# The contribution of the CEA marker to CA 15.3 in the follow-up of breast cancer

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**Summary**

*Purpose of investigation:* The clinical use of tumor markers during breast cancer follow-up is still surrounded by controversy. The objective of this study consisted of determining the contribution of the CEA marker to CA 15.3 in the follow-up of breast cancer patients as applied to clinical practice.

*Methods*: Three hundred and eighteen cases of women with breast cancer were analyzed retrospectively as far as the sensitivity, the specificity and the positive and negative predictable values of the CA 15.3 and CEA markers.

*Results*: Of the 318 patients, 59 suffered a relapse during the study. After evaluation of both markers the sensitivity was 56.8% (CA 15.3: 47.4%), the specificity 85.3% (CA 15.3: 88.4%), the positive predictable value was 46.4% (CA 15.3: 48.2%) and the negative predictable value was 89.41% (CA 15.3: 88%).

*Conclusions*: The low sensitivity of studied tumor markers proved of limited use on a clinical scale.

*Key words:* Breast cancer; Tumor markers; CA 15.3; CEA; Follow-up.

## Introduction

Even after breast cancer treatment geared at complete recovery the risk of relapse persists for a long time, well within 30 years or beyond [1], although in the immense majority of cases this happens in the first ten years of initial intervention.

The tumor markers are substances that denote the existence and the growth of a tumor [2]. Easily detectable in organic fluids they are used for screening during follow-up. They also help speed up the tasks of cancer relapse detection. One of these markers is the carcinoembrionic antigen (CEA), first described by Gold and Freedman in 1965 [3]. It belongs to an interrelated family of macromolecules with interlaced immunological reactivity and a wide, variable distribution range in different normal tissues, be it fetal or mature, and especially in cancerous tissues. Thus, CEA has been intensively studied and employed due to its vast diffusion in organic fluids and serves as a reference for other, newly discovered markers. Another such a marker is CA 15.3, which was initially described by Kufe *et al.* in 1984 [4] and now is recognized as a circulating antigen defined by two monoclonal antibodies, 115D8 and DF3.

The objective of this study consisted of determining the contribution of the CEA marker to CA 15.3 in the follow up of breast cancer patients as applied to clinical practice.

## Materials and methods

In total, 2,093 serum level determinations of CA 15.3 and 1,920 of CEA were carried out retrospectively within the framework of follow-up after 318 breast cancer operations. The average age of intervened patients was 55 years (with age limits between 26 and 91). All the patients had previously been diagnosed with breast cancer and operated on accordingly for therapeutic purposes, after discarding the existence of regional metastasis. Anamnesis, exploration and thorax X-rays were carried out biannually supplanted by annual mammography, while other tests were reserved for the appearance of symptoms or suggestive signs of relapse. The two mentioned markers were routinely incorporated into the follow-up protocol at the beginning of 1994, and their levels were checked during each biannual control. Thirteen cancer patients were excluded from the study because their blood showed high levels of the markers in the routine analysis prior to the intervention. The determination of CEA and CA 15.3 levels in blood were carried out by relying on the commercial enzyme-immunoassay kit (analyzer ES-300, Boehringer Mannheim, Germany). Marker levels beyond 30 U/ml and 5 ng/ml, respectively, were considered pathological in all cases.

To confirm false increases of the marker levels, their presence was scrutinized for at least 12 months in patients with pathological readings in absence of metastasis. Likewise, the patients with confirmed metastasis and normal levels of CEA and CA 15.3 were regularly screened up to their exitus, discontinuation of the follow-up or termination of the study. The average period of patient follow-up lasted 60.9 months, counted from the moment of intervention (ranging between 6 and 120 months). During the last 12 months of the follow-up we continued clinical checkups and marker screening of all patients but without including the findings in the discussed follow-up or final marker levels.

## Results

From the total of 318 patients included in the current study, 256 (80.5%) remained disease-free, while 59 (18.5%) suffered a relapse that culminated in exitus of 25 patients. Another three patients died during follow-up but for causes not related to breast cancer.

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The levels of CA 15.3 rose in 28 cases of confirmed metastasis or local relapse, and among them in 16 patients before symptoms had appeared or we could establish the diagnosis. The CEA levels rose in 15 cases with eight of them accompanied by a simultaneous or posterior increase of CA 15.3 levels, whereas in two cases this occurred six months before, and in five cases the CEA levels rose in patients with relapses or metastases, but where CA 15.3 levels had not risen a minimum of six months later or until the patient's exitus (Table 1).

