

Gynecological characteristics related to breast cancer in pre and postmenopausal women

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Background. The objective of this study was two fold: to identify gynecological characteristics that distinguish women diagnosed with early-stage breast cancer from those at more advanced stages; to identify distinguishing characteristics between premenopausal and postmenopausal women diagnosed with the same stage.

Population and method. 186 incident cases diagnosed with breast cancer were identified out of the 685 patients who were seen to in 2000-2001. The variables to be studied were obtained by means of a specific questionnaire which collected data concerning reproductive characteristics and contraceptive types.

Results. Significant differences in the mean age were found, since the early-stage group was younger (57.01 ± 12.82 vs. 65.06 ± 15.11). Characteristical factors found in pre-menopausal women were: early menopause, they either had no children or a single child, no breastfeeding practice and a more extensive use of contraceptives. Postmenopausal women presented more advanced stages, more pregnancies and less abortions.

Conclusions. By taking the obtained results into consideration, it would be recommendable to bring forward the age at which women are to be included in early detection programmes, and to conduct a follow-up of those women who present such factors to favour an earlier diagnosis of the disease.

Key words: breast cancer, menopause, risk factors.

Pastor Climente IP, Morales Suárez Varela MM, Magraner Gil JF, Llopis González A. Gynecological characteristics related to breast cancer in pre and postmenopausal women. *Clin Transl Oncol.* 2006;8(6):416-22.

INTRODUCTION

In Spain, breast cancer is the main cause of death due to cancer in women^{1,2}. The highest breast cancer rates have been observed in the North of Europe, whereas in our country it is comparatively at the lowest levels of Europe together with France and Greece, in agreement with the social and economic level development²⁻⁴, although it is growing as shown by the mortality rates published in Spain that turned from 19.19 cases per 100,000 women in 1980 to 24.22 cases per 100,000 women in 1990 and to 24.75 cases per 100,000 women in 1995⁵, and reaching 28.07 cases in 2000⁶. Despite of the efforts done, the morbidity and mortality due to breast cancer have been continuously increasing in Spain in the recent years, and they are expected to keep increasing⁵.

To diminish breast cancer incidence, research is aimed to modify risk factors when possible². Risk factors for breast cancer, include characteristics inherent to the patients that can not be modified and also characteristics that can be modified. Among the first we would include the age and genetic factors, such as breast cancer family history; and hormonal factors, such as early menarche and a late menopause, nulliparity, pregnancy, advance age and abortions. Whereas the occupation lifestyle, nutritional factors or oral contraceptive intake could be modified. It has been said thereof, that the reproductive factors could play an important role in its etiology but there are contradictory results about its role⁷⁻⁹. Relationship between nulliparity or early menarche in pre-menopausal woman and breast cancer is not clear either. Also, the breast-feeding has historically been considered as a protector factor, although nowadays this association can be only confirmed for pre-menopausal women. The same happens between breast cancer and abortion, or with the role on hormonal contraceptives consumption^{5,7,10}.

Together with the increase of the breast cancer incidence a social change has been observed in the recent years that influences on the woman's behaviour. This different lifestyle can modify the presentation characteristics and disease detection. To characterize the incident case at the present moment would allow us to make an earlier diagnose, specially bearing in

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Received 11 May 2005; Revised 17 November 2005; Accepted 21 December 2005.

mind that diagnosis at early stages is related to the woman's survival, as well as to know those factors that we could use or modify with the aim of improving the primary prevention.

For all before mentioned, it could be possible that risk factors would be different depending on the menopausal status¹¹. Different studies show that the early menarche is an important risk factor for pre-menopausal women, and not such important for post-menopausal, for whom the Quetelet index and the education are more important than for pre-menopausal women^{4,10,12}.

The main aim of this study is to identify those gynecological characteristics that differentiate women at early stages from those at more advanced stages, as well as to identify the differential characteristics between pre-menopausal and pos-menopausal patients with a same stage with the aim that results may favour an earlier diagnose.

MATERIAL AND METHODS

Hospital Clínico Universitario de Valencia is the reference hospital of Health Area number 4 of the *Comunidad Valenciana* with a total population of 500,528 habitants of which 155,836 habitants (51.8%) are women, according to the SIP (Population Information System) from year 2001.

