Evaluation of risk factors in survival of breast cancer patients

Sandra Ramírez [1], **Luis Cid** [2], **Marcela Valdés** [2]
[1]Pontificia Universidad Javeriana seccional Cali, Cali, Colombia
[2]Universidad del Bio Bio, Concepción, Chile

Abstract
A sample of 1200 breast cancer patients with complete follow up from 1978 to 2002 was used to assess the evolution survival of patients over time using several survival estimators: Kaplan and Meier´s, Cox´s proportional hazards regression, multinomial logit regression model, median-quartiles residual life time. Patients were classified into groups according to risk factors and results for the groups were compared through standard ad-hoc tests and confidence bands, obtained using bootstrap re-sampling methods. The analysis of effect of risk factors considered only non metastatic patients since the presence of metastasis overcome all possible factors affecting survival. The results showed that patients at stage three of the disease present a differential result in survival when considering factors such as age at detection and age at first child birth, which are considered also as risk factors.

Key Words: Breast cancer, survival estimation, product limit estimator, proportional hazard models, residual median lifetime, bootstrap.

1. Introduction

There exist many factors that have been identified and associated with the development of breast cancer. Among the most relevant, are those related to the reproductive life of women, including age, age of the first pregnancy, absence of pregnancy and hence of lactation, early menarche, late menopause, etc. These risk factors are linked to the exposition to estrogens, which are assumed to be one of the main causes of the high incidence of the disease. There also exist factors acting as protection against the disease, such as first pregnancy before 30 years old, age at detection and, etc. Some of the described conditions constitute valid information that could be associated to the prognostic of the disease, measure as life expectation after the disease has been detected and the treatment initiated. In this research we intend to elucidate which of the risk and/or protection factors have some influence in the prognostic of the disease, measured as the residual life time after detection.

1.1 Risk factors
The National Cancer Institute, in its Breast Cancer Risk Assessment Tool (BCRAT), includes several variables, of interest to be analyzed in this context.These are personal history of breast cancer, age at detection (AD), age at menarche(AM), age at menopause(AMP), age at first live birth of a child (AFLB), first degree relatives with a history of breast cancer, positive breast biopsy and race. Some of these factors are directly related to the reproductive life of the patient, others are not. Although the BCRAT is widely used, there are other factors involved which are not considered, including genetics, endocrinology, sexual activity, age related, pregnancy history, among others (Arraztoa, 2004), although not all of them need to be present for the disease to appear, and in a significant portion of women with the disease, none of the previous risk factors is present. Moreover, the reproductive conditions of women determine a long exposition to sometimes high concentrations of collagens and estrogens which constitute a risk factor (Eliassen et al., 2006; Novoa et al.,2006). This is also related, to high numbers of menstrual cycles which, has been demonstrated, have a significant correlation with the presence of breast cancer (Ardí et al.,1993).

Starting from the time of the menarche when the risk is the lowest, the risk increases with age, reaching the maximum, after 65 years of age. With a risk two to four times higher when the cycles start before being 12 years

old compared with whose cycles start after 13 years. (Ortiz et al., 2007; Novoa et al., 2006; Salas,2006). Two years of retardation of the menarche could reduce in as much as a 10% the risk of breast cancer (Clavel-Chapelon, 2002). Due to similar reasons, the end of the menstrual cycle will be an indication of the length of time during which the woman organism has been exposed to higher concentration of estrogens so that delayed menopause is considered to be a risk factor. In fact women with late menopause appear to be at higher risk. At 55 years the risk is twice as high that women under 55 (Novoa et al.,2006; Salas,2006; Ewertz and Duffy,1988).

Age is one the factors that contributes the most to increase the risk of breast cancer (Morales et al., 1999) mainly due to what is called cumulative risk factor, representing the accumulation of several risk factors along time (Novoa et al.,2006). This is in addition to an oncogenic stimulation for which older women are less prepared to react along with the loss of efficiency of mechanisms of cell restoration. In fact, the risk of developing breast cancer between 20 and 40 years is 0.49% and 5.5% between 65 and 85 years of age (Peralta, 2002). The risk of breast cancer at 50 years of age is approximately of 1 in 400 women and is ten times higher than at age 30. This is strongly related to hormone, estrogen and progestagen effects (Vazquez et al.,2005; Salas et al., 2006).

Temperature of the tumor has been also used both as detection and survival prediction tool. In fact it is well known that differences in energy consumption exist for normal and cancerous tissue. These differences lead to small but detectable local temperature changes Since the emissivity of the human skin is extremely high, within 1% of that of a black body, measurements of infrared radiation emitted by the skin can be converted directly into accurate temperature values (González, 2007). Infrared imaging was introduced into medicine in the late 1950s. there are differences in energy consumption of normal and cancerous tissue that lead to small but detectable local temperature changes (Gore and Xu, 2003). Temperature of the tumor can also been used as a detection tool. A typical infrared image of a breast tumor reveals a 1-2◦C elevation in skin surface temperature at the periphery of the tumor, with the tumor mass often being associated with a corresponding reduction in skin surface temperature (Xie, et al., 2004). Since it is relted to groing rate of the tumor, a phenomenon know to be an exothermal process. This is ore formed by computing the difference in temperature (D2) between the area of the tumor and a similar area in the opposite breast. But the temperature of the tumor has been primarily used to estimate the type of tumor, and consequently the prognosis of the disease.

Current demographic data confirm the inverse correlation between the number of live births and the presence of breast cancer. For women without live births, the estimated relative risk is about twice as high when compared with women with five or more children (Becher et al.,2003). It has also been verified that the reduction of natality rates in Canada could produce an increment of the breast cancer incidence (Lopez-Rios et al.,1997).

1.2 Protection factors

As protection factors against the risk of getting the disease, we consider the same variables used to assess risk, regarding the variables that can influence the prognostic of the disease, they are summarized in the classification of the disease according to the TNM definitions of stages (Breast. In: American Joint Committee on Cancer, 2002; Singletary et al., 2002). We do not consider at this stage the histologic classifications.

In this research, we intend to determine if there exist an association between some of the risk factors and life expectation. We intend to demonstrate that although some of the risk factors constitute a menace toward the women exposed, there are situations in which those risk factors can evolve into protection factors, providing the patients with longer life expectations after the disease has been detected, if the treatment protocols applied to patients under similar disease conditions are equivalent. Alternatively, some of the risk factors are proven to act against the life expectations. We also analyzed the effect of D2, in estimating survival probabilities.

2. Methodology and patients

The objective of this study is to evaluate the effect of the risk factors on the life expectation of breast cancer patients, considering both exact life time, for patients who actually died of breast cancer during the period of study, and censored values, corresponding to patients that either were alive at the time evaluation or they died of a cause different from breast cancer, including those patients with incomplete follow up, and for whom we

ignore the survival status at evaluation time. To estimate survival, we used Kaplan and Meier's product limit estimator (PLE) (Kaplan and Meier, 1958), percentile residual life time (Jeong, et al., 2009) and Cox´s proportional-hazard model (Cox, 1972) to evaluate the effect different covariates, related to the risk factors. Test statistics to establish differences between survival functions associated with different levels of the risk factors, were conducted using flexible testing strategies provided by the Log rank and Tarone Ware test which allow to give different weight to early or late years of the follow up (Martínez et. al.,2009; Bellon, n.d, 2011). We also included the estimates of residual life time, to provide complementary information regarding life expectations (Jeong, et al., 2009; Fleming and Harrington, 1981) and estimates of conditional probabilities of the various categories of variable survival time conditioned to the categories of the predictor variable using logit model (Agresti, 2012).We also analyzed the effect of D2, in estimating survival probabilities.

