

AD \_\_\_\_\_

MIPR NO: 93MM3507

TITLE: ROLE OF BONE MARROW MICROMETASTASES IN BREAST CANCER

PRINCIPAL INVESTIGATOR: Kenneth A. Bertram, M.D., Ph.D.

CONTRACTING ORGANIZATION: Madigan Army Medical Center  
Reid Street, Building 9070  
Tacoma, Washington 98431-5000

REPORT DATE: October 22, 1994



TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick  
Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;  
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

DTIC QUALITY INSPECTED 3

19950501 035

# REPORT DOCUMENTATION PAGE

OMB No 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE <b>October 22, 1994</b>	3. REPORT TYPE AND DATES COVERED <b>Final Report (20 Oct 92 - 30 Sep 94)</b>	
4. TITLE AND SUBTITLE <b>Role of Bone Marrow Micrometastases in Breast Cancer</b>		5. FUNDING NUMBERS <b>MIPR No. 93MM3507</b>	
6. AUTHOR(S) <b>Kenneth A. Bertram, M.D.; Katherine H. Moore, Ph.D.; Mark Brissette, M.D.</b>		8. PERFORMING ORGANIZATION REPORT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Commander Madigan Army Medical Center Reid Street, Bldg 9070 Tacoma, WA 98431-5000</b>		10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) <b>U.S. Army Medical Research &amp; Materiel Command Ft Detrick Frederick, MD 21702-5012</b>		11. SUPPLEMENTARY NOTES	
12a. DISTRIBUTION / AVAILABILITY STATEMENT <b>Approved for public release; distribution unlimited</b>		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) <b>Although most women with breast cancer present with local disease, 30-40% of these women will develop advanced disease. Several tumor characteristics have been suggested to be predictive of disease recurrence, among them the presence of micrometastatic disease in the bone marrow. The purpose of this research proposal was to determine if adjuvant therapy could alter this risk factor, that is, will standard adjuvant therapy eliminate these metastatic cells. Additionally this project was going to examine the same questions in patients who presented with metastatic disease or with metastatic disease recurrence. Unfortunately, the study was significantly handicapped by the reluctance of women to have a non-treatment related bone marrow donw, even when the procedure was made available during general anesthesia. Therefore, we did no have sufficient patient accrual to fulfill our study objectives. Our data would suggest, however, that the incidence of bone marrow micrometastases is not as frequent as suggested by some authors in the literature.</b>			
14. SUBJECT TERMS <b>Breast cancer, metastases, bone marrow</b>		15. NUMBER OF PAGES <b>18</b>	
17. SECURITY CLASSIFICATION OF REPORT <b>Unclassified</b>		18. SECURITY CLASSIFICATION OF THIS PAGE <b>Unclassified</b>	
19. SECURITY CLASSIFICATION OF ABSTRACT <b>Unclassified</b>		20. LIMITATION OF ABSTRACT <b>Unlimited</b>	

## FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

\_\_\_\_\_ Where copyrighted material is quoted, permission has been obtained to use such material.

\_\_\_\_\_ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

\_\_\_\_\_ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

\_\_\_\_\_ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

KB For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

\_\_\_\_\_ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

\_\_\_\_\_ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

\_\_\_\_\_ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Accession For	
NTIS CRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification _____	
By _____	
Distribution / _____	
Availability Codes	
Dist	Avail and/or Special
<b>A-1</b>	

*Herbert A. [Signature]*      10/23/94  
PI - Signature                      Date

## Table of Contents

	Page
Front Cover	1
SF 298	2
Foreword	3
Table of Contents	4
Introduction	5
Methods	7
Results (text)	8
Discussion	9
Conclusion	10
References	10
Figures	13
Appendix	15

## INTRODUCTION

Breast cancer. The American Cancer Society estimates there will be 183,000 women who will hear that diagnosis in 1994. Breast cancer is the second most common malignancy in women and it is estimated to kill 46,000 women in 1994 (1). The risk for breast cancer continues to increase, such that one in eight women in the United States will develop breast cancer during their lifetime. Currently, approximately 40% of women with breast cancer present with disease confined to the chest and another 40% of women present with disease confined to the chest and axillary lymph nodes. These women are treated with surgery, radiation therapy and subsequent adjuvant therapy. Despite these therapeutic interventions, metastatic disease will develop in approximately 30-40% of both groups of these women (2).

