

Breast and cervical cancer mortality in the western Amazon

A time series study between 1980 and 2014

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Abstract

Among the main types of neoplasms in the female population, breast and cervical cancers are the most important due to their high morbidity and mortality rates. The mortality has been proportionally higher in developing countries. Analysis of the trend of cancer mortality in Brazil revealed a considerable difference in the pattern of deaths between the regions.

To analyze the trend of mortality due to breast and cervical cancers in women.

Retrospective study of a series of death cases, using secondary data from the mortality information system (SIM) of the Ministry of Health. The deaths were identified as the underlying cause of breast and cervical cancers, including malignant neoplasms of the uterus without other specifications, occurring from 1980 to 2014. Thus, the annual standardized age-specific mortality rates by the world population were applied. For trend analysis, regression models were utilized in which the mortality rates were considered dependent variables and years the independent variable. Polynomial regression models and a Prais–Winsten regression model were adopted.

Cervical cancer presented a mortality rate ranging from 2.15 to 10.69 per 100,000 women from 1980 to 2014, with a tendency for stability.

Breast cancer mortality rate varied from 3.81 to 11.47 per 100,000 women from 1981 to 2014, indicating a growing trend.

There is a significant increase in the mortality rate for breast cancer and stability of cervical cancers in the State of Acre from 1980 to 2014, evidencing a concern in their care and monitoring. Above all, guaranteed access, especially to the population of women at social risk, and the search for effective screening should be emphasized in the formation of the care line and the Health Care Network in the State of Acre.

Abbreviations: α = constant, β = regression coefficient, C50 = malignant breast cancer, C53 = malignant cervical cancer, C55 = malignant neoplasm of the uterus without further specification, CID = International Classification of Diseases, HPV = human papillomavirus, IBGE = Brazilian Institute of Geography and Statistics, INCA = National Cancer Institute, r = square of Pearson's correlation coefficient, R^2 = coefficient of determination, SIM = mortality information system.

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Ethical approval and consent to participation:

This is a retrospective study of time series about death cases of the Mortality Information System of the Ministry of Health of the Department of Informatics of SUS (DATASUS). Data were collected by place of occurrence and residence for the city of Rio Branco, Acre, Brazil.

All sources of information are of the public domain and freely accessible. No additional information that is not freely accessible was collected. It should be noted that no information, such as the individual identification of the subjects, was obtained for this study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee, Opinion No. 253.096 and CAAE No: 14873013.2.0000.5180.

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

The leading causes of death among women older than 50 years are cardiovascular diseases and malignant neoplasms. According to data from the Instituto Nacional de Câncer (INCA - National Cancer Institute), the most common types of cancer in women, except non-melanoma skin cancer, are breast (29.7%), colon and rectum (9.2%) cancers, cervix (7.4%), lung (5.6%), and thyroid (5.4%).^[1,2]

In 140 of 184 countries worldwide, breast cancer is the most commonly diagnosed cancer among women.^[3] The annual incidence rate has increased by 3.1% since 1980. Breast and cervical cancers are the most frequently diagnosed cancers in Latin America and the Caribbean, Africa, and most of Asia (Torre et al^[4]).

The breast cancer is still responsible for a significant number of deaths in women, despite the recognized methods of prevention and early detection.^[5] Breast cancer mortality rates increase with age, with 97% of breast cancer-related deaths in women over 40.^[6]

For cervical cancer, 200,000 deaths of women aged 15 to 49 were related in developing countries in 2010.^[3,7]

The mortality has been proportionally higher in developing countries, a disparity that primarily reflects differences in disease profiles and the access to diagnosis and treatment.^[8]

In Latin America, breast cancer mortality has increased in recent years, unlike other where mortality rates are declining.