The sample of breast cancer patients used for this study has 1215 patients and was developed with a protocol established in 1978 by the Breast Cancer Center of Concepción, Chile. Patients in the study were required to have at least 24 months of follow up. Approximately 70% of the cases were right censored observations. Due to the characteristics of the disease at diagnostic time, the study was performed separately for patients at stage I and II, and III and IV because at advanced stages of the disease, like stage IV, the survival expectations are clearly determined by the degree of progression of the disease at detection without considering any other factor. In fact, metastatic tumors characterize stage IV and that overcomes any other consideration regarding the nature on the tumor. Based on this consideration, the results of this study consider only patients at stages I, II and III of the disease.

To determine differences between different risks classes, the risk factors were classified each into two groups, i.e., age at detection (AD) was grouped into AD≤50 and AD> 50 years. The cutting point for Age at first delivery of a live child (AFLB) was 30 years, for age at menopause (AMP) was 50 years, for age at menarche (AM) was 12 years and temperature difference between healthy and diseased breast (D2) was 2.5 ºC. Other strictly categorical factors such as parity, lactation, etc., were considered as binary variables. The rankings were made due to medical interest (Table 1)

Table 1: Risk factors were classified each into two groups

Risk factors	*Two groups*	
Age at detection (AD)	*≤50 >50*	
Age at the fisrt live birth of a child(AFLB)	*≤30 >30*	
Age at menarche (AM)	*≤12 >12*	
Age at menopause(AMP)	*≤50 >50*	
Temperature difference (D2)	*≤2.5 >2.5*	
Time of exposure to estrogen (TS)	*≤40 >40*	
Parity(P)	*With birth*	*without birth*
Family antecedents (F)	*With*	*without*

3. Results

3.1 Product limit estimator PLE

3.1.1 Global

In what follows we will analyze the results of the PLE. Initially we analyzed the survival of the entire group, with special emphasis in 60, 90 and 120 months of survival after tumor detection. Figure 1 shows the PLE for the entire group of patients with no group separation, probability of survival at 60, 90 and 120 months survival were approximately 0.733, 0.681 and 0.64 respectively.

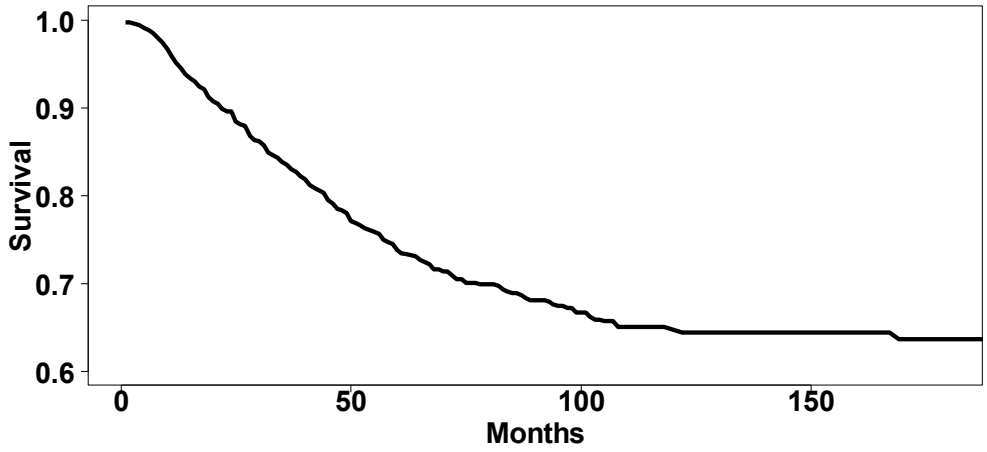

Figure 1: PLE for all patients.

3.1.2 Factors

Figure 2, shows the differences in survival expectations using the PLE which shows clear differences in survival expectation between stages, survival at 60 months for patients at stages I, II, III and IV was approximately 0.94, 0.81, 0.47 and 0.17.

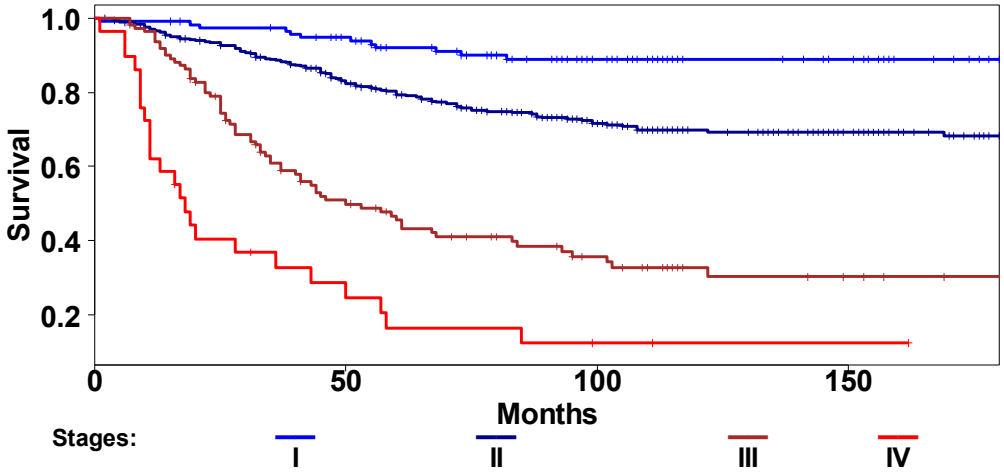

Figure 2. PLE separately for stages I, II, III and IV of the disease.

Figure 3 shows the PLE for each of the two groups of age at detection (AD) of the disease, considering only patients at stages I, II and III of the disease. The first group corresponds to patients with AD ≤ 50 years and the second to those with AD > 50 years. The result of this analysis shows that patients in the second group (AD > 50) have significantly higher life expectations than the first group. The risk factor AD constitutes a protection factor, with survival probability at 60 months of about 0.79 for the AD>50 and 0.63 for the AD ≤50. At stage III and IV the same trend is observed, but is not significant possibly due to the reduced number of samples in this group.

