluation (SCORE) models. The agreement between cardiovascular risk models was analyzed by calculating a kappa coefficient and its 95% confidence interval (CI). **RESULTS:** Mean subject age was 53.2±6.0 years, with rates of obesity, hypertension, and dyslipidemia of 25, 34 and 90%, respectively. The most frequent lipid abnormalities were high total cholesterol (70%), high LDL-C (51%) and high non-HDL-C (48%) concentrations. Based on the Framingham score, 22% of the participants had a high risk for coronary artery disease. According to the SCORE model, 100 and 93% of the participants were at low risk for fatal CVD in populations at low and high risk, respectively, for CVD. The agreement between the Framingham and SCORE risk models was poor (kappa: 0.1; 95%CI 0.01–0.2) for populations at high risk for CVD. **CONCLUSIONS:** These findings indicate the need to include lipid profile and CVD risk assessment in the follow-up of BCS, focusing on adequate control of serum lipid concentrations.

Keywords
Breast neoplasms
Cardiovascular diseases
Coronary artery disease
Dyslipidemias
Hypertension
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Models, cardiovascular

Palavras-chave
Neoplasias da mama
Doenças cardiovasculares
Doença da artéria coronariana
Dislipidemias
Hipertensão
Radioterapia
Modelos cardiovasculares

Resumo

OBJETIVO: Avaliar o risco de doença cardiovascular (DCV) em mulheres com câncer de mama. **MÉTODOS:** Foi conduzido estudo de corte transversal, com 67 mulheres com câncer de mama, entre 45 e 65 anos, tratamento oncológico completo, não usuárias de terapia hormonal, tamoxifeno ou inibidores da aromatase nos últimos 6 meses. Foram avaliados o perfil lipídico e o risco de DCV. Para avaliar o risco de DCV, foram utilizados os modelos *Framingham* e *Systematic COronary Risk Evaluation* (SCORE). Para investigar a concordância entre os modelos de risco cardiovascular, foi calculado o coeficiente kappa com seu respectivo intervalo de confiança (IC) de 95%. **RESULTADOS:** A média de idade das participantes foi de 53,2±6,0 anos. A prevalência de obesidade, hipertensão e dislipidemia foi 25, 34 e 90%, respectivamente. A prevalência de dislipidemia foi 90%. As anormalidades mais comuns do perfil lipídico foram: alto colesterol total (70%), alto LDL-C (51%) e alto não HDL-C (48%). Baseado no escore de *Framingham*, 22% das mulheres com câncer de mama apresentaram alto risco de doença arterial coronariana. De acordo com o modelo SCORE, 100 e 93% das participantes apresentaram baixo risco de DCV fatal, considerando populações de baixo e alto risco de DCV, respectivamente. A concordância entre os modelos de *Framingham* e SCORE foi ruim (kappa: 0,1; IC95% 0,01–0,2), considerando populações de alto risco de DCV. **CONCLUSÕES:** Esses dados indicam a necessidade de incluir a avaliação do perfil lipídico e do risco de DCV na rotina de seguimento de mulheres com câncer de mama, sendo observadoo adequado controle dos níveis séricos de lipídios.

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Introduction

There are currently millions of women diagnosed with breast cancer, who are going through a phase termed the menopause transition, in which there is an increased susceptibility to cardiovascular events[1]. Coronary heart disease (CHD) and cerebrovascular disease are the main cardiovascular diseases. Cardiovascular disease (CVD) is the leading cause of death in women worldwide, competing with breast cancer as the primary cause of death in breast cancer survivors (BCS)[2].

Dyslipidemia, obesity, age, smoking, sedentary lifestyle, hypertension and diabetes mellitus are known risk factors for CVD[1]. Previous studies have identified the high prevalence of CVD risk factors in middle-aged women[3,4]. Elevated serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were described in perimenopausal women[5,6]. The behavior of high-density lipoprotein cholesterol (HDL-C) levels in the menopause transition is less clear and reports have described that HDL-C concentration is not correlated with menopause status[6].