Six hundred and eighty five patients were attended by the Oncology Service of the *Hospital Clínico* due to breast cancer during the period since January 2000 to December 2001.

Women with breast cancer coming to *Hospital Clínico* with residence in the metropolitan area of and municipalities corresponding to Health Area number 4, were considered as incident cases. 186 women filling the established criteria were identified.

Staging was performed according to the American Joint Committee on Cancer classification¹⁵.

For the study, there were gathered those data which, after an exhaustive review of the literature were considered as oncogenic factors in breast cancer^{4,14}. Data were obtained through a questionnaire filled in by the doctor in the personal interview during the patient's first visit at the hospital. The questionnaire included questions on reproductive characteristics (menarche age, numbers of pregnancies, number of children, number of abortions, age at first pregnancy, age at last pregnancy, breast-feeding, and age of menopause) and use of contraceptives.

The series was divided into seven groups depending on the stage in which the patients were diagnosed. At the same time, these stages were grouped into two groups, one which included the earliest stages with better prognosis 0, I, IIA and IIB, which will be called group DIS; and a second which included stages IIIA, IIIB and IV, with worse prognosis, which will be called group DAS.

TABLE 1. Comparison of hormonal and reproductive variable averages in mamma cancer of women in Valencia

Variable	Average	SD	Value p*
Age years			
Group DIS	57.01	12.821	0.002
Group DAS	65.06	15.11	
Menarche (years)			
Group DIS	12.61	1.73	0.472
Group DAS	12.33	1.63	
Menopause (years)			
Group DIS	50.12	4.61	0.267
Group DAS	48.76	4.51	
Number of pregnancies			
Group DIS	2.85	1.68	0.874
Group DAS	2.79	1.41	
Living children			
Group DIS	2.42	1.46	0.855
Group DAS	2.29	0.85	
Abortions			
Group DIS	1.44	0.59	0.348
Group DAS	1.75	0.96	
First pregnancy (years)			
Group DIS	26.05	4.12	0.1
Group DAS	27.64	4.04	
Last pregnancy (years)			
Group DIS	32.35	4.79	0.803
Group DAS	33.00	3.87	

SD: standard deviation; *: χ^2 test; DIS: diagnosis at initial stage; DAS: diagnosis at advanced stage.

At the same time, it was stratified between pre-menopausal and pos-menopausal patients at diagnosis.

The descriptive analysis, once checked the normal distribution by the Kolmogorov-Smirnov method, the average value, standard deviation (SD) and confidence level (CI) of 95% for the quantitative variable was used.

For the analysis of two parametric variables the Student's t-test was used and for variables with more than two categories, the ANOVA test was used. In case of non parametric variables we used the Mann-Whitney U test or the Kruskal-Wallis H test, for two or more variables, respectively.

For the comparison of proportions among groups, the χ^2 test was used with a CI of 95%.

RESULTS

The incidence rate was 59.6 patients with breast cancer per each 100,000 women. The 80.9% of our patients were diagnosed at initial stage (stages 0, I, IIA, IIB) whereas the rest (19.1%) were diagnosed at an advanced stage (IIIA, IIIB y IV).

The average and the standard deviation of the total population of the study divided into two groups, DIS and DAS, is described in table 1. The average age of the group of patients diagnosed at initial stages was statistically lower then that of the group diagnosed at

TABLE 2. Relative frequencies for mamma cancer grouped by menopausal status, at the moment of diagnosis

