Prognostic Value of Chorionic Gonadotropin β Gene Transcripts in Human Breast Carcinoma

Ivan Bièche, Vladimir Lazar, Catherine Noguès, Thierry Poynard, Yves Giovangrandi, Dominique Bellet, Rosette Lidereau, and Michel Vidaud

Laboratoire de Génétique Moléculaire [I. B., Y. G., M. V.] and Unité de Recherche Associée 1484 Centre National de la Recherche Scientifique [V. L., T. P., D. B.], Faculté des Sciences Pharmaceutiques et Biologiques de Paris, 75006 Paris; and Laboratoire d’Oncogénétique [I. B., R. L.] and Département de Statistiques Médicales [C. N.], Centre René Huguenin, 92211 Saint Cloud, France

ABSTRACT

The β subunit of human chorionic gonadotropin is potentially encoded by six genes, which can be categorized into two types based on a sequence change at codon 117: GCC for the type I and GAC for the type II genes. We previously showed that, whereas type I genes were exclusively expressed in normal breast tissues, expression of type II genes was associated with malignant transformation (Bellet, D., et al. Cancer Res., 57: 516–523, 1997). We designed a simple and robust test (the CG117 assay) that measures the percentage of type II over both types of chorionic gonadotropin β mRNAs. Normal breast tissues consistently had a negative CG117 index, whereas cancer breast tissues showed indexes ranging from 0 to 100%.

The prognostic significance of the CG117 index was investigated in a series of 99 unilateral invasive primary breast cancer patients with known long-term outcome (median follow-up, 9 years).

The CG117 index was positive in 48 (48.5%) of the 99 tumor mRNA samples. The index was not significantly associated with standard prognostic parameters, including clinical and macroscopic tumor size, histopathological grade, and lymph node status or steroid receptor status. Patients with a positive CG117 index in primary tumor mRNA had significantly shorter metastasis-free survival (P = 0.014) and overall survival (P = 0.038) after surgery, compared to patients with a negative index. The prognostic significance of the CG117 index persisted in Cox multivariate regression analysis, both for metastasis-free survival (P = 0.008) and overall survival (P = 0.016), together with lymph node status (P = 0.027 and P = 0.009, respectively).

These findings indicate that the CG117 index may contribute to the identification of high-risk breast cancer patients.

INTRODUCTION

Human CGβ belongs to a glycoprotein hormone family that also includes LH, follicle-stimulating hormone, and thyrotropin and is composed of two noncovalently bound subunits, designated α and β (1). The α subunit is common to the four hormones, and the β subunit confers biological specificity. CG is synthesized by trophoblast cells in the very first stages of pregnancy. Consistent production of this hormone is essential for the growth, development, and maintenance of the embryo during pregnancy. Besides these classical endocrine functions, CG appears to be involved in paracrine regulation of the growth of various cell types (1).

Numerous immunochemical studies of tissue or body fluids have pointed to the β subunit of CG as a significant indicator of malignant transformation, not only in trophoblastic and germ cell tumors but also in a wide range of nongonadal epithelial tumors (2–9). Serum levels of free CGβ subunit (but not intact CG or free CGα) could, like two other embryonically related cancer biomarkers (carcinoembryonic antigen and α-fetoprotein), be useful for the monitoring of patients with certain solid malignancies, such as bladder, pancreas, and cervical carcinomas (3). However, given the lack of sensitivity of immunoassays, it is unclear whether CGβ-based studies could also be of clinical relevance with regard to other solid tumors, such as breast cancer. We recently used RT-PCR analysis to assess CGβ mRNA in nontrophoblastic normal and cancer tissues of different histological origins, including breast tissue (10, 11). The subunit is composed of 145 amino acids and is coded by at least six genes, two of which are allelic (βA, β5, β7, or β6 and β3 or β9; Ref. 11). All are contained in a single cluster on chromosome 19 (12). Three other genes are also located in this cluster: the β1 and β2 genes, encoding unidentified proteins, and the LH (or β4) gene, encoding the LHβ subunit.

Surprisingly, we were able to detect CGβ mRNAs not only in malignant cells but also in normal cells (11). Interestingly, normal breast tissues were found to express only CGβ7 (or CGβ6), whereas malignant transformation was associated in about half the breast samples with the emergence of the CGβ

Received 10/20/97; revised 12/31/97; accepted 12/31/97.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This work was supported by the Ligue Nationale de Lutte Contre le Cancer, the Comités Régionaux des Hauts de Seine et des Yvelines, and the Association pour la Recherche sur le Cancer.