At midlife, BCS may present the same risk factors for CVD as women without breast cancer. As a result, BCS may develop CHD. A higher measurement of TC, LDL-C and TG was reported in BCS, when compared to non-BCS[7,8]. Furthermore, a relationship between obesity and unfavorable lipid profilehas been demonstrated in BCS[8,9]. Correlations between obesity[10-12], higher blood pressure and lipid levels[11]with worse survival rates in BCS were observed. The addition of traditional risk factors for CVD to chemotherapy[13-15], radiotherapy[14], targeted therapy[16] and endocrine therapy[17] may increase CVD risk in BCS. Use of endocrine therapy may be associated with favorable or unfavorable alterations in lipid profile[17,18].

CVD risk may be assessed by algorithms or mathematical models. Among the cardiovascular risk assessment models, the Framingham Risk Score (FRS)[19] and the Systematic COronary Risk Evaluation (SCORE)[20] are highlighted. The FRS, developed in the United States, is the most widely used algorithm worldwide[19] for calculation of CHD risk[19]. On the other hand, European guidelines recommend the application of the SCORE system, developed and validated in European countries[20]. The SCORE system estimates the risk of fatal CVD[20]. The prognostic performance of CVD risk assessment models may vary according to the population studied[21,22] and the clinical condition of the patients[23,24].

Therefore, the aim of the present study was to investigate the prevalence of CVD risk factors, estimate cardiovascular risk according to the FRS and SCORE model, and evaluate the agreement between these two cardiovascular risk estimation models in middle-aged BCS.

Methods

Patients

Participant selection has been previously described in detail[25]. Briefly, the current sample originated from the Brazilian Breast Cancer and Menopause (BBCAM) study. BBCAM study had a cross-sectional design and was conducted to investigate the prevalence of menopause symptoms, sexual activity, quality of life, bone mineral density and CVD risk in middle-aged BCS[25].We focused on the cardiovascular risk factors found in this study.

Participants of this study were selected among patients consecutively treated in the Menopause and Breast Cancer Outpatient Facilities in the Women's Hospital, located at the Universidade Estadual de Campinas, Brazil, between August 2002 and June 2003. During outpatient consultation, patients who met the inclusion criteria were invited to participate in the study. BCS, aged 45–65 years, who had not received menopause hormone therapy, tamoxifen or aromatase inhibitors in the last 6 months, and had no history of other malignant tumors were included in the study. Women were invited to participate regardless of menopause status. One hundred BCS were consecutively invited to participate in the study. Three patients refused due to lack of time. Twenty-two patients were undergoing oncology treatment and eight had no record of lipid profile. Sixty-seven BCS comprised the present study sample.

Participants provided information on their sociodemographic characteristics, including age, race/ethnicity, and marital status. Clinical characteristics included body mass index (weight in kg/height in m^2), smoking status, diabetes mellitus, blood pressure levels, time since breast cancer diagnosis, tumor stage, chemotherapy, and radiotherapy. Overweight and obese patients were defined asthose having a body mass index (BMI) between 25.0–29.9 kg/m^2 and ≥30 kg/m^2, respectively. Blood pressure was measured after rest. Hypertension was defined as a self-reported and/or blood pressure measurement ≥140 and/or ≥90 mmHg. Diabetes mellitus was defined as a self-reported medical diagnosis. The study was approved by the internal review board of the institution. All women signed an informed consent term.

The mean age of the participants was 53.2±6.0 years and mean time since breast cancer diagnosis was 67.7±55.0 months. The mean BMI was 27.8±5.7 kg/m^2. Seventy percent of the participants reported having one partner, 73% were white, and 84% were postmenopausal. Seventy-two per cent of the participants underwent chemotherapy, and 72% received radiotherapy. Other characteristics of the participants are shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of middle-aged breast cancer survivors

Characteristics	n	%
Race		
White	49	73
Non-white	18	27
Marital status		
With partner	47	70
Without partner	20	30
Menopause status		
Premenopause	11	16
Postmenopause	56	84
Type of surgery		
Mastectomy	36	54
Breast-conserving surgery	31	46
Chemotherapy	48	72
Radiotherapy	48	72
Chemotherapy + Radiotherapy	38	57
Tumor stage		
0	8	12
I	11	16
II	37	56
III	11	16