	Pre-menopausal women			Post-menopausal women		
	n	RF	CI 95%	n	RF	CI 95%
Menarche						
< 12	16	41.03	25.98-57.81	23	58.97	42.19-74.02
12	10	23.26	12.28-39.00	33	76.74	61.00-87.62
13	13	40.63	24.22-59.21	19	59.38	10.79-75.78
14	5	25.00	9.59-49.41	15	75.00	50.59-90.41
> 14	6	30.00	12.84-54.33	14	70.00	45.67-87.16
Pregnancies						
0	11	57.89	33.97-78.88	8	42.11	21.12-63.03
1	12	50.00	29.65-70.35	12	50.00	29.65-70.35
2	14	28.57	17.03-43.47	35	71.43	56.53-82.97
3	13	35.14	20.72-52.58	24	64.86	47.42-79.28
> 3	3	8.82	2.31-24.81	31	91.18	75.19-97.69
Children						
1	15	55.56	35.64-73.96	12	44.44	26.04-64.36
2	17	27.42	17.22-40.44	45	72.58	59.56-82.78
3	7	29.17	13.44-51.25	17	70.83	48.75-86.56
> 3	1	5.00	0.26-26.94	19	95.00	73.06-99.74
Abortions						
No	30	32.97	23.88-43.71	61	67.03	56.29-76.32
First pregnancy						
< 20	2	66.67	12.53-98.23	1	33.3	1.77-87.47
20-24	19	38.78	25.54-53.78	30	61.22	46.24-74.46
25-29	17	27.87	17.51-41.03	44	72.13	58.97-82.49
> 29	4	17.39	5.72-39.54	19	82.61	60.45-94.28
Last pregnancy						
< 25	0	0	0	2	100.0	19.79-100.0
25-29	8	30.77	15.09-51.90	18	69.23	48.10-84.91
30-34	12	35.29	20.30-53.53	22	64.71	46.47-79.70
> 34	4	10.81	3.52-26.36	33	89.19	73.64-93.48
Breastfeeding						
Yes	30	28.85	20.59-38.69	74	61.54	51.41-70.76
Breastfeeding duration						
0-3	0	0	0	4	100.0	39.58-100.0
4-12	4	22.22	7.37-48.08	14	77.78	51.92-92.63
12-24	2	33.33	6.00-75.89	4	66.67	24.11-94.00
> 24	0	0	0	1	100.0	5.46-100.0
Contraceptive						
N	18	27.69	17.65-40.39	47	72.31	59.61-82.35

n: number of sample; RF: relative frequency; CI: confidence index.

advanced stages. The rest of studied variables did not show any differences.

Pre-menopausal and post-menopausal women represented the 35.1% and 66.9% of the patients respectively. Table 2 describes the relative frequency and the confidence level index of each of the study's variables, grouped by menopausal status. Significant differences have been obtained at the variable «menarche age at 12 years old», where the proportion of post-menopausal is higher ($p = 0.004$); the number of children, where the group of post-menopausal more frequently have «2 children» ($p = 0.005$); the women «not having undergone any abortion» is lower in the pre-menopausal group ($p = 0.002$); as for the age of first pregnancy, proportion of post-menopausal women who had her «first child between 25-29 years» is higher ($p = 0.001$).

They were also more frequent in post-menopausal women group: the breast-feeding ($p = 0.002$) and the non use of anticonceptive ($p = 0.001$). The rest of the variables did not show significant differences between the two groups or could not be compared due to a lack of sample.

Table 3 describes the study series dividing, at the same time, the pre and post-menopausal groups into two, corresponding to groups DIS and DAS sub-groups. Significant differences have been obtained between pre-menopausal women from group DIS and those from group DAS in: no abortions ($p = 0.015$) and breastfeeding ($p = 0.016$), being both more frequent in the group DIS of pre-menopausal women. In the group of post-menopausal, differences between groups DIS and DAS were considered statistically significant in «menarche age at 12 years»

TABLE 3. Relative frequency for mamma cancer grouped by stages depending on selected reproductive variables of the Spanish women

