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Overall survival analyses of female malignancies in Southern Brazil during 2008–2017: A closer look at breast, cervical and ovarian cancer

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ABSTRACT

Background: The aim of this study was to report the overall survival and baseline factors associated with OS for breast, cervical and ovarian cancer in Florianópolis, Southern Brazil, a region with quality-of-life indicators comparable to high-income countries.
Methods: Cohort study was performed from probabilistic record linkage of the Mortality Information System and the Population-based cancer registry of Florianópolis. It was included breasts, cervical and ovarian cancer diagnosis during the period of 2008–2012 with a follow up of 60 months. Cox regression and Kaplan-Meier method were used for associations with overall survival and risk factors.
Findings: 1857 cases of the three malignancies were included in the analysis. We identified 202 deaths in breast cancer subjects, 53 for cervical cancer and 51 for ovarian cancer. Metastatic disease at diagnosis was present in 31%, 9.6%, and 55% of the cases, respectively. Overall survival was statistically correlated with age, educational level and stage for breast cancer; age and stage for cervical cancer; age and stage for ovarian cancer.
Interpretation: Metastatic disease and age are the main prognostic factors for the malignancies studied, as they were associated with both overall survival and risk of death. Better screening and preventive tests for early diagnosis are needed.
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Abbreviations: OS, overall survival; HDI, Human Development Index; ICD, International Statistical Classification of Diseases and Related Health Problems; RCBP, Population-based cancer registry; IARC, International Agency of Research Cancer; INCA, National Institute of Cancer of Brazil; GNI, gross national income; DATASUS, SUS Computer Department.

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1. Introduction

Cancer is one of the major public health problems worldwide. It has taken a higher position at the causes of death ranking, from third to second place in the last years, remaining only behind cardiovascular diseases [1,2]. However, in high-income countries and some upper-middle-income countries, recent evidence has shown that deaths due to cancer will become the leading cause of death in some years [3]. Additionally, the number of cancer diagnosis are increasing along the time [4,5].

Brazil is classified as a country with a high human development index (HDI) [6]. However, the incidence and mortality due to cancer in women differ from what is expected. CONCORD-3, the global program for worldwide surveillance of cancer survival, estimated that for high HDI countries, cervical cancer should not be listed in the main causes [5]. In Brazil, cervical cancer is the third cause of cancer incidence and mortality due to cancer in women [7,8]. Notably, Brazil is marked by a high level of income and social inequalities (Gini coefficient = 0,533) [9], and the spatial distribution of cancer incidence and mortality is different in its regions [7,8].

In the South of Brazil, the state of Santa Catarina presents indicators of quality of life comparable to high-income countries, with an elevated HDI when compared to the other Brazilian states and its capital, Florianópolis, has the third highest HDI among all 5570 municipalities in Brazil [6]. And breast cancer is the most common cancer in women in Florianópolis with 47·8 cases 100 thousand inhabitants of incidence. Cervical cancer is in the fifth position (13·3 cases per 100 thousand inhabitants) while ovarian cancer is in the ninth position (6.6 cases) [7]. Regarding overall mortality due to cancer, in 2016, 16·0% was relative to breast, 4·8% cervical, and 3·6% ovarian cancer [8].

Florianópolis is one of the few municipalities in Brazil which counts with a population-based cancer registry. More than that, in order to identify the determinants of health disparities and to improve survival after a cancer diagnosis it is important to evaluate the data from cancer registries [10]. The aim of the present study was to evaluate the overall survival (OS) after cancer diagnosis in women diagnosed with breast, cervical and ovarian cancer in the city of Florianópolis and to identify baseline factors associated with OS.

2. Methods

2.1. Study design and study population

This is a historic cohort study with data retrieved from the city of Florianopolis, the capital of the Santa Catarina state, in the south of Brazil. Its population is of 421,240, according to the latest Brazilian census [11], and its HDI is of 0·847, considered very high by the sum of life expectancy at birth of 0·87, followed by the gross national income (GNI) per capita of 0·87 and education index of 0·80 [12].

The study population is characterized by the cancer registries coded by the international statistical classification of diseases and related health problems (ICD) as breast cancer (C50), cervical cancer (C53) and ovarian cancer (C56) included in the population-based cancer registry of Florianopolis, during the period of 2008 until 2012. We excluded the case were diagnosed by death verification service or because the diagnostic method was not available.

2.2. Data source

Data were retrieved from the Population-based cancer registry (RCBP), which is a database built to estimate cancer incidence, mortality, and survival of a target population through the collection, analyses, interpretation, and propagation of the data systematically, during specific pre-defined periods [13]. The data collection by the RCBP started in 2008 and it is still active. The quality of the data is certified by the National Cancer Institute of Brazil (INCA) and it follows the standards of the International Agency for Research Cancer (IACR): histopathologic diagnosis (>70%), notification only by death certificate (<20%), ignored age (<10%), nonspecific location (<10%) and mortality/incidence ratio (between 20 and 30%) [14].

Deaths were captured by the national Mortality Information System: “Sistema de Informação sobre Mortalidade”, a database created by DATASUS (SUS Computer Department) for the regular collection of mortality data in the country, based on the death certificate [15]. The quality of this database in Santa Catarina is one of the highest in Brazil based on the following indicators: >90% of the deaths occurring in the state are registered in the system [15,16].