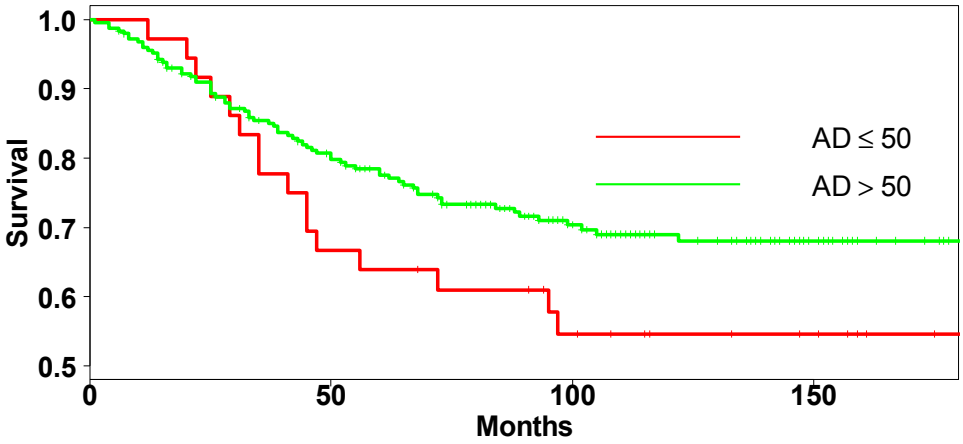

Figure 3. EPL the two age groups showing higher life expectation for patients with AD>50 for stages I, II and III.

Figure 4 shows the PLE for each of the two groups of age at detection (AD) of the disease, considering only patients at stages I, II. The survival probability at 60 month of about 0.85 for the AD>50 and 0.75 for the AD ≤50.

Age at first delivery of a live child (AFLB) showed significant differences in survival probabilities for the two groups considered in stage I- II-III (Figure 5). The first group considered AFLB ≤ 30 and the second AFLB > 30. The group corresponding to early first pregnancy showed significantly higher survival than the group of late first pregnancy. For each stage (I, II, III) this observation is significant when considered separately. For stages I,II is significant too while for stages III,IV significant difference cannot be observed between groups.

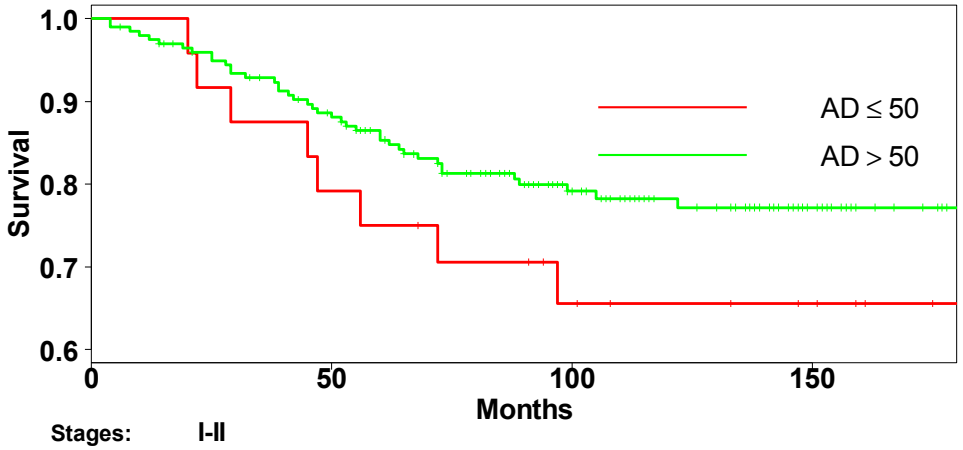

Figure 4. EPL the two age groups of AD for stages I and II.

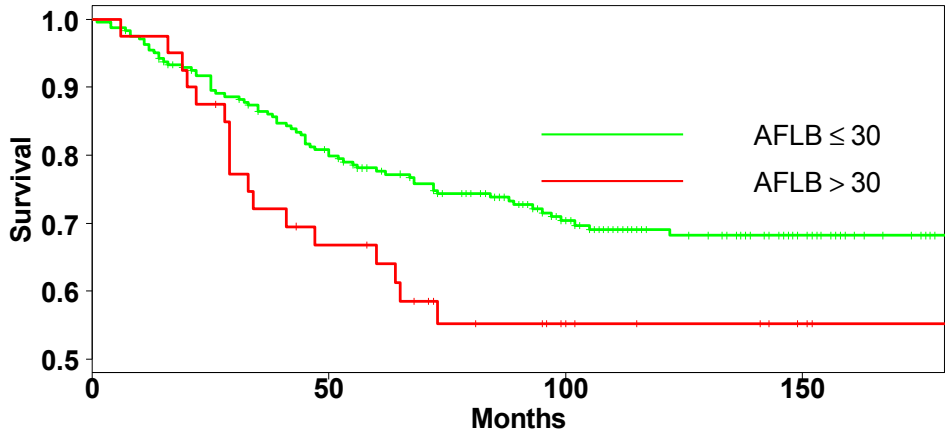

Figure 5. EPL the two age groups showing higher life expectation for patients with AFLB≤30 for stage I-II-III.

Figure 6 shows the PLE for each of the two groups of whose temperature difference D2, considering only patients at stages I, II and III. It shows significant differences in survival probabilities for the two groups considered showing higher life expectation for patients with D2 between 0 and 2.5 ºC. Considering each stage separately, stages I and II were significant while in stage III and IV significant difference cannot be observed between groups.

According to the survival curves women who are of 50 years of age at diagnosis or older or those who had their first live birth at the age of 30 or less or those whose temperature difference between healthy and diseased breast is less than 2.5 ° C have greater survival (Figures 3,4,5 and 6). The remaining factors such as age at menopause (AMP), age at menarche (AM), lactation and number of children do not exhibit clear differences between survival curves.

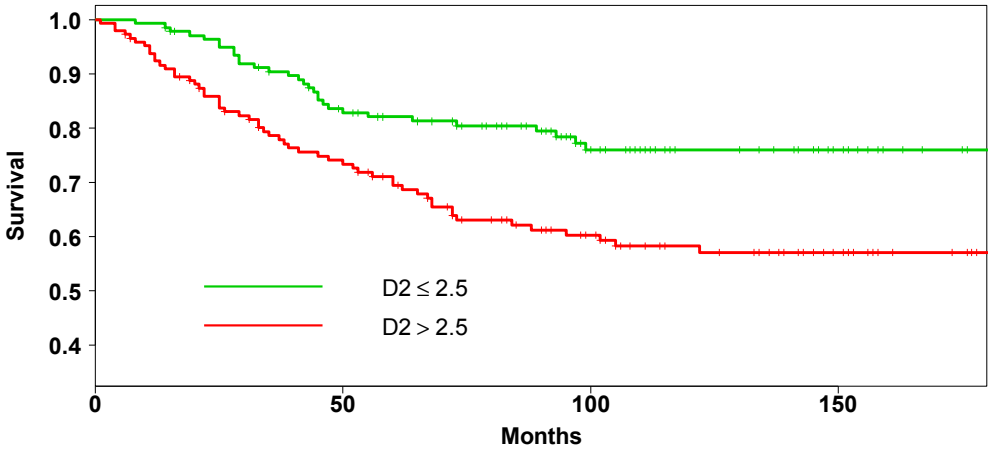

Figure 6. EPL the two age groups showing higher life expectation for patients with D2 between 0 and 2.5 ºC.