	Pre-menopausal women						Post-menopausal women					
	Group DIS			Group DAS			Group DIS			Group DAS		
	n	RF	CI 95%	n	RF	CI 95%	n	RF	CI 95%	n	RF	CI 95%
Menarche												
< 12	15	93.75	67.71-97.67	1	6.25	0.33-32.29	18	78.26	55.79-91.71	5	21.74	8.29-44.21
12	8	80.00	44.21-96.45	2	20.00	3.54-55.78	27	81.82	63.92-92.38	6	18.18	7.62-36.08
13	11	84.62	53.66-97.29	2	15.38	2.71-46.34	16	84.21	59.51-95.83	3	15.79	4.17-40.49
14	4	80.00	29.88-98.95	1	20.00	1.05-70.12	13	86.67	58.39-97.66	2	13.33	2.34-41.61
> 14	5	83.33	36.48-99.12	1	16.67	0.88-63.52	13	92.86	64.17-99.63	1	7.14	0.37-35.83
Pregnancies												
0	10	90.91	57.12-99.52	1	9.09	0.48-42.88	6	75.00	35.58-95.55	2	25.00	4.45-64.42
1	12	100.0	69.87-100.0	0	0	0	11	90.91	57.12-99.52	1	9.09	0.48-42.88
2	11	78.57	48.82-94.29	3	21.43	5.71-51.18	25	71.43	53.48-84.76	10	28.57	15.24-26.53
3	10	76.92	45.98-93.84	3	23.08	6.16-54.02	21	87.50	66.54-96.71	3	12.50	3.29-33.46
> 3	3	100.0	31.00-100.0	0	0	0	27	87.10	69.24-95.78	4	12.90	4.22-30.76
Children												
1	15	100.0	74.65-100.0	0	0	0	10	83.33	50.88-97.06	2	16.67	2.94-49.12
2	14	82.35	55.80-95.33	3	17.65	4.67-44.20	32	71.11	55.48-83.16	13	28.89	16.84-44.52
3	4	57.14	20.24-89.19	3	42.86	11.81-79.76	16	94.12	69.24-99.69	1	5.88	0.31-30.76
> 3	1	100.0	5.46-100.0	0	0	0	17	89.47	65.46-98.16	2	10.53	1.84-34.54
Abortions												
No	24	80.00	60.87-91.60	6	20.00	8.40-39.13	48	78.69	65.98-87.74	13	21.31	12.26-34.02
First pregnancy												
< 20	2	100.0	19.79-100.0	0	0	0	1	100.0	5.46-100.0	0	0	0
20-24	17	89.47	65.46-98.16	2	10.53	1.84-34.54	27	90.00	72.32-97.38	3	10.00	2.82-27.68
25-29	14	82.35	55.80-95.33	3	17.65	4.67-44.20	37	84.09	69.32-92.84	7	15.91	7.16-30.67
> 29	3	75.00	21.94-98.68	1	25.00	1.32-78.06	13	68.42	43.50-86.44	6	31.58	13.56-56.5
Last pregnancy												
< 25	0	0	0	0	0	0	2	100.0	19.79-100.0	0	0	0
25-29	7	87.50	46.68-99.34	1	12.50	0.66-53.32	16	88.89	63.93-98.05	2	11.11	1.95-36.07
30-34	9	75.00	42.84-93.31	3	25.00	6.94-57.16	17	77.27	54.18-91.31	5	22.73	8.69-45.82
> 34	4	100.0	39.58-100.0	0	0	0	27	81.82	63.92-92.38	6	18.18	7.62-36.08
Breastfeeding												
Yes	25	83.33	64.55-93.70	5	16.67	6.30-35.45	62	83.78	72.99-90.98	12	16.22	9.02-27.01
Duration of breastfeeding												
0-3	0	0	0	0	0	0	4	100.0	39.58-100.0	0	0	0
4-12	3	75.00	21.94-98.68	1	25.00	1.32-78.06	14	100.0	73.24-100.0	0	0	0
12-24	1	50.00	2.67-97.33	1	50.00	2.67-97.33	3	75.00	21.94-98.68	1	25.00	1.32-78.06
> 24	0	0	0	0	0	0	1	100.0	5.46-100.0	0	0	0
Contraceptive												
N	15	83.33	57.73-95.59	3	16.67	4.41-92.27	40	85.11	71.08-93.31	7	14.89	6.69-28.92

DIS: diagnosis at initial stage; DAS: diagnosis at advance stage; RF: relative frequency; n: sample number; CI: confidence index.

($p = 0.008$); number of children, where the group DIS has a higher frequency of «2 children» ($p = 0.01$); «not having undergone abortions» ($p = 0.0005$); the «age of first abortion between 25-29 years» ($p = 0.0009$), and the «pregnancy age > 34 years» ($p = 0.008$) being all of them more common on women of group DIS. Breast-feeding ($p < 0.05$) and the non use of contraceptive ($p = 0.0005$) were also more common in post-menopausal women from group DIS.

The rest of the variables did not show significant differences between the two groups or it could not be possible to calculate because the sample was insufficient.