Lipid profile

After a 12 hour-fast, blood samples were collected for analysis of serum TC, HDL-C and TG levels. Plasma levels of TC, HDL-C and TG were measured by an enzymatic colorimetric method (Roche Modular system, Roche Diagnostics, Indianapolis, IN), using the Hitachi Modular Analytics system (Roche Diagnostics, Mannheim, Germany). Non-high density lipoprotein cholesterol (non-HDL-C) values were obtained by subtracting HDL-C from TC values[26]. LDL-C concentration was calculated with the Friedewald formula. TC/HDL-C, LDL-C/HDL-C and TG/HDL-C ratios were calculated by dividing TC, LDL-C and TG by HDL-C, respectively.

Dyslipidemia was classified according to the National Cholesterol Education ProgramAdult Treatment Panel III (NCEP-ATP III) guidelines[26], which considered the following levels elevated: TC ≥200 mg/dL, LDL-C ≥130 mg/dL, TG ≥150 mg/dL and non-HDL-C ≥160 mg/dL. HDL-C values<50 mg/dL were considered low. Ratios were considered high when the following values were observed: TC/HDL-C >4.5, LDL-C/HDL-C >3.0 and TG/HDL-C >4.0.

Cardiovascular risk assessment

The FRS was validated in a cohort of 5,345 US adults (2,856 women and 2,489 men), aged between 30 and 74 years, followed for12 years[19]. The FRS was developed to assess the relative importance of CHD risk factors and measure the absolute risk of CHD in each patient. The variables used to calculate the FRS were age, gender, smoking status, blood pressure levels, diabetes and values of TC and HDL-C. The10-year CHD riskis classified as low (<10%), moderate (10–20%) and high (>20%)[19].

The SCORE project assembled a pool of datasets from 12 European cohort studies, including 205,178 people (88,080 women and 117,098 men), aged between 45 and 64 years[20]. The SCORE project estimated the total 10-year risk of developing fatal CVD based on age, gender, systolic blood pressure, smoking status and TC level or TC/HDL-C ratio. There are versions for low- and high-risk regions. The 10-year risk of fatal CVD is classified as low (<3%), moderate (≥3 and <5%) and high (≥5%)[20].

Statistical analysis

Results were presented as means and standard deviations (SD) or as absolute and relative frequencies, according to the type of variable. The prevalence of CVD risk factors was calculated. The kappa coefficient was used to measure the degree of agreement between cardiovascular risk estimated by the Framingham and SCORE risk assessment models. The kappa coefficient and its respective 95% confidence interval (CI) were estimated using SAS software.

Results

The prevalence of overweight, obese and hypertensive patients was 43, 25 and 34%, respectively. The overall prevalence of dyslipidemic patients was 90%. The most common lipid disorders were high TC (70%), high LDL-C (51%) and high non-HDL-C (48%). The prevalence of high non-HDL-C in BCS with TG ≥200 mg/dL was 3%. The prevalence of other CVD risk factors is shown in Table 2.

Based on the FRS, 22% of BCS had a high10-year risk for CHD. According to the SCORE model, 100 and 93% of BCS had a low10-year risk of fatal CVD, considering populations at low and high risk for CVD, respectively. Considering Brazilian BCS as population at low or high risk for CVD, none of the participants were classified as high risk by the SCORE system (Table 3).

Considering populations at high risk for CVD, 30 BCS were classified as having a low 10-year risk of CVD and 4 BCS were classified as having a moderate 10-year risk of CVD by both cardiovascular risk models. Agreement between the FRS and SCORE system was poor (kappa: 0.1; 95%CI 0.01–0.2).

Based on the SCORE system, none of the participants had a moderate or high10-year risk of developing fatal CVD, considering populations at low risk for this condition. Thus, a kappa coefficient could not be obtained for populations at low risk for CVD.