3.2 Residual life time

In this part the residual lifetime is shown according to each of the stages in which women were diagnosed. This corresponds to the time for future survival given that they have survived up to a point

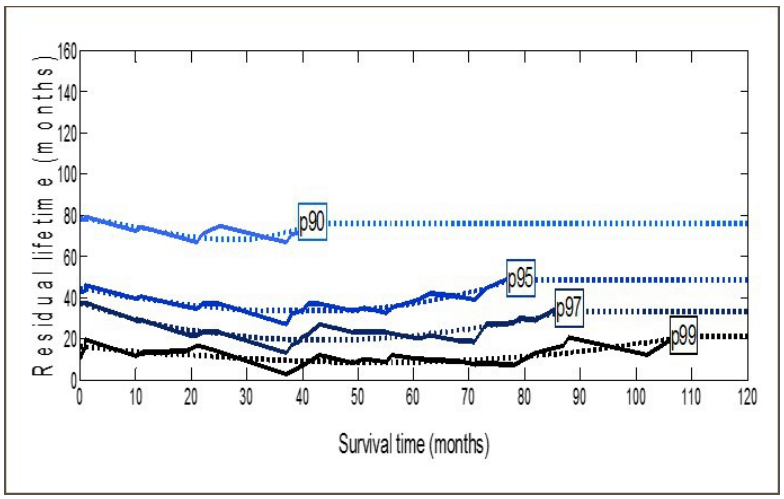

Figure 7. Residual life time for stage I.

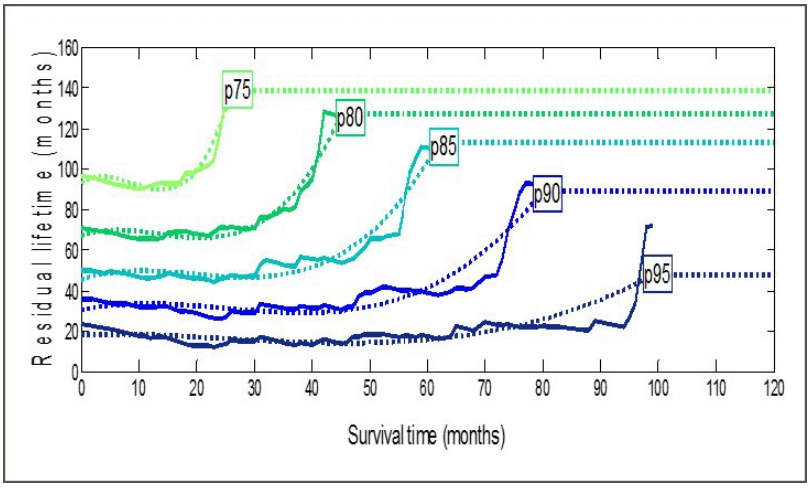

Figure 8. Residual life time for stage II.

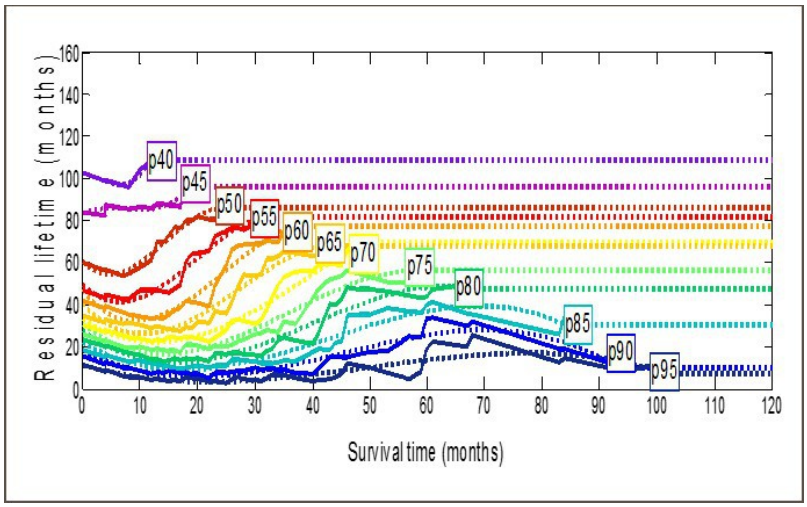

Figure 9. Residual life time for stage III

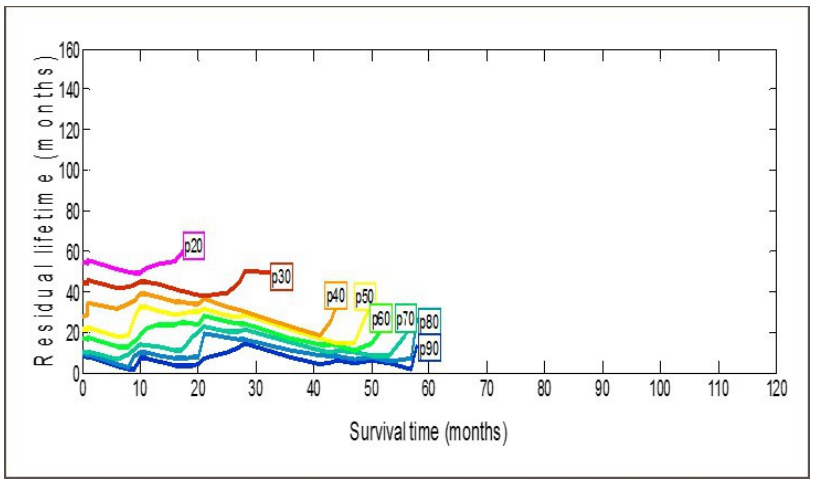

Figure 10. Residual life time for stage IV

The residual life time according to each of the stages in which the women were diagnosed. In stage I (Figure 7) it was only possible to calculate the residual life time for 95 and 90 percentiles, given the fact that regardless of which point in time we choose, in the future fewer than 10% of patients alive at the time of testing would have died. From the figure we could rescue that 90% of the women diagnosed at stage I, who had survived 36 months would survive at least another 72 months. For patients diagnosed at stage II (Figure 8) it was possible to calculate up to percentile 75 this is to say that regardless of the time a patient survived, fewer than 25% of the patients who were in this condition would have died in the future due to breast cancer. For example, 95% of the women who were classified as a stage I and had survived for 5 years would live at least 20 months, 90%, 40 months, 85%, 110 months. For stage III patients, (Figure 9) it is possible, unlike prior stages, to find the residual 50, in the first months of survival. It shows that for those patients who have survived 24 months after their diagnosis, 50% will die within 80 months, 25% before 20 months, 10% before 8 months. Only 50% of women who were classified as stage IV (Figure 10) survived more than 22 months. 50% of those who have survived 24 months will die within the next 30 months.

3.3 Cox proportional hazards model

We performed similar analysis using Cox´s regression model using AD, D2 and AFLB as covariates, both jointly and using independent models, to verify the previous results. The Figure 11 shows the probability of survival for different age groups, as estimated by the Cox´s regression model using AD as predictor. To analyze the age at the moment of the diagnosis, the Cox regression was analyzed for all the set of data, without difference of stages, for each stage individually and putting stages I and II together. In the cases: all the set of stages, stage I and stage I-II the p-value for the Cox model was meaningful. The p-value for each cases were 0.036, 0.027 y 0.021 respectively. According to the models, and also with the PLE, the Survival rate is greater when the age of the diagnosis is higher. Cox's regression coefficients for the age at detection of the diagnosis in stages I-II. Hence, the model is:

$$h_i(t) = h_0(t)\, e^{-0.018\,AD} \quad , e^{-0.018} = 0.982$$

According to the models the risk of dying for a 41 year old woman at the moment of the detection is of 98.2% of the risk of women who were diagnosed at the age of 40. This means that the risk diminishes when the age at the moment of the diagnosis is higher, as seen in Figure 12.

