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Research Article

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Prevalence of Comorbidity and Impact On Survival in Women with Lung, Breast and Cervical Cancer

Madelaine Sarria Castro[1*], Orlando Parellada Joa[1], Shivani Samlall[2], Juan Jesus Lence Anta[1], Priscila Torres Barbie[1], Solveing Rousseaux Lamothe[1], Eldier Rodriguez Herrera[1], Luis Eduardo Martin Rodriguez[1] and Juan Mario Silveira Pablos[1]

[1]*National Institute of Oncology & Radiobiology, Havana, Cuba.*
[2]*Ministry of Health, Guyana*

[*]Corresponding author
Dr. Madelaine Sarria Castro, National Institute of Oncology & Radiobiology, Havana, Cuba. https://orcid.org/0000-0002-1798-5259.

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Abstract

Background: *The relationship between cancer incidence and mortality, and the resulting comorbidities of the elderly reflects current demographics trends*

Objective: *The study aimed to investigate the prevalence of comorbidities and their impact on survival of women diagnosed with: NSCLC, breast and cervical cancer, at the National Institute of Oncology and Radiobiology in Havana, Cuba.*

Methods: *Data were collected retrospectively from patients' clinical charts. The study involved 138 NSCLC, 1 598 breast cancer and 631 cervical cancer registered during 2007-2011. Comorbidity was classified according to the ICD-10 diagnosis code and was measured using Charlson Comorbidity Index. Associations between comorbidities and mortality by all causes were analyzed in Cox regression models.*

Results: *The highest prevalence of comorbidities was in NSCLC (68.8%). The 3-year OS for NSCLC were 44.5% (95%CI: 29.3–59.7) and 23.3% (95%CI: 13.2–33.4) in patients without and with comorbidity, respectively (p=.01). The 5-year OS for breast cancer in the no comorbidity group was 91.4% (95%CI: 89.6–91.6) compared with 37.2% (95%CI: 32.7-59.9) in the comorbodity group (p=.00). The 5-year OS for cervical cancer in patients without diseases was (55.8% [95%CI: 50.7 – 59.9]), in women with comorbidity (27.7% [95%CI: 15.9–29.5]) (p =.00). Comorbidity was an independent predictor for overall survival: NSCL (HR Adjusted: 2.28 [95%CI: 1.43 - 3.65], p=.000), breast cancer (HR Adjusted: 3.16 [95%CI: 2.69–3.71], p=.000), cervical cancer (HR Adjusted: 1.38 [95%CI: 1.10–1.86], p=.032)*

Conclusions: *Comorbidity is an important prognostic factor for women diagnosed with lung, breast and cervical cancer.*

Keywords: Lung cancer, Cervical cancer, Breast cancer, Charlson Comorbidity Index, Survival

Abbreviations: NSCLC, non-small-cell lung cancer; COPD, Chronic Obstructive Pulmonary Disease; CCI, Charlson comorbidity index, OS, overall survival; HR, hazard ratio; CI, confidence interval

Introduction

Cancer is a global health issue that imposes a huge economic burden with its associated care. It is estimated that each year in Latin America and the Caribbean there are approximately 900 000 new cases, 542 000 deaths, and more than two million people that are living with the disease. Projections for the coming decades estimate that the number of female cancer cases from Latin America will double and mortality will increase by more than 40%. Currently, the highest incidence rates of cancer in women are breast and colorectal followed by cervical and lung cancer.

In Cuba, since 1958, cancer is the second cause of death in women, and has maintained an elevated incidence. Annually, more than 20 000 new cases are diagnosed in the country. Cancer of the breast, lung, and cervix represent approximately 50% of all new cases diagnosed each year. Female mortality rate reflects a similar trend; approximately 50% of deaths are identified in these cancer locations [1].

The relationship between cancer incidence and mortality, and the resulting comorbidities of the elderly reflects current demographics trends. Population aging is undoubtedly one of the most transformative social phenomena of the century. All regions of the world are experiencing population aging, although the rates of increase differ across regions. Currently, large sections of populations are over 60 years, thus presenting important challenges to healthcare systems. Although Latin American countries are still younger than most advanced economies, population aging is expected to accelerate. This is because it is an emerging region with substantial socio-political changes in the last decade. In Cuba, since 2017, the percentage of older adults have increased by 20.1% and in the last decade, life expectancy of women was 80 years [1].

These changes in the demographic and socioeconomic profiles have caused the expected effects in the epidemiological profiles. Chronic diseases, specifically cancer, highlights cause of mortality. The binomial between age and comorbidity factors is essential for the analysis of cancer mortality and other indicators related to resources, hospital stay of patients and medical care costs [2, 3].

Since the beginning of the 1990s, there have been "warning calls" from the medical literature regarding the treatment of the elderly with cancer due to the multiple pathologies that are common in this group; for which numerous reasons have been adduced to justify the poor therapeutic results and their exemption from clinical trials. The risk of death by cancer is higher in patients who suffer from chronic concomitant diseases, and which occurs independently of clinical tumor stage and the therapeutic management.

