

## RESEARCH ARTICLE

# Relation of Alcohol/Tobacco use with Metastasis, Hormonal (Estrogen and Progesterone) Receptor Status and c-erbB2 Protein in Mammary Ductal Carcinoma

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### Abstract

**Background:** An association between alcohol/tobacco use and risk of metastasis in breast cancer has been clearly shown. **Materials and Methods:** The present study explored, in 48 samples of tissue from mammary ductal carcinoma (taken from Mexican women with an average age of 58.2±10.9 years), the association of risk of metastasis with the status of hormonal receptors and the c-erbB2 protein (by immunohistochemistry) as well as clinical, histopathological and sociodemographic factors. **Results:** Of 48 patients, 41.6% (20/48) presented with metastasis, 43.8% were positive for the estrogen receptor (RE+), 31.3% for the progesterone receptor (RP+) and 47.7% for c-erbB2 (c-erbB2+). The following combinations were found: RE+/RP+/c-erbB2+ 8.3%, RE+/RP+ 22.9%, RE+/RP- 20.8%, RE-/RP+ 8.3%, RE-/RP-/c-erbB2- 22.9% and RE-/RP- 47.8%. There were 12 patients who used alcohol/tobacco, of which 91.6% did not present metastasis and 81.9% were RE-/RP-. Compared to the RE-/RP-/c-erbB2+, the RE+/RP+/c-erbB2+ group had a 15-fold greater risk for metastasis (95% CI, 0.9-228.8, p=0.05). The carriers of the double negative hormonal receptors had a 4.7 fold greater probability of being (or having been) smokers or drinkers (95% CI, 1.0-20.4, p = 0.03). **Conclusions:** There was a clear protective effect of using alcohol and/or tobacco, in the cases included in the present study of mammary ductal carcinoma, associated with double negative hormonal receptors. However, this association could be due to a protective factor not measured (Neyman bias) or to a bias inherent in the rate of hospitalization (Berkson fallacy). This question should be explored in a broad prospective longitudinal study.

**Keywords:** Breast cancer - alcoholism - tobacco use - hormonal receptors - metastasis - Her/neu

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### Introduction

The incidence of breast cancer (BCa) has increased in Mexico during last one decade, especially among older women, while the downturn observed in mortality mainly reflects improved survival as a result of earlier diagnosis and better cancer treatment (Anaya-Ruiz et al., 2014) and multiples dietary factors such as soy food, fish and fruit consumption, dairy products, health status indicators, academic education, and some diseases like diabetes mellitus can affect the BCa incidence, although the results of ecologic studies like this must naturally be interpreted with caution (Abbastabar et al., 2013; Liu et al., 2014a). However, since the end of the 1980's, a multitude of articles have been published about the fact that the regular

consumption of alcohol and use of tobacco represent risk factors for breast cancer (Stefani et al., 2011; Cardenas-Rodriguez et al., 2012; de Menezes et al., 2013; Gao et al., 2013; Gou et al., 2013). Interestingly, some of the first studies actually showed a reduction of the risk of breast cancer with tobacco use (Meara et al., 1989) or alcohol consumption (Adami et al., 1988; Liu, M. et al., 2014b), or no association between smoking and breast cancer (Smith et al., 1994), further more, did not find any association between alcohol consumption and an increased risk of cancers of the lung, bladder, endometrium and ovary (de Menezes et al., 2013), and it was also observed that alcohol consumption may be inversely related to thyroid cancer. And on the other hand, in certain study suggest that cigarette smoking is associated with an elevated risk

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of breast cancer among former smokers in Serbia (Ilic et al., 2013). However, the authors identified probable factors of confusion that they recommended be taken into account and controlled in future studies.

By the end of the 1990's, the reports gave support to the hypothesis that the use of tobacco and alcohol increased the risk of breast cancer (Enger et al., 1999; Johnson et al., 2002), associated with tumors double positive to hormonal receptors of estrogen (ER+) and progesterone (PR+), although women having shorter menstrual cycles (<26 days) spend more time in the luteal phase when estrogen and progesterone levels are high and when breast mitotic activity is at its peak, compared to women with longer cycle length (Babu et al., 2013). Nevertheless, the polemic about factors of confusion continued (Hamajima et al., 2002). As of 2004, there was an increase in the number of individual studies and systematic reviews with meta-analysis, and they left little doubt about the association between breast cancer and the use of tobacco and/or alcohol. Alcohol consumption above all was clearly associated with this malady (de Menezes et al., 2013; Gao et al., 2013; Gou et al., 2013).