A study about breast cancer mortality at Brasil profile from 1987 to 2016 showed an increase of >45% in mortality rates. It estimated even more significant growth in the number of cases in the coming years.^[9]

Rates have also decreased in some high-incidence areas, including India and Brazil, possibly due to improved socio-economic conditions or screening.^[4]

Analysis of the trend of cancer mortality in Brazil and geographic regions between 1996 and 2010 revealed a considerable difference in the pattern of deaths between the country's regions, with a significant increase throughout the historical series. Evince that this disparity in access to health services also directly influences mortality according to the regions of Brazil. From 2011 to 2030, a trend of increased cancer mortality for the north and northeast regions was estimated. For the other regions, the trend was stable or decrease.^[10]

Despite the epidemiological importance of cervical and breast cancers worldwide and in Brazil, studies describing and analyzing the mortality trend from these cancers are still scarce, especially in Brazilian states of the western Amazon. Therefore, this study aims to analyze the mortality from cervical and breast cancers in women living in the western Amazon.

2. Methods

2.1. Study design

We conducted a retrospective time-series study from 1980 to 2014 of deaths from breast and cervical cancers in Acre State, Brazil.

2.2. Context (setting)

The data were retrieved from the “Sistema de Informações sobre Mortalidade” (SIM). SIM is the official source from the Brazilian Ministry of Health, which reports data concerning mortality. This system is fed by the death certificate, a mandatory civil document in the country.^[11]

There were included the deaths that have breast cancer as the underlying cause, defined by code 174 of the International Classification of Diseases (9th revision) (ICD-9) and C50 (C50: malignant breast cancer) of ICD-10 (10th revision). Also, there were extracted codes 179 and 180 of ICD-9 and C53 (C53: malignant cervical cancer) and C55 of ICD-10, thus including deaths coded as malignant neoplasm of the uterus without further specification (uterus not otherwise specified [NOS]).

This strategy was chosen, in agreement with other studies,^[12,13] because the use of the code for uterus NOS, in large part, means advanced and challenging to classify cervical disease, or even fails to attest death, being declared only uterine cancer.

2.3. Participants

Information on the population was obtained from the Department of Health Care of the Ministry of Health website. It was based on the 2010 demographic censuses, and the estimates for the interstate years were made by the Instituto Brasileiro de Geografia e Estatísticas (IBGE: Brazilian Institute of Geography and Statistics).

2.4. Variables

Age-specific annual breast and cervical cancer mortality rates, standardized by world population, from 1980 to 2014. Trend analysis was based on annual standardized mortality rates by the direct method and the world population proposed by Segi^[14] and modified by Doll et al.^[15]

2.5. Bias

The present study's main biases refer to the use of secondary data, especially in the fields to fill in the primary causes of death and the Acre State SIM coverage during the study period.

2.6. Statistical analysis

The Prais–Winsten method was applied for generalized linear regression. This test corrects the first-order autocorrelation effect and quantifies the annual rate variation, which is the most suitable for the time series analysis.^[16] A trend is considered stationary whose regression coefficient was not non-zero ($P > .05$), and the confidence intervals were also calculated (95%).

In the analysis with a polynomial regression model, annual mortality rates were considered dependent variables (y), and the mean and the years of study from 1980 to 2014 were explanatory variables (x).^[16] The year variable was transformed to the year-centralized variable ($x = \text{year} - 1997$) to avoid serial correlation between the regression equation terms.

Due to the oscillation of the points and the small number of cases in certain strata, the moving average centered in 3 terms was calculated to smooth out the historical series. Initially, the annual mortality rates were analyzed in a scatter plot to see which function best fit the rate distribution. The simplest model tested was the linear model ($y = \alpha + \beta x$), where α is the constant and β is the regression coefficient, followed by the second-order ($y = \alpha + \beta 1x + \beta 2x^2$) and third-order ($y = \alpha + \beta 1x + \beta 2x^2 + \beta 3x^3$) parabolic models.

The regression model's adequacy to the distribution of mortality rates was assessed by the coefficient of determination (R^2), which is the square of Pearson correlation coefficient (r), and estimates how much of the series can be explained the respective regression model. A value of R^2 equal to 1.0 means that all rates are on the regression line, and values close to 0.0 (zero) represent a weak explanatory relationship between the regression model and the rate distribution.

The null hypothesis of no regression of mortality rates over the years of the series (regression coefficient $\beta = 0$) was then tested. The presence of a significant trend ($P < .05$) was considered the best model to the one with the lowest P -value.