2 These authors contributed equally to this work.

3 To whom requests for reprints should be addressed, at Laboratoire de Génétique Moléculaire, JE DRED 351, Faculté des Sciences Pharmaceutiques et Biologiques de Paris, 4 Avenue de l’Observatoire, 75006 Paris, France.

4 The abbreviations used are: LH, luteinizing hormone; RT-PCR, reverse transcriptase-PCR; CG, chorionic gonadotropin; MFS, metastasis-free survival; OS, overall survival.
Prognostic Value of CGβ in Breast Cancer

Efficiency, and so on) do not affect this index because the results are expressed as a ratio, with each type of CGβ transcript serving as a control for the other types of CGβ transcripts. The index ranges from 0%, in tissues in which only type I CGβ genes are transcribed, to 100%, in tissues in which only type II CGβ genes are transcribed.

Here, we present an investigation of the prognostic value of the CG117 index in a series of 99 unilateral invasive primary breast cancer patients with known long-term outcome. The significance of CG117 index as a prognostic factor is discussed.

PATIENTS AND METHODS

Patients and Treatment. Primary breast tumor specimens were obtained from 99 patients treated at the Center René Huguenin from 1979 to 1988. These patients (mean age, 57.6 years; range, 34–83 years) treated during this period met the following criteria: primary unilateral breast carcinoma; no other primary cancer or metastasis (supraclavicular nodes included); no radiation therapy or chemotherapy before surgery; and complete collection of clinical, histological, and biological data. All patients selected for this study had undergone either total or partial axillary lymph node dissection (mean number of nodes examined, 16). The main classifying prognostic factors are presented in Table 1. Seventy-three women had undergone simple mastectomy and lymph node dissection, and 26 had had lumpectomy with axillary clearance. Seventy-seven tumors (77.8%) were infiltrating ductal carcinomas. Fifty-four patients had received postoperative radiation therapy as part of their locoregional treatment. Sixty-two high-risk patients had received adjuvant therapy, consisting of chemotherapy (mainly a combination of fluorouracil, methotrexate, and cyclophosphamide; n = 19), hormone therapy (n = 17), or both (n = 26). All underwent a physical examination and routine chest radiography every 3 months for the first year, every 6 months for the next year, and then annually. Liver scintigraphy, bone scans, and mammograms were carried out annually. The median follow-up was 9 years (range, 1.0–16.2 years). The cutoff date for this analysis was January 1996. Forty-two patients relapsed (distribution of first relapse events among patients was as follows: 8 local and/or regional recurrences, 25 metastases, 4 both, and 5 contralateral breast tumors). Three second invasive cancers occurred (not considered as relapse events). All but two of the 32 deaths were related to breast cancer.

Evaluation of ‘Classical’ Prognostic Factors. The histological type and steroid hormone receptor status of each tumor and the number of positive axillary nodes were established at the time of surgery. The malignancy of infiltrating carcinomas was scored according to the histoprognostic grading of Bloom and Richardson (13). Estrogen and progesterone receptors were assayed as described by the European Organization for Research and Treatment for Cancer (14), with a detection threshold of 10 fmol/mg cytosolic protein.

RNA Extraction. Immediately after surgery, the tumor samples were placed in liquid nitrogen until extraction of RNA. Patients were included in this study if the tumor sample used for RNA preparation contained more than 60% of tumor cells (by histological analysis).