Survival analysis studies and cancer mortality studies are frequent in the Hispanic medical literature. However, only a few of these studies analyze the impact of associated comorbidities as a prognostic factor. Clinicians often intuitively underestimate this parameter. Similarly, this knowledge framework has vital importance for health managers and administrators to help in resource planning, due to the additional costs of treatment and follow-up of oncological patients.

The objective of this study is to determine the prevalence of comorbidities and their impact on survival of women with lung, breast and cervical cancer at the National Institute of Oncology and Radiobiology in Havana, between 2007 and 2011. This entity is the referral center for cancer patients in Cuba and guarantees the care of more than 20% of the population diagnosed with cancer.

Patient and Methods

Study design and data source. The present study is based on the analysis of data collected retrospectively in women diagnosed with primary tumors: non-small-cell lung cancer (NSCLC), breast and cervical cancer, at the National Institute of Oncology and Radiobiology in Havana, Cuba between January 1st, 2007 and December 30th, 2011. Women with multiple cancers, metastatic diseases and those with missing data were excluded from the study.

A total of 2 367 women were studied, 138 NSCLC, 1 598 breast cancer and 631 cervical cancer diagnosed during five years of study. Follow-up period ranged from 0 to 144 months (median 57.5 months).

Clinical and epidemiological data were collected from patients' clinical charts. Based on the topography of the primary tumor, the following data were gathered: clinical and histological variables of the tumor, therapeutic management (protocolized treatment was established as first-line, and treatment recommendations were based on NCCN (National Comprehensive Clinical Network; NCCN 2019), and those of the National Institute of Oncology and Radiobiology.

Classification of comorbidity. Comorbidities were defined as a set of diseases concomitant to the disease under study, where, each of the diagnoses was based on internationally established and recognized criteria. The diagnosis of comorbidity must be made before the cancer diagnosis, namely, the personal pathological history must have at least 1 year of evolution. Comorbidity was classified, using the hospital events data registered at patients' clinical charts, according to the ICD-10 diagnosis code. A widely known measure of comorbidity was used. The Charlson Comorbidity Index[2] (CCI) covers 19 selected conditions scored by degree of severity. Since cancer was the disease of interest in this study, lung cancer and metastatic tumor codes were excluded as clinical conditions based on the CCI. The occurrence of comorbidities was assessed from one year prior to the date of cancer diagnosis. The CCI score per patient was calculated as the sum of the weighted scores of all the comorbid conditions. Subsequently, they were categorized as: no comorbidity (CCI =0), low to moderate comorbidity (CCI, 1–3), and severe comorbidity (CCI ≥4). The study was approved by the Research Ethic Committee of the National Institute of Oncology and Radiobiology, Havana, Cuba.

Statistical Analysis

Descriptive statistics were used to present the frequency distribution of the baseline study characteristics as numbers and percentages or as the mean ± standard deviation. Kaplan-Meier survival curves were developed, and a log-rank test was used for the comparison of survival functions. Cox proportional hazard models were used to identify the prognostic factors of survival. Statistically significant variables in the univariate Cox Regresion analysis were included in a multivariate analysis. Multivariate Cox regression models were used to estimate hazard ratios (HRs) which were adjusted for selected comorbidities. 95% confidence intervals (CIs) were calculated for the HRs with the Wald test of the Cox regression parameter. $p<.05$ was considered statistically significant. In Cuba, there are no antecedents of published research that uses comorbidity measures (CCI or any other) to assess the role of comorbidities on cancer survival.

Results

Demographic and clinical-pathologic characteristics of the patients are summarized in Table 1. The mean age of these women

exceeded the fifth decade of life for all anatomic locations (lung, breast and cervix). The oldest women were those diagnosed with NSCLC (Mean age, 60.5 years; SE ± 0.8). Regarding performance status, 58.9% of the women with lung cancer were classified as level 1 (symptomatic patients, ambulatory but with restriction of vigorous physical activities, able to do light work of a sedentary nature); and this corresponds with localized and locally advanced (regional) disease. Physical and functional deterioration was only observed in 1.3% of the patients, and this was consistent with patients with metastatic disease. In the case of breast cancer, 45.3% of women were classified as level 0 (patients that were capable of carrying out unrestricted physical activity); consistent with the high percentage of cases with localized clinical stages. The most representative group of women with cervical cancer were classified as functional status scale 1 (44.5%).

Table 1: Descriptive statistics of women with NSCLC, breast and cervical cancer diagnosed between 2007 and 2011.

Characteristics	NSCLC N=138		Breast N=1598		Cervical N=631	
	No.	%	No.	%	No.	%
Age (years)						
<50	15	10.9	505	31.6	274	43.4
50 – 64	72	52.2	540	33,8	220	34.9
65 – 74	40	29.0	352	22.0	103	16.3
≥ 75	11	8.0	201	12.6	34	5.4
Performance Status						
0	25	18.0	723	45.3	236	31.4
1	81	58.9	627	39.2	281	44.5
2	20	14.1	166	10.4	74	11.7
3	10	7.7	68	4.2	33	5.3
4	2	1.3	14	0.9	7	1.1
Tumor histology (NSCLC)						
Squamous cell carcinoma	75	54.3	NA		NA	
Adenocarcinoma	53	38.4	NA		NA	
Small-cell carcinoma	4	2.9	NA		NA	
Other	6	4.3	NA		NA	
Tumor histology (Breast)						
Ductal carcinoma	NA		1321	82,7	NA	
Other	NA		277	17,3	NA	
Tumor histology (Cervical)						
Squamous cell carcinoma	NA		NA		575	91,2
Adenocarcinoma	NA		NA		33	5,2
Adenosquamous carcinoma	NA		NA		23	3,6
Clinical Stage						
Local	44	31,9	709	44,4	99	15,7
Regional	39	28,3	788	49,3	516	81,8
Distant	55	39,9	101	6,3	16	2,5
Therapeutic Management						
Protocolized treatment	103	74,6	1228	76,8	578	91,6
Other therapies	22	15,4	301	18,8	47	7,4
Palliative Care	13	9,4	69	4,3	6	1,0