2.7. Ethical and legal aspects of the research

This study used secondary data, involving the description and analysis of population data present in public databases. All these sources of information are in the public domain and freely accessible. Included were those data from the general population and death census, collected from the Mortality Information System. It should be noted that no information, such as the individual identification of the subjects, was obtained for this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee, Opinion No. 253.096 and CAAE No: 14873013.2.0000.5180.

3. Results

From 1980 to 2014, there were 257 deaths from breast cancer in the State of Acre. The average was 7.34 deaths per year, and a significant increase in the number of deaths, from 5 deaths in 2010 to 33 in 2014 (Table 1).

For breast cancer, the best model ($R^2 = 49.4\%$, $P < .001$), according to the polynomial regression, represents the mortality

Table 1

Breast cancer mortality rates by 2010 world and Brazilian populations per 100,000 women. Acre-Brazil. 1980–2014.

Year	No. of cases	Gross rate	World age-adjusted rate	Age-adjusted rate Brazil
1980	0	0	0	0
1981	2	1.33	3.81	3.24
1982	3	1.92	4.69	6.13
1983	1	0.62	0.7	0.91
1984	1	0.6	1.35	1.45
1985	2	1.15	2.33	2.52
1986	5	2.79	6.85	6.76
1987	2	1.08	2.68	2.55
1988	2	1.05	1.48	1.72
1989	4	2.05	3.69	4.09
1990	7	3.50	5.32	5.79
1991	1	0.49	1.06	1.63
1992	0	0	0	0
1993	3	1.39	2.31	2.62
1994	2	0.91	2.41	2.05
1995	5	2.23	4.22	4.12
1996	4	1.67	3.22	3.45
1997	8	3.23	6.49	6.9
1998	5	1.97	3.32	3.44
1999	4	1.53	2.7	3.06
2000	7	2.53	4.09	4.52
2001	8	2.81	4.69	4.84
2002	9	3.09	5.22	5.94
2003	7	2.35	4.53	4.43
2004	5	1.64	2.51	2.54
2005	11	3.31	5.26	5.53
2006	11	3.23	5.44	5.82
2007	10	2.86	4.3	4.52
2008	6	1.78	2.57	2.78
2009	5	1.46	2.34	2.57
2010	5	1.37	2.19	2.27
2011	17	4.57	6.27	6.99
2012	32	8.47	11.32	12.47
2013	30	7.94	11.21	11.81
2014	33	8.73	11.47	12.45

Gross and age-adjusted breast cancer mortality rates by 2010 world and Brazilian populations per 100,000 women, Acre, Brazil, 1980–2014.

Source: MS/SVS/DASIS/CGIAE/Sistema de Informação sobre Mortalidade - SIM

Table 2**Cervical cancer mortality rates by the 2010 populations per 100.000 women. Acre-Brazil from 1980 to 2014.**

Year	No. of cases	Gross rate	World age-adjusted rate	Age-adjusted rate Brazil
1980	2	1.37	2.15	2.51
1981	7	4.64	11.19	11.87
1982	6	3.83	9.23	11.19
1983	14	8.63	18.88	20.35
1984	11	6.56	15.86	17.23
1985	11	6.34	14.34	14.58
1986	8	4.47	9.01	9.81
1987	7	3.79	7.44	8.17
1988	10	5.27	9.89	10
1989	9	4.61	8.66	10.14
1990	9	4.49	9.39	9.53
1991	15	7.28	15.26	15.23
1992	15	7.07	14.29	14.58
1993	20	9.27	15.52	18.57
1994	15	6.81	12.68	13.44
1995	18	8.01	16.23	17.84
1996	17	7.11	11.73	12.81
1997	16	6.47	11.15	12.41
1998	15	5.9	9.3	10.61
1999	8	3.06	5.97	6.03
2000	13	4.7	8.13	8.69
2001	10	3.51	6.37	6.69
2002	14	4.81	8.55	9.02
2003	18	6.04	9.85	10.57
2004	16	5.25	9.11	9.53
2005	15	4.51	7.72	8.05
2006	20	5.87	8.8	10.47
2007	22	6.29	9.25	10.08
2008	15	4.44	6.92	7.27
2009	6	1.75	2.46	2.95
2010	17	4.65	6.61	6.83
2011	29	7.8	10.4	11.44
2012	41	10.85	13.81	15.4
2013	38	10.06	15.43	15.41
2014	31	8.21	10.69	12.06

Gross and age-adjusted cervical cancer mortality rates by the 2010 world and Brazilian populations per 100,000 women, Acre, Brazil, from 1980 to 2014.