2.3. Statistical analysis

The database created for this analysis was based on the probabilistic record linkage technique, which attempts to link two pieces of information together, using multiple possible non-unique keys [17,18]. For this study, the merging of the data was performed using the software Open*Reclink* [19]. In order to assure correct data pairing, the following variables were used: full name, mother's name, sex, and date of birth. After the linkage, one unique database was created containing all relevant information for the study.

Independent study variables included age (categorized by the registry for each cancer type), race/ethnicity (white, other ethnic groups, missing data), educational level (≥ 9 years of school, ≤ 8 years of school, missing data), marital status (with a partner, without a partner, missing data), and disease extension (in situ, localized, metastatic, missing data).

OS was calculated as the interval of time between the date of cancer diagnosis and the date of death at the end of follow up, that was 60 months. Subjects that did not present an event regarding death until the end of follow-up were considered as censured. All cases that were not found in the Mortality Information System were considered alive and censored at the end of follow up. Database lock was performed on the 31 of December of 2018.

The probability of survival rates was estimated using the Kaplan-Meier method. Comparisons between survival curves, stratified by independent variables were performed using the Log-rank test. Cox proportional hazard model was used to access the effect of the independent variables in overall survival. Post-estimation analysis using the Test of proportional-hazards assumption showed that the model was proportional over time [20]. Analyses were performed using Stata SE 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) This research project respected the ethical principles, based on the Federal Resolution number 466, of the National Health Council and was approved by institutional review board and national ethics committee (CAAE: 53518116.1.0000.0121).

3. Results

During the period of first of January of 2008 until 31 of December of 2012, 1,913 cases of cancer with the three selected typologies were registered by the RCBP at the city of Florianopolis. Of those, 1,857 cases fulfilled the criteria regarding data availability and were included in this analysis (1,270 cases of breast cancer, 480 of cervical cancer and 107 of ovarian cancer).

Breast cancer was more prevalent in women older than 50 years, of white ethnicity, with 9 or more years of school, classified as having a

Table 1
Descriptive and 5-years survival analyses of breast cancer, overall and by stage, Florianópolis, 2008–2017.

Variables	Overall					In situ			Local/regional			Metastatic		
	n (%)	Deaths (%)	*p*-value*	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	p-value†
Age group			<0·001		<0·001			0·264			<0·001			0·002
39 years or less	125 (9·9)	20 (16·0)		84·0 (76·3;89·4)		12 (8·16)	100·0		40 (9·1)	90·9 (77·6;96·5)		25 (9·0)	65·8 (48·5;78·5)	
40 to 49 years	300 (23·6)	33 (1·1·0)		89·0 (84·9;92·1)		35 (23·8)	100·0		109 (24·8)	95·6 (89·8;98·1)		71 (25·6)	74·7 (64·7;82·3)	
50 to 69 years	635 (50·0)	78 (12·3)		87·7 (84·9;90·0)		86 (58·5)	98·9 (92·1;99·8)		239 (54·4)	95·6 (92·2;97·5)		147 (53·1)	72·4 (65·7;78·0)	
70 years or more	209 (16·5)	71 (34·0)		66·0 (84·9;72·0)		14 (9·52)	93·3 (61·3;99·0)		51 (11·6)	73·9 (61·8;82·7)		34 (12·3)	50·8 (38·3;61·9)	
Median age (IRQ)	55 (46;65)					54 (48;63)			55 (46;64)			55 (46;66)		
Ethnic group			0·028		0·370			0·752			0·354			0·515
White	1585 (85·4)	271 (17·1)		83·6 (81·3;85·6)		116 (77·9)	98·3 (93·3;99·6)		430 (90·2)	91·9 (88·9;94·1)		357 (88·6)	69·2 (64·1;73·7)	
Other groups	123 (6·6)	22 (17·9)		85·5 (74·7;91·9)		9 (6·0)	100·0		20 (4·2)	100·0		30 (7·4)	70·0 (50·3;83·1)	
No information	140 (8·0)	13 (8·7)		88·9 (80·8;93·7)		24 (16·1)	100·0		27 (5·7)	88·9 (69·4;96·3)		16 (4·0)	56·3 (29·5;76·2)	
Educational level			<0·001		<0·001			0·479			0·087			0·020
9 years or more	956 (51·5)	121 (12·7)		88·0 (85·4;90·2)		86 (57·7)	97·7 (91;99·4)		280 (58·7)	94·3 (90·8;96·5)		224 (55·6)	74·6 (68·3;79·8)	
8 years or less	623 (33·6)	150 (24·1)		74·8 (70·0;79·0)		29 (19·5)	100·0		116 (24·3)	87·9 (80·5;92·7)		144 (35·7)	61·8 (53·4;69·2)	
No information	278 (15)	35 (12·6)		87·1 (81·4;91·1)		34 (22·8)	100·0		81 (17·0)	90·1 (81·2;94·9)		35 (8·7)	60·0 (42·0;74·0)	
Marital status			<0·001		<0·001			0·360			0·172			0·737
Partnered	848 (45·7)	127 (15·0)		85·3 (82·3;87·9)		74 (49·7)	97·3 (89·6;99·3)		235 (49·3)	94·0 (90·2;96·4)		206 (51·1)	70·4 (63·6;76·1)	
Without partnered	740 (39·9)	152 (20·5)		80·2 (76·3;83·5)		40 (26·9)	100·0		171 (35·9)	88·9 (83·1;92·8)		165 (40·9)	67·3 (59·5;73·9)	
No information	269 (14·5)	27 (10·0)		90·1 (84·7;93·6)		35 (23·5)	100·0		71 (14·9)	93·0 (83·9;97·0)		32 (7·9)	65·6 (46·6;79·3)	
Status														
Censored	1068 (84·1)					147 (98·7)			439 (92·0)			277 (68·7)		
Death	202 (15·9)					2 (1·3)			38 (8·0)			126 (31·3)		
Stage at diagnosis			<0·001		<0·001									
In situ	149 (11·7)	2 (1·3)		98·7 (94·7;99·7)										
Local/regional	477 (37·6)	38 (8·0)		92·0 (89·2;94·1)										
Metastatic	403 (31·7)	126 (31·3)		68·7 (64·0;73·0)										
No information	241 (19·0)	36 (14·9)		85·1 (79·9;89·0)										