Several characteristics of breast cancer have been suggested to be risk factors for breast cancer recurrence and decreased survival. Among these characteristics are the size, histology, and hormonal status of the original tumor and the presence of positive lymph nodes or metastases (3). Although these factors have helped determine the breast cancer populations at risk for recurrence or early death, they are not sufficient to define the risks for an individual patient. Evidence is accumulating that other features of a patient's tumor, such as S-phase analysis (4), expression of selected oncogenes (5), and the presence of bone marrow micrometastases (BMM), may have prognostic significance for that patient's individual risk of recurrence and survival (6-8).

Redding et al from the Ludwig Institute for Cancer Research (United Kingdom) examined bone marrow from 110 patients with primary breast cancer for the presence of micrometastases (6). Bone marrow was obtained from each patient (2-4 ml aspirate) from several sites. Mononuclear and malignant cells were isolated by Ficoll gradient centrifugation, placed onto glass slides and wet-fixed in absolute ethanol. The slides were then stained immunocytochemically with an antibody probe which recognized an epithelial membrane antigen present on breast cells in order to detect the presence of breast cancer cells. Breast carcinoma cells were detected in the bone marrows from 31 of the 110 patients (28%). None of these patients had malignant cells in their marrow as detected by conventional Giemsa staining.

In a follow-up report, 81 of 307 patients (26.4%) evaluated as outlined above had bone marrows positive for micrometastases (7). The correlations previously noticed between the presence of BMM, advanced T stage, and vascular invasion became stronger, reaching P values  $<0.05$ . Additionally, it was noted that although only 19% of lymph node negative

patients had BMM, 33% of lymph node positive patients had BMM ( $p=0.013$ ). With a median follow-up time of 27 months, 32 of the 81 patients with positive marrows (29.5%) had recurrent breast cancer, while only 45 of 226 (19.0%) whose marrows were antibody negative had recurred. A total of 36 patients died. Of these, 15 deaths occurred in the group of 81 patients who had BMM at presentation (18.5%), and the other 21 deaths occurred in the 226 initially free of BMM (9.3%). The difference in the two groups reached a P value of  $< 0.05$ . However, BMM could not be shown to be an independent prognostic factor for either disease free survival (DFS) or overall survival (OS).

Cote et al from Memorial Sloan-Kettering recently reported follow-up data (median follow-up of 29 months) on their patients evaluated for BMM (8). Recurrences occurred in 7 of the 18 patients with BMM at initial presentation and in 5 of the 31 patients without BMM. The estimated 2-year recurrence rate in patients with BMM was 33% and for those patients without BMM, it was 3%. When BMM status was combined with lymph nodal (LN) status, the difference in recurrence rates became even more striking. Those patients who were BMM+ and LN+ had a 42 percent 2-year recurrence rate, while those who were BMM- and LN- had a zero 2-year recurrence rate. This data indicated that the combination of positive BMM status and positive nodal status was a significant prognostic indicator for early recurrence. No overall survival data was presented.

The above studies suggest several interesting events in breast cancer. First, the data from Cote et al (8) suggests that patients with BMM are at risk for early recurrence. Second, BMM occur very early in certain, but apparently not all, patients, as evidenced by finding BMM in Stage I breast cancer patients. Third, BMM probably occur as a result of hematogenous spread, as evidenced by finding BMM in lymph node negative patients.

Although the available data suggests that BMM may have an effect on DFS and OS, the effects of adjuvant therapy (chemotherapy or hormonal therapy) on the presence of BMM remains unclear (9). The status of BMM in relapsed patients and the effects of therapy on BMM in these patients has not been reported.

The purpose of this work was therefore twofold. One, to determine if hormonal therapy or chemotherapy would eradicate BMM in women with breast cancer in either the adjuvant or advanced disease setting. Two, to determine if failure to eradicate BMM with systemic therapy was a prognostic factor for decreased disease-free survival or overall survival.

The method of approach was to enroll eligible women with breast cancer into the study protocol where they have bone marrow aspirates done prior to the beginning of hormonal or chemotherapy and at specific times

after their therapy in order to look for BMM using antibodies which recognize breast cancer cells. The pre- and post-therapy presence or absence of BMM was then correlated with the disease-free and overall survival in this group of breast cancer patients.