Total RNA was prepared using the acid-phenol guanidium method (15). The quality of RNA samples was determined by electrophoresis through denaturing agarose gels, staining with...
Table 1  Characteristics of the 99 patients and relationship to MFS and OS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MFS</th>
<th></th>
<th></th>
<th></th>
<th>OS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients (%)</td>
<td>No. of events</td>
<td>5-yr rate (%)</td>
<td>15-yr rate (%)</td>
<td>P (15 yr)</td>
<td>No of events</td>
<td>5-yr rate (%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>37 (37.4)</td>
<td>14</td>
<td>81.1 (6.4)</td>
<td>44.6 (12.3)</td>
<td>0.27</td>
<td>8</td>
<td>94.6 (3.7)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>62 (62.6)</td>
<td>28</td>
<td>76.5 (5.5)</td>
<td>46.6 (7.5)</td>
<td></td>
<td>22</td>
<td>85.2 (4.6)</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11 (11.8)</td>
<td>3</td>
<td>100</td>
<td>30.0 (23.9)</td>
<td>0.028</td>
<td>4</td>
<td>90.3 (5.3)</td>
</tr>
<tr>
<td>III</td>
<td>50 (53.8)</td>
<td>23</td>
<td>73.4 (6.3)</td>
<td>47.7 (8.3)</td>
<td></td>
<td>17</td>
<td>85.9 (5.0)</td>
</tr>
<tr>
<td>Lymph node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-negative</td>
<td>31 (31.6)</td>
<td>7</td>
<td>76.7 (7.7)</td>
<td>76.7 (7.7)</td>
<td>0.90</td>
<td>35</td>
<td>78.6 (5.1)</td>
</tr>
<tr>
<td>Node-positive</td>
<td>67 (68.4)</td>
<td>26</td>
<td>87.9 (4.0)</td>
<td>51.0 (7.7)</td>
<td></td>
<td>26</td>
<td>87.9 (4.0)</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ (≥10 fmol/mg)</td>
<td>64 (66.0)</td>
<td>29</td>
<td>79.1 (5.2)</td>
<td>40.2 (8.6)</td>
<td></td>
<td>20</td>
<td>90.5 (3.7)</td>
</tr>
<tr>
<td>− (&lt;10 fmol/mg)</td>
<td>33 (34.0)</td>
<td>13</td>
<td>75.0 (7.7)</td>
<td>54.2 (10.0)</td>
<td></td>
<td>10</td>
<td>84.5 (6.4)</td>
</tr>
<tr>
<td>PR status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ (≥10 fmol/mg)</td>
<td>60 (61.9)</td>
<td>28</td>
<td>76.2 (5.6)</td>
<td>37.5 (9.8)</td>
<td>0.33</td>
<td>22</td>
<td>88.2 (4.2)</td>
</tr>
<tr>
<td>− (&lt;10 fmol/mg)</td>
<td>37 (38.1)</td>
<td>14</td>
<td>80.5 (6.6)</td>
<td>53.3 (9.9)</td>
<td></td>
<td>8</td>
<td>89.0 (5.2)</td>
</tr>
<tr>
<td>Macrosopic tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 mm</td>
<td>63 (65.6)</td>
<td>26</td>
<td>78.7 (5.3)</td>
<td>49.8 (7.8)</td>
<td></td>
<td>18</td>
<td>87.0 (4.2)</td>
</tr>
<tr>
<td>&gt;30 mm</td>
<td>33 (34.4)</td>
<td>15</td>
<td>75.2 (7.6)</td>
<td>39.0 (12.3)</td>
<td></td>
<td>12</td>
<td>90.8 (5.1)</td>
</tr>
</tbody>
</table>

The number of patients for each parameter does not necessarily equal 99 because status was not known for all patients.

The Kaplan-Meier estimate.

The log-rank test.

The Scarff-Bloom-Richardson classification.

ER, estrogen receptor; PR, progesterone receptor.

---

ethidium bromide, and visualization of the 18S and 28S RNA bands under UV irradiation. The extraction yield was quantified spectrophotometrically.

RT-PCR. Total RNA (1 μg) was reverse-transcribed using the oligo(dT)16 primer and Moloney murine leukemia virus reverse transcriptase according to the protocol supplied with the GeneAmp RNA PCR Core kit (Perkin-Elmer Corp.).

