Risk assessment for breast cancer and BRCA mutations in women with personal and familial history

Leandro da Silva Clementino[1], Edinei Hideki Suzuki[2] and Karen Brajão de Oliveira[1*]

[1]Curso de Biomedicina, Centro de Ensino Superior de Maringá, Av. Guedner, 1610, 87050-390, Maringá, Paraná, Brazil. [2]Curso de Psicologia, Faculdade de Apucarana, Apucarana, Paraná, Brazil. *Author for correspondence. E-mail: karen_brajao@hotmail.com

ABSTRACT. Risk estimation tools can be used in clinical practice to promote the counseling, prevention, or increase the surveillance against breast cancer development. The present study aimed to estimate the risk for breast cancer and the odds for BRCA1/2 mutations, and to correlate the values found by the different models. Breast cancer risk was determined by the models of Gail, Claus, BRCAPRO and Boadicea; and for the mutations, Myriad II, Penn II BRCAPRO, and Boadicea models were utilized, in women who have or had the disease (n = 16) and their respective first degree female relatives unaffected (n = 25). Considering non affected women 16% were categorized as high risk for breast cancer development in five years by the Gail model, and all values presented significant correlation among the models (p < 0.05). Among the participants, 12% (5/41) were considered high risk for BRCA mutations. All the models presented significant correlation between the odds of BRCA1/2 mutation risk, except between Myriad II and Boadicea models. Since there is no model that includes all the variables influencing the development of this disease, it is essential to estimate the risk by more than one model before initiating any clinical intervention.

Keywords: breast neoplasms, risk factors, genetic variation.

Avaliação de risco para câncer de mama e mutações dos genes BRCA em mulheres com histórico pessoal e familiar

RESUMO. Ferramentas de estimativa de risco podem ser utilizadas na prática clínica para promover o aconselhamento, prevenção, ou aumentar a vigilância contra o desenvolvimento do câncer de mama. O presente estudo teve como objetivo estimar o risco de câncer de mama e a probabilidade de risco para mutação BRCA1/2, e correlacionar os valores encontrados pelos diferentes modelos. O risco de desenvolvimento do Câncer de mama foi estimado pelos modelos de Gail, Claus, BRCAPRO e Boadicea, e para as mutações, os modelos Boadicea Myriad II, Penn II BRCAPRO foram utilizados, em mulheres que têm ou tiveram a doença (n = 16) e seu respectivos parentes de primeiro grau do sexo feminino afetados (n = 25). Considerando-se as mulheres não afetadas 16% foram categorizadas como de alto risco para o desenvolvimento de câncer de mama em cinco anos pelo modelo de Gail, e todos os valores apresentaram correlação significativa entre os modelos (p < 0,05). Entre as participantes, 12% (5/41) foram consideradas de alto risco para mutações dos genes BRCA. Todos os modelos apresentaram correlação significativa entre as probabilidades de risco para a mutação BRCA1/2, exceto entre os modelos Boadicea Myriad e II. Uma vez que não existe um modelo que inclui todas as variáveis que influenciam o desenvolvimento da doença, é essencial estimar o risco por mais de um modelo antes do início de qualquer intervenção clínica.

Palavras-chave: neoplasias de mama, fatores de risco, variação genética.

Introduction

Breast cancer is the second most frequent cancer worldwide, the most common among women, relatively rare before 35 years old; above this age its incidence grows rapidly and steadily until 50 years, and later its prevalence progresses slowly. In Brazil, death rates from breast cancer are still high, with an estimate of 49,240 new cases in 2010, accounting for 11,860 deaths in 2008 (11,735 women and 125 men), which can be explained by the high rate of diagnoses at advanced stages of the disease. In the world population, the median survival after five years of diagnosis is 61%, and its incidence has grown both in developed and in developing countries (GONÇALVES et al., 2009; INCA, 2010).

Breast cancer is considered a multifactorial and complex disease, related to the process of industrialization, and other classical risk factors such as gender, age, ethnicity, overweight, alcoholism, hormonal factors, related to low parity, early menarche, late menopause, breastfeeding, hormone replacement

therapy (HRT), use of hormonal contraceptives, high-risk breast lesions, and the existence of close relatives affected by the disease (GUERRA et al., 2005; DANTAS et al., 2009; INCA, 2010).

About 15-20% of people affected by breast cancer may have a first- or second-degree relative also affected, characterized as familial breast cancer. This can emerge as a result of the interaction between multiple genes and environmental factors, or of a gene that promotes susceptibility, but with low penetrance (HEMMINK; ENG, 2004), however only 5-10% of this population present inherited predisposition (RUISÁNCHEZ et al., 2000).

The most common occurrence of hereditary breast cancer is its association with ovarian cancer, called Hereditary Breast and Ovarian Cancer Syndrome (HBOC) caused by mutations in BRCA1 and BRCA2 genes, which represent at least 30% of all hereditary breast cancers (LYNCH et al., 2008). Meanwhile, the sporadic breast cancer corresponds to the vast majority of cases (70%) and has no clinical features associated to inheritance (EWALD et al., 2011).

Women with mutations in BRCA1 have 87% chance of developing breast cancer, and 40-60% chance of developing an ovarian carcinoma along lifetime, and 65% chance of developing a second breast cancer if they live up to 70 years, while the risk for general population ranges from 8 to 10% (DANTAS et al., 2009), whereas the presence of mutations in BRCA2 promotes around 85% chance of developing a breast cancer throughout the life (DANTAS et al., 2009) and a risk of 15-30% for ovarian cancer (EWALD et al., 2011). Also there is a 6%-risk for breast cancer in male (CANCER GENETICS, 2003).