Source: MS/SVS/DASIS/CGIAE/Sistema de Informação sobre Mortalidade - SIM.

rate behavior, was the second-order, representing a growth trend; however, it was not constant, where alternating periods of reduction. Attention is drawn to the year 2008, where the mortality rate standardized by the world population was 2.57/100,000 inhabitants, rising to 11.47/100,000 inhabitants in 2014.

According to the data in Table 2, between 1980 and 2014, 538 women died of cervical cancer. There was a significant increase in this category from 6 deaths in 2009 to 41 in 2012 (an average of 15.37 per year).

For cervical cancer, the best model was the linear model, which has a decreasing and non-constant rate and revealed oscillations in the studied period, with some stabilization in recent years, confirmed by the regression of Prais–Winsten: annual average variation (VAM) = -1, 74% 95% CI (-3.57, -0.12) (Tables 3 and 4).

The trend of increasing mortality for breast cancer and stable mortality for cervical cancer in Acre's State is similar to that observed in most Brazil studies (Table 5).

4. Discussion

The trend analysis of the standardized breast cancer mortality rates in Acre, state of western Amazonia, showed an average

annual positive variation in the period 1980 to 2014, which showed a constant growth in mortality rates. As for cervical cancer, both models described a drop in mortality rates. However, the trend was not constant, with rate stability in the last years of the series.

The trend of increasing mortality for breast cancer is similar to that observed in most Brazil studies (Table 5). An evolution of mortality rates from breast cancer was observed by Guimarães et al^[19] in 3 census years (1991, 2000, and 2010). Breast cancer had the highest mortality rates due to neoplasms in women, observed in all Brazilian states.^[20]

Although not expressive, all states of the north and northeast regions showed a percentage increase in the period, with the highest increases seen in Amapá, Piauí, and Acre.^[20] Our findings indicate a significant increase in mortality from breast cancer, mainly from 2010 to 2014 for the state of Acre.

Risk factors for cancer development have consequently increased with aging and lifestyle, which would not be different in the State of Acre. Girianelli et al^[21] also use the aging of the population to justify the high mortality rates due to the influence of habits and changes in reproductive and sexual aspects during life.^[22]

Table 3
Standardized trend results for polynomial regression of breast and cervical cancer mortality rates* in the State of Acre, Brazil, 1980–2014.

Location	Type	Model	R ² (%)	P value (R ²)	P value (β)
Breast	Linear	$Y=3.91+0.14x$	43.7	<.001	$\beta^1 < .001$
	Second order	$Y=3.27+0.14x+0.006x^2$	49.4	<.001	$\beta^1 < .001$ $\beta^2 = .038$
	Third order	$Y=3.27-0.001x+0.006x^2+0.001x^3$	57.2	<.001	$\beta^1 = .992$ $\beta^2 = .025$ $\beta^3 = .013$
Uterus	Linear	$Y=10.23-0.14x$	20.9	.003	$\beta^1 = .003$
	Second order	$Y=10.25-0.14x-0.001x^2$	18.5	.014	$\beta^1 = .004$ $\beta^2 = .922$
	Third order	$Y=10.25-0.31x-0.001x^2+0.001x^3$	21.8	0.014	$\beta^1 = .012$ $\beta^2 = .920$ $\beta^3 = .137$

* Cervical cancer mortality rates NOS (CID-9 179+180; CID-10 C53+C55).

Acre has increased in breast cancer cases in recent years, which may be related to exposure to risk factors and the precariousness of health services offered, reducing the chances of detection and treatment.^[23] Other factors that may contribute to this increase are exposure to chemicals, including exogenous hormones, pesticides, obesity, and dietary factors.