In the middle of the decade of 2000-2010, a great emphasis was given to the analysis of hormonal receptors and other tumor markers related to the regular use of tobacco and alcohol (Cui et al., 2008; Suzuki et al., 2008; Singhai et al., 2011; Liu et al., 2012). Later, there was a boom in triple negative studies (Phipps et al., 2008b; 2008a; Reis-Filho and Tutt, 2008; Rakha and Ellis, 2009; Li et al., 2013) that aimed to associate breast cancer with stress and the use of tobacco and alcohol (Tan et al., 2009b; Kabat et al., 2011; Islam et al., 2012).

The report by the panel of experts on tobacco use and the risk of breast cancer in Canada (Johnson et al., 2011) established without any doubt that there is an association of this malady with smoking and drinking. Nonetheless, the relation of hormonal receptors and other tumor markers with breast cancer has still not been clearly established for the diverse subtypes of cancer, the genes involved and other clinical and environmental factors (Larsson et al., 2010; Li et al., 2010; Hemmati et al., 2011; Marian et al., 2011; Park et al., 2012; Seitz et al., 2012).

In Mexico studies have shown that a high consumption of vitamin B12 is associated with a lower risk of breast cancer (Cox et al., 2011), while alcohol consumption and low levels of folates is related to an increased risk (Lajous et al., 2006), although it is polemic (Liu et al., 2013; Liu et al., 2014b). Studies in Mexico have also indicated a probable association between alcohol consumption and polymorphisms of the FGFR2 gene that increase the risk of breast cancer (Beasley et al., 2010).

The aim of the current study was to evaluate the association between the use of tobacco/alcohol, the status of hormonal receptors and the c-erbB2 protein (also known as Her/neu, a member of the epidermal growth factor receptor family), whose overexpression of this gene is related in the development and progression of breast cancer and its protein is an important marker target of breast cancer therapy (Jamal et al., 2009; Munjal et al., 2009; Tan et al., 2009a; Mitri et al., 2012), and the risk of metastasis in Mexican patients with mammary ductal

carcinoma, the most common type of breast cancer.

## Materials and Methods

### *Biological samples*

Forty eight samples of mammary ductal carcinoma in Mexican women were obtained and processed in the Pathology Department in the Specialty Clinic for Women of the Secretary of Defense (SEDENA). The age of the patients ranged from 31 to 87 years, with an average age of 58.2±10.9 years. The clinical and socio-demographic data related to these samples were taken from clinical files after obtaining the signed informed consent from all the corresponding patients. A patient was excluded from the study in case of having previously received antineoplastic treatment. The protocol of this research was approved by the Ethics Committee of the aforementioned clinic (number of Document SI-378).

### *Immunohistochemistry study*

Immunohistochemical analysis had been previously conducted in the Pathology Department in the Specialty Clinic for Women of the Secretary of Defense. An expert pathologist was always in charge of carrying out the analytical procedure according to the quality criteria of the hospital. For the present study the results of this analysis were found in the files of the aforementioned hospital department. Cases were considered positive to hormonal receptors if they complied with the standards established by the hospital for the immunohistochemical test conducted by the pathologist.

### *Statistical Analysis*

In the contingency tables of 2x2, the associations were contrasted with the Chi Squared test, or if appropriate with Fisher's exact test. The OR was calculated with 95%CI. For comparison of two averages, the U test of Mann-Whitney was applied. For comparison of three averages, the H test of Kruskal-Wallis was employed. Multivariate analysis was done with the model of unconditional logistical regression. In all cases the  $\alpha$  error tolerated was 0.05.

## Results

In 20 cases (41.7%) metastasis was found in axillary ganglia. Of these cases, 81.3% were menopausal, 95.8% sedentary, 72.9% with comorbidity (20.8% with diabetes mellitus), 37.5% with a family background of cancer, and 50.0% with 3 or more pregnancies. Additionally, 20.8% were smokers, 16.7% alcoholics and 14.6% exposed to biomass. The tumors ranged in size from 0.8 to 22.5 cm, with an average size of 3.2±3.9 cm. The Bloom-Richardson grading system was used to classify the cases of breast cancer, finding 18.8% in grade I, 35.4% in grade II and 45.8% in grade III. According to the Nottingham index, 87.4% of patients were classified as having a poor and 19.6% a regular prognostic. According to the TNM staging system, 74% were classified as grades II-III.