In general, the mutations in BRCA1 and BRCA2 genes confer a risk much higher than other factors like age, family history, menarche age, menopause age, age at first birth, benign breast disease or hormone replacement therapy (GOMY; ESTEVEZ DIZ, 2013). This high risk could be explained by the high penetrance of these mutations. Besides these, but with lower frequency are those genes associated with other syndromes that also confer increased risk of breast cancer: TP53 (Li-Fraumeni Syndrome), CHEK2 (hereditary breast and colon cancer syndrome) and PTEN (Cowden Syndrome) (MANN et al., 2006; DANTAS et al., 2009).

Patients carrying such mutations have some specific aspects of clinical and family history. The major criteria used for clinical diagnosis of HBOC are those from National Comprehensive Cancer Network (NCCN)

and American Society of Clinical Oncology (ASCO), which briefly include: personal or family history of early breast cancer (before 50 years), family history of ovarian and breast cancer in an individual, bilateral breast cancer in male, ashkenazi Jewish descent (Central and Eastern Europe) (EWALD et al., 2011). These characteristics can be used to select individuals that should be submitted to molecular tests to identify mutations in these genes (DUFLOTH et al., 2005).

The purpose of the risk assessment for breast cancer is to personalize management strategies for all women, in order to increase survival in high-risk women, and reduce the cost and complications in low-risk women (DOMCHEK et al., 2003). The detection of families with high risk of developing breast cancer, especially the carriers of genetic disorders, would be helpful for there to be a follow-up more specific, rigorous and effective (ROUKOS; BRIASOULIS, 2007).

Risk assessment models can be used to assist clinical examination and patient management. Different models for cancer risk can help determining when perform genetic tests, determine eligibility for chemoprevention, and provide accurate information to the patients about their individual risk, which can be evaluated as the probability of developing breast cancer or as the probability to detect a mutation in BRCA1 or BRCA2 (using prior probability models) (DOMCHEK et al., 2003).

These theoretical models population-based are tools used in risk assessment, developed to help estimate the risk of breast cancer, of an individual, or the chance of presenting a genetic mutation that predisposes to disease. Gail and Claus models were specifically develop to estimate the individual risk of a woman to develop breast cancer, while the Myriad II and Penn II models were designed to estimate the chance of a woman or a man to have the BRCA1 or BRCA2 mutation. The models BRCAPRO, Tyrer-Cuzick and Boadicea estimate both (EVANS; HOWELL, 2007; READY; ARUN, 2008; PANCHAL et al., 2008).

On the one hand, there are models like Gail, which take into account the personal risk factors, and in a less comprehensive way the family history, underestimating genetic risk, while the other studies investigate the genetic risks for breast cancer without considering hormonal and reproductive factors (TYRER et al., 2004). The patients whose family histories suggest a high-risk gene should be referred to a genetic clinic, where the evaluation will be more adequate. There are not yet precise data that allow incorporating conventional epidemiological risk factors into a general genetic model (ECCLES et al., 2000). The applicability

and ease of risk assessment models are listed in Table 1.

It is of paramount importance to consider the strengths and weaknesses of each model to select one tool with which it will be estimated the risk of breast cancer or the probability of BRCA1 or BRCA2 mutation, once the same model will not be appropriate for all patients. Thus, due to the low concordance among the methods used to determine the risk of developing breast cancer or having some BRCA germline mutation, Gomy and Esteves Diz (2013) recommends that individuals included in such research should be evaluated by several methods.

Recent studies have reinforced the importance of risk assessment for breast cancer, such as: chemoprevention with tamoxifen and raloxifene and surgical approaches (bilateral mastectomy or oophorectomy). These approaches are recommended only for women at high-risk for developing cancer, and therefore the proper calculation of risk is essential to identify women that can get benefit from these preventive measures (HOOKS, 2010). Besides integrate these patients into programs for monitoring and control as well as to perform educational programs that influence breast self-examination and genetic counseling (READY; ARUN, 2008; DANTAS et al., 2009).

This research aimed at determining, through an epidemiological survey, the prevalence of women with high risk of developing breast cancer and of carriers of mutations in genes BRCA1 and BRCA 2, in a population sample, selected with base on personal and family history of cancer, and to correlate the risk, according to the models of Gail, Claus, Miriad II, Penn II, BRCAPRO and Boadicea.

Material and methods

Study population

The study applied a descriptive methodology for the selected population that included women diagnosed with breast cancer (n = 16) treated in a hospital of Maringá city (Paraná State), in October 2010, in addition to their respective first-degree female family members (n = 25) over 18 years, totaling 41 individuals. The epidemiological data related to breast cancer for each woman were collected by means of a questionnaire after signing the Consent Form. The present study was approved by the Ethics Committee of the University Center of Maringá – Cesumar, in 8/6/2010, certification no. 246/2010, CAAE 0271.0.299.000-10.