## METHODS

**Patient characteristics.** Women who were: (1) between the ages of 18 and 70 years with newly diagnosed or recurrent breast cancer, (2) were to receive hormonal or chemotherapy and (3) gave informed consent, were eligible for the study. Patients were entered into the study within two months of primary diagnosis or recurrence. Patients with prior radiation to the iliac crests or who had known metastatic disease to the iliac crests were excluded. Bone marrow samples (2-3 mls per iliac crest) from eligible patients were obtained at the time of their entry onto the study. Bone marrow aspirates were to be repeated after completing each chemotherapy regimen, after six months of hormonal therapy, or after a change in hormonal therapy. All treatment, clinical follow-up, and other care decisions remained the responsibility of the patient and her physicians.

**Prestudy evaluation.** All patients had a physical examination, chest x-ray, bone scan, CBC, electrolytes, BUN and creatinine, and liver function test panel.

**Marrow processing.** The marrow samples were diluted with PBS and layered onto a Ficoll-Hypaque density gradient and centrifuged. The cells at the interface layer were collected and then washed three times with RPMI-1640 plus 5% FCS. The cells (which consist of mononuclear cells and tumor cells) were then suspended at  $1 \times 10^7$  cells/ml in PBS and placed, by single drops, onto microscope slides and dried. Two slides from each patient were stained with Wright's stain for cytological examination. Ten to twelve slides from each patient were used for identification of breast cancer cells by indirect immunoglucose oxidase studies (10,11). The anti-cytokeratin mouse monoclonal antibodies 35BH11 (provided by Dr. Allen Gown) or CAM 5.2 (Becton-Dickinson) were used as the primary antibodies to detect the presence of breast cancer cells in the bone marrow (10,12).

**Indirect immunoglucoseoxidase assay.** Slides with cells were incubated with a primary antibody for 30-60 minutes, followed by washing 3 times with PBS. Specimens were then incubated 30 minutes

with a glucose oxidase conjugated secondary antibody (Cappel, Durham, NC). Next, the specimen was washed 3 times with PBS and incubated with the chromogen phenazine methosulfate/two,2-di-p-nitrophenyl-5,5-diphenyl-3,3'(3,3-dimethoxy-4,4'-diphenylene)-ditetrazolium chloride (PMS/NBT) for 8-10 minutes. The glucose oxidase enzyme label oxidizes the glucose substrate resulting in the reduction of NBT through the intermediate electron carrier PMS. Upon reduction of NBT, a highly colored, insoluble product is formed which allows the localized glucose oxidase to be visualized. Slides were rinsed in distilled water, counterstained with methyl green for 5 minutes, dehydrated and coverslips applied. Control slides included specimens treated with (1) no primary antibody, (2) normal peripheral blood, and (3) normal peripheral blood seeded with MCF-7 cells (11).

**Statistical Analysis.** Tumor staging, histology, and hormonal status were obtained from pathology and surgical reports. Hospital and clinic records were reviewed to obtain data on patient's clinical course to include treatment, DFS and OS. The Chi-squared test was to be used to evaluate the relationship between the presence of BMM and other known prognostic factors. Standard survival analyses was to be used to evaluate the relationship between BMM and DFS and OS.

## RESULTS

Seventeen patients were enrolled on the study. Four of the patients were stage I at the time of study entry, five were stage II, one was stage III and the remaining seven were all stage IV (metastatic disease). An example of a completed patient data collection form is provided in Appendix 1. Figure 1 is a picture of a positive immunocytochemistry control (MCF cell mixed with normal peripheral blood cells) stained with the anticytokeratin antibody, 35BH11. Figure 2 is a negative control. Figure 3 is a patient bone marrow sample showing no staining in the absence of a cytokeratin primary antibody. Figure 4 is a patient bone marrow sample positively staining for breast cancer cells as detected by CAM 5.2

Of the seventeen patients studied, there were two patients with evidence of breast cancer cells in their bone marrow based on the immunocytochemistry results. A third patient had an indeterminate response. All three of these patients were known to have metastatic disease in other sites of their body at the time of study entry.