Besides, early menarche, late menopause, late pregnancy, nulliparity, contraception, and hormone replacement use are directly related to developing some cases of breast cancer.^[24,25] Mutations in the BRCA1 and BRCA2 suppressor genes, widely studied in recent decades, also have a strict relationship with breast cancer.^[2]

In cervical cancer, risk factors include human papillomavirus (HPV)-related infections, which, when not appropriately treated, can progress to cancer; early sexual initiation; the number of sexual partners; a large number of pregnancies; smoking; and unfavorable socioeconomic conditions.^[2,26]

The standardized uterine cancer mortality rates did not show a definite trend, with a considerable reduction in Brazil. The regions with the highest mortality rates are the poorest, with vulnerable conditions. A study whose data were projected for 2030 described the continuing reduction in the trend of this mortality. Between 2008 and 2012, the average cervical cancer mortality rate by age ranged from 4.6 to 22.9 cases per 100,000 women per year.^[4,21]

Mortality due to cervical cancer was the fourth cause of death due to cancer in women in 2015. The mortality rate studies showed a marked reduction in Brazil from 1980 to 2014 (Table 5).^[12,13,27–29] However, the rates described in these series represented values that are still high in respect to those verified in European and North American countries.^[10]

The highest mortality rates in 2015 were observed in the north and northeast regions, especially in Amazonas, reflecting the

regional inequality of access to preventive measures that are still present in Brazil.

Analysis of cervical cancer mortality between 1996 and 2010 found stability in the north and northeast Brazilian regions.^[9] Another study found a decline in the country's mortality (1980–2010), except in distant municipalities in the north and northeast regions.^[21] This result is reinforced by this study, which showed the trend of stable mortality for cervical cancer in the State of Acre.

The regional differences observed in the epidemiological profile of breast and cervical cancers in Brazil can be attributed to the distinct economic, cultural, regional, and intra-urban characteristics influencing exposure to recognized cancer risk factors.^[10] There is epidemiological evidence that socioeconomic and demographic factors influence breast and cervical cancers and related survival. De Carvalho et al^[30] showed that the incidence prevailed in women older than 49 years with low education and low family income, reflected in mortality. Social determinants such as family income, education, and occupational issues impact cancer cases as a whole, especially on breast cancer.^[31]

The low-to-medium income population's socioeconomic transition reduces the prevalence of infectious diseases and increases those related to dietary, reproductive, metabolic, hormonal, and behavioral factors. Therefore, there is a tendency to reduce cervical cancer incidence and increase breast cancer incidence in Brazil, especially in cities with lower socioeconomic development.^[32] The socioeconomic condition of the population combined with the low effectiveness of public policies was evidenced in the findings by Guimarães et al,^[33] in which the highest percentage of deaths from cervical cancer (53.3%) occurred in residents of neighborhoods belonging to the worst living strata of the municipality, suggesting the role of poverty in determining the disease. Difficulties in accessing health services

Table 4
Prais-Winsten regression trend in breast and cervical cancer mortality rates^[18] in the State of Acre, Brazil, 1980–2014.

Location	Average annual change%	CI 95%		P value	Interpretation
		Inferior	Superior		
Breast	+3.28	1.63	6.05	$P < .001$	Crescent
Uterus	-1.74	-3.57	0.12	$P = .066$	Stable

* Cervical cancer mortality rates NOS (CID-9 179+180; CID-10 C53+C55).

Table 5
Comparison of mortality rates for breast and cervical cancer in Brazil in selected studies.

Breast cancer Study	Location	Period	Tendency
Cecilio et al ^[24]	Brazil	1980–1995	Crescent
Andrade et al ^[25]	Salvador	1979–1996	Stable
Nakashima et al ^[26]	Santos	1979–1999	Crescent
Arruda et al ^[22]	Paraná	1980–2002	Crescent
	Rio Grande do Sul	1980–2002	Crescent
	Santa Catarina	1980–2002	Crescent
Study	Acre	1980–2014	Crescent
Cervical cancer BRASIL ^[2]	Belém*	1980–1997	Decrescent
	Para*	1980–1997	Decrescent
Wunsch and Moncau ^[27]	São Paulo*	1980–1999	Stable
Penha et al ^[23]	Rio Grande do Sul*	1979–1998	Crescent
Fonseca et al ^[28]	Salvador†	1979–1997	Decrescent
World Health Organization (WHO) ^[18]	Rio Grande do Sul†	1979–1995	Stable
Alves et al ^[29]	Minas Gerais†	1980–2005	Decrescent
De Carvalho et al ^[30]	Acre†	1980–2014	Decrescent. Stable
Cecilio et al ^[24]	Brasil*	1980–1995	Decrescent

* Cervical cancer mortality rates (CID-9 180; CID-10 C53).