Abbreviations: NA, not applicable

Treatments were categorized according to what is established by the NCCN guidelines and those of the National Institute of Oncology and Radiobiology. The majority of patients received their first line of oncology specific treatment. The percentage of patients that received their treatment as per protocol was more than 70% for all cancer sites. However, there was greater adherence to treatment protocols in patients diagnosed with cervical cancer (91.6%).

Table 2 indicates the prevalence of comorbidities in each cancer studied. The highest frequency was observed in women with NSCLC (68.8%). Breast and cervical cancers had a similar percentage of comorbidity distribution, while the majority of women had no comorbidities in both (breast: 71.6%; cervix: 73.9%). The proportion of women with moderate comorbidity barely reached a quarter of the total number of women studied (breast: 25.7%; cervix: 24.7%).

Table 2: Charlson comorbidity scores: Category and Prevalence for Clinical disorders in NSCLC, breast and cervical cancer.

Charlson Comorbidity Index (CCI) Categories and scores		NSCLC N=138		Breast N=1598		Cervical N=631	
		No.	%	No.	%	No.	%
Presence of comorbidity							
Yes		95	68.8	454	28.4	165	26.1
No		43	31.2	1144	71.6	466	73.9
Levels of comorbidity (CCI)							
0		43	31.2	1144	71.6	466	73.9
1 – 3		81	58.7	411	25.7	156	24.7
≥4		14	10.1	43	2.7	9	1.4
CCI scores[a]	**Comorbidities**						
1	Myocardial infarction	3	2.2	11	0.7	2	0.3
	Congestive heart failure	15	10.9	50	3.1	13	2.1
	Peripheral vascular disease	13	9.4	126	77.9	64	10.1
	Cerebrovascular disease	5	3.6	33	2.1	29	4.6
	Dementia	0	0.0	0	0.0	1	0.2
	Chronic Obstructive Pulmonary Disease (COPD)	49	35.5	26	1.6	16	2.5
	Connective tissue disease	11	8.0	24	1.5	16	2.5
	Ulcer disease	7	11.9	51	3.2	23	3.6
	Mild liver disease	6	4.3	14	0.9	3	0.5
	Diabetes mellitus	20	14.5	185	11.6	90	14.3
2	Hemiplegia	0	0.0	0	0.0	0	0.0
	Moderate or severe renal disease	8	5.8	33	2.1	36	5.7
	Diabetes mellitus with end-organ damage	17	12.3	78	4.9	14	2.2
3	Moderate or severe liver disease	3	2.2	9	0.6	4	0.6
6	AIDS	2	1.4	0	0.0	0	0.0

[a] Scores assigned for each condition that a patient has.

The most prevalent comorbid illness was diabetes mellitus. In women with lung cancer, chronic obstructive pulmonary disease (COPD) was the most frequent disease (35.5%), followed by diabetes mellitus without chronic complications (14.5%) and diabetes mellitus with chronic complications (12.3%). In breast cancer, the most prevalent disorders were: diabetes mellitus without chronic complications (11.6%), peripheral vascular disease (7.9%) and diabetes mellitus with chronic complications (4.9%). In patients with cervical cancer: diabetes mellitus without chronic complications (14.5%), peripheral vascular disease (10.1%) and moderate or severe renal disease (5.7%).

The comorbidity levels (CCI) associated with age groups according to cancer location are provided in Figure 1. The percentage of patients with comorbidities increased markedly with advanced age, in all the studied. In NSCLC, there was an increase from 40%

for women aged <50 years to 100% for women aged ≥75 years. This increase was also observed in breast and cervical cancer; from 9.9% for women aged <50 years to 84.6% for women aged ≥75 years and from 3.6% for women aged <50 years to 100% for women aged ≥75 years, respectively. Similarly, worsening comorbidity was associated with age for the three types of cancer (p<.001). Among patients with NSCLC, results ranged from 60% for women with no comorbidity, aged <50 years to 63.6% for women aged ≥75 years with severe comorbidity (*p*<.001). In breast cancer, the percentage of patients aged <50 years with no comorbidity was 91.1% compared with 9.5% for patients aged ≥75 years with severe comorbidity (*p*<.001). In women with cervical cancer, a big decline was observed from 97.4% for women with no comorbidity aged <50 years to 14.7% for women aged ≥ 75 years with severe comorbidity (*p*<.001).