S(t): survival rate; * χ^2 test; † Log-rank test.

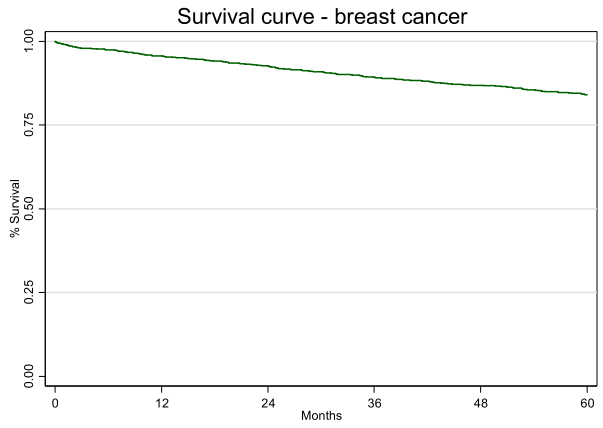
partner and with localized disease. During the follow-up period, there were 202 deaths. The OS was significantly lower in women with age ≥ 70 years, lower educational level (8 years or less of school), without a partner, and with metastatic disease (Table 1 and Fig. 1). When analyzing the registries according to the stage at diagnosis, for *in situ* breast cancer, there were only two related deaths and there were no factors associated with OS. For subjects diagnosed with localized disease, worse survival rates were observed in older women (≥70 years). In the metastatic setting, OS was statistically correlated with age ($p = 0{\cdot}002$) and educational level ($p = 0{\cdot}020$), in the crude and adjusted analyses (Table 1 and Fig. 1).

The cases of cervical cancer are reported in Table 2. It was more frequently diagnosed in women with age ≤ 39 years, of white ethnicity and most of the cases diagnosed as *in situ*. During the follow-up, 53 deaths occurred among women diagnosed with cervical cancer, 0·7% in the cases registered as *in situ*, 18·2% in the localized cases and 45·7% for metastatic disease. The survival curves after cancer diagnosis in the overall population and stratified by stage at diagnosis is shown in Fig. 1.

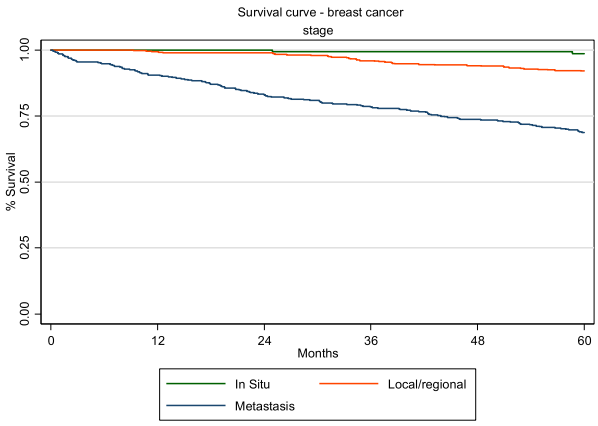
Table 3 details the cases of ovarian cancer. This malignancy was more frequently observed in women of ≤59 years, without a partner and most of the women presented metastatic disease at the moment of diagnosis. During the follow-up, among the subjects diagnosed with ovarian cancer, we observed 51 deaths (47·7%), most frequently in the cases of metastatic disease (57·6%). The survival probability of the subjects classified as having metastatic disease was of 42·4% after 5 years of diagnosis, and it presented a statistically significant association with age (p = 0·005) (Table 3 and Fig. 1).

Table 4 depicts the proportional risks of dying for each one of the selected cancer types (breast, cervical, and ovarian) in general and stratified by the extent of disease (localized vs metastatic). In our analyses, older age and lower educational level were statistically significant worse prognostic factors for breast cancer: HR 2·53; 95% CI 1·75–3·67 and HR 1·59; 95% CI 1·13–2·25, respectively. When analyzing stage at diagnosis, having the diagnosis of metastatic disease increased in 4.49 the risk of dying independently of other factors (HR 4·46; 95% CI 3·09–6·44).