CG117 Assay. CG117 was assayed as described elsewhere (11), with the addition of minor modifications. Briefly, PCR was carried out in a final volume of 50 μl containing 10 μl of the reverse transcription reaction mix, 10 pmol of each primer common to all CGβ transcripts (primers CG1 and CG2), 200 μM each dNTP (Pharmacia), 1.5 mM MgCl2, 10 mM Tris-HCl (pH 8.3), 50 mM KC1, and 2.5 units of Taq DNA polymerase (Perkin-Elmer). Amplification reactions were carried out in 30 sequential cycles of 94°C for 30 s, 65°C for 30 s, and 72°C for 30 s in a Perkin-Elmer 9600 DNA thermal cycler. Amplification products (347 bp) were diluted 104-fold, and 2 μl of the dilution used for a second round of PCR amplification (20 cycles) using two allele-specific nested primers (primers CG3 and CG4) labeled with TET and FAM, respectively, and primer CG2. PCR amplifications were carried out in a 20-μl final volume containing 0.1 pmol of each allele-specific primer (CG3 and CG4), 0.1 pmol of the common primer CG2, 50 μM each dNTP (Pharmacia), 3 mM MgCl2, 10 mM Tris-HCl (pH 8.3), 10 mM KC1, and 2 units of the Stoffel fragment of Taq DNA polymerase (Perkin-Elmer). Each run consisted of 20 cycles of 90°C and 30 s at 94°C and 30 s at 65°C in a Perkin-Elmer 9600 DNA thermocycler. PCR products were diluted 50-fold and analyzed on a 373A DNA sequencer (Perkin-Elmer) as described previously (11). The relative fluorescent intensities of the two resulting blue and green peak areas of the 119-bp PCR products were representative of the relative expression levels of type I and type II CGβ genes, respectively, and were used to define the CG117 index, as follows:

\[
CG117 \text{ index} = \frac{\text{Type II CGβ mRNA}}{\text{Type I CGβ mRNA} + \text{Type II CGβ mRNA}} \times 100
\]

The CG117 index ranges from 0% in tissues in which only type I CGβ genes are transcribed, to 100%, in tissues in which only type II CGβ genes are transcribed.

Statistical Methods. MFS was determined as the interval between diagnosis and detection of the first metastasis or breast cancer-related death without apparent metastasis, and OS was determined as the interval between diagnosis and death. Clinical, pathological, and biological parameters were compared using the most appropriate among the \( \chi^2 \) test, Fisher's exact test, Mann-Whitney U test, Student's t test, and Wilcoxon test. Survival distributions were estimated by the Kaplan-Meier method (16), and the significance of differences between survival rates was ascertained using the log-rank test (17). Multivariate analysis using the Cox proportional hazards model (18) was used to assess the independent contribution of each variable to MFS and OS.

RESULTS

The CG117 index was determined for tumor mRNAs from 99 primary breast cancer patients. In a previous study, this index was demonstrated to be negative in a series of normal breast specimens obtained after cosmetic surgery, as well as in a series of normal breast specimens obtained after cosmetic surgery, as well as in a...
of normal breast tissue adjacent to breast cancer in patients who had a positive index in their tumors (11). A positive CG117 index was found in 48 (48.5%) of the 99 tumor mRNAs. The CG117 index ranged from 2 to 95% in the series of 48 positive CG117 breast tumors; 4 tumors showed a CG117 index above 50%. Table 1 summarizes the frequency of events in the 99 patients according to the usual prognostic characteristics. Univariate analysis of the 99 patients showed that positive lymph node status was the only classical explanatory variable associated with reduced MFS and OS. CG117 index positivity was not significantly associated with menopausal status or standard prognostic factors, such as macroscopic tumor size, histopathological grade, or lymph node or steroid receptor status. Patients with positive CG117 had a higher risk of relapse [54.2% (26 of 48) versus 31.4% (16 of 51)] and of death relapse [39.6% (19 of 48) versus 21.6% (11 of 51)] than those with a negative CG117 index. CG117 index positivity was associated with reduced MFS (P = 0.014) and OS (P = 0.038; Fig. 2). The outcome for the 48 patients with a positive CG117 index was significantly worse than that of the 51 patients with a negative CG117 index in terms of MFS [5-year MFS, 68.1% (SE = 6.8%) versus 87.8% (SE = 4.7%); and 15-year MFS, 29.6% (SE = 9.5%) versus 62.4% (SE = 7.8%)] and OS [5-year OS, 81.1% (SE = 5.7%) versus 96.0% (SE = 2.7%); and 15-year OS, 52.2% (SE = 9.1%) versus 69.2% (SE = 8.6%)]. A therapeutic treatment bias was unlikely to account for the significant difference observed between the two populations because CG117 index positivity was as frequent in patients who received postoperative adjuvant chemotherapy and/or hormone therapy (32 of 62, 51.6%) as it was in those who did not (16 of 37, 43.2%).