Of the two patients with positive immunocytochemistry studies, one had evidence of gross metastatic disease in her bone marrow by standard histological review (thus did not have "micrometastatic" disease) and the

second subsequently had a bone scan with evidence of disease in the iliac crest (which was evidence of gross, not micrometastatic, disease in the area of bone marrow aspiration). The patient with an indeterminate response was subsequently sent to Brooke AMC for bone marrow transplant. Therefore none of these patients qualified for continued study on this protocol.

## DISCUSSION

The natural history of breast cancer is not well understood and consequently, many patients receive therapy that does not work for them (as evidenced by relapses) while other patients receive treatment they may not need (which patients really benefit from years of adjuvant tamoxifen?). By learning more about the biology of breast cancer in the individual patient, the treatment of breast cancer can be refined and tailored for that patient. This will help to ensure that an optimal regimen is utilized and eliminate unnecessarily treating certain patients. BMM has been suggested to be a prognostic indicator of increased risk of breast cancer recurrence (8,13). The purpose of this research project was to determine if adjuvant hormonal therapy or chemotherapy can alter this risk factor, that is, would standard adjuvant therapy eliminate these metastatic tumor cells. Additionally, this project was seeking to determine if patients in whom these cells were not eliminated have a greater risk of tumor recurrence than the patients in whom the micrometastatic cells were eliminated. To accomplish this project, bone marrow aspirates were screened for micrometastases using highly sensitive immunological techniques prior to the initiation of and after completion of adjuvant therapy. The patient's course (disease free and overall survival) was then be followed for at least five years. This project was also to explore the effect of therapy on marrow micrometastases in patients with advanced disease in a similar manner.

Seventeen patients were enrolled in the study, but none of them had evidence of BMM without also having evidence of gross metastatic breast cancer in the same area. Therefore no observation of the effect of therapy upon BMM was possible. Of the ten patients without metastatic disease at the time of study entry, none had evidence of micrometastatic disease. We were surprised at the absence of BMM in this population since the reports by Cote et al (8) and Kirk et al (14) would suggest rates of 30-50% positivity. After twelve patients had been enrolled without any true BMM, we contacted Dr. Gown's laboratory and found that they did not see BMM rates as high as reported above and Giai et al (15) note they only found 2 out of 45 patients to have bone marrow positive for micrometastases by

immunocytochemistry. Thus, our results would agree with other investigators that BMM may not be as common as reported by some authors.

Madigan Army Medical Center (MAMC) has consistently been a leader in enrolling patients to Southwestern Oncology Group breast cancer study protocols. Based on this history and the number of breast cancer patients seen at MAMC, we thought that patient accrual to this study would be relatively easy. After the study started, we discovered that patients, with all the other issues of their care concerning them, were basically of no mind to have a procedure done which was not required for their own treatment (especially when all their "friends", relatives, next-door neighbors, National Enquirer, etc had told them how painful a bone marrow aspirate would be). For example, one of the first patients approached about being on the study replied with "not only no, but hell no". When we recognized that patient accrual was going to be less than anticipated, we made two significant changes to the protocol. We amended the study protocol so that the bone marrow aspirates could be done in the operating room during the patients' diagnostic/definitive surgical procedure at MAMC and added the University of Washington as a second source of patients. We essentially doubled our MAMC enrollment from year 1 to year 2 by doing the bone marrows in the operating room but no patients were enrolled from the University of Washington. Unfortunately when even active duty nurses and doctors with breast cancer were unwilling to have a bone marrow done and to participate in the study, this is evidence that it is difficult to accrue patients.

## CONCLUSIONS

From our data and experience, we would conclude that metastatic breast cells can be detected in the bone marrow of patients by using immunocytochemistry. However we found the incidence of BMM in breast cancer patients to be smaller than reported by some authors in the literature. We would also conclude that it is difficult to overcome both the pre-existing prejudices that patients have about bone marrows (even when using a supportive multidisciplinary team) and the feeling that patients have of being overwhelmed at the time of diagnosis and not wanting to consider anything not part of their treatment plan.