For cervical cancer, having 40 years or more and the extension of disease were the main factors related to the risk of death (Table 4). The independent variables associated with OS after ovarian cancer diagnosis were



a



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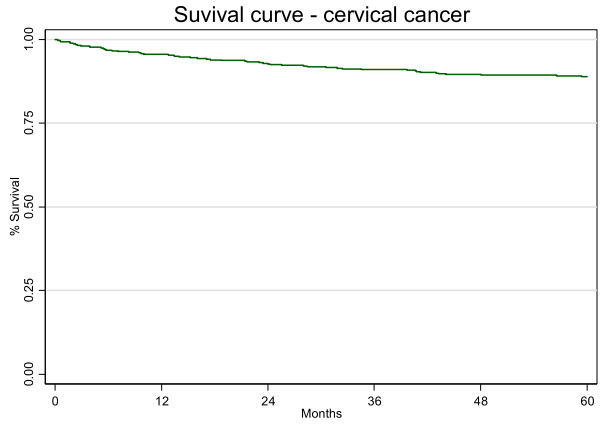

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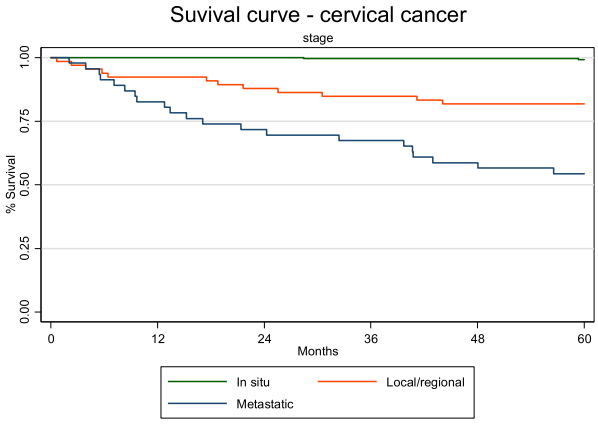

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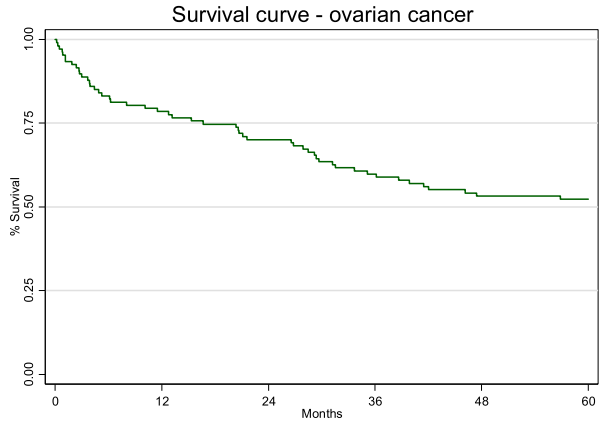

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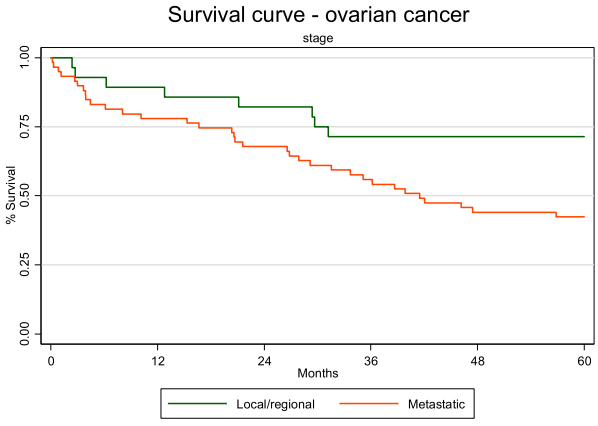

f

Fig. 1. Survival rates for breast, cervical and ovarian cancer, overall (a, b, c, respectively) and by stage (d, e, f, respectively), Florianópolis, 2008–2017. S(t): survival rate; * χ^2 test; † Log-rank test.

age (≥60 years: HR 2·18; 95% CI 1·09–4·35), being classified as without a partner (HR 2·28; 95% CI 1·17–4·44) and the presence of metastatic disease (HR 2·93; 95% CI 1·24–6·94) (Table 4).

4. Discussion

In the present manuscript, we describe the registered cases of breast, cervical, and ovarian cancer in the city of Florianópolis, the capital of the Santa Catarina state, in the south of Brazil during the period of 2008–2017. We also report OS rates for the three cancer types and factors associated with OS. It is already well established in the literature the fact that both geographic and demographic factors may influence the incidence and prevalence of certain types of cancer (e.g. genetic and behavioral risk factors, adherence to screening policies, etc.) [21–23]. Also, access to diagnosis and treatment might be different in each geographic region [5,24,25]. All these factors can play an important role in the clinical outcomes of cancer subjects after the diagnosis of a malignancy. Brazil is the largest country in Latin America and the fifth largest country in the world in terms of population, it is divided into five regions which present important differences regarding economic and social development as well as demographic

Table 2
Descriptive and 5-years survival analyses of cervical cancer, overall and by stage, Florianópolis, 2008–2017.