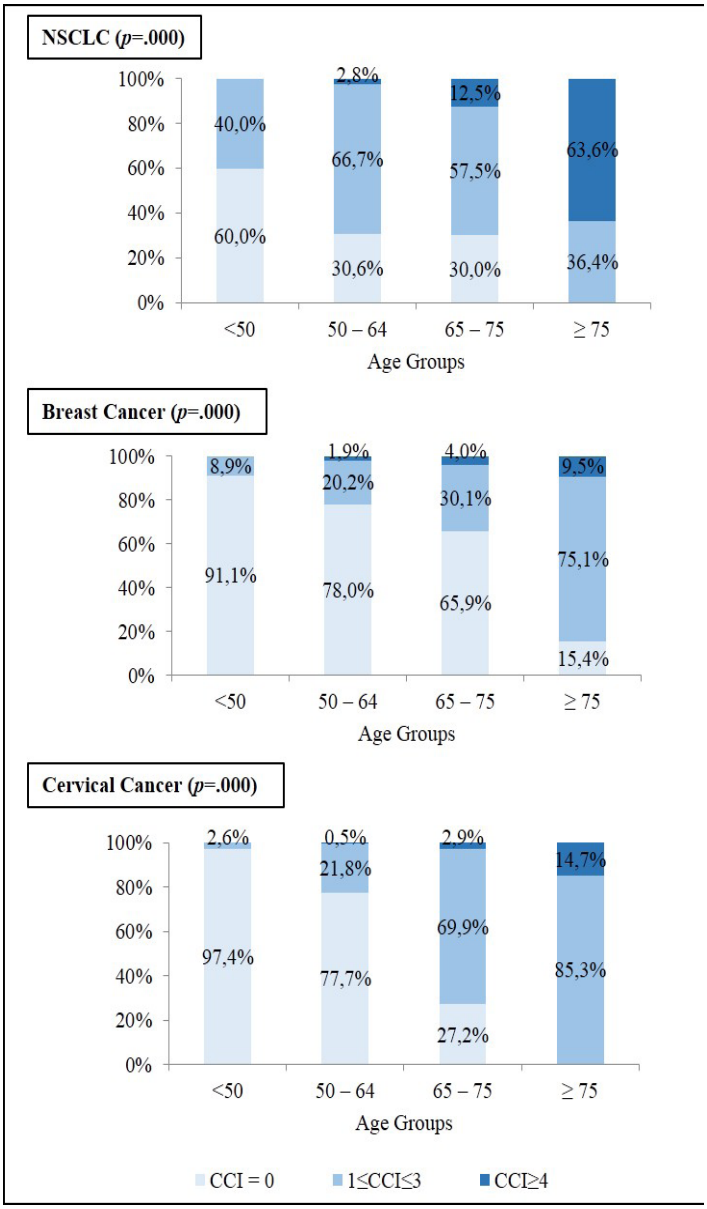

Figure 1: Comorbidity scores (CCI) according to age groups and cancer location.

Survival Analyses

Survival analysis revealed that for patients with NSCLC, the 3 years OS was 30.1% (95%CI: 29.3–30.8) whereby the 5-year overall rates were 71.6% (95%CI: 74.1–78.1) for breast cancer and 46.7% (95%CI: 42.6–50.8) for cervical cancer.

The effect of comorbidity on survival of women was assessed by Kaplan-Meier method and Log-Rank test. The study estimated overall cancer survival based on the presence of comorbidity diseases. The difference in OS for all women who had no comorbidity versus women with comorbidities was statistically significant for all cancer sites (p<.05) (Table 2, Figure 2).

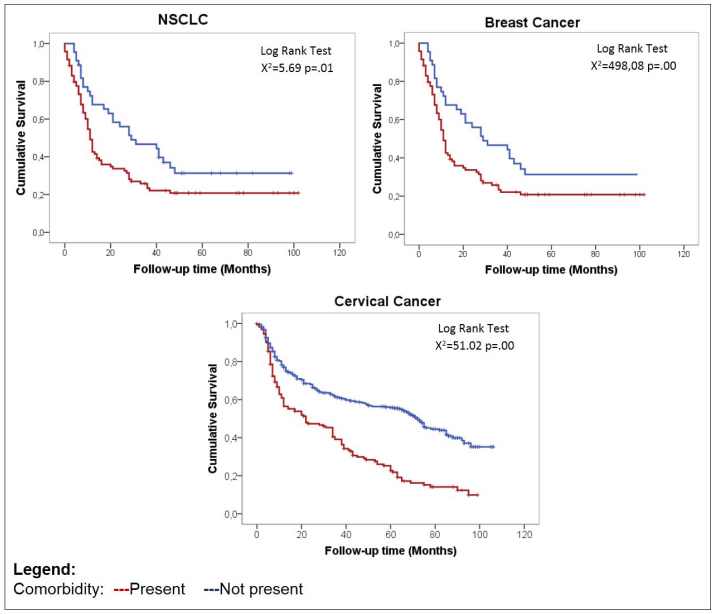

Figure 2: Kaplan Meier survival function according to presence or absence of comorbidity among women with NSCLC, breast and cervical cancer.