Regarding proteins, 43.8% were positive to RE, 31.3% to RP and 45.7% to c-erbB2. Additionally, 22.9% were

**Table 1. Combinations of Tumor Markers (RE and RP Hormonal Receptors and c-erbB2) Associated with Ganglion Metastasis in Mammary Ductal Carcinoma**

Combinations of tumor markers	Metastasis		Probability quotient	Logistical regression	
	Si (n = 20)	No (n = 28)		ORa	Pb
Triple negative	3 (15.0%)	8 (28.6%)	0.52	15	0.05
Triple positive	3 (15.0%)	1 (03.6%)	4.16	6.6	0.08
Double negative/erbB2 positive	2 (10.0%)	10 (35.7%)	0.28	6.6	0.04
Double positive/erbB2 negative	4 (20.0%)	3 (10.7%)	1.86	1.87	0.54
Other combinations	8 (40.0%)	6 (21.4%)	1.86	0.2	0.03
RE and RP negative	5 (25.0%)	18 (64.3%)	0.38	6.3	0.022
RE and RP positive	7 (35.0%)	4 (14.3%)	2.44	3.6	0.114
RE positive and RP negative	5 (25.0%)	5 (17.9%)	1.39	10.8	0.059
RE negative and RP positive	3 (15.0%)	1 (3.6%)	4.16	0.27	0.011

\*aOdds ratio that calculates the risk with the Exp(B) estimator; \*Significance determined by the Wald estimator

**Table 2. Semi-Quantitative Percentages and Punctuations of the Hormonal Receptors and Clinical and Sociodemographic Factors Associated with Ganglion Metastasis in Mammary Ductal Carcinoma**

Hormonal receptors or factors	Metastasis		P
	Yes (n = 20)	No (n = 28)	
Average percentage RE (DS)	60.2 (42.8)	32.9 (42.9)	0.02
Average Punctuation RE (DS)	1.7 (1.0)	0.8 (1.1)	0.01
Average percentage RP (DS)	38.5 (38.5)	16.3 (30.8)	0.006
Average Punctuation RP (DS)	1.7 (1.8)	0.7 (1.0)	0.006
Tobacco use	0 (0.0%)	10 (37.0%)	0.002
Alcohol use	1 (5.0%)	7 (25.9%)	0.06
Menopause	20 (100.0%)	20 (74.1%)	0.02
Age of first pregnancy < 20 years	15 (75.0 %)	12 (42.8)	0.02

triple negative, 8.3% triple positive, 47.8% double RH negative, 22.9% double RH positive, 20.8% RE+/RP- and 8.3% RE-/RP+.

There was no significant correlation between the status of the tumor markers studied and age, weight, height or IMC ( $p > 0.05$ ). Considering the three markers together (Table 1), the triple positive tumors had the highest metastasis probability quotient.

Taking the RE-/RP-H/c-erbB2+ (those with the least risk of metastasis) as a reference, in the model of logistical regression (Table 1) the triple positive samples had an OR with 15 times greater risk of metastasis ( $p=0.05$ ), and the other combinations had an OR of 6.6 ( $p=0.04$ ). It is noteworthy that the triple negative samples had a low risk of metastasis.

Analyzing only the hormonal receptors (Table 1), the combinations in which both values were positive (e.g., RE+/RP+) as well as RE-/RP+ show the greatest risk of metastasis, while the combinations in which both values were negative apparently have a protective role in this sense.

Taking the RE-/RP- (the tumors with the least risk of metastasis) as a reference for the model of logistical regression (Table 1), the double positive have an OR of 6.3 times greater risk of metastasis ( $p=0.02$ ) and the RE-/RP+ 10.8 times greater risk of metastasis ( $p=0.05$ ). The averages and percentages of semi-quantitative punctuations of RE and RP were significantly greater among the patients with metastasis (Table 2).

**Table 3. Averages of RE and RP According to Alcohol/Tobacco use in Patients with Mammary Ductal Carcinoma**

	Alcohol/tobacco use	N	Mean		P
			Typical deviation		
RE%	Both negative	36	51.5	44.4	0.03
	Positive to at least one	12	20	36.4	
RE#	Both negative	36	1.3	1.2	0.05
	Positive to at least one	12	0.67	0.98	
RP%	Both negative	36	29.7	37.1	0.03
	Positive to at least one	12	11.6	27.2	
RP#	Both negative	36	1.3	1.1	0.04
	Positive to at least one	12	0.58	1.084	

Regarding clinical, histopathological and socio-demographic factors, the use of tobacco and alcohol were apparently protective factors in relation to the risk of metastasis. Contrarily, menopause and an early age of the first pregnancy increased this risk (Table 2). The first pregnancy  $\leq 20$  years of age implied a risk of metastasis 4.0 times greater than the overall risk in the study (95%CI, 1.1-14.0).