## REFERENCES

1. Anonymous. Cancer Facts and Figures-1994. American Cancer Society. p. 12-13. 1994.
2. Carter SK, Glatstein E, Livingston RB. Principles of Cancer Treatment. New York: McGraw-Hill, 1982; 291-295.
3. Merkel DE, Osborne CK. Prognostic factors in breast cancer. Hematology/Oncology Clin of N Am. 1989; 3: 641-652.
4. Clark GM, Mathieu MC, Owens MA, et al. Prognostic significance of S-phase fraction in good-risk node-negative breast cancer patients. J Clin Onc 1992; 10:428-432.
5. Paterson MC, Dietrich KD, Danyluk J, et al. Correlation between c-erbB-2 amplification and risk of recurrent disease in node-negative breast cancer. Cancer Res 1991; 51:556-567.
6. Redding WH, Monaghan P, Imrie SF, et al. Detection of micrometastases in patients with primary breast cancer. Lancet 1983; 1271-1274.
7. Mansi JL, Berger U, Easton D, et al. Micrometastases in bone marrow in patients with primary breast cancer: evaluation as an early predictor of bone metastases. Br Med J 1987; 295:1093-1096.
8. Cote RJ, Rosen PP, Lesser ML, et al. Prediction of early relapse in patients with operable breast cancer by detection of occult bone marrow micrometastases. J Clin Onc 1991; 9:1749-1756.
9. Shpall EJ, Jones RB, Bast RC, et al. 4-Hydroperoxycyclophosphamide purging of breast cancer from mononuclear cell fraction of bone marrow in patients receiving high-dose chemotherapy and autologous marrow support: a phase I trial. J Clin Onc 1991; 9:85-93.
10. Ellis G, Ferguson M, Yamanaka E, et al. Monoclonal antibodies for detection of occult carcinoma cells in bone marrow of breast cancer patients. Cancer 1989; 63: 2509-2514.
11. Gown AM, Vogel AM. Monoclonal antibodies to human intermediate filament proteins: III. Analysis of tumors. Am J Clin Pathol 1985; 84:413-424.
12. Gown AM. Immunoglucose oxidase methods in immunohistochemistry. In DeLellis RA, ed. Advances in Immunohistochemistry. Raven Press. p. 31-45, 1988.
13. Mansi, JL, et al. Bone marrow micrometastases in primary breast cancer: prognostic significance after 6 years' follow-up. Eur. J. Cancer 1991; 27:1552-1555.

14. Kirk, SJ, et al. The prognostic significance of marrow micrometastases in women with early breast cancer. *Eur. J Surg. Oncol* 1990; 16:481-485.
15. Giai, M, et al. Bone marrow micrometastases detected by a monoclonal antibody in patients with breast cancer, 1990; 10:119-121.

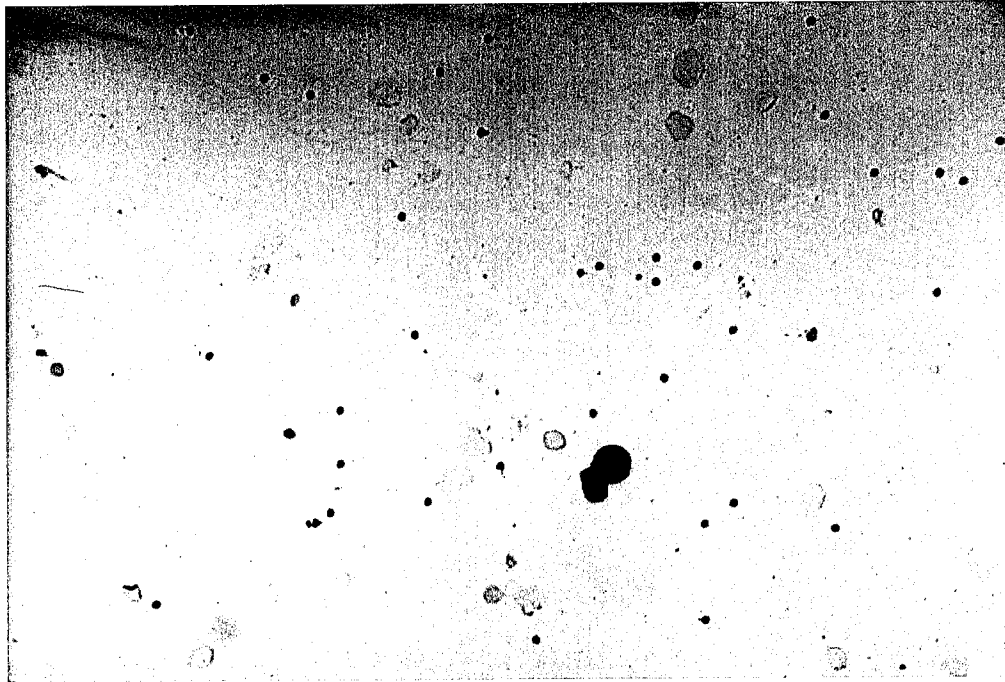


Figure 1. An MCF-7 cell mixed with normal peripheral blood cells and positively stained with the anti-cytokeratin antibody, 35BH11.