The cumulative 3-year OS rates for NSCLC were 44.5% (95%CI: 29.3–59.7) and 23.3% (95%CI: 13.2–33.4) in patients without and with comorbidity, respectively. A comparison of Kaplan–Meier curves for OS showed a significant difference between the two groups (p=.01). The cumulative 5-year OS rate of women with breast cancer in the no comorbidity group was 91.4% (95%CI: 89.6–91.6) compared with 37.2% (95%CI: 32.7–59.9) for those in the comorbidity group (*p=.00*). This research also showed a significant difference in OS between the two groups (Comorbidity/ No comorbidity) for cervical cancer. The cumulative 5-year OS was significantly higher (p =.00) in patients without clinical disorders (55.8% [95%CI: 50.7 – 59.9]) than patients with comorbidity (27.7% [95%CI: 15.9–29.5]). A comparison of Kaplan–Meier curves for OS demonstrated that the association between presence of comorbidity disorder and cancer overall survival was statistically significant for the three topographies studied.

Similarly, a significant statistical association (p<.05) was observed between the level of comorbidity (CCI) and survival. Both the median and the survival rate significantly decreased as the level of comorbidity increased in those three cancer sites (Table 2, Figure 3). Figure 3 shows overall survival function for cancer patients diagnosed by topography according to Charlson comorbidity score category. In all patients (with NSCLC, breast or cervical cancer) OS were significantly higher for patients with ICC=0 (no comorbidity) compared with Charlson score 1-2 (light or moderate comorbidity) for three cancer locations. A worse OS was noted among patients with ICC≥4 (severe comorbidity). A significant statistical association (p<.05, log-rank test) was observed between the level of comorbidity (Charlson comorbidity score category) and survival.

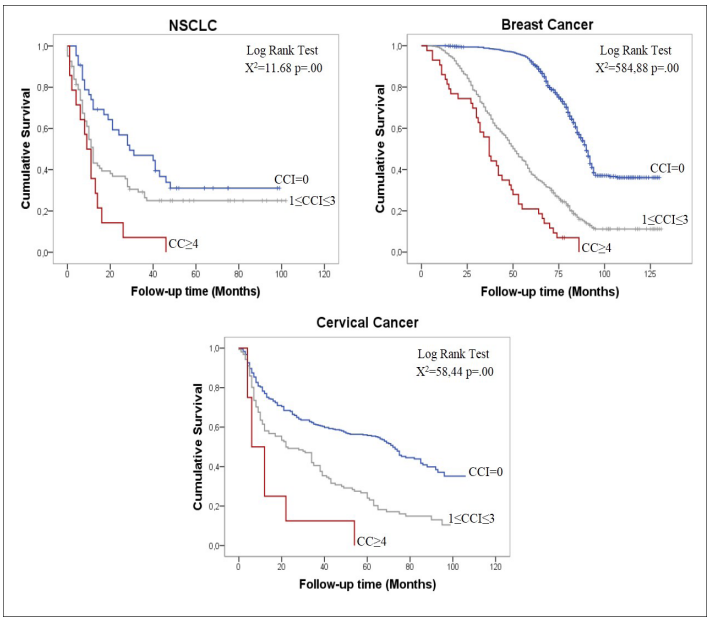

Figure 3: Kaplan Meier survival function of ranking comorbidity (CCI) for women with NSCLC, breast and cervical cancer.

Multivariate Analysis

Cox proportional hazard models were used to identify predictor factors for OS. These were included to estimate Hazard Ratios adjusted for comorbidity (CCI).

For NSCLC, the following independent prognostic factors for OS were identified: clinical stage (HR: 4.3 [95%CI: 2.99 - 5.96], p=.000), comorbidity (HR: 2.28 [95%CI: 1.43 - 3.65], p=.000), therapeutic management (HR: 1.58 [95%CI: 1.02 - 2.45], p=.009) and age (HR: 1.03 [95%CI: 1.01 - 1.05] p=.03). Table 3 illustrates the HRs by comorbidity adjusted for independent prognostic factors previously recognized. Three of individual comorbid conditions showed significant increases in the mortality risk: congestive heart failure (HR: 1.93 [95%CI: 1.06 – 3.51]), chronic obstructive pulmonary disease (HR: 1.81 [95%CI: 1.16 - 2.83]), and AIDS (HR: 1.43 [95%CI: 1.12 – 1.84]). Kaplan-Meier analysis revealed that in women with congestive heart failure (n=3), the 3-year OS (0.0% vs. 34.7% [95%CI: 26.1–43.3], p=.000) was significantly poorer in comparison with those without it. Also, OS rate in patients with COPD (n=49, OS: 42.2% [95%CI: 31.9–52.5]), was lower than women without disease (OS: 10.0% [95%CI: 1.8–19.0]) (p=.000). Only two patients with AIDS were registered and died before 6 months; the 3-year OS was 23.6% (95% CI: 19.1–28.1).