DISCUSSION

First of all it is to stress the fact that this study has been performed in one only health area and in one only hospital, which ensures the same access to the health services to all population, as well as an uniformity of criteria for diagnosis and staging as a result of working with one only medical team under the same protocol.

Besides sex, age is the most important risk factor in breast cancer. Breast cancer increases rapidly with the age during the fertile years and, subsequently continues increasing in a lower proportion^{2,14}. The average age of cancer detection in our patients was of

57.14 years, similar to the 56 years described by Zorzona et al¹⁵. However, grouped stage by stage, this value differs in women diagnosed at early stages with an average age of 57.01 years compared to the 65.06 years of those who have been diagnosed at more advanced stages, which could indicate a delay in diagnosis. Although it has been indicated that the risk of developing a breast cancer is more frequent at advanced ages¹⁶, it is possible that younger women, possibly due to a higher awareness, goes to the doctor earlier than older women and therefore, is also diagnosed at earlier stages; what would explain this age difference. Also the fact that the 66.9% of the patients in this study were menopausal women is related to the high average in which the cancer was diagnosed¹⁷.

The early menarche constitutes one of the main endogenous risk factors for breast cancer⁵, possibly due to the fact that it increases the years of exposition to the estrogens which are directly related with the risk of breast cancer^{1,9,14,18}. Any difference was found in the menarche age stage by stage, although in both groups it was slightly lower than in the results referred by Tovar-Guzmán et al¹¹. The fact that significant differences were detected in the menarche age at 12 years in the post-menopausal women does not seem to be a very important differential factor, although further studies would be necessary.

However, although with no significant differences, it should be stressed that in pre-menopausal women early menarche is more frequent, whereas in post-menopausal women late menarche has a major importance. This seems to indicate that late menopause protects, in a certain way, from developing breast cancer, because it seems to delay its appearance. On the contrary, women with an early menarche possibly start very early to be exposed to progesterone, and develop the disease at a younger age.

At the same time, early menarche could be related with cancer diagnosis at more advanced stages, given that in post-menopausal women, group DIS (stages 0,I and II) have a later menarche than group DAS (stages III and IV). However, this situation does not seem to occur in pre-menopausal women.

In other studies, women with late menopause presented a higher risk of cancer¹¹. This fact could be due to the fact that a late menopause also increases the exposition time to progesterone¹⁴. On the contrary, a surgically induced menopause (by oophorectomy or hysterectomy) before the age of 35 years seems to produce a decrease of the risk¹. It also seems that post-menopausal women have a more advanced stage than the pre-menopausal women¹⁷. In our study, it seems that this tendency also occurs with 7 (14%) pre-menopausal women with stages III and IV and 21 (18.9%) post-menopausal women with advanced stages, with no significant differences.

Regarding the number of pregnancies it is proven that the risk of developing breast cancer increases with the nulliparity^{10,11} and decreases with the number of pregnancies¹⁴, with the exception that the protecting effect is just observed in pregnancies that end with the born of a viable fetus¹⁶. Other studies indicate that the following normal term pregnancies also have influence in the risk¹⁴. There are no differences between stages in our study and the existing differences between the pre-menopausal and post-menopausal group indicate that post-menopausal women have 2 pregnancies more frequently than pre-menopausal women. It is to stress the fact that in our study post-menopausal woman had more than three pregnancies in 31 cases (27.9%) compared to 3 (5.6%) of the pre-menopausal women, being the nulliparity much more common in pre-menopausal women. This is in agreement with that pregnancies protect from breast cancer or at least it delays its onset, thus developing it at older ages. Also, post-menopausal women of group DIS seem to have a higher number of pregnancies than those of group DAS, but differences were not found to be significant.

Bearing in mind that the risk reduction only takes place in normal term pregnancies, the existence of abortions was studied. Zornoza et al reported a 37% of abortions in its series¹⁵ and different studies seem to indicate an association between abortions and mamma cancer, although there is no agreement on this point¹². In our study a 34% of the patients have undergone at least one abortion, although no differences were found between the DIS and the DAS groups, being the average rate of abortion slightly higher for the group of advanced stages. The proportion of post-menopausal who have not undergone abortions is higher, what coincides with the literature, indicating that not having undergone abortions is a protector factor¹⁴. On the other side, women of the group DIS at early stages have not undergone abortion than those of DAS group, which could be related to the most advanced stages.