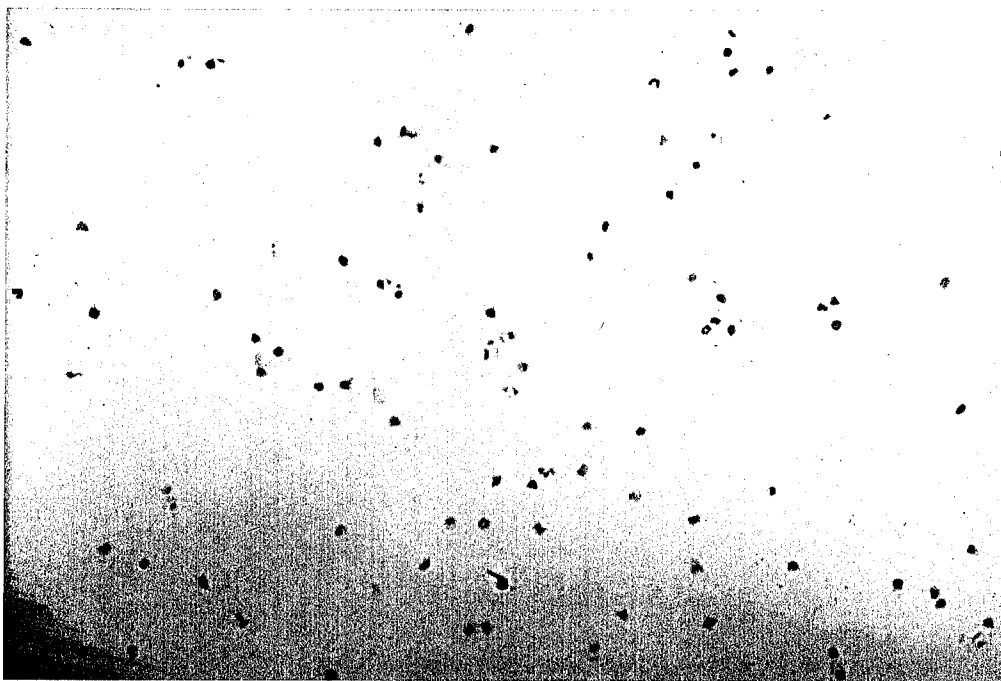


Figure 2. Negative control. No staining of peripheral blood cells alone with the anti-cytokeratin antibody, 35BH11.