† Cervical cancer mortality rates NQS (CID-9 179+180; CID-10 C53+C55).

for women from a lower social class influence the necessary examinations and treatments in breast and cervical cancers, generating severe consequences for these women, which delays their diagnosis and treatment.

The National Health Survey of 2013 found a high screening coverage throughout the country, but it found higher proportions of women with lower educational levels and no private health plan in the north and northeast regions, and these variables showed an inverse association with performing the test.^[34]

The absence or insufficiency of a screening program that targets the entire susceptible female population, coupled with poor therapeutic care, is likely to contribute to the tendency for mortality to continue to increase for years to come. Screening is offered to healthy people (without disease symptoms) to select those most likely to have a disease because they have abnormal or suspicious tests and should therefore be referred for diagnostic investigation.^[2] Cervical cancer screening is recommended for a Pap smear, the primary method of prevention and early detection. The test is recommended for every woman who has had sex and is aged between 25 and 59. It is to be performed at least once a year. Performing the test as recommended helps change the incidence and mortality rates.^[35,36]

The American Cancer Society^[10] recommends starting optional mammography screening for women ages 40 to 44, annual screening for women ages 45 to 54, and screening every 2 years for women over 55 years of age. Progress in reducing breast cancer mortality rates may be accelerated by the increased number of women screened from 40. Findings show that mammographic screening in women aged 40 to 69 years is a protective factor against breast cancer death.^[30]

In Sweden, for example, the reduction in mortality reached 40% after the implementation of mammographic screening. In addition to the reduction in mortality, it was observed that the diagnosis in mammographic screening campaigns showed a decrease in cases at an advanced stage, compared with cases diagnosed by other methods.^[37]

Thus, survival related to both breast and cervical cancers is related to the disease stage and the diagnosis, which makes the

strategies aimed at early detection the most effective for reducing the mortality rate. To this end, screening through mammography and Pap smears has as its primary objective the detection of clinically occult breast and cervical cancers in the expectation of disrupting the natural history of the disease.

After the deconcentration of public policies related to the pregnancy-puerperal cycle and contraception, the Ministry of Health, through the National Cancer Institute (INCA),^[32] launched the Viva Mulher Programme in 1996 intending to reduce mortality and the physical, psychic, and social issues of breast and cervical cancers, offering prevention and early detection services. Besides, the Pact for Life was developed, which is a program also aimed at reducing mortality from breast cancer and where mammograms are offered to reach as many women as possible.^[6]

Expanding access to health care, including Pap smears and disease information, is likely to explain the stability in mortality rates observed in this study. However, despite the increase in the number of exams, cervical cancer control actions have not been able to intervene in the pattern of mortality from the disease constantly and satisfactorily as expected, keeping it constant at high values, compared with the results obtained in developed countries in previous decades. In this context, it can be seen from the results found in this study that cancer mortality in the State of Acre suggests an ongoing epidemiological transition process, representing significant mortality rates from diseases associated with better socioeconomic conditions, such as breast cancer and persistence of high rates for tumors that are generally related to poverty.

The limitations of this study include the use of secondary databases. Breast and cervical cancer mortality depend on intrinsic and extrinsic factors that were not addressed in this study.

The finding of increased mortality rates from breast cancer shows the importance that should be given to the Health Care Network in Acre and the infrastructure, diagnosis, and treatment currently available in the state to fight and combat this disease. The development of public health infrastructure plays a vital role

in maintaining health actions, health promotion, and contributing to individuals' quality of life.^[38] Given the increase in mortality rates from breast cancer in the State of Acre, it is necessary to intensify the search for early diagnosis in the preclinical phase and universalize access to local services with medicine-based practices.

5. Conclusion

There is a significant increase in the mortality rate for breast cancer and cervical cancer stability in the State of Acre from 1980 to 2014, evidencing a concern in their care and monitoring. Above all, guaranteed access, especially to the population of women at social risk, and the search for effective screening should be emphasized in the formation of the care line and the Health Care Network in the State of Acre.

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