Table 1. — *True positive cases detected by the levels of CEA but not by CA 15.3 levels.*

| Patient | Origin of metastasis | CEA values in U/ml | Time of increase |
|---|---|---|---|
| 1 | Lung | 8.9 | = |
| 2 | Lung | 5.2 | = |
| 3 | Local relapse | 7.7 | = |
| 4 | Supraclavicular | 5.2 | – 4 months |
| 5 | Local relapse | 7.4 | + 4 months |

Where the increase could have occurred before (-) coinciding with (=) or after (+) the diagnosis of metastasis.

CA 15.3 screening generated 30 false positive cases, since in spite of the increased levels above 30 U/ml we could not confirm any metastasis during follow-up a minimum of one year later. CEA confirmed an additional eight cases, besides three cases that coincided with false increases of CA 15.3. The average false positive CA 15.3 reading was 35.4 U/ml (within the limits of 30.1 and 58.4), whereas this average for CEA was 6.6 ng/ml (within the limits of 5.3 and 10.2). We did not find pathological levels of CA 15.3 in 31 patients with confirmed metastasis throughout the follow-up period superior to one year, even though 21 of them suffered tumor relapses. The ten remaining patients had died or abandoned the follow-up before the year's end. In the total of 31 cases there were five where CEA rose as shown in Table 1. In 26 cases, where none of the tumor markers could be determined, 53.8% or 14 cases accounted for local relapses, with five of these constituting bone, four lung and three regional metastases. Considering both markers, the sensitivity was 56.8% (CA 15.3: 47.4%), the specificity 85.3% (CA 15.3: 88.4), the positive predictable value 46.4% (CA 15.3: 48.2%) and the negative predictable value 89.4% (CA 15.3: 88%), respectively.

## Discussion

Many studies emphasize the fact that almost all breast cancer relapses manifest early with signs and symptoms [5]. The early detection of metastasis triggered by the breast cancer in an asymptomatic stage does not improve the disease-free survival or the global survival [6] rates, which questions the concentrated efforts of precociously diagnosing metastases. The oncological follow-up of patients treated for breast cancer is utterly useful for screening against a local relapse diagnosed precociously. It is also helpful in screening against the relapse risk of breast cancer treated in a conservative way and against the increased risk of appearance of a primary breast cancer in the healthy breast [7]. The other usages of these markers are still debatable, at least until we will dispose of more effective therapeutic means against breast cancer metastasis. In 1996 the American Clinical Oncological Society fashioned out and distributed a practical clinical guide for the employment of tumor markers in screening for breast as well as colorectal cancers. Thus, this guide recommended that the CEA and CA 15.3 markers should not be used for screening, diagnosis, grading or follow-ups after the primary treatment of the tumor [8], which reflect low sensitivity and lack of reliability when it comes to these markers; an update enforcing the clinically negative conclusions appeared later [9]. Diverse studies have established that sensitivity of CA 15.3 for detecting relapses during breast cancer follow-up is around 61-79% (10,11). In our study this sensitivity was found to merely reach 47.4%; in addition to the fact that in five cases CA 15.3 did not rise, but CEA rose indeed, while only in one case did this happen ahead of the diagnosis. Indeed, Sütterlin *et al.* [12] found results that matched ours in their study on sensitivity of CEA and CA 15.3 during 1,228 determinations in 664 patients. Thus the authors concluded that the clinical advantage of using this marker is rather limited.

The presence of false positives reinforce the issue since they generate a series of inconveniences such as repetitive blood analyses without protocols, complementary tests that are not routine and in general, a great anxiety to which affected patients are submitted unnecessarily. By adding the CEA determination to our study it increased to eight false positive cases. When we raised the limit of the pathological level of CA 15.3 from 30 to 35 U/ml and that of CEA from 5 to 10 ng/ml we were able to observe a decrease in the number of false positive cases, however 18 patients with metastasis were not diagnosed at that moment, but much later on. The solution may rest in the generally agreed on proposal offered during the Berlin meeting in February 1995 [13] that suggested determining the tumor markers only in cases with obvious symptoms, signs of relapse or regional metastasis. In addition, by incorporating into the protocol information that contributes to the determination of the C-erbB-2 (HER2) oncogenes, it may increase the sensitivity of breast cancer relapse detection up to 10.5% [14]

We have begun to determine the C-erbB2 marker, because in clinical practice the low sensitivity of the breast cancer marker CA 15.3 for the detection of metastasis, even when complemented with the determination of CEA, limits the clinical usefulness and puts into doubt the effectiveness of routine determinations during the follow-up of all affected patients.

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