For the regular use of tobacco and/or alcohol, there are combinations of variables that show confusion. Indeed, smokers had an OR=27 (95%CI, 4.1-181.3) of simultaneous alcoholism. Therefore, patients were classified as follows: both factors positive, both factors negative and mixed. Patients positive to both factors or only to one had a 4.7 fold greater probability (95%CI, 1.0-20.4) of being double RH negative ( $p=0.03$ ) compared to patients with any other combination. Moreover, the average percentage and punctuation of the RH were systematically lower in patients that used both tobacco and alcohol compared with those that consumed neither (Table 3).

Except for an association with protection against metastasis, the patients using both tobacco and alcohol did not show a relation with any other clinical or histopathological factor or any tumor marker.

When stratifying the analysis, in the group that did not use tobacco or alcohol, the presence of triple positive tumor markers implied a greater risk of metastasis, while the erbB2 positive combined with an absence of the two RH showed greater protection. In the group with either tobacco or alcohol use positive (but not both), with triple

negative markers there was an association with greater protection against metastasis. Isolating only the RH, among patients that did not use tobacco or alcohol, there was a greater risk of metastasis with both RH positive and a protective role with both RH negative. Contrarily, with patients positive for the use of both tobacco and alcohol, all combinations indicated a protective role, with the greatest protection found in the group with both RH negative.

## Discussion

The majority of authors hold that use of either tobacco or alcohol constitutes a risk factor for breast cancer, for a prognostic of a shorter survival time after a mastectomy, and for an increase in rates of tumor recurrence, based on empirical conclusions from large population studies and meta-analysis (Stefani et al., 2011; Park et al., 2012; Gou et al., 2013). However, the risk of metastasis and the status of the tumor markers associated with the use of alcohol and/or tobacco has been less studied.

Larsson et al. (2010) and Cui et al. (2008) reported an increased risk of double RH- tumors associated with the consumption of beta carotenes, which the former research team attributed to the fact that such elevated consumption is more common in smokers (Cui et al., 2008; Larsson et al., 2010). Similarly, Beasley et al. (2010) in Mexico followed the line of research begun by Lajous et al. (2006), and confirmed that alcohol consumption is associated with lower levels of folates, which in turn increases the risk of breast cancer (Lajous et al., 2006; Beasley et al., 2010).

In the present study we found that patients with breast cancer and without any previous treatment who regularly use alcohol and/or tobacco systematically show lower percentages of the expression of both hormonal receptors, and consequently a greater risk of being double RH-. This finding is in contradiction to the results of Suzuki et al. (2008), Enger et al. (1999) and Johnson et al. (2000), who reported that the consumption of alcohol is associated with diverse combinations of RH positive and negative, but not with double RH- (Enger et al., 1999; Johnson et al., 2000; Suzuki et al., 2008). On the other hand, the most recent report by Li et al. (2010) coincides with our results that RE- is present in patients with mammary ductal carcinoma who regularly consume alcohol; it is noted that patients presenting with ductal carcinoma in situ associated with comedo necrosis or hormone receptor negativity are more likely to have a microinvasive component in definitive pathology following surgery, and should be considered for sentinel lymph node biopsy procedure along with patients who will undergo mastectomy due to ductal carcinoma in situ (Li et al., 2010; Ozkan-Gurdal et al., 2014). Li et al. (2010) also observed that, in the case of invasive lobular carcinoma, there is an association with an increased frequency of RE+ among patients who regularly consume alcohol compared to those who never drink (Li et al., 2010).

Seitz et al. (2012) suggests that RE+ is more common in those who consume alcohol because this habit increases the levels of estrogens. However, it is not known why this tendency exists in patients with invasive lobular carcinoma and not with mammary ductal carcinoma (Seitz

et al., 2012).