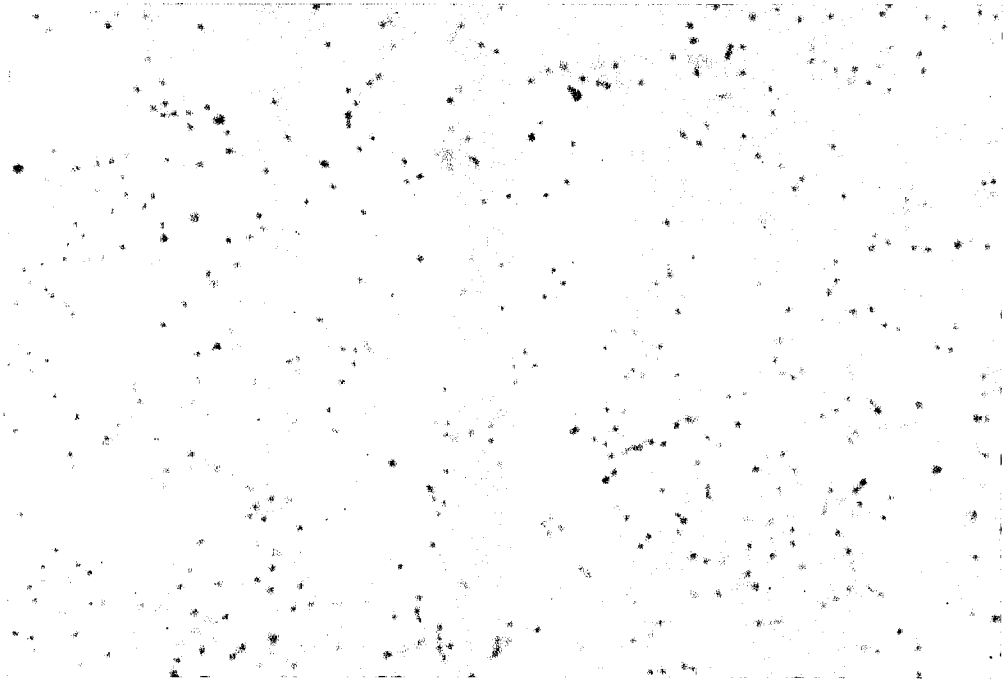


Figure 3. Patient bone marrow sample shows no positive cells in the absence of an anti-cytokeratin antibody.

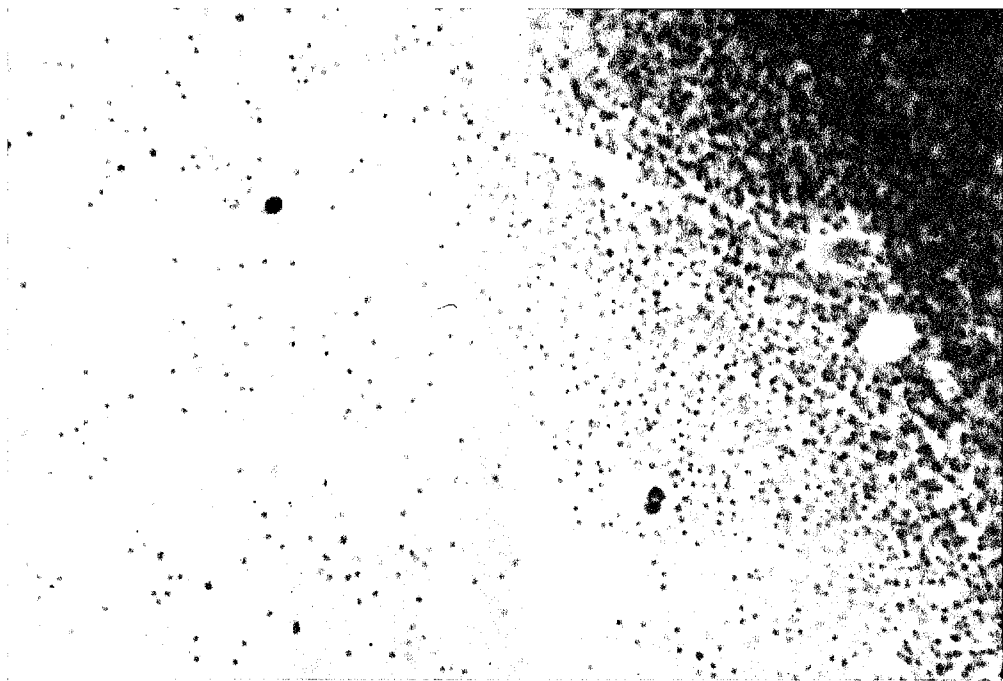


Figure 4. Patient bone marrow sample showing breast cancer cell staining with the anti-cytokeratin antibody CAM 5.2

APPENDIX 1  
Patient Data Collection Form

Bone Marrow Micrometastases Study '94

**DATA OBTAINED @ INITIAL  
DIAGNOSIS of Breast CA**

**Breast Cancer Type**

Metastatic

Patient ID MC #14

DOB 05/02/51  
(m/d/y)

Race Hawaiian

Date of initial dx 09/09/91

Study Entry Number 14

Date of entry 04/06/94

**PRE**

**POST**

BMM result

Pos  
 Indeterminate  
 Neg

Pos  
 Indeterminate  
 Neg

# Positive Cells  
w/ ICC (per 50µl  
drop)

8

Histology Results  
(BM)

Pos  
 Neg

Pos  
 Neg

Primary site(s)/Laterality

L-breast

Histology & grade  
(PD,MD,WD)of (tumor)

ductal adenoca.;  
PD

Tumor size (cm)

1.5

Tiss. bx date

09/91

Tiss.bx access.#

S-8687-91

Primary surgical procedure/date

L-MRM;12/17/91

Surg. access.#

S-12351-91

Regional nodes: pos./ total

4/4

AJCC staging system  
(TNM;stage)

T3N1M1; IV

ER value

suboptimal specimen

ER interp.