The most important prognostic factors for mortality in women with breast cancer were: clinical stage (HR: 3.39 [95%CI: 2.99– 3.83], p=.000), comorbidity (HR: 3.16 [95%CI: 2.69–3.71], p=.000), therapeutic management (HR: 1.16 [95%CI: 1.03–1.29], p=.004) and age (HR: 1.03 [95% CI: 1.02–1.04], p=.000). The adjusted HR of comorbidities was positive and statistically significant for diabetes mellitus (HR: 1.91 [95% CI: 1.55–2.33], p=.000). The probability of overall survival was significantly different (p=.000) between women with diabetes (n=185, 5-year OS: 31.3% [95%CI: 25.6–37.0]) and those without diabetes (OS: 85.0% [95%CI: 83.0–87.0]).

The clinical stage (HR: 2.23 [95%CI: 1.59–3.12], p=.000), therapeutic management (HR: 1.82 [95%CI: 1.37–2.42], p=.000), comorbidity (HR: 1.38 [95%CI: 1.10–1.86], p=.032) and age (HR: 1.02 [95% CI: 1.00–1.03], p=.001), had a consistent correlation with poorer OS, suggesting that these were independent predictor variables for survival in cervical cancer. With this, the prognostic factors identified were included to assess the diagnostic categories of the CCI. After adjustment for other prognostic factors, multivariate analysis demonstrated that moderate or severe kidney disorder increased the risk of death in women with cervical cancer (HR: 1.22 [95%CI: 1.01–1.49], p=.03). The cumulative 5-year OS of women with kidney illness was 23.3% (n=36, [95%CI: 13.2–33.4]) compared with 44.5% (95%CI: 29.3–59.7) for patients without this comorbidity. The Log rank test demonstrated a statistically significant difference between groups (p=0.000).

Table 3: Overall Survival according to comorbidity index (CCI) levels in women with NSCLC, breast and cervical cancer.

Cancer Site	Median (95%CI)	Overall Survival Rates (OS) (95%CI)	Log Rank test *p*-value
NSCLC		3 year survival rate	0.00
CCI = 0	29.0 (9.23 – 48.7)	44.5% (29.3 – 59.7)	
1≤CCI≤3	12.0 (10.2 – 13.8)	26.4% (16.8 – 36.0)	
CCI≥4	9.0 (5.3 – 12.7)	23.3% (13.2 – 33.4)	
Breast cancer		5 year survival rate	0.00
CCI = 0	90.0 (88.4 – 91.6)	92.2% (90.6 – 93.8)	
1≤CCI≤3	51.0 (47.0 – 54.9)	37.2% (32.5 – 41.9)	
CCI≥4	37.0 (31.8 – 42.1)	18.6% (7.1 – 30.1)	
Cervical cancer		5 year survival rate	0.00
CCI = 0	72.0 (65.1 – 78.8)	55.8% (60.7 – 59.9)	
1≤CCI≤3	22.0 (11.8 – 32.2)	24.0% (16.8 – 31.2)	
CCI≥4	6.0 (0.45 – 11.5)	0.0%	

*p value based on Log Rank test (statistical significant $p<.05$)

Table 4: Comorbidity diseases and Hazard Ratios adjusted for selected prognostic factors in women with NSCLC, breast and cervical cancer.

Comorbidity Diseases	NSCLC			Breast			Cervical		
	HR[a]	(95%CI)	*P*-value	HRb	(95%CI)	*P*-value	HR[c]	(95%CI)	*p*-value
Myocardial infarction	1.50	(0.44 – 5.10)	0.51	0.86	(0.47 – 1.59)	0.65	2.91	(0.40 – 21.0)	0.29
Congestive heart failure	1.93	(1.06 – 3.51)	0.03	0.82	(0.59 – 1.15)	0.26	1.60	(0.84 – 1.87)	0.25
Peripheral vascular disease	1.72	(0.89 – 3.33)	0.10	1.09	(0.79 – 1.15)	0.61	1.09	(0.79 – 1.51)	0.58
Cerebrovascular disease	1.90	(0.69 – 5.21)	0.21	1.04	(0.82 – 1.33)	0.05	1.11	(0.71 – 1.73)	0.65
Dementia	NA			NA			0.03	(0.01 – 0.06)	0.98
Chronic Pulmonary Disease	1.81	(1.16 – 2.83)	0.05	1.67	(0.95 – 2.27)	0.07	1.67	(0.95 – 2.27)	0.07
Connective tissue disease	1.06	(0.51 – 2.21)	0.86	1.33	(0.76 – 2.86)	0.31	1.33	(0.76 – 2.86)	0.31
Ulcer disease	1.18	(0.42 – 3.29)	0.74	1.03	(0.62 – 1.69)	0.90	1.03	(0.62 – 1.69)	0.90
Mild liver disease	1.44	(0.14 – 0.79)	0.47	1.39	(0.90 – 2.15)	0.14	2.19	(0.70 – 6.88)	0.18
Diabetes mellitus	1.37	(0.72 – 2.62)	0.34	1.91	(1.55 – 2.33)	0.00	0.94	(0.69 – 1.28)	0.70
Moderate or severe renal disease	1.18	(0.74 – 1.88)	0,48	1.00	(0.82 – 1.22)	0.97	1.22	(1.01 – 1.49)	0.03
Diabetes mellitus with end-organ damage	1.29	(0.99 – 1.69)	0.05	1.01	(0.72 – 1.41)	0.95	1.01	(0.72 – 1.41)	0.94
Moderate or severe liver disease	1.25	(0.84 – 1.84)	0.27	1.14	(0.82 – 1.60)	0.41	1.14	(0.82 – 1.60)	0.41
AIDS	1.43	(1.12 – 1.84)	0.00	NA			NA		