Variables	Overall					In situ			Local/regional			Metastatic		
	n (%)	Deaths (%)	p-value*	S(t) (95%CI)	P-value†	n (%)	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	P-value†	n (%)	S(t) (95%CI)	p-value†
Age group			<0·001		<0·001			0·021			0·103			0·057
39 years or less	270 (56·3)	8 (3·0)		97·0 (94·2;98·5)		204 (72·6)	100·0		66 (37·9)	92·0 (71·6;97·9)		13 (28·3)	76·9 (44·2;91·9)	
40 years or more	210 (43·8)	45 (21·4)		78·6 (72·4;83·5)		77 (27·4)	97·4 (90·0;99·3)		41 (62·1)	75·6 (59·4;86·1)		13 (71·7)	45·5 (28·2;61·2)	
Median age (IRQ)	37 (30;48)					33 (27;41)			44·5 (36;55)			46·5 (39;58)		
Ethnic group			0·018		0·018			0·134			0·349			0·040
White	385 (80·2)	42 (10·9)		89·1 (85·5;91·8)		222 (79)	99·6 (96·9;99·9)		57 (86·4)	79·0 (65·9;87·5)		37 (80·4)	56·8 (39·4;70·8)	
Other groups	49 (10·2)	10 (20·4)		79·6 (65·4;88·5)		26 (9·3)	96·2 (75·7;99·5)		6 (9·1)	100·0		6 (13·0)	16·7 (0·80;51·7)	
No information	46 (9·6)	1 (2·2)		97·8 (85·6;99·7)		33 (11·7)	100·0		3 (4·6)	100·0		3 (6·5)	100·0	
Educational level			0·021		0·020			0·240			0·329			0·383
9 years or more	193 (40·2)	14 (7·3)		92·8 (88·1;95·6)		123 (43·8)	100·0		26 (39·4)	88·5 (68·4;96·1)		14 (30·4)	64·3 (34·3;83·3)	
8 years or less	213 (44·4)	33 (15·5)		84·5 (78·9;88·7)		116 (41·3)	98·3 (93·3;99·6)		27 (40·9)	74·1 (53·2;86·7)		26 (56·5)	46·2 (26·6;63·6)	
No information	74 (15·4)	6 (8·1)		91·9 (82·8;96·3)		42 (15·0)	100·0		13 (19·7)	84·6 (51·2;95·9)		6 (13·0)	66·7 (19·5;90·4)	
Marital status			0·400		0·382			0·317			0·798			0·614
Partnered	186 (38·8)	19 (10·2)		89·8 (84·5;93·4)		104 (37·0)	100·0		22 (33·3)	86·4 (78·6;95·4)		22 (47·8)	59·1 (36·1;76·2)	
Without partnered	216 (45·0)	28 (13·0)		87 (81·8;90·9)		131 (46·6)	98·5 (94;99·6)		30 (45·5)	80·0 (60·8;90·5)		19 (41·3)	47·4 (24·4;67·3)	
No information	78 (16·3)	6 (7·7)		92·3 (83·7;96·5)		46 (16·4)	100·0		14 (21·2)	78·6 (47·3;92·5)		5 (10·9)	60·0 (12·6;88·2)	
Status														
Censored	427 (89·0)					279 (99·3)			54 (81·8)			25 (54·4)		
Death	53 (11·0)					2 (0·7)			12 (18·2)			21 (45·7)		
Stage at diagnosis			<0·001		<0·001									
In situ	281 (58·5)	2 (0·7)		99·3 (97·2;99·8)										
Local/regional	66 (13·8)	12 (18·2)		81·8 (70·2;89·2)										
Metastatic	46 (9·6)	21 (45·7)		54·4 (39;67·4)										
No information	87 (18·1)	18 (20·7)		79·3 (69·2;86·4)										

S(t): survival rate; * χ^2 test; † Log-rank test.

distribution [26] For these reasons, the knowledge of local data regarding cancer prevalence and mortality is paramount; in order to acquire a closer look into the real situation in the country, build future preventive and educational strategies, screening policies, and optimization of the access to diagnosis and treatment.

Genetic factors and family history should be considered as malignancies in this study. However, the biological mechanisms do not show much similarity between them. Age is one of the most relevant factors for breast and ovarian cancer, as mutations in genes such as BRCA1 and BRCA2 increase the risk factor for both [27–29]. On the other hand, while cervical cancer has an increased risk factor with the increased the duration of the use of oral contraceptive [30], the same reason appears as a protective factor for ovarian cancer [31].

We recognize that, in general, stage at diagnosis is the most important factor associated with OS in cancer subjects and this was highly striking in the overall survival analyses of our study. Regarding the three female malignancies analyzed in this study, we observed that for breast cancer, only half of the cases were diagnosed in early stage (in situ + local/regional: 49·3%), highlighting an important part of the population being diagnosed with metastatic disease (31·7%). For cervical cancer, around 10% of the cases presented metastatic disease at the moment of diagnosis. These findings are important since both breast [32] and cervical [33] cancer are contemplated by the national screening policies, and they call attention for the need of better educational strategies, access and compliance with screening programs. The low proportion of women diagnosed with breast cancer through screening programs in Brazil has been reported previously [34], reinforcing the results of our study. For ovarian cancer, we observed metastatic disease at diagnosis for 55% of the cases, this finding is not unexpected, given the lack of an effective screening tool for this malignancy worldwide [35]. The risk of death from the metastatic stage remains significant for all three malignancies, even when the cases registered as in situ or no information were excluded in our analysis (Table 4). It can be noted that the other variables in the analysis models suffered small changes in the hazard ratio. This reinforces the need to carry out early diagnosis to improve the survival of women.