<input type="radio"/> Positive	<input type="radio"/> Positive	<input type="radio"/> Positive
<input type="radio"/> Indeterminate	<input type="radio"/> Indeterminate	<input type="radio"/> Indeterminate
<input checked="" type="radio"/> Negative	<input type="radio"/> Negative	<input type="radio"/> Negative

PR value

ND

PR interp.

<input type="radio"/> Positive	<input type="radio"/> Positive	<input type="radio"/> Positive
<input type="radio"/> Indeterminate	<input type="radio"/> Indeterminate	<input type="radio"/> Indeterminate
<input type="radio"/> Negative	<input type="radio"/> Negative	<input type="radio"/> Negative

Patient ID MC #14

**DATA @ RECURRENCE OR RELAPSE**

<b>Date/site(s) of recurrence or relapse</b>	09/17/91; subclavicular LN	11/93; R-parietal subdural mass	11/93; brain	03/94; R-hip
<b>Tissue bx confirmation (Y,N)</b>	Y	Y	MRI	N
<b>Bx access.#</b>	S-9075-91	S-12324-93		
<b>Histology</b>	mets. adenoca.; PD	mets. adenoca.	suggestive of mets.tumor	

**DATA OBTAINED @ TIME OF STUDY**

**CXR result**     Normal     Abnormal    **CXR-comments**    ND

**MMG result**     Normal     Abnormal    **MMG-comments**    ND

**Bone scan**     Normal     Abnormal    **B.scan-comments**   

**WBC (x10<sup>9</sup>/L)**    2.6                      **ALT/ AST**    29/31

**HGB/HCT**    10.3/29.8                      **ALK PHOS**    108

**Platelets(x10<sup>9</sup>/L)**    153                      **Gamma GT**    51

**Electrolytes(Na,K,Cl)**    143,3.7, 107                      **T Bili**    1.0

**BUN/Ca**    --/8.9

**TREATMENTS**

	PRE	TX	POST
<b>Date/dose of rad. tx(rads)</b>	04/92-05/92, L-chest 5040; 11/93-12/93-brain		
<b>Date of 1st tx (chemo/horm)</b>	09/91-03/92	12/93	
<b>Type of 1st tx (chemo/horm)</b>	<input checked="" type="checkbox"/> Cytoxan <input checked="" type="checkbox"/> Adriamycin <input checked="" type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input type="checkbox"/> Tamoxifen <input type="checkbox"/> Methotrexate	<input checked="" type="checkbox"/> Cytoxan <input type="checkbox"/> Adriamycin <input checked="" type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input type="checkbox"/> Tamoxifen <input checked="" type="checkbox"/> Methotrexate	<input type="checkbox"/> Cytoxan <input type="checkbox"/> Adriamycin <input type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input type="checkbox"/> Tamoxifen <input type="checkbox"/> Methotrexate
<b>Date of 2d (chemo/horm) tx</b>	04/92-10/92	02/94	
<b>Type of 2d (chemo/horm) tx</b>	<input checked="" type="checkbox"/> Cytoxan <input type="checkbox"/> Adriamycin <input checked="" type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input type="checkbox"/> Tamoxifen <input checked="" type="checkbox"/> Methotrexate <input type="checkbox"/> Mitoxantione	<input type="checkbox"/> Cytoxan <input type="checkbox"/> Adriamycin <input type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input checked="" type="checkbox"/> Tamoxifen <input type="checkbox"/> Methotrexate <input type="checkbox"/> Mitoxantione	<input type="checkbox"/> Cytoxan <input type="checkbox"/> Adriamycin <input type="checkbox"/> 5-Flouracil <input type="checkbox"/> Leukoran <input type="checkbox"/> Tamoxifen <input type="checkbox"/> Methotrexate <input type="checkbox"/> Mitoxantione

Patient ID

PRE

TX

POST

Date of last contact

Status of patient and cancer  
(alive,dead,NED,metastasized)

Misc.comments

KEY:

NA=not  
available  
ND=not done  
L=left  
R=right