Table 2. Prevalence of cardiovascular risk factors in middle-aged breast cancer survivors

Cardiovascular risk factors	n	%
Obesity	17	25
Hypertension	23	34
Diabetes mellitus	7	10
Smoking status	8	12
Dyslipidemia	60	90
High total cholesterol (≥200 mg/dL)	47	70
High LDL-cholesterol (≥130 mg/dL)	34	51
Low HDL-cholesterol (<50 mg/dL)	27	40
High non-HDL-cholesterol (≥160 mg/dL)	32	48
High triglyceride (≥150 mg/dL)	27	40
High TC/HDL-C ratio (>4.5)	24	36
High LDL-C/HDL-C ratio (>3.0)	19	28
High triglyceride/HDL-C ratio (>4.0)	18	27

Table 3. Risk of cardiovascular disease in middle-aged breast cancer survivors, according to Framingham and Systematic Coronary Risk Evaluation risk assessment models

Cardiovascular risk	Framingham		SCORE[a]		SCORE[b]	
	n	%	n	%	n	%
Low	30	45	67	100	62	93
Moderate	22	33	–	–	5	7
High	15	22	–	–	–	–

[a]Ten-year risk of fatal cardiovascular disease in populations at low risk for cardiovascular disease; [b]ten-year risk of fatal cardiovascular disease in populations at high risk for cardiovascular disease.

SCORE: Systematic COronary Risk Evaluation.

Discussion

The prevalence of CVD risk factors in our study participants was high, with 68% of these women being overweight or obese, slightly higher than the 56% of BCS previously reported to be overweight or obese[9]. Moreover, the prevalence of metabolic syndrome among 158 postmenopausal Brazilian BCS was found to be 48.1%[27]. Abdominal fat was the most frequent diagnostic criterion of metabolic syndrome in BCS, occurring in 54.4% of participants[27]. BCS may gain weight after diagnosis and treatment[10,27], with each 5 kg weight gain associated with a 12% increase in all-cause mortality, a 13% increase in breast cancer-specific mortality and a 19% increase in mortality from CVD[10].

Furthermore, obesity may be associated with hypertension. High blood pressure was common in our sample, affecting 34% of BCS. In a study of 494 BCS, the most common comorbid condition was hypertension, with a rate of 19%[9]. Other studies reported hypertension in 26[14] and 50.6%[27] of BCS. In the Shanghai Breast Cancer Survival (SBCS) study, hypertension was the most common comorbid condition, affecting 22.4% of the participants[28]. In the Life after Cancer Epidemiology (LACE) study, hypertension was independently associated with an increased risk of all-cause mortality, due to causes both related and unrelated to breast cancer[29]. This association disappeared, however, after adjusting for antihypertensive medication[29]. The prevalence of hypertension in our sample and in other studies is of concern, indicating the need to control blood pressure to minimize the deleterious effects of hypertension.

Another CVD risk factor was diabetes mellitus, reported by 10% of the participants. Similarly, other studies have reported diabetes mellitus in 6.2[28], 8[11] and 9%[14] of BCS. In the SBCS study, diabetes was associated with a 40% higher risk of total mortality and death unrelated to breast cancer, but not breast cancer-specific mortality[28]. In another study of BCS, diabetes was associated with a 39% increased risk of all-cause mortality, similar to rates observed in diabetics without breast cancer[30]. These data indicate an association between diabetes and poorer outcomes in breast cancer patients. A worse prognosis in BCS may be due to diabetes-related complications, such as insulin resistance and/or hyperinsulinemia[30].

Dyslipidemia, which may be associated with obesity, hypertension and diabetes[8,9], was detected in 90% of our study participants. The prevalence of dyslipidemia in middle-aged women without breast cancer was shown to be 71.5% in Chile[3] and 63.4% in Iran[4]. The most common lipid disorders were high TC, LDL-C and non-HDL-C concentrations. LDL-C is a major cause of CHD, as well as the primary target of lipid-lowering therapy[26]. BMI has been found to be related to TC[8,9] and LDL-C[8] concentrations in BCS, similar to findings in non-BCS[6]. A study of 104 Brazilian postmenopausal BCS found that the rates of high TC and high LDL-C were 56.7 and 83.4%, respectively[31]. Moreover, a prospective study of non-BCS found that the menopause transition was associated with significant increases in TC and TG concentrations[6]. The Study of Women's Health Across the Nation (SWAN) found that TC, LDL-C and TG levels peaked during late perimenopause and early postmenopause[5]. These findings may explain, at least in part, the prevalence of dyslipidemia in our study cohort and emphasize the importance of evaluating lipid profiles in middle-aged BCS.