Access to cancer treatment is still a challenge in Brazil, [25,36] and because of this, the federal government decreed in 2012, the "Law of 60 days" (Federal Law number 12·732/12). This law came into effect in 2013 and regulates the maximum period that a subject with cancer may wait before initiating its treatment, an attempt to reduce the interval of time between diagnosis and treatment as well as the consequences of late-stage diagnosis. Because of possible misinterpretations of the law, in March 2014, the Ministry of Health amended an Administrative Order MS/GM 876/13, determining that the count of the maximum period of 60 days should begin from the signature of the pathological report until first treatment received.

Table 3
Descriptive and 5-years survival analyses of Ovarian cancer, overall and by stage, Florianópolis, 2008–2017.

Variables	Overall					Local/regional			Metastatic		
	n (%)	Deaths (%)	p-value*	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	p-value†	n (%)	S(t) (95%CI)	p-value†
Age group			0·003		0·001			0·948			0·005
59 years or less	70 (65·4)	26 (37·1)		62·9 (50·4;73·0)		21 (75·0)	71·4 (47·2;86·0)		39 (66·1)	53·9 (37·2;67·9)	
60 years or more	37 (34·6)	25 (67·6)		32·4 (18·2;47·5)		7 (25·0)	71·4 (25·8;92·0)		20 (33·9)	20·0 (6·2;39·3)	
Median age (IRQ)	61 (54;72)	69 (64;77)			<0·001	60 (54;72)			65 (52;72)		
Ethnic group			0·604		0·662			0·397			0·247
White	98 (91·6)	48 (49·0)		51·0 (40·8;60·4)		26 (92·9)	69·2 (47·8;83·3)		54 (91·5)	42·6 (29·3;55·2)	
Other groups	5 (4·7)	2 (40·0)		60·0 (12·6;88·2)		;	;		4 (6·8)	50·0 (5·8;84·5)	
No information	4 (3·7)	1 (25·0)		75·0 (12·8;96·1)		2 (7·1)	100·0		1 (1·7)	0	
Educational level			0·521		0·497			0·660			0·977
9 years or more	47 (43·9)	21 (44·7)		55·3 (40·1;68·1)		14 (50·0)	78·6 (47·3;92·5)		28 (47·5)	42·9 (24·6;60·0)	
8 years or less	49 (45·8)	26 (53·1)		46·9 (32·6;60·0)		8 (28·6)	62·5 (22·9;86·1)		29 (49·2)	41·4 (23·7;58·3)	
No information	11 (10·3)	4 (36·4)		63·6 (29·7;84·5)		6 (21·4)	66·7 (19·5;90·4)		2 (3·4)	50 (0·60;91·0)	
Marital status			0·108		0·053			0·266			0·211
Partnered	43 (40·2)	17 (39·5)		60·5 (44·3;73·3)		8 (28·6)	87·5 (38·7;98·1)		28 (47·5)	50·0 (30·6;66·6)	
Without partnered	54 (50·5)	31 (57·4)		42·6 (29·3;55·2)		14 (50·0)	57·1 (28·4;78·0)		29 (49·2)	34·5 (18·2;51·5)	
No information	10 (9·4)	3 (30·0)		70·0 (32·9;89·2)		6 (21·4)	83·3 (27·3;97·5)		2 (3·4)	50·0 (0·60;91·0)	
Status											
Censored	56 (52·3)					20 (71·4)			25 (42·4)		
Death	51 (47·7)					8 (28·6)			34 (57·6)		
Stage at diagnosis					0·077						
Local/regional	28 (26·2)	8 (28·6)		71·4 (50·9;84·6)							
Metastatic	59 (55·1)	34 (57·6)		42·4 (29·7;54·5)							
No information	20 (18·7)	9 (45·0)		55·0 (31·3;73·5)							

S(t): survival rate; * χ^2 test; † Log-rank test.

Aiming to increase the proportion of diagnosis at early stages, recently, in October 2019, another law was decreed (Federal Law number 13·896/2019), in order to guarantee that patients with a suspicion of cancer have prompt access to a biopsy procedure within 30 days. These political actions may change the prevalence of late-stage diagnosis in the country, and this should be further assessed after appropriated follow-up.

When analyzing other factors associated with overall survival besides stage at diagnosis, for breast cancer, we observed higher mortality in women older than 70 and with lower educational level. Due to increasing life expectancy worldwide and ageing of the population, the prevalence of breast cancer in geriatric patients is increasing. A recent Dutch study of a large cohort of breast cancer subjects followed by 10 years has also shown higher mortality associated with older age that was not outweighed by a substantially higher other cause mortality [37]. It is already reported that older patients might receive less aggressive treatment when compared to younger patients with breast cancer [38–41]. Currently, better assessment of the prognostic factors for other cause mortality along with prognostic factors for breast cancer mortality should be carefully performed in order to improve the balance between undertreatment and overtreatment in this population [42,43]. Regarding the higher mortality in women with lower educational levels, this can be associated with lower knowledge and/or compliance to screening policies, disparities, and difficulties regarding access to diagnosis and treatment as already shown in Brazil [25] and globally [44]. A major effort should be made to improve access to diagnosis along with educational policies highlighting the importance of mammography screening and early seeking for appropriate care when an alteration is noticed during breast palpation for this at risk population. Interestingly, there was no difference in overall survival regarding ethnicity, which can reflect the low proportion of patients of other ethnic groups present in this analysis.