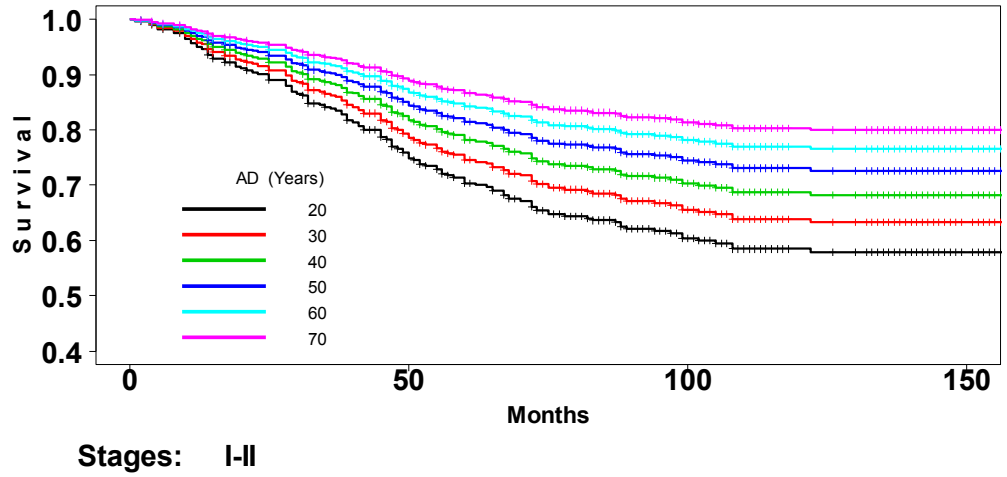

Figure 11. Survival probabilities using Cox's regression models with age at detection as covariate, for values between 20 and 70 years.

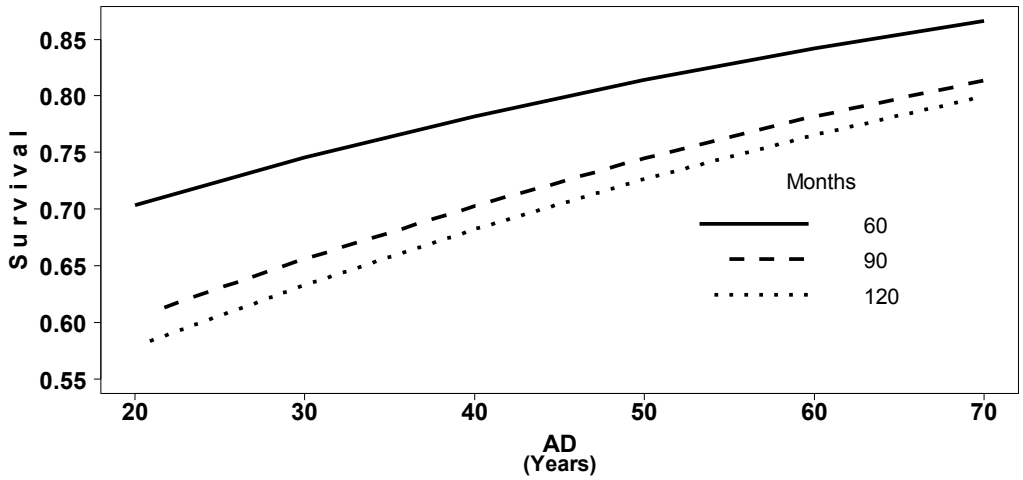

Figure 12. Survival probabilities using Cox's regression models with age at detection as covariate, for survival of 60, 90 and 120 months.

Age of first live birth (AFLB) turned out to be an important factor for survival classified in stage II. A meaningful model was found when analyzing the complete set of data by stages and for stage II, p-value were 0.00194. The model for stage I is $h_i(t) = h_0(t)e^{(0.0444AFLB)}$. For AFBL=1, this means that a woman with a first live birth at the age of 31, has greater risks than a woman who had her first live birth at the age of 30. That is to say, the risk diminishes as the age of the first live birth is lower as it can be seen in Figures 13 and 14.

To analyze the effect of D2 between the healthy breast and the sick breast affected by cancer, the Cox's regression was calculated for all the set of data (without difference per stage) and for each stage separately. A meaningful model was found when analyzing the complete set of data by stages and for stage I, p-value were $(6.3)10^{-3}$ and 0.0093 respectively. The model for stage I is

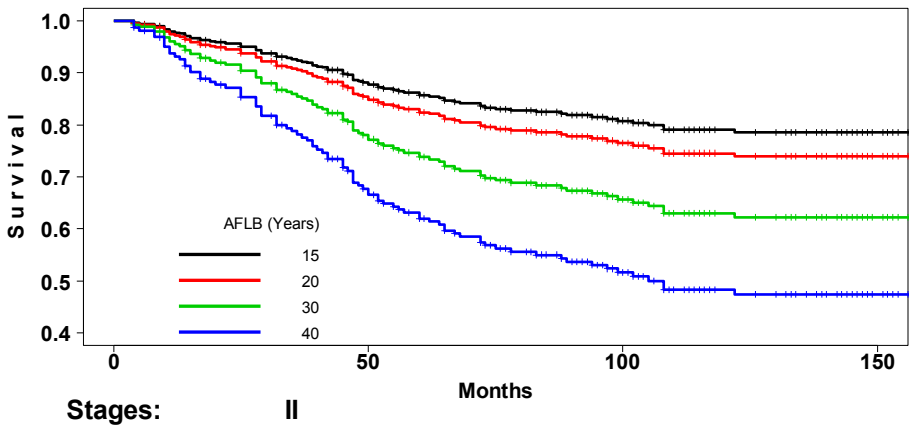

Figure 13. Survival probabilities using Cox's regression models with age at detection as covariate, for values between 20 and 70 years.

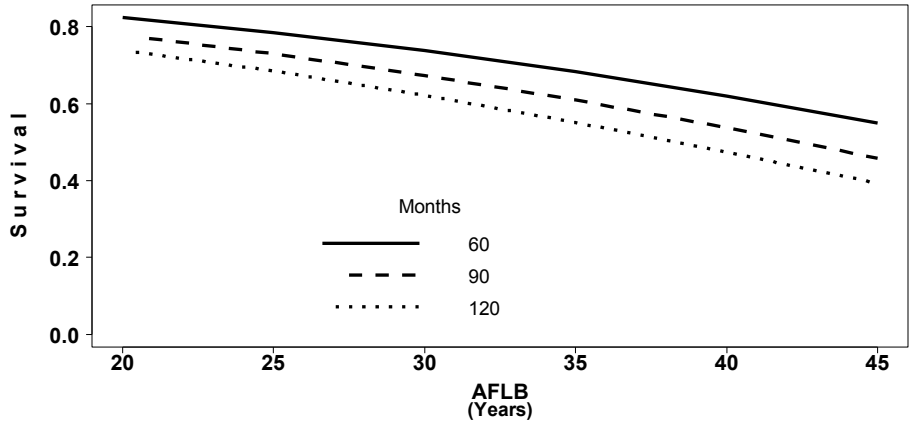

Figure 14. Survival probabilities using Cox's regression models with age at detection as covariate, for survival of 60, 90 and 120 months.