Risk analysis

The risk of breast cancer in five years was given only for unaffected women (n = 25) by means of the risk models: Gail, Claus, BRCAPRO and Boadicea, while the probabilities for both BRCA1/2 mutations were determined for all women (n = 41) performed by the models Myriad II, Penn II, BRCAPRO and Boadicea, using CaGene5 software for the calculation of Gail, Claus, BRCAPRO and Myriad II. The models Penn II (2010) and Boadicea (ANTONIOU et al., 2008b) are available online at: http://www.afcri.upenn.edu/itacc/penn2/andhttp://ccge.medschl.cam.ac.uk/boadicea/ respectively.

Table 1. Applicability and ease of use of risk assessment models Gail, Claus, Myrad II, Penn II, BRCAPRO, BOADICEA, Tyrer-Cuzick.

Model	Personal risk factors	Family history	Cancers included	Inclusiveness	Calculation method	Data entry
Risk of breast cancer						
Gail	Age, age at menarche, age at first birth, prior breast biopsy	1st-degree relatives	Female breast cancer	Unaffected women	CaGene5 software or Web-page	One-page questionnaire
Claus	Age	1st- and 2nd-degree relatives	Female breast cancer in maternal and paternal family line	Unaffected women	CaGene5 software	CaGene5 software
Probability of being carrier of BRCA mutation						
Myriad II		1st- and 2nd-degree relatives	Male and female breast and ovarian cancer	Any individual	CaGene5 software	CaGene5 software or prevalence tables
Penn II		1st-, 2nd- and 3rd-degree relatives	Male and female breast, ovarian, prostate and pancreatic cancer	Excludes of individuals from families with no cases of breast cancer	Available online	One-page questionnaire
Risk of breast cancer and of being carrier of BRCA1/2 mutation						
BRCAPRO	Age	1st- and 2nd-degree relatives	Male and female breast and ovarian cancer	Any individual	CaGene5 software	Complete pedigree data for affected and unaffected family members
BOADICEA	Age	1st-, 2nd- and 3rd-degree relatives	Male and female breast, ovarian, prostate and pancreatic cancer	Any individual	Available online	Complete pedigree data for affected and unaffected family members
Tyrer-Cuzick	Age, age at menarche, age at menopause, age at first birth; HRT, body mass index	1st-, 2nd- and 3rd-degree relatives	Female breast, ovarian cancer	Only women	Requires download from the software IBIS	One-page questionnaire

Source: Modified from Panchal et al. (2008) and Ready and Arun (2008). Data of both studies were pooled and organized into a single comparative box.

Those women with a percentage ≥ 10% were categorized as high-risk patients for hereditary breast cancer. The risk of breast cancer was given as the probability of developing breast cancer in five years (calculated only for unaffected women). And women with a relative risk (RR) ≥ 1.66, determined by the Gail model, were classified as high-risk for breast cancer.

Statistical analysis

The risk values were mutually correlated through the Spearman correlation coefficient using the software SPSS Statistics 17.0 (SPSS STATISTICS, 2008/2009), and the significance level adopted was $p < 0.05$.

Results

In this study, 16 women participated, being carriers of malignant breast tumors (mean age 53 ± 9.7 years) and 25 non-carrier women (mean age 43 ± 11.8 years), but with family history of cancer. Most participants considered white (58.5%), followed by brown (36.6%) and black (4.9%). The mean menarche age was 13 (± 1.7) years for both groups, and the mean menopause age was 45 (± 6.5) years, and 44% (18/41) were in menopause and the majority (83%; 15/18) entered menopause aged ≤ 50 years, among them 44.4% (8/18) reported using HRT for less than five years. The mean age at first birth was 23 (± 5.4) years, and most (94%; 32/34) had children before age 30.

In this study, it have participated 16 women carriers of malignant breast tumors (mean age 53 ± 9.7 years) and 25 non-carrier women (mean age 43 ± 11.8 years), but with family history of cancer. Most participants considered white (58.5%), followed by brown (36.6%) and black (4.9%). The mean menarche age was 13 (± 1.7) years for both groups, and the mean menopause age was 45 (± 6.5) years, and 44% (18/41) were in menopause and the majority (83%; 15/18) entered menopause aged ≤ 50 years, among them 44.4% (8/18) reported using HRT for a period shorter than five years. The mean age at first birth was 23 (± 5.4) years, and most (94%; 32/34) had children before age 30.

Of the 25 unaffected women, only four (16%) were classified as high-risk for developing breast cancer in five years by the Gail model (RR ≥ 1.66). Of the 41 women (affected and unaffected), only five (12%) were considered as high-risk for BRCA1/2 mutations (≥ 10%). These data are listed in Table 2.

Only one patient was considered as high-risk by Myriad II, four by Penn II, one by BRCAPRO, and none by Boadicea (Figure 1).

It was verified a considerable divergence in the risk classification among the models, since five patients have been considered as high-risk by at least one of the models, and none patient has been considered as high-risk by all models.

Table 2. Epidemiological characteristics related to breast cancer in high-risk women.