Regarding cervical cancer, attention should be given for the fact that about 10% of the cases were diagnosed with metastatic disease. This is alarming because it is a disease that can easily be prevented by early detection of pre-malignant cervical alterations. Although the south of Brazil is recognized to have a cervical cancer screening program of better quality and performance, on a national level, the cervical cancer screening program is still far from being considered efficient [45,46]. More than that, the prognosis for patients diagnosed with metastatic disease is poor with high mortality rates and it is probably related to the lack of effective systemic therapies in this scenario [47]It is estimated that annually, 8414 women die from cervical cancer in Brazil and 18,503 cases are diagnosed, classifying cervical cancer as the 3rd most frequent cancer among Brazilian women [7,8]. HPV vaccination (quadrivalent) is available in the National Immunization Program in Brazil since 2014 for girls of 9 to 13 years old and, since 2017, it was extended to boys of 11 to 13 years old. Hopefully, this action might change the current scenario, and further analysis of cervical cancer incidence and mortality in Brazil must be performed after adequate follow up. It is of our concern, however, that the coverage of HPV vaccination is still low in the country and Latin America [48].

Table 4
Unadjusted and adjusted proportional hazard risk of death for breast cancer, cervical and ovarian, overall and according to local/regional and metastatic staging, Florianópolis, 2008–2017.

Variables	Overall		Local/regional and Metastatic	
	HR unadjusted (95%CI)	HR adjusted (95%CI)	HR unadjusted* (95%CI)	HR adjusted* (95%CI)
Breast cancer				
Age group				
39 years or less	1·42 (0·83;2·41)	1·39 (0·84;2·29)	1·42 (0·83;2·41)	1·45 (0·84;2·49)
40 to 49 years	0·94 (0·61;1·45)	0·95 (0·63;1·43)	0 93 (0·60;1·45)	1·01 (0·64;1·56)
50 to 69 years	1·00	1·00	1·00	1·00
70 years or more	2·89 (2·01;4·16)	2·66 (1·90;3·70)	2 88 (2 00;4·16)	2·53 (1·75;3·67)
Ethnic group				
White	1·00	1·00	1·00	1·00
Other groups	0·87 (0·46;1·64)	0·72 (0·38;1·38)	0·97 (0·50;1·91)	0·75 (0·38;1·49)
No information	0·66 (0·36;1·21)	1·03 (0·44;2·38)	1·30 (0·69;2·47)	1·58 (0·67;3·97)
Educational level				
9 years or more	1·00	1·00	1·00	1·00
8 years or less	2·29 (1·7;3·07)	1·76 (1·30;2·41)	1·97 (1·42;2·73)	1·59 (1·13;2·25)
No information	1·07 (0·69;1·67)	2·15 (1·12;4·14)	1·32 (0·82;2·12)	2·01 (1·01;3·97)
Marital status				
Partnered	1·00	1·00	1·00	1·00
Without partnered	1·39 (1·04;1·85)	1·17 (0·87;1·58)	1·31 (0·95;1·81)	1·17 (0·84;1·63)
No information	0·65 (0·39;1·08)	0·46 (0·20;1·05)	0·89 (0·52;1·53)	0·52 (0·22;1·24)
Stage at diagnosis				
In situ	1·00	1·00		
Local/regional	6·09 (1·47;2·52)	5·28 (1·27;21·93)	1·00	1·00
Metastatic	27·95 (6·91;112·98)	23·10 (5·70;93·66)	4·62 (3·21;6·64)	4·46 (3·09;6·44)
No information	12·22 (2·94;50·74)	9·49 (2·28;39·50)		
Cervical cancer				
Age group				
39 years or less	1·00	1·00	1·00	1·00
40 years or more	8·04 (3·79;17·06)	3·15 (1·42;6·97)	3·42 (1·32;8·85)	3·20 (1·16;8·79)
Ethnic group				
White	1·00	1·00	1·00	1·00
Other groups	1·96 (0·98;3·91)	1·75 (0·86;3·57)	1·51 (0·58;3·91)	1·32 (0·49;3·59)
No information	0·19 (0·03;1·39)	0·30 (0·04;2·24)		
Educational level				
9 years or more	1·00	1·00	1·00	1·00
8 years or less	2·25 (1·20;4·20)	1·28 (0·66;2·46)	2·46 (1·09;5·56)	1·69 (0·72;3·94)
No information	1·14 (0·44;2·96)	0·72 (0·16;3·27)	1·29 (0·39;4·29)	0·48 (0·09;2·70)
Marital status				
Partnered	1·00	1·00	1·00	1·00
Without partnered	1·3 (0·73;2·33)	1·65 (0·91;2·99)	1·30 (0·61;2·74)	1·65 (0·77;3·53)
No information	0·74 (0·30;1·86)	1·84 (0·41;8·18)	1·10 (0·39;3·13)	3·57 (0·73;17·44)
Stage at diagnosis				
In situ	1·00	1·00		
Local/regional	28·25 (6·32;126·25)	18·82 (4·13;85·78)	1·00	1·00
Metastatic	82·18 (19·25;350·75)	58·46 (13·41;254·92)	3·05 (1·5;6·2)	3·02 (1·43;6·36)
No information	33·14 (7·69;142·86)	21·72 (4·95;95·42)		
Ovarian cancer				
Age group				
59 years or less	1·00	1·00	1·00	1·00
60 years or more	2·56 (1·48;4·45)	2·81 (1·54;5·11)	2·15 (1·17;3·98)	2·18 (1·09;4·35)
Ethnic group				
White	1·00	1·00	1·00	1·00
Other groups	0·74 (0·18;3·03)	0·86 (0·20;3·66)	1·01 (0·24;4·16)	0·86 (0·20;3·72)
No information	0·45 (0·06;3·25)	0·73 (0·06;8·42)	0·66 (0·09;4·81)	2·20 (0·23;2·14)
Educational level				
9 year or more	1·00	1·00	1·00	1·00
8 year or less	1·34 (0·76;2·39)	0·97 (0·52;1·79)	1·33 (0·71;2·49)	0·96 (0·49;1·90)
No information	0·86 (0·29;2·49)	1·50 (0·38;5·95)	0·85 (0·25;2·88)	5·45 (0·67;44·48)
Marital status				
Partnered	1·00	1·00	1·00	1·00
Without partnered	1·93 (1·07;3·49)	2·42 (1·30;4·50)	1·86 (0·98;3·53)	2·28 (1·17;4·44)
No information	0·86 (0·25;2·95)	1·06 (0·19;5·84)	0·64 (0·15;2·78)	0·22 (0·02;2·43)
Stage at diagnosis				
Local/regional	1·00	1·00	1·00	1·00
Metastatic	2·38 (1·10;5·14)	2·62 (1·15;5·96)	2·41 (1·11;5·21)	2·93 (1·24;6·94)
No information	2·00 (0·77;5·19)	2·10 (0·77;5·76)		