HR[a]: Hazard Ratio adjusted for age, clinical stage and therapeutic management
HR[b]: Hazard Ratio adjusted for age, hormonal therapy personal antecedents, clinical stage and therapeutic management
HR[c]: Hazard Ratio adjusted for age, clinical stage and therapeutic management
NA: Not applicable

Discussion

The change in population demographics in terms of population aging has resulted in an increased proportion of elderly cancer patients, many of whom present with comorbid diseases. The high incidence of cancer in advanced ages is evident and emphasizes the need for corresponding research. The higher incidence observed in women over age 50 with lung, breast and cervical cancer highlights the importance of age as a prognostic factor. Besides age, clinical disease stage and therapeutic management are prognostic factors which have a significant impact on cancer survival and mortality. All of which are recognized by diverse authors [5-8]. Similarly, comorbidity disorders play an important role in cancer survival. Their presence can affect the choice of conventional cancer therapies, irrespective of tumor staging. This affirmation is frequently emphasized in the Clinical Practice Guidelines in Oncology (National Comprehensive Clinical Network, NCCN 2020) [5]. Fortunately, comorbidity studies in cancer patients have increased in the last decade. However, it remains challenging to analyze trends or establish comparisons between studies due to the methodological differences that exist in the recording of information on the subject and in the statistical analysis. The current study noted a higher prevalence of patients with comorbidities among older women. It was observed that the frequency of comorbidity is three times higher in people older than 60 years [9].

Edwards B, in a study on the prevalence of comorbidities in patients with Lung, Colorectal, Breast and Prostate Cancer, diagnosed in the period 1975 -2010, concluded that lung cancer (52.9%) was the topographic diagnosis with the highest prevalence of comorbidity [10]. Similar findings were obtained in the present study. The frequency of comorbidities varies and depends on the cancer location and the population studied. Cardiopulmonary Diseases and Diabetes Mellitus were the most frequent comorbidities in all three locations. This outcome is consistent, with results reported by numerous studies and European Registries [10-14].

Lung cancer is a major cause of death and imposes a significant burden on healthcare systems throughout the world. Furthermore, with the increase in smoking and in life expectancy, lung cancer will likely place an increasing burden on healthcare services in developing countries. Factors such as age, performance status, and social conditions are often seen as correlates for comorbidity [15].

With regards to lung cancer, comorbidity may differ in important ways from comorbidity in patients with cancer from other sites. Firstly, lung cancer is strongly associated with smoking, which is a major cause of comorbidity. Hence, the diversity and number of comorbidities may be greater in lung cancer patients. Secondly, this disease has a relatively short course, and indolent comorbidities may not have the opportunity to exert deleterious effects. The findings of the current study support this view. For example, peripheral vascular disease, cerebrovascular disease, connective tissue illness and diabetes, perceived to be of major importance in other studies or in established comorbidity indexes were not found to be important predictors of survival in lung cancer [16]. Despite an increased recognition of the importance of comor¬bidities in the long term prognosis of lung cancer patients, there is insufficient evidence in the literature of the causal link between comorbidities and the risk of lung cancer specific mortality. However, in recent years, there has been an increase in the number of studies aimed at investigating comorbidities in this cancer topography. Various researchers have identified comorbidity as a negative prognostic factor for lung cancer survival [17-19]. In a population-based cohort study by Deleuran Thomas et al. which included 9 369 patients diagnosed with lung cancer from 2000 to 2011, in the Central Region of Denmark, revealed improvements in the overall survival of younger women without comorbidity compared to those with associated comorbidity [19, 20]. Other authors like Birim et al. evaluated the impact of the CCI on long-term survival in NSCLC [19]. Using multivariate analysis, it was shown that for a CCI score ≥3, the relative risk of death was 2.2 (95% CI, 1.5-3.1). However, when the ICC score was 1 or 2, the relative risk was reduced to 1.4 (95% CI, 1.0-1.8). In this analysis, severe comorbidity had a significant negative impact on long-term survival when comorbidity was assessed according to the CCI.

The current study evaluated medical conditions as prognostic factors of overall survival using the Cox proportional hazards analysis. It was found that Congestive Heart Disease, Chronic Obstructive Pulmonary Disease and Acquired Immune Deficiency Syndrome (AIDS) significantly increase the relative risk of death. Previous studies have recognized that these disorders have the highest prognostic value [16]. In general, a significant number of authors have found that medical conditions and the Charlson Comorbidity Index score were predictors of overall survival in NSCLC, but have only described a discreet percentage of survival variation.

Breast cancer is primarily a disease of older women, who frequently have other associated diseases. When present, these diseases may not only affect breast cancer treatment choices but also adherence to treatment regimens, resulting in a direct impact on both breast cancer mortality and overall survival. The presence of comorbidities was statistically significantly associated with cancer survival in women with breast cancer, and the risk of death was also significantly higher in these patients, independent of diagnostic age, stage and treatment modality [21-25].