According to the models, and also with the PLE, the survival rate is greater when the D2 is lower (Figure 15 and 16). A woman with a 1°C difference between the sane and the affected breast by cancer, has approximately a 82% probability to survive 60 months, i.e. a probability of not dying before 60 months after being diagnosed. A woman who has 6°C of difference has a estimated survival rate for 60 months of 60% (Figure 17).

3.4 Linear regression model

Considering the joint information of stages I, II and III or the joint information of stage I and II or stage III by itself, the model turned out out to be significant, from which it is concluded that when the temperature difference is of low level it is more probable the patient will survive a longer amount time. When the temperature difference is higher it is more probable that the patient will survive a shorter amount of time (Figure 18 y 19).

We have demonstrated, using four different statistical methodologies, that there exist significant differences in survival expectations for patients according to their risk conditions, namely, age at time of detection, age at first delivery of a live child and temperature difference between breasts.

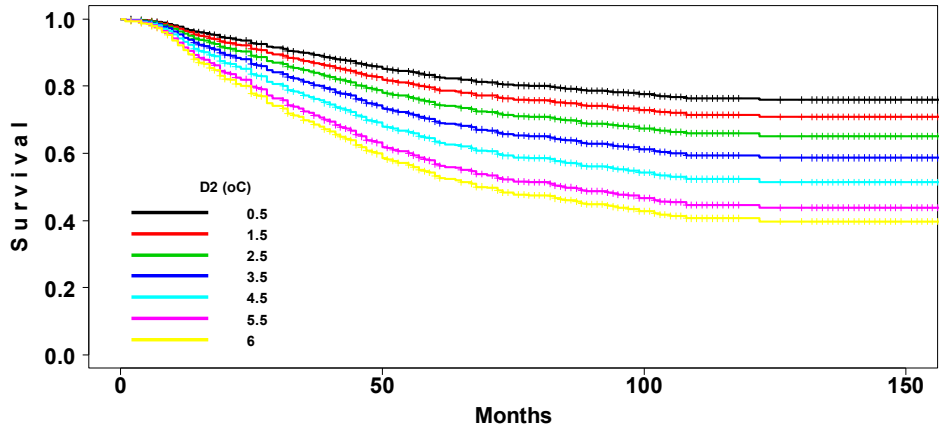

Figure 15. Survival probabilities using Cox's regression models with D2 as covariate, for values between 0.5 and 6 ºC.

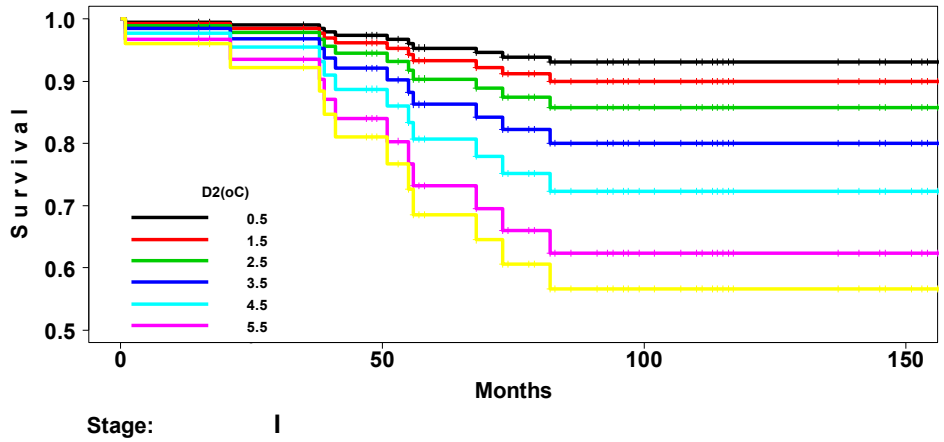

Figure 16. Survival probabilities using Cox's regression models with D2 as covariate, for values between 0.5 and 6 ºC.

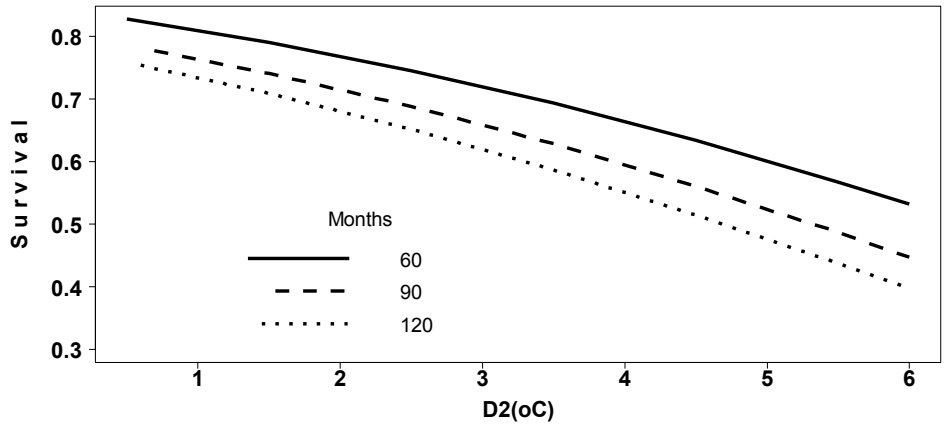

Figure 17. Survival probabilities using Cox's regression models with D2 as covariate, for survival of 60, 90 and 120 months.

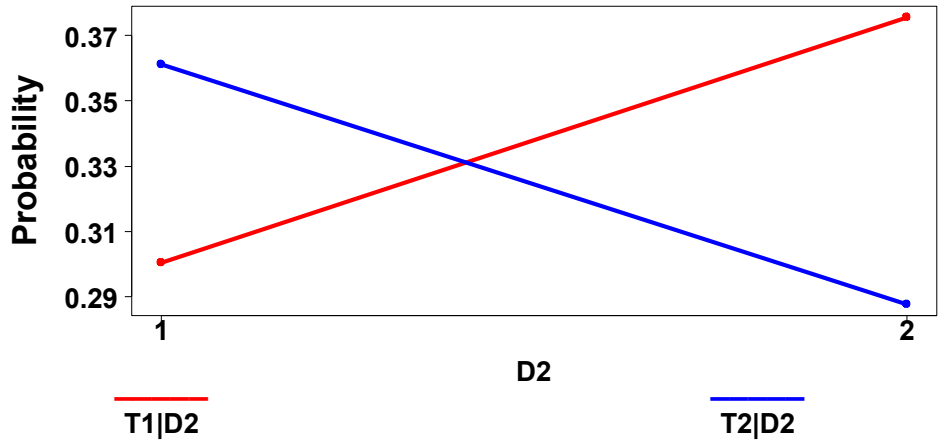

Figure 18. For stages I-II-III, conditional probabilities of time of life (T) with conditioned to D2 (for D2=≤2.5 and D2>2.5) using linear regression model where the function for this model is the logit link.