	RR ≥ 1.66 in 5 years[a]		Probability of mutation BRCA1/2 ≥ 10%[d]	
N	4		5	
	Mean (years)	Interval (years)	Mean (years)	Interval (years)
Age	49.25	(34-68)	39.2	(40-60)
Race	All white		3 brown/ 2 white	
Age at menarche	11.5	(10-13)	13,2	(12-15)
Age at first birth	27.7[b]	(20-38)	22.8	(16-29)
Age at menopause	47.7[c]	(45-50)	46[c]	-
Use of HRT up to 5 years	2 women		-	
Breast biopsy	2 women		4 women[f]	
Age at diagnosis of breast cancer	-		34.5	(18-46)
Diagnosed relatives < 50 years	2 women		1 woman	

[a]Included only unaffected women. [b]3 women had children. [c]3 women were menopausal. [d]4 women had breast cancer, and 1 not. [e]Only 1 woman was menopausal. [f]Women diagnosed with breast cancer.
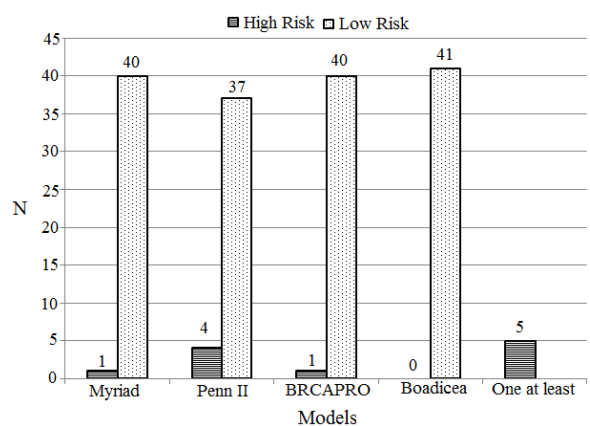
Figure 1. Risk of BRCA1/2 mutation. Classification of the 41 patients evaluated according to the risk of BRCA1/2 mutation by the models Myriad II, Penn II, BRCAPRO and Boadicea. The last column ('in one') indicates the number of cases where the risk is high by at least one model.

Significant correlations ($p < 0.05$) were detected between the percentage values of risk in five years, for all risk assessment models for breast cancer, the highest correlation was observed between Gail/ Boadicea (rho = 0.918; $p < 0.001$), followed by Claus/ Boadicea (rho = 0.879; $p < 0.001$), Gail/ BRCAPRO (rho = 0.858; $p < 0.001$), Gail/ Claus (rho = 0.808; $p < 0.001$), BRCAPRO/ Boadicea (rho = 0.736; $p < 0.001$) and Claus/ BRCAPRO (rho = 0.702; $p < 0.001$).

The average risk in five years for breast cancer was estimated at 1.35% by Gail model, and 0.93% by Claus model, 0.57% by BRCAPRO and 1.14% by Boadicea.

The risk probabilities for BRCA1/2 mutation had no correlation between the models Myriad II and Boadicea, while for the other models, significant correlations (p <0.05) have been verified: Penn II/BRCAPRO (rho = 0.871; p < 0.001), Myriad II/Penn II (rho = 0.815; p < 0.001), Myriad II/BRCAPRO (rho = 0.704; p < 0.001), BRCAPRO/Boadicea (rho = 0.494; p = 0.001) and Penn II/Boadicea (rho = 0.449; p = 0.003).

The average risk for BRCA mutation for all individuals was estimated at 4.38% by Myriad II, 5.51% by Penn II, 1.74% by BRCAPRO and 1.4% by Boadicea. The risk probabilities calculated by Penn II were higher than the other models.

Considering non-carrier women (n = 25), it was observed a significant correlation (p < 0.05) between the age at breast cancer diagnosis of first-degree relatives and the risk for BRCA1/2 mutation of all models: Penn II (rho = 0.781; p < 0.001), BRCAPRO (rho =0.714; p < 0.001), Myriad II (rho = 0.605; p = 0.001) and Boadicea (rho = 0.417; p = 0.038). There was also significant correlation (p < 0.05) between the values of risk for mutation and the age at diagnosis of carrier women (n = 16): Myriad II (rho = 0.925; p < 0.001), Penn II (rho = 0.873; p < 0.001) and BRCAPRO (rho = 0.740; p = 0.001), except for Boadicea model.

Discussion

Most cases of breast cancer occur in women over 50 years of age, and the risk for its development increases with age. White women have a slightly higher risk when compared to African-American, Asian and Hispanic women, although black women diagnosed with breast cancer have a worse prognosis (GUERRA et al., 2005; DANTAS et al., 2009). In the present study we observed similar data, since the average age of women with cancer was 53 years, and 58.5% were white.

Women considered at high-risk for breast cancer presented: early menarche, late age at first birth and menopause in relation to the total population; also, half of these women had at least one particular characteristic, such as the use of HRT (not longer than 5 years), prior breast biopsy or a relative diagnosed with breast cancer before age 50 (Table 2).

Several authors reported that hormonal and reproductive factors are of great relevance, since the prolonged exposure to estrogen confers increased risk of breast cancer. Thus, the early menarche (< 12 years) and late menopause (> 55 years) increase the risk through extending the exposure to these hormones. The hormone replacement therapy (HRT) seems to increase the cumulative risk of 1-2% per year, with extended use and combined formulations of estrogen and progesterone, but the risk appears to return to that of general population, after suspension for five years or more. There is also an increase of 24% in the risk of breast cancer by the use of combined oral contraceptives for more than ten years. Nulliparous women and those who had their first child over age 30 have twice the risk of women that had their first child under the age 20. The age at first birth influences the relative risk of breast cancer, since it maintains more stable the breast parenchyma cells, resulting in a reduced proliferation in the second half of the menstrual cycle (AMIR et al., 2003; EVANS; HOWELL, 2007; KOLLING; SANTOS, 2009; HOOKS, 2010).