The numbers of BCS in this study with high TC/HDL-C, LDL-C/HDL-C and TG/HDL-C ratios were not negligible. LDL-C/HDL-C ratio was shown to increase following menopause[32], whereas TG/HDL-C[33] and TC/HDL-C[6,32] ratios were found to increase during the menopause transition and postmenopausal periods, two phases the BBCAM study participants were going through. Considering the predictive capacity of CVD risk ratios, our results merit attention in clinical practice, since a considerable proportion of women in our study cohort BCS had elevated ratios, indicating that these women were at higher risk of CVD.

Tobacco smoking, another established CVD risk factor, was reported by 12% of the women in our study cohort. Tobacco smoke may lead to coronary endothelial dysfunction and atherosclerosis, possibly via oxidative stress[34]. Furthermore, cigarette smoking may be associated with increased mortality in BCS[35]. For example, results from the LACE study showed that current smokers were at a twofold increased risk of breast cancer-specific mortality and a fourfold higher risk of death unrelated to breast cancer[35] than never smokers. The mechanism relating smoking to poorer outcomes in BCS is not completely understood.

The combination of smoking and radiotherapy has been found to have a more than additive effect on the risk of myocardial infarction[14]. Radiotherapy was employed to treat 72% of our participants. Radiation-related heart toxicities include diseases of the pericardium and myocardium, coronary artery disease, valvular dysfunction and conduction abnormalities[14,36]. A population-based case-control study involving 2,168 breast cancer patients found that women irradiated for cancer in the left breast had significantly higher rates of major coronary events (*i.e.*, myocardial infarction, coronary revascularization, or death from ischemic heart disease) than those irradiated for cancer in the right breast[37]. Morphology was similar in patients with radiation-related CHD and spontaneous atherosclerosis[36].

Other therapeutic modalities commonly used to treat breast cancer patients include chemotherapy, targeted therapy and endocrine therapy. Anthracyclines are the most frequently used chemotherapeutic agents for breast cancer. Anthracycline cardiotoxicity is related to cumulative dose, increasing the risk of cardiomyopathy and congestive heart failure[13]. Chemotherapy-related cardiac ischemia is uncommon. However, associations between 5-fluorouracil use and myocardial ischemia have been reported[15]. Data on the chemotherapy agents used in our patients could not be retrieved. Although the targeted therapy trastuzumab has been associated with an increased risk of heart failure[16], this agent was not available to treat BCS at the time this study was performed. Endocrine therapy with tamoxifen may reduce TC and LDL-C, while increasing TG levels[18]. A systematic review found that the use of aromatase inhibitors, compared with tamoxifen, was associated with increased odds of developing CVD and hypercholesterolemia[17].

BCS have multiple risk factors for CVD, including both traditional and treatment-related factors. Despite the elevated prevalence of risk factors, none of the participants was categorized using the SCORE model as being at highrisk of CVD, whereas 22% were found to be at highrisk according to the FRS model. FRS and SCORE models may overestimate or underestimate CVD risk in different scenarios[21,22]. A recent systematic review evaluating the use and validity of CVD risk prediction models in Latin America and the Caribbean and among Hispanic populations in the United States reported that FRS overestimates CVD risk among Hispanics when not adequately recalibrated[22]. We found that the agreement between the two risk models was poor. Although no previous studies evaluated the FRS and SCORE risk models in middle-aged BCS, similar results have been reported in other settings[23,24]. For example, the agreement between FRS and SCORE models in poor Spanish middle-aged women[23] and in HIV-positive Brazilian patients[24].

This study had several limitations, including its cross-sectional design and relatively small sample size. To our knowledge, this is the first study from Latin America to evaluate the agreement between two CVD risk models in BCS. Routine follow-up of BCS should include lipid profiles and CVD risk assessment.

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