It has to be taken into account that the biggest limitation has been to do not know if abortions were spontaneous or not.

Also, the number of children and the normal term pregnancies of the patients were studied, because in different studies a risk reduction of 3% for each normal term pregnancy was observed^{10,15}. Again, no differences between the DIS and the DAS groups were found, although the average was slightly higher for the group of early stages. The fact that a higher percentage of women who had two children were post-menopausal could also be related with the higher age of the group, and also that two children is the most common number of children in the population. It is very outstanding that pre-menopausal women of our series have in 15 cases (57.5%) just one child, com-

pared to the 12 cases (12.9%) of the post-menopausal women; being the proportion of women in this group much higher (66.9%). Again, this could indicate that having a normal term infant is a factor that delays the onset of breast cancer.

Early maternity reduces the risk of breast cancer, which could probably be explained by an early maturity of the breast tissue due to the hormonal changes associated to a normal term pregnancy. This process could be protective by diminishing the epithelium susceptibility against further dysplastic processes^{15,19,20}. The age of first pregnancy is lower, but not statistically significant for initial stages, which would be an interesting characteristic in order to differentiate both groups. Between pre and post-menopausal women a significant difference in the age of first pregnancy between 25 and 29 years was found; the higher proportion was for post-menopausal women within a tendency of the post-menopausal woman to have children at an older age. Having children at a younger age seems to be here a factor that predisposes the appearance of cancer at early ages.

Regarding the age of the last pregnancy, it establishes a difference between post- and pre-menopausal woman given that the first represents a higher proportion of women who have had her last child after 34 years old. This difference does not exist at comparing per stages.

Classically, women who did not breastfeed have been included in the group of risk of breast cancer¹⁵. The comparative analysis of our population depending on early or advanced stages does not show significant differences. Only the post-menopausal population group and the post-menopausal DIS group presented a percentage significantly higher than for the positive breastfeeding compared to pre-menopausal women? In both cases, DIS group has breastfed in a higher proportion than the DAS group, with significant differences; therefore breastfeeding, in addition to protect against breast cancer, it would allow to diagnose at earlier stages in case of developing cancer.

The hypothesis that the prolonged breastfeeding protects against breast cancer is based on the epidemiological evidence that countries with lower rates of mortality due to breast cancer have as a common practice the prolonged breastfeeding²¹. In some studies a relationship between dose response between the number months of breastfeeding and a lower proba-

bility of mamma cancer in women younger than 40 years old^{22,25} has been found. On the other side, other studies have shown that this relationship does exist but just in post-menopausal women^{22,24}. We could not study this aspect because sufficient data was lacking for performing a comparable sample but, however, most of these women belong to the post-menopausal group, thus it seems, at least, that it does protect or delay in a certain way the onset of breast cancer.

About the association of the use of oral contraceptives and breast cancer, results are contradictory. It is well-known that oral contraceptives produce a stimulation of the proliferative activity of the stem cells of the lobular epithelium, while the progesterone increases, at the same time, the alveolar cell growth. Some studies show an increase of breast cancer risk in women taking oral contraceptive, regardless of the dose, age of first use or time of use^{1,23,26}. The major effect was observed in women regularly taking oral contraceptive (24% of risk increase) and the risk descends after 10 years of not taking it^{1,25}. Other studies have also observed a great increase of risk in women who started using this medication before 25 years old and with a prolonged use¹¹. On the contrary, other studies do not evidence this relationship. It is possible that breast cancer is more related with the sort of hormone than with the duration of treatment¹⁵. In our population it became evident that post-menopausal women have not consumed contraceptives in a higher proportion than pre-menopausal women. We, once more, insist on the age as a possible explication to these differences. However, it could also indicate that the fact that not consuming contraceptives delays the disease development.

In this study a series of variables have been identified that, according to the results, seem to influence in the appearance of breast cancer and in the development thereof at one or other stage, thus it could be used for incorporating it to early detection programmes. Therefore, having detected the early menopause and the nulliparity or only one child as characteristics that influence on breast cancer appearance in pre-menopausal women, it would be recommendable to put forward the age when the women are included in early detection programmes, and perform a follow-up in those who present these factors in order to advance the diagnosis.

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