Besides reproductive factors that can contribute up to 30% of cases of breast cancer, it is known that a sedentary lifestyle, obesity and poor eating habits can raise this risk by 40%, besides smoking and alcoholism (KOLLING; SANTOS, 2009). Other factor such as family history (including inherited mutations in genes predisposing to cancer), exposure to radiation therapy during breast development (breast radiation therapy for lymphoma treatment), breast density, lesions including lobular carcinoma in situ (LCIS), atypical hyperplasia and ductal carcinoma in situ (DCIS) are associated with a risk two to three times higher for invasive breast cancer (READY; ARUN, 2008; GARBER, 2009).

The studies carried out by Amir et al. (2003) and Gareth et al. (2007) evaluated the number of expected and observed cases of breast cancer in women with family history of disease, and it was observed that the models of Gail, Claus and BRCAPRO had underestimated the risk in women with a first-degree relative affected with breast cancer. On the other hand, all the models have predicted accurately the risk in women with multiple relatives affected. The models of Gail, Claus and BRCAPRO also had underestimated the risk in nulliparous women or those whose first birth occurred after age 30 and in women whose menarche occurred before age 12. Furthermore, the Gail model tends to underestimate the protective effect of the early first pregnancy in women with first-degree relatives affected.

For the Boadicea model, the first validation studies were performed for mutation probability, but not for the prediction of risk for cancer. The BRCAPRO and Boadicea were useful to evaluate the risk of genetic abnormalities in Jewish and non-Jewish women with family history of breast or ovarian cancer. The BRCAPRO model produced less accurate estimates of risk of breast cancer, while the Boadicea model predicted values closer to the observed than those

obtained by models of Claus and BRCAPRO (GARETH et al., 2007).

In contrast to the validation where the predicted risk is compared to the observed number of clinical diagnosis, the reliability indicates how closely two measures are in accordance, which is extremely important for scientific applications and counseling clinics, since two methods that measure the same subject should provide similar estimates.

The average risk in five years, of the patients of this study, presented higher estimates when evaluated by the Gail method. The determination of the risk by this method is based on hormonal and reproductive factors, family history, and clinical risk. However only first-degree relatives are included, underestimating the risk in 50% of families with cases of cancer in paternal line, and it also does not consider the age at onset of cancer. The Claus model uses genetic risk models based on the number of first- and second-degree relatives affected and the age at diagnosis of breast cancer. The main shortcoming of Claus model is the non-inclusion of any other risk factor except the heredity (GARETH et al., 2007). Thus, the Gail model is useful to assess the risk of a woman in the general population, without an extended family history, while the Claus model may be better to evaluate the risk of breast cancer in women with several relatives affected (DOMCHEK et al., 2003; HOOKS, 2010).

According to Evans and Lalloo (2002), hormonal factors, despite their relevance, alters minimally the risks in most cases, since in carriers of genetic mutations that confer higher risk for breast cancer, an early pregnancy does not provide protection against the disease. Then the risk increases with increasing number of relatives affected and with reduced age at diagnosis of affected relatives. Therefore, the best way to assess the risk is to consider first the family history, which is the major risk factor, and then make small adjustments based on other factors.

The Gail model is widely used, especially in studies focused on prevention of breast cancer in high-risk women, currently being the best model for risk assessment. Our study evidenced that, although mainly based on hormonal and reproductive factors, the risk values estimated by Gail, in five years, were very similar to other models, with significant correlation ($p < 0.05$) with Boadicea, BRCAPRO and Claus, which estimate the risk based only on family history and age at diagnosis of affected relatives. Moreover, Gail tends to estimate higher risks than the other models, but taking into account that all the 25 analyzed women presented one first-degree relative affected, this observation had not been relevant for the present study.

Panchal et al. (2008) showed that when considered the risk threshold as 10%, the sensitivity and specificity of the conventional tests to determine mutations in BRCA genes, were, respectively: BRCAPRO (0.75; 0.62), Penn II (0.93; 0.31), Myriad (0.71; 0.63), and Boadicea (0.70; 0.65). The model Penn II, besides being the most accessible due to its easy insertion of data, was the only one able to reach high sensitivity (90%) consistently in study population, therefore the widespread use of 10% is not suitable for all models (PANCHAL et al., 2008).

In the validation of risk estimates for BRCA1/2 mutations, Kang et al. (2006) achieved an optimal concordance between the values observed for risk of mutation for each proband for the models Penn II and Manchester, while the models Myriad and BRCAPRO presented areas of disagreement, related to clinical trial in the choice of proband, the estimation of age of the relatives, and the inclusion of paternal and maternal relatives.

If possible, the mutation analysis should be provided to all women at risk, but the low prevalence of carriers of BRCA mutation in the general population and the considerable costs prevent large-scale genetic screening. Based on family and personal history, age at diagnosis of cancer and estimates of prevalence, it is suggested that the genetic test should be provided to women with probability equal to or greater than 10% of having a BRCA mutation, where the probability thresholds should be less stringent for high-risk populations, such as Ashkenazi Jewish women (DOMCHEK et al., 2003; KANG et al., 2006; MANN et al., 2006; ROUKOS; BRIASOULIS, 2007; PANCHAL et al., 2008; EVANS et al., 2009).

Eventually, all the models have limitations, once very small families and the lack of knowledge about family history diminish the value of all models to some degree. Several models incorporate only information about first- or second-degree relatives of the proband, which can underestimate the risk of cancer when there are more family members or third-degree relatives affected by breast or ovarian cancer, and other cancers, such as prostate and pancreas, which are known to be influenced by BRCA1 or BRCA2 mutations (DOMCHEK; ANTONIOU, 2007).