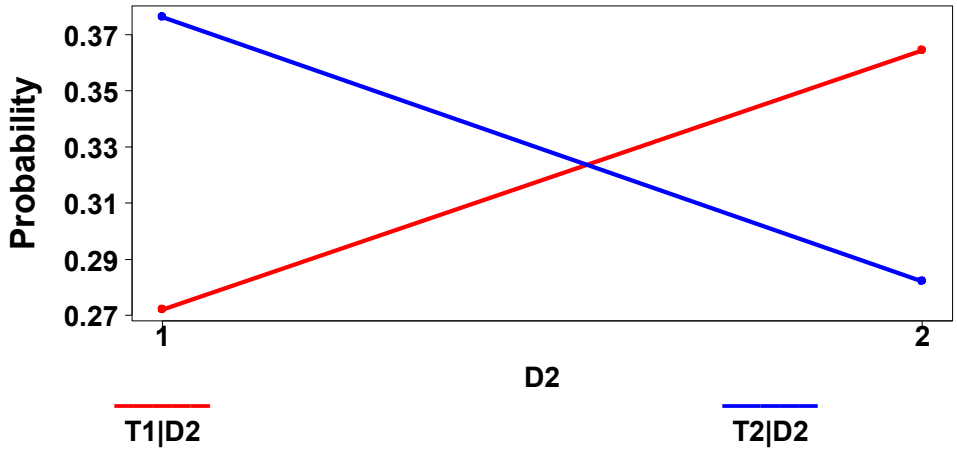

Figure 19. For stages I-II conditional probabilities of time of life (T) with conditioned to temperature difference (for D2=≤2.5 and D2>2.5) using linear regression model where the function for this model is the logit link.

4. Discusion

Breast cancer is one of the main causes of death at international level, so is of primary importance to advance in determine the factors influencing the prognosting of the disease as well as investigating the importance of controlling the risk factors as well as the risk factors. In this respect, this study confirms the hypothesis that some of the risks factors have an important contribution in the life expectations of patients after the disease has been diagnosticated. The age at diagnostic, age at first delivery of a live child, temperature difference between healthy and affected breast, and cancer stage, are relevant for prediction. This varies according to cancer stage.

Owed to population growth and aging, cancer mortality is expected to rise a 45% worldwide, from 7.9 to 11.5 millions of deaths, between 2007 y 2015 (WHO, 2014 c). Survival is increasing too, because of better detection protocols and treatments. Breast cancer, the most frequent in women and third at global incidence, has a survival rate at 5 years of 76% in Chile (Serra et al, 2009). The number is expected to increase in 2015 with the inclusion of breast cancer in the group of GES pathologies, a classs of diseaese that guarantees the diagnostic and treatment of women over 15 years.

Proper estimators for survival must be used to analyze pathology with a low mortality rate, that implies a high percentage of censored observations – of 73.59% in our sample–. Kaplan and Meier Product-Limit Estimator is useful to describe life and death events with censored data, but in some cases the survival curves obtained might

not be so different. Curve comparison tests as Log-Rang, and Breslow and Tarone-Ware help to determine if the observed difference is significant as long as curves do not cross or get too close. If this occurs the ignore differences that could be clinically interesting.

We added residual lifetime analysis by percentiles as residual lifetime is not too precise with a high percentage of censorship, Cox risk proportional model and a linear regression model with a logit link function.

We found that out of the 12 variables in the sample, only age at diagnostic, age at first childbirth, temperature difference between healthy and affected breast and cancer stage diagnosed are factors to forecast patients survival. Stage and ganglionic affectation are considered the main forecast factors for breast cancer (Cavada, s.f.; González et al, 2011; Murillo, 2003; Vásquez et al, 2005).

Age over 50 at diagnostic (AD) is a factor that contributes to survival if the disease is in stage I, II or III. González et al (2011) remark that age is a controversial forecast factor while Garicochea et al (2009) found that women AD over 40 survive more at any stage, and even more if they are in stage I.

The age at first live child birth (AFLB) also affects survival in stages I, II and III. Survival es lower if the AFLB is over 30 years.

Temperature difference between the healthy and affected breast (D2) is a forecast factor for stages I and II. When D2 is higher, there are more deaths. This is expected as the tumor growing faster presents a higher temperature. To measure this variable an infrared thermometer and visual inspection were used. There are more precise methods that can be used in the future.

Established risk factors like family antecedents, evolution time, parity, lactation, menarche age and menopause age have no relevance for survival. For instance, a woman with breast cancer in her family has twice the risk of developing the disease than a woman with no family antecedents, but, when diagnosed, the survival is not affected by this factor. Only in stage III we observed a relation between survival and the factors mentioned. This agrees with González et al. (2011), conducted in La Habana, where they found null influence of parity over survival and Flores-Luna et al. (2008), conducted in México, in which they concluded that menarche age and parity are no influential.

PLE curves for stage IV are not interpreted as forecast factor because the sample included only 47 patients (3.87% of sample size).

Of 1215 patients we found: 23,6% in stage I; 55,9% in stage II; 13,7% in stage III; and 3,9% in stage IV. This results differ to Serra et al. (2009) results with patients in two public hospitals in Santiago de Chile, between 1994 y 2005, where they found a higher percentage of patients in stages, III and IV (4,8% in stage I; 15,6% in stage II, 45,5% in stage III; 4,0% in stage IV). As Serra et al.(2009) study has more recent patients, we expected to find more patients in eary stages of cacer, but that is not the case. This difference could be attributed to the limited access the patients had to public health services and their sociocultural level. Martins and Radunz (2012) analyze the sociocultural effect on survival.

González et al. (2011) realizes that all patients in stage IV die before 2 years after diagnostic. When our study concluded we found 7 censored cases, and only one with information, is alive with a survival of 16 months.

Survival at 5, 10 y 15 years does not present big differences for Serra et al. (2009) de 76,2% y 78,2%; 69,0% and for our study: 68,2%; 63,6% y 66,3%, respectively. As there is no additional information at a national level, it is important to integrate more data from public and private health institutions and conduct more studies.

For the past two decades, breast cancer stage and treatment was analyzed from tumor size and the number of lymph nodes compromised. We found that age at diagnostic, age at first delivery of a live child, temperature difference between healthy and affected breast, and cancer stage, are relevant for prediction. This varies according to cancer stage.

For future work we propose to analyze the properties of the employed survival estimators and include new ones. We want to compare the survival of this sample with more recent patients to determine if the new national policies of early detection, diagnostic and treatment are affecting survival. And, we want to include new tumor molecular markers in our methodology.

5. Conclusions

Breast cancer is one of the main causes of death at international level, so is of primary importance to advance in determine the factors influencing the prognosting of the disease as well as investigating the importance of controlling the risk factors as well as the risk factors. In this respect, this study confirms the hypothesis that some of the risks factors have an important contribution in the life expectations of patients after the disease has been diagnosticated. The age at diagnostic, age at first delivery of a live child, temperature difference between healthy and affected breast, and cancer stage, are relevant for prediction. This varies according to cancer stage.