HR: Proportional hazard survival rate;

* Excluded cases recorded as *in situ* and missing data about stage.

In relation to ovarian cancer, we observed higher mortality in older patients with a marital status classified as without a partner, which might reflect the treatment burden related to an extensive surgery (debulking) [49], followed must of the times by adjuvant chemotherapy [50], which may be more difficult to perform in older subjects due to decreased physiological reserve or in patients with social difficulties experienced by the lack of optimal family support [51]. Interestingly, in our cohort, 65.4% of the subjects diagnosed ovarian cancer with an age lower than 60 years, which is uncommon and might be related to a higher prevalence of genetic mutations in the south of Brazil that could confer major risk of ovarian cancer in younger age such as BRCA1 and BRCA2 [52] and this should be further evaluated.

As for the risk of death, the findings are like other studies [53–55]. Metastatic cancer was the common risk factor for breast, ovarian and cervical cancer. This finding is related to the aggressiveness of the tumor at the time of diagnosis and reiterates the need for mammographic screening and preventive exams, as other studies have already pointed out [33,56]. Another factor that increased the risk of death for breast cancer and ovarian cancer was advanced age. Although it is the most prevalent age group, due to the hormonal relationship, especially in breast cancer, the diagnosis at an advanced age may reflect in cases that were discovered at an advanced stage [31,37]. In turn, low education was associated with death, specifically from breast cancer and agrees with other studies that show an inverse relationship between better prognosis and better socioeconomic status [57]. Living without a partner, although statistically significant only for ovarian cancer, increased the risk of death for all cancer sites in both crude and adjusted analyses. It should be noted that the absence of social support is related to several negative health outcomes [51,58].

Several important limitations of our work should be acknowledged since the data was retrieved from the population-based cancer registry. First, for breast cancer, we do not have data regarding breast cancer subtypes (Luminal, HER2 positive and triple negative) and for all cancers, the tumor characteristics were not available (grade, size, hormone receptors). Second, the cancer registry does not provide the information regarding which type of treatment was delivered (surgery, chemotherapy, endocrine therapy and or target therapy). Third, we have a percentage of data classified as missing data (reported in the results) that should also be considered. Fourth, the data of death, we had not accessed the cause of death. Therefore, it is not possible to claim that malignancy was the primary cause of death. However, two of these three malignancies are the main causes of death cancer-related in women in Brazil. In addition, some women may have the death record in other cities and, therefore, we have not had access to this record and have been censored. It is known that cases of migration in Santa Catarina are higher to Florianópolis from other cities, especially for those who need access to health services. In this way, our loss may have occurred but in very few cases. The coverage of Mortality Information System in Santa Catarina is very high. Then for women who died and were registered as residents in Florianópolis, regardless of city of death in the Santa Catarina, we had access to this register. Importantly, we recognize that there is a notable gap between private and public health system in Brazil, and this was already shown to influence overall survival in cancer patients [59]. In this database, we could not retrieve the information regarding in which type of institution the patient actually received her treatment. Finally, stage at diagnosis was classified in the database as: in situ, local/regional and metastatic with no distinction between stage I, II and stage III.

5. Conclusions

In conclusion, metastatic disease was the main risk factor for death and is statistically correlated with overall survival. The results should be used to improve the screening and treatment of these neoplasms.

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Data availability statement

The data can be accessed from http://www.pmf.sc.gov.br/sites/ses/index.php?cms=capps&menu=0.

Credit authorship contribution statement

Ione Jayce Ceola Schneider: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision. **Tauana Prestes Schmidt:** Conceptualization, Formal analysis, Writing – original draft. **Ana Maria Martins dos Santos:** Conceptualization, Writing – original draft. **Vanessa Pereira Correa:** Conceptualization, Writing – original draft. **Leandro Pereira Garcia:** Conceptualization, Writing – original draft. **Cesar de Oliveira:** Conceptualization, Writing – original draft. **Maria Alice Franzoi:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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