As the selection criteria and the fact that some models are developed from studies on a set of high-risk families, such as Myriad II and Penn II, these frequently produce estimates with greater probability than other models (ANTONIOU et al., 2008a). Since most models of risk prediction was not validated for many populations, the predictor variables among models tend to be similar but not

identical, thus it is unclear whether they can be applied to other populations beyond those for which were designed (DOMCHEK; ANTONIOU, 2007).

Moreover, the greater number of relatives with cancer in addition to the younger ages at diagnosis, the higher the risk for mutation. The present study showed no correlation of the risk values for BRCA mutation only between the models Myriad II and Boadicea, but for the other models there were significant correlations (p < 0.05), however regarding the classification of the risk there was considerable divergence among the models (Table 2). The model Penn II seems to provide greater estimates of risk than the other models, and had classified women as being at high-risk of BRCA mutations, at 10% threshold, evidencing the divergences and limitations that should be considered before using these models.

The confirmation of women carriers of BRCA mutations considered at high-risk in the study would be required to determine the most accurate model. As well as it would be necessary further studies on larger populations in Brazil to determine the frequency of these mutations and the most suitable model. In the present study, the average risk of BRCA mutation for all individuals was estimated at 4.38% for Myriad II, 5.51% for Penn II, 1.74% for BRCAPRO and 1.4% for Boadicea. In this way, it was possible to notice that the probabilities of risk estimated by Penn II were higher than the other models.

New studies are underway to determine whether the inclusion of additional elements into existing models, especially Gail model, such as mammographic density, weight gain, serum level of steroid hormones, and genetic variations (SNP-single nucleotide polymorphisms) associated with breast cancer (including the genes CASP8, MAP3K1, RAD51L1 and others) will improve the risk prediction (GARETH et al., 2007; WACHOLDER et al., 2010).

The Tyrer-Cuzick model is the most consistent and accurate to predict breast cancer, since it is the only one that combines extensive family history, exposure to endogenous estrogens, benign breast disease, body mass index and HRT. Nevertheless, this model is not yet widely used, despite being the most precise according to a validation study performed by Amir et al. (2003) in determining the risk of breast cancer, but this model was not available on our computers.

Few data are available about black women and from other ethnicities, especially as for prevalence of BRCA mutations in these populations, once all the current models of probability include data almost exclusively of white women of North America and Europe (DOMCHEK et al., 2003). The models also can be improved, by introducing specific population risks, like prevalence of mutation, or specific characteristics of the tumor. For instance, around 80% BRCA1 breast cancer have histopathology of basal type, i.e., are negative for estrogen receptors (ER), progesterone receptors (PR) and HER2, so-called triple negative, while BRCA2 tumors are carriers of the luminal subtype that frequently are ER positive, which can be important for decision-making regarding the admission of preventive strategies (DOMCHEK; ANTONIOU, 2007; ROUKOS; BRIASOULIS, 2007).

When determined risk factors that increase the probability of developing breast cancer, it is imperative the discussion and offering effective methods to these women to prevent the disease. The surveillance of breast cancer can be improved with MRI (magnetic resonance imaging), while the prophylactic oophorectomy reduces significantly the risk of ovarian cancer by 90%, when performed before menopause may reduce the risk of breast cancer by 50%; and the prophylactic mastectomy diminish the risk of breast cancer in more than 90%, and these are options for only women with BRCA mutations (EVANS; LALLOO, 2002; DOMCHEK et al., 2003; GARBER, 2009).

In general, women at lower risk can be better served by the breast self-examination, characterized by the ease and low cost, systematic clinical examination performed by a specialized professional, in addition to mammography and ultrasonography (identify non-palpable tumors), which although reduce the risks also allow early detection of disease, where the expectations of cure are higher (NASCIMENTO et al., 2009).

As with any preventive intervention, the doctor role is to inform high-risk women about the benefits of any intervention (MORROW; GRADISHAR, 2002). The screening for BRCA1 and BRCA2 mutations should be done in the context of genetic counseling (DUFLOTH et al., 2005). The genetic screening is a method used to pre-symptomatic detection and prevention of genetic diseases so that they can start an early treatment and prevent or mitigate worse consequences of the disease (DANTAS et al., 2009). Moreover, the determination of risk for women with high chances of developing breast cancer or with a genetic mutation that make them more susceptible to this disease, may decrease the doubts, increase the perception of support and alleviate anxiety (GOMY; ESTEVEZ DIZ, 2013).

Conclusion

The present study showed that despite limitations, especially due to the low number of individuals included, the risk assessment models for breast cancer and for mutations have presented a good concordance among their values. In this way, it is recommended to

include other risk factors in order to increase the accuracy of these models. Eventually, it would be required the adaptation and validation of risk models in Brazil and diverse populations. The computer models to estimate the risks of BRCA mutations can be used in clinics to produce and store genealogical data and information about family members. In clinical practice, the risk analysis for breast cancer may be more useful than the evaluation of BRCA mutations, since the high cost of genetic tests prevents the management and counseling of all women with high probability for these mutations.

References

AMIR, E.; EVANS, D. G.; SHENTON, A.; LALLOO, F.; MORAN, A.; BOGGIS, C.; WILSON, M.; HOWELL, A. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. **Journal of Medical Genetics**, v. 40, n. 11, p. 807-814, 2003.