To analyze the CG117 index as a continuous variable, the patients with a positive CG117 index (n = 48) were subdivided into three equal groups (16 patients each) with tumors of low (2–12%), intermediate (13–24%), and high (25–95%) indices. The outcomes of the patients in the three groups were not found to differ. Using the Cox proportional hazards model, we also assessed the prognostic value of parameters that were found to be significant or nearly significant (P ≤ 0.15) after univariate analysis, i.e., menopausal status, histological grade, lymph node status, progesterone receptor status, and CG117 index status (negative or positive) for OS and lymph-node status and CG117 index status for MFS. This multivariate analysis showed that positive lymph node status and CG117 index positivity were the only independent variables that were predictive of both MFS and OS (Table 2); high histological grade and postmenopausal status were independently predictive of OS, but progesterone receptor status was not. Histological grade, menopausal status, and progesterone receptor status were not predictive of MFS (data not shown).

Because of the major interest in identifying a marker that might contribute to the identification of node-negative patients at high risk of recurrence, we assessed the effect of CG117 index status on MFS in this subgroup. Although few patients fell into this category (31 cases) and few events had occurred (7 relapses), the results of univariate analysis were close to significance (P = 0.07). Six of the 7 patients who had relapsed had a positive CG117 index. The CG117 index was also predictive of reduced MFS in the 67 node-positive patients (P = 0.04).

**DISCUSSION**

Numerous immunochemical studies based on both tissue samples and body fluids have pointed the CGβ subunit as a diagnostic and prognostic marker and as a predictor of the response to adjuvant therapy (2–9, 19). However, results are sometimes in conflict in terms of both the frequency of CGβ-positive patients and its clinical value. This may be due to the limited sensitivity of most immunohistostaining methods, such as macroscopic tumor size, histopathological grade, or lymph node or steroid receptor status. Patients with positive CG117 had a higher risk of relapse [54.2% (26 of 48) versus 31.4% (16 of 51)] and of death relapse [39.6% (19 of 48) versus 21.6% (11 of 51)] than those with a negative CG117 index. CG117 index positivity was associated with reduced MFS (P = 0.014) and OS (P = 0.038; Fig. 2). The outcome for the 48 patients with a positive CG117 index was significantly worse than that of the 51 patients with a negative CG117 index in terms of MFS [5-year MFS, 68.1% (SE = 6.8%) versus 87.8% (SE = 4.7%); and 15-year MFS, 29.6% (SE = 9.5%) versus 62.4% (SE = 7.8%)] and OS [5-year OS, 81.1% (SE = 5.7%) versus 96.0% (SE = 2.7%); and 15-year OS, 52.2% (SE = 9.1%) versus 69.2% (SE = 8.6%)]. A therapeutic treatment bias was unlikely to account for the significant difference observed between the two populations because CG117 index positivity was as frequent in patients who received postoperative adjuvant chemotherapy and/or hormone therapy (32 of 62, 51.6%) as it was in those who did not (16 of 37, 43.2%).

To analyze the CG117 index as a continuous variable, the patients with a positive CG117 index (n = 48) were subdivided into three equal groups (16 patients each) with tumors of low (2–12%), intermediate (13–24%), and high (25–95%) indices. The outcomes of the patients in the three groups were not found to differ. Using the Cox proportional hazards model, we also assessed the prognostic value of parameters that were found to be significant or nearly significant (P ≤ 0.15) after univariate analysis, i.e., menopausal status, histological grade, lymph node status, progesterone receptor status, and CG117 index status (negative or positive) for OS and lymph-node status and CG117 index status for MFS. This multivariate analysis showed that positive lymph node status and CG117 index positivity were the only independent variables that were predictive of both MFS and OS (Table 2); high histological grade and postmenopausal status were independently predictive of OS, but progesterone receptor status was not. Histological grade, menopausal status, and progesterone receptor status were not predictive of MFS (data not shown).

Because of the major interest in identifying a marker that might contribute to the identification of node-negative patients at high risk of recurrence, we assessed the effect of CG117 index status on MFS in this subgroup. Although few patients fell into this category (31 cases) and few events had occurred (7 relapses), the results of univariate analysis were close to significance (P = 0.07). Six of the 7 patients who had relapsed had a positive CG117 index. The CG117 index was also predictive of reduced MFS in the 67 node-positive patients (P = 0.04).