Ahern TP et al. conducted a study within an ongoing prospective cohort of older women diagnosed with early-stage breast cancer [25]. The authors suggested that the statistical adjustment for such variables would be expected to attenuate the observed hazard ratio when associating comorbidity with mortality by removing a portion of the total causal effect. They tested this expectation adjusting for histologic grade, estrogen receptor status, surgery type, receipt of adjuvant tamoxifen, and receipt of adjuvant chemotherapy (HR: 1.4, 95%CI: 1.2–1.6). Adjustment for these variables reduced the comorbidity hazard ratio in each of the three models by 5% or less. The three modeling strategies yielded similar results. This result was consistent with findings from earlier studies.

Diabetes Mellitus was identified as the disease which significantly increased the risk of death in breast cancer. The trend of higher mortality among diabetic women remained the same after adjusting for diagnostic age, tumor stage and treatment. The results of the study are concordant with previous literature investigating comorbidities in women with breast cancer and their association with mortality. Patnaik JL et al. studied a series of 96 954 women, aged 65 years and older, diagnosed with breast cancer between 1992 and

2000 (based on statistics obtained from the Population Registry of the National Cancer Institute of the United States) [26, 27]. This large population size allowed the investigators to study the association between rare conditions and overall survival in older breast cancer patients in the United States and to assess the impact of age and tumor stage. They found that all of the comorbidities studied (CCI) were associ¬ated with increased all-cause mor¬tality in the study population. Partially and fully adjusted (for age, race and/or ethnic, stage, grade, estrogen receptor status, surgery, chemotherapy, radiation, and all other individual comorbid condition) hazard ratios of comorbidities were all positive and statistically significant (e.g., fully adjusted hazard ratios: for diabetes mellitus, HR of death: 1.41; 95%CI: 1.36–1.45). An important number of studies have reported that type 2 diabetes increased the risk of incident breast cancer and a recent meta-analysis indicated that diabetes was associated with increased mortality in breast cancer (HR: 1.61; 95%CI: 1.46–1.78) [24, 29, 30]. Another contribution was that age at diagnosis modified these relationships. Patients with comorbidities diagnosed with early-stage breast cancer had survival outcomes similar to or worse than that of patients with no comorbidities diagnosed with later-stage tumors [27].

Cervical cancer is a leading cause of cancer death in women in developing countries. Recognizing this, Cuba introduced a National Cervical Screening Program in 1967 [30]. Despite having this program, cervical cancer still represents a great disease burden, with a high incidence of 24.9/100 000 and a mortality rate of 9.1/100 000 [1].

Because Cuba is an old population, the prevalence of many chronic diseases such as cardio-vascular disease, diabetes, renal disorders, etc. is higher for Cuban women including those with cervical cancer. However, the impact of these comorbidities on cervical cancer survival in Cuban women has never been examined. To date, there have been few publications which have assessed the role of comorbid conditions on cervical cancer survival.

The present study has shown that having increased comorbidity is associated with a reduction in the five-year all-cause survival of these women. These findings coincide with previous findings reported from studies of New Zealand, Australian and Danish women [31-33].

Diaz A. et al examined the impact of comorbidity on cervical cancer survival in Australian women, in a study which included 4 467 women [32]. In this research, comorbidity was measured using both the Charlson Comorbidity Index and the Elixhauser Index. The investigation found that the all-cause survival followed similar patterns to cause-specific survival and mortality: higher comorbidity score was associated with higher mortality. The authors also found that the five–year survival rate was lowest in women with ICC score ≥4.

There is evidence which shows that a higher comorbidity burden is associated with worse survival in cervical cancer patients [31-34]. Importantly, the prevalence of comorbidity varies between population groups and countries, and may contribute to disparities in cancer survival rates.

This study revealed that moderate or severe renal disease was the comorbidity associated with the highest mortality. The difference in survival rates between women with kidney illness and those without said comorbidity exceeded 20%. Similar results were published by Brewer N et al. who estimated the cervical cancer-specific survival (HRs) adjusted for age, year of diagnosis, stage, ethnicity, and urban/rural residence, for individual medical conditions included in the Elixhauser instrument [31]. Thirteen of the individual comorbid conditions showed HRs of ≥1.5. Renal diseases in the year before diagnosis were associated with cervical cancer–specific survival (HR: 4.27; 95%IC: 2.01-8.08). Other publications have agreed with this finding and have reported that mortality was associated with other frequent disorders, such as: cardiovascular diseases, diabetes mellitus, cerebrovascular and liver diseases.

Conclusions

The prevalence of comorbid diseases in cancer women is extremely high. Comorbidities were found to be present in the majority of women of advanced age. The effect of comorbidity on overall survival rates vary depending on the comorbid condition and the topography of cancer. Comorbidity is an important prognostic factor for women diagnosed with lung, breast and cervical cancer. Further research is needed to investigate the underlying mechanisms of this relationship. A higher comorbidity burden was associated with a wider survival disparity among women with comorbidity and those without. The Comorbidity Charlson Index (CCI) is a good predictor of overall cancer survival and mortality for the three cancer locations. The use of comorbidity burden in the clinical management of women diagnosed with cancer is recommended.

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