ANTONIOU, A. C.; HARDY, R.; WALKER, L.; EVANS, D. G.; SHENTON, A.; EELES, R.; SHANLEY, S.; PICHERT, G.; IZATT, L.; ROSE, S.; DOUGLAS, F.; ECCLES, D.; MORRISON, P. J.; SCOTT, J.; ZIMMERN, R. L.; EASTON, D. F.; PHAROAH, P. D. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. **Journal of Medical Genetics**, v. 45, n. 7, p. 425-431, 2008a.

ANTONIOU, A. C.; CUNNINGHAM. A. P.; PETO, J.; EVANS, D. G.; LALLOO, F.; NAROD, S. A.; RISCH, H. A.; EYFJORD, J. E.; HOPPER, J. L.; SOUTHEY, M. C.; OLSSON, H.; JOHANNSSON, O.; BORG, A.; PASSINI, B.; RADICE, P.; MANOUKIAN, S.; ECCLES, D. M.; TANG, N.; OLAH, E.; ANTON-CULVER, H.; WARNER, E.; LUBINSKI, J.; GRONWALD, J.; GORSKI, B.; TRYGGVADOTTIR, L.; SYRJAKOSKI, K.; KALLIONIEMI, O.-P.; EEROLA, H.; NEVANLINNA, H.; PHAROAH, P. D. P.; EASTON, D. F. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. **British Journal of Cancer**, v. 98, n. 8, p. 1457-1466, 2008b.

CANCER GENETICS. Physician and patient educational site of câncer genetics. **Breast Cancer Genetics**. 2003. Available from: <http://www.umdnj.edu/cigenweb/health_pro/breast_cancer.htm.>. Access on: Aug. 15, 2010.

DANTAS, E. L. R.; SÁ, F. H. L.; CARVALHO, S. M. F.; ARRUDA, A. P.; RIBEIRO, E. M.; RIBEIRO, E. M. Genética do câncer hereditário. **Revista Brasileira de Cancerologia**, v. 3, n. 55, p. 263-269, 2009.

DOMCHEK, S. M.; ANTONIOU, A. Cancer risk models: translating family history into clinical management. **Annals of Internal Medicine**, v. 147, n. 7, p. 515-517, 2007.

DOMCHEK, S. M.; EISEN, A.; CALZONE, K.; STOPFER, J.; BLACKWOOD, A.; WEBER, B. L. Application of breast cancer risk prediction models in clinical practice. **Journal of Clinical Oncology**, v. 21, n. 4, p. 593-601, 2003.

DUFLOTH, R. M.; CARVALHO, S.; HEINRICH, J. K.; SHINZATO, J. Y.; DOS SANTOS, C. C.; ZEFERINO, L. C.; SCHMITT, F. Analysis of BRCA1 and BRCA2 mutations in Brazilian breast cancer patients with positive family history. **Sao Paulo Medical Journal**, v. 123, n. 4, p. 192-197, 2005.

ECCLES, D. M; EVANS, D. G. R; MACKAY, J. Guidelines for a genetic risk based approach to advising women with a family history of breast cancer. **Journal of Medical Genetics**, v. 37, n. 3, p. 203-209, 2000.

EVANS, D. G. R.; LALLOO, F. Risk assessment and management of high risk familial breast cancer. **Journal of Medical Genetics**, v. 39, n. 12, p. 865-871, 2002.

EVANS, D. G. R.; HOWELL, A. Breast cancer risk assessment models. **Breast Cancer Research**, v. 9, n. 5, p. 213, 2007.

EVANS, D. G. R.; LALLOO, F.; CRAMER, A.; JONES, E. A.; KNOX, F.; AMIR, E.; HOWELL, A. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. **Journal of Medical Genetics**, v. 46, n. 12, p. 811-817, 2009.

EWALD, I. P.; IZETTI, P.; VARGAS, F. R.; MOREIRA, M. A.; MOREIRA, A. S.; MOREIRA-FILHO, C. A.; CUNHA, D. R.; HAMAGUCHI, S.; CAMEY, S. A.; SCHMIDT, A.; CALEFFI, M.; KOEHLER-SANTOS, P.; GIUGLIANI, R.; ASHTON-PROLLA, P. Prevalence of the BRCA1 founder mutation c.5266dupin Brazilian individuals at-risk for the hereditary breast and ovarian cancer syndrome. **Hereditary Cancer Clinical Practice**, v. 20, n. 1, p. 9-12, 2011.

GARBER, J. E. Identifying and assessing women at high risk for breast cancer. **Breast Cancer Research**, v. 11, suppl. 1, S1-S20, 2009.

GARETH, D; EVANS, R; HOWELL, A. Breast cancer risk-assessment models. **Breast Cancer Research**, v. 9, n. 5, p. 213-220, 2007.

GOMY, I.; ESTEVEZ DIZ, M. D. P. Hereditary Cancer Risk Assessment: How Best can we Achieve it? **Genetics**, S2: 003, p. 1-5, 2013.

GONÇALVES, L. L. C.; LIMA, A. V.; BRITO, E. S.; OLIVEIRA, M. M.; OLIVEIRA, L. A. R.; ABUD, A. C. F.; DALTRO, A. S. T.; BARROS, A. M. M. S.; GUIMARÃES, U. V. Mulheres portadoras de câncer de mama: conhecimento e acesso às medidas de detecção precoce. **Revista de Enfermagem**, v. 17, n. 3, p. 362-367, 2009.