**DISCUSSION**

Numerous immunochemical studies based on both tissue samples and body fluids have pointed the CGβ subunit as a diagnostic and prognostic marker and as a predictor of the response to adjuvant therapy (2–9, 19). However, results are sometimes in conflict in terms of both the frequency of CGβ-positive patients and its clinical value. This may be due to the limited sensitivity of most immunohistostaining methods, as well as to their variable specificity, based on the different antibodies used. Recent immunohistochemical studies demonstrated that CG and CGβ protein production was not restricted to malignant cells (20–22). Using immunohistochemical analysis, we also confirmed the presence of either CG or CGβ protein in normal prostate and testis tissues.5 Taken together, these results advocate revisiting CGβ
This was in keeping with a previous report from our group, in classical parameters as well as with prognosis. The CO117 index positivity was significantly related to early relapse and death and was the only independent factor, apart from lymph node status, to be linked to both parameters. Our results also suggest that the CG117 index could be a useful molecular marker in node-negative breast cancer patients. Only 7.1% (1 of 14) of node-negative patients with CG117-negative tumors relapsed, as compared with 35.3% (6 of 17) of node-negative patients with CG117-positive tumors.

The latter finding will need confirmation from study of a larger series of node-negative patients. The main interest of such a marker, applied to this particular population, is in identifying patients at high risk of relapse, who, therefore, require systemic adjuvant therapy.

It remains to be determined whether the emergence of type II CGβ gene transcripts, which are normally observed only in trophoblastic cells, simply reflects phenotypic transformation to malignancy or whether it has biological relevance in terms of malignant cell growth. Crystallographic studies of CG and its subunits showed striking structural similarities between the free CGβ subunit and other growth factors, such as nerve growth factor, transforming growth factor β, and platelet-derived growth factor β, which have the ability to bind to their receptor as homodimers (23). It is noteworthy that the only known CG receptor (LH/CG receptor), also recently detected in normal and malignant breast cells (24), exclusively binds the heterodimer (CG), whereas free CGβ has extremely poor binding and stimulating capacities regarding this receptor. Several authors have suggested that the CGβ subunit or smaller variants might have angiogenic activity (25) or might induce apoptosis (26). This study strongly supports an additional level of complexity for CGβ activity because a subtype of CGβ transcripts was identified in association with the most aggressive breast tumors. Further investigations will focus on the promoters of the CGβ gene cluster and the regulation of mRNA stability and translation of these distinct CGβ transcripts, as well as on the specific functions of the type I and type II CGβ genes. Gillot et al. (27) found that placental CGβ (encoded by type II CGβ genes) but not dimeric CG, CGs, or the β-core affected the growth of different bladder cancer cell lines in vitro. More interestingly, they showed that the degree of CGβ stimulation was maximal in the T24 line and lower in the RT112 line, which have negative and positive CG117 indices, respectively (11).

These findings raise the possibility that type I and II CGβ genes encode molecules or smaller variants that act as growth factors of variable specificity via unidentified receptors.

In conclusion, using a highly sensitive, specific, and simple test to assess a CG117 index, we found that CGβ gene mRNA status was a potentially exciting new tool for defining prognosis in human breast cancer. These findings must now be confirmed in a larger series of breast cancer patients and in a large subpopulation of node-negative patients. It will be tempting to

<table>
<thead>
<tr>
<th>Variable</th>
<th>MFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td>CG117 index status (positive vs. negative)</td>
<td>0.85</td>
<td>2.33 (1.23–4.41)</td>
</tr>
<tr>
<td>Lymph node status (positive vs. negative)</td>
<td>0.92</td>
<td>2.51 (1.10–5.75)</td>
</tr>
<tr>
<td>Histological grade (III vs. II vs. I)</td>
<td>0.88</td>
<td>2.41 (1.23–4.70)</td>
</tr>
<tr>
<td>Menopausal status (postmenopausal vs. premenopausal)</td>
<td>0.86</td>
<td>2.36 (0.92–6.06)</td>
</tr>
</tbody>
</table>

* CI, confidence interval; PR, progesterone receptor.
investigate the prognostic significance of the CG117 index in cancers of other histological origin (prostate, bladder, thyroid, colon, uterus, and so on), in which the expression of CGβ genes was demonstrated to be altered alongside malignant transformation. Additional studies are also warranted to understand the particular contribution of these distinct CGβ genes to breast carcinogenesis.

ACKNOWLEDGMENTS

We thank Quanta Medical for assistance in performing the study and Michel Bahua for help in preparing this manuscript. We also thank the Center René Huguenin staff for assistance in specimen collection and patient care.

REFERENCES

Prognostic value of chorionic gonadotropin beta gene transcripts in human breast carcinoma.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/4/3/671

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.