Finding good estimators for low death rate pathology is challenging because there is a high proportion of censored observations. Although PLE describes well survival and death events, when used to compare survival curves the difference might not be clear. The Breslow Tarone-Ware test helps to determine the significance of the difference. However, if the curves cross or come too close, the tests are not sensitive to differences.

As there is high censorship in the data, the residual survival lifetime was used, in percentiles.

The adjustment of linear regression model offers coherent results with PLE and Cox models.

Acknowledgements

This research was partially funded by grant # 4129, from the Pontificia Universidad Javeriana seccional Cali.

References

Agresti, A., 2012. *Categorical data analysis*. Ed.Wiley, New Jersey.

Ardí, E., J. Pinotti, M.Osis, and A. Faúndes, 1993.Variáveis Reproductivas e Risco para Cancer de Mama: Estudo caso-controle Desenvolvido no Brasil / Reproductive variables and the risk of breast cancer: Case-control study conducted in Brazil. *Boletín de la Oficina Sanitaria Panamericana (OSP)*.115(2), 93-102.

Arraztoa , J. 2004. *Factores Epidemiológicos y Biológicos del Cáncer de Mama. La Mama*. Ed. Mediterreano, 2nd Ed, 139-202.

Becher, H., S.Schmidt, and J.Chang-Claude, 2003. Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene–environment interaction. *International Journal of Epidemiology*. 32, 38-48.

Bellón, J.(n.d). Análisis de supervivencia. Epidemiología molecular de enfermedades infecciosas.Available in *http:\\epidemiologiamolecular.com\analisissupervivencia-ii*.

Breast. 2002. *American Joint Committee on Cancer*: *AJCC Cancer Staging Manual*. 6th ed. New York, NY, VA: Springer.

Cavada, G., I. Schiattino, M. Berríos, and L. Derio. (n.d.). *Sobrevida del cáncer de mama en Chile*, 1990- 2011.

Clavel-Chapelon , F. 2002. E3N-EPIC Group. Differential Effects of Reproductive Factors on the Risk of Pre- and Postmenopausal Breast Cancer. Results From a Large Cohort of French Women. *Br J Cancer*.4, 86(5), 723-7.

Cox, D.1972. Regression models and lifetables. J R Stat Soc. 34(B), 187-220.

Eliassen , A., Heather, Colditz , Graham , and Cols. 2006. Adult Weight Change and Risk of Postmenopausal Breast Cancer. *J Am Med Assoc,* 296(2), 193-201.

Ewertz M., S. Duffy, 1988. Risk of Breast Cancer in Relation to Reproductive Factors in Denmark. 58(1), 99-104.

Fleming T. R., and D. P. Harrington, 1981. A class of hypothesis tests for one or two samples of censored survival da.ta. *In Communications in Statistics.*

Flores-Luna, L., Salazar-Martínez, E., Duarte-Torres, R., Torres-Mejía, G., Alonso-Ruíz, P. y Lazcano- Ponce, E., 2008. Factores pronósticos relacionados con la supervivencia del cáncer de mama. *Salud Pública Mex, 50*, 119-125.

Garicochea, B., A. Morelle, A. Andrighetti, A. Cancella, A. Bós, and G. Werutsky, 2009. Age as prognostic factor in early breast cancer. *Rev Saúde Pública, 43*(2).

González, F. J., 2007. Thermal simulation of breast tumors. *Rev. Mexicana de Física*. 53(4), 323,326.

González, J., M. Morales, Z.López, and M. Díaz. 2011. Factores pronósticos del cáncer de mama. *Revista Cubana de Cirugía*, 50(1), 130-138. [on line]. http://www.redalyc.org/articulo.oa?id=281223026013.

Gore J. P., L.X. Xu, 2003. Thermal Imaging for Biological and Medical Diagnostics. *Biomedical Photonics Handbook*, CRC Press.

Jeong, J-H., S-H., Jung, and JP. Constantino, 2009. Nonparametric inference on median residual life function. Biometrics. (64), 157-163.

Kaplan, E.L., and P. Meier. 1958.Nonparametric estimator from incomplete observations. *In J Am Stat Assoc* 53, 457-481.

Lopez-Rios, O., E. Lazcano-Ponce, V., Tovar-Guzamn. 1997. La Epidemia de Cáncer de Mama en México: ¿Consecuencia de la Transición Demográfica?. *Salud Pública Méx*. 39(4).

Martínez, C., G. Ramírez, and M. Vazquez. 2009. Pruebas no paramétricas para comparar curvas de sobrevivencia de dos grupos que experimentan eventos recurrentes. *Revista ingeniería UC*, 16(3), 58-71.

Martins, L., V. Radunz. 2012. Survival rates to woman with breast cancer: Review. *Text Context Nursing, Florianópolis, 21*(4), 980-989.

Morales, G., A. Pollan. 1999. Morbilidad del Cáncer de Mama en la Mujer. *Rev Cubana Med Gen Integr*. 15(3), 247-252.

Murillo, M. 2003. Factores pronósticos en la recidiva local y a distancia en el tratamiento conservador del cáncer de mama. Trabajo de grado, Doctor en Medicina, Facultad de Medicina, Universidad Complutense, Madrid, España.

Novoa, A., M. Pliego, B. Malagon, and B. Bustillos B. 2006.Historia Natural del Cáncer de Mama. Ginecol Obstet Mex. 74(2), 115-120.

Ortiz, C., 2007. E, and Galván. 2007. Factores de Riesgo Reproductivos para Cáncer de Mama en Pacientes Atendidas en un Hospital Urbano de Segundo Nivel. *Ginecol Obstet Mex*. 75, 11-16.

Peralta, O. 2002. Cáncer de Mama en Chile: Datos Epidemiológicos. *Rev. Chil. Obstet. Ginecol*. 67(6), 439-445.

Salas, I., B. Ramirez, and E. Apodaca. 2006. Factores de riesgo para la presentación de cáncer de mama en Centro Médico Nacional Siglo XXI. Chihuahua, México. CIMEL. 11(2), 62-66.

Serra I., R. Martínez, X. Mimica, G. Cavada, C. Aguayo. Cáncer de mama en Chile. Un aporte clínico y epidemiológico según un registro poblacional metropolitano: 1.845 pacientes. *Revista Chilena de Cirugía, 61*(6), pp.507-514. [on line]. http://www.scielo.cl/pdf/rchcir/v61n6/art03. [consulted january 3 2013].

Singletary, SE., C. Allred, P. Ashley, et al.2002. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol*. 20 (17), 3628-3636.

Vázquez, T., G. Krygier, E. 2005. Barrios. Análisis de Sobrevida de una Población con Cáncer de Mama y su Relación con Factores Pronósticos: Estudio de 1.311 Pacientes seguidas durante 230 meses. *Rev Med Uruguay*. 21, 107-121.

WHO, 2014. World Health Organization. *Are the number cases increasing or decresing in the world?,* [on line]. *In http://www.who.int/features/qa/15/en/.*

Xie, W., P. Mccahon, K. Jakobsen, and C. Parish, 2004. Evaluation of the ability of digital infrared imaging to detect vascular changes in experimental animal tumours. *Int. J. Cancer*, 108(5). 790-794.