GUERRA, M. R.; GALLO, C. V. M.; MENDONÇA, G. A. S. Risco de câncer no Brasil: tendências e estudos epidemiológicos mais recentes. **Revista Brasileira de Cancerologia**, v. 51, n. 3, p. 227-234, 2005.

HEMMINKI, K.; ENG, C. Clinical genetic counselling for familial cancers requires reliable data on familial cancer risks and general action plans. **Journal of Medical Genetics**, v. 41, n. 11, p. 801-807, 2004.

HOOKS, M. A. Breast cancer: risk assessment and prevention. **Southern Medical Journal**, v. 103, n. 4, p. 287-288, 2010.

INCA-Instituto Nacional do Câncer. **Estimativa de incidência e mortalidade por câncer no Brasil**. 2010.

Available form: <http://www.inca.gov.br>. Access on: Apr. 25, 2010.

KANG, H. H.; WILLIAMS, R.; LEARY, J.; RINGLAND, C.; KIRK, J.; WARD, R. Evaluation of models to predict BRCA germline mutations. **British Journal of Cancer**, v. 95, n. 7, p. 914-920, 2006.

KOLLING, F. L.; SANTOS, J. S. A influência dos fatores de risco nutricionais no desenvolvimento de câncer de mama em pacientes ambulatoriais do interior do Rio Grande do Sul, Brasil. **Scientia Medica**, v. 19, n. 3, p. 115-121, 2009.

LYNCH, H. T.; SILVA, E.; SNYDER, C.; LYNCH, J. F. Hereditary breast cancer: diagnosing hereditary breast cancer syndromes henry journal compilation. **The Breast Journal**, v. 14, n. 1, p. 3-13, 2008.

MANN, G. J.; THORNE, H.; BALLEINE, R. L.; BUTOW, P. N.; CLARKE, C. L.; EDKINS, E.; EVANS, G. M.; FEREDAY, S.; HAAN, E.; GATTAS, M.; GILES, G. G.; GOLDBLATT, J.; HOPPER, J. L.; KIRK, J.; LEARY, J. A.; LINDEMAN, G.; NIEDERMAYR, E.; PHILLIPS, K. A.; PICKEN, S.; PUPO, G. M.; SAUNDERS, C.; SCOTT, C. L.; SPURDLE, A. B.; SUTHERS, G.; TUCKER, K.; CHENEVIX-TRENCH, G.; CUNINGHAM, K. Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource. **Breast Cancer Research**, v. 8, n. 1, R12, 2006.

MORROW, M; GRADISHAR, W. Breast cancer. **British Medical Journal**, v. 324, p. 404-410, 2002.

NASCIMENTO, T. G; SILVA, S. R; MACHADO, A. R. M. Auto-exame de mama: significado para pacientes em tratamento quimioterápico. **Revista Brasileira de Enfermagem**, v. 62, n. 4, p. 557-561, 2009.

PANCHAL, S. M; ENNIS, M.; CÂNON, S; BORDELEAU, L. J. Selecting a BRCA risk assessment model for use in a familial cancer clinic. **BMC Medical Genetics**, v. 9, p. 116, 2008.

PENN II Risk Model. University of Pennsylvania. Available from: <http://www.afcri.upenn.edu/itacc/penn2/>. Access on: Oct. 10, 2010.

READY, K. J.; ARUN, B. The evaluation and management of familial and genetic risk in individuals at high risk for breast cancer. **Medscape Oncology**. 2008. Available from: <http://www.cme.medscape.com/viewarticle/576353>. Access on: Apr. 18, 2010.

ROUKOS, D. H.; BRIASOULIS, E. Individualized preventive and therapeutic management of hereditary breast ovarian cancer syndrome. **Nature Clinical Practice Oncology**, v. 4, n. 10, p. 578-590, 2007.

RUISÁNCHEZ, P. N.; ALVAREZ, B. M. T.; MENÉNDEZ, A. I.; RAMÍREZ, B. I. Alternativas preventivas en cáncer de mama. **Revista del Instituto Nacional de Cancerología**, v. 46, n. 4, p. 232-236, 2000.

SPSS STATISTICS. **SPSS Statistics Base 17.0**. User's guide, version 17.0. Illinois: SPSS inc., 2008/2009.

TYRER, J.; DUFFY, S. W; CUZICK J. A breast cancer prediction model incorporating familial and personal risk factors. **Statistics in Medicine**, v. 23, n. 7, p. 1111-1130, 2004.

WACHOLDER, S.; HARTGE, P.; PRENTICE, R.; GARCIA-CLOSAS, M.; FEIGELSON, H. S.; DIVER, W. R.; THUN, M. J.; COX, D. G.; HANKINSON, S. E.; KRAFT, P.; ROSNER, B.; BERG, C. D.; BRINTON, L. A.; LISSOWSKA, J.; SHERMAN, M. E.; CHLEBOWSKI. R.; KOOPERBERG, C.; JACKSON, R. D.; BUCKMAN, D. W.; HUI, P.; PFEIFFER, R.; JACOBS, K. B.; THOMAS, G. D.; HOOVER, R. N.; GAIL, M. H.; CHANOCK, S. J.; HUNTER, D. J. Performance of common genetic variants in breast-cancer risk models. **The New England Journal of Medicine**, v. 362, n. 11, p. 986-993, 2010.