Neither is the reason clear for the probable interaction of the polymorphism of the N-acetyltransferase 2 gene, tobacco use and the risk of breast cancer. More recent systematic reviews with meta-analysis (Zhang et al., 2010b) and individual studies (Zhang et al., 2010a) suggest that in the long run a history of smoking in women with a polymorphism of the N-acetyltransferase 2 gene can contribute to susceptibility to cancer. On the other hand, in our university there was an unpublished study by Marian et al. (2011) with solid evidence showing that in Mexican women the polymorphism of the FGFR2 gene mediates the increased risk of cancer produced by alcohol use. Is it then possible that in the current study the use of alcohol and/or tobacco is actually being confused with the status of folates and the FGFR2 gene polymorphism in relation to an increased risk of metastasis of mammary ductal carcinoma (Marian et al., 2011).

It is known that the double RH- are less responsive to hormonal treatments and that, together with triple negative tumors, are more aggressive and have a graver prognosis (Phipps et al., 2008b; 2008a; Reis-Filho and Tutt, 2008; Rakha and Ellis, 2009; Islam et al., 2012). Contrarily, the double RH+ respond better (Gonzalez-Angulo et al., 2007). Similar to the studies by Kabat et al. (2011) and Islam et al. (2012) the use of alcohol/tobacco was not related in the present study to an increased risk of metastasis with triple negative tumors, but did indeed lead to an increased risk with triple positive, double RH+ and above all RE-/RP+ tumors. Contrarily, a strong protective effect was apparently exercised by alcohol/tobacco use with double RH-/erbB2+ and double RH- tumors (Kabat et al., 2011; Islam et al., 2012).

Perhaps a certain proportion of mammary ductal carcinoma patients who use alcohol and/or tobacco generate double or triple negative tumors with greater frequency, as reported in other studies (Li et al., 2010; Singhai et al., 2011; Liu et al., 2012). We would add the possibility that they could be resistant to metastasis as well. It is also worth considering whether the aforementioned differences in susceptibility to metastasis according to tumor type could represent a typical bias due to the rate of hospitalization (Berkson Fallacy).

In a cross-sectional or retrospective study it is less likely to find hospitalized patients that are smokers or drinkers and have one of the more aggressive types of breast cancer (such as double or triple negative). It is more likely that these patients would have died relatively soon due to the primary tumor or metastasis. In fact, among patients with metastasis the rate of survival over a 5-year period is 20%, with an average survival of 12 to 24 months (Gonzalez-Angulo et al., 2007); such patients also have the possibility of dying even sooner due to diseases related to the use of alcohol and/or tobacco, including cardiovascular disease, cirrhosis, and cancer of the mouth, larynx or esophagus, as suggested by Collaborative Group on Hormonal Factors in Breast Cancer (Hamajima et al., 2002). All of these factors can cause the mistaken conclusion that alcohol and tobacco use have little effect on the incidence of metastasis or rate of survival of breast cancer patients.

If we compare our results with those of the majority of reports on the use of alcohol and tobacco as risk factors for cancer, it appears quite likely that the Berkson Fallacy is at play in the present study. It is commonly reported (e.g., see Hemmati et al., 2011) that the rate of survival after a mastectomy is notably lower among smokers, and that the rate of recurrence is higher among drinkers.

The Berkson Fallacy would explain why in the current contribution patients who use alcohol and/or tobacco (but have not shown evidence of metastasis) are more likely to be found in a cross-sectional or retrospective study. Contrarily, patients who do not use alcohol or tobacco and are double positive to hormonal receptors (those with the best prognostic in respect to a primary tumor) would have survived long enough to be hospitalized. Therefore, in a cross-sectional study it would be more likely to find such patients with a greater risk of metastasis.

It is also possible that the bias of Neymann is at play here. That is, the patients in our sample that regularly use tobacco and/or alcohol (even those who are double or triple negative) may have survived and avoided metastasis due to the protective influence of some other factor that was not measured.

In conclusion, the patients in the present sample who used alcohol and/or tobacco had a lower average percentage of expression of tumor markers, and therefore a greater proportion of double and triple negative tumors (associated with a null risk of metastasis). This result could mean that in Mexico patients who use alcohol and/or tobacco and have mammary ductal carcinoma tend to generate double or triple negative tumors with greater frequency (and therefore be resistant to metastasis) due to a protective factor not measured (Neyman bias) in the present study or to a bias inherent in the rate of hospitalization (Berkson Fallacy). These possibilities suggest the importance of a prospective longitudinal study of Mexican women with diverse types of breast cancer to explore the possible influence of alcohol and/or tobacco use as well as levels of folates and polymorphisms of the FGFR2 gene on hormonal markers and the risk of metastasis.

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