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*Clin Cancer Res* 2001;7:1843-1849.

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*Special Article*

# The Cooperative Breast Cancer Tissue Resource: Archival Tissue for the Investigation of Tumor Markers<sup>1</sup>

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## Abstract

Investigators continue to search for reliable markers of prognosis of breast cancer. For many analyses, laboratory techniques permit the use of archival paraffin-embedded tissue collected years previously and readily linked to clinical and follow-up information. Laboratory investigators have often expressed the need for such a tissue resource. We have developed a publicly available resource of archival breast cancer specimens. The pathological material has been collected and reviewed by investigators at four institutions and currently includes breast cancer specimens from more than 9300 cases. Institutional pathologists reviewed slides and blocks using a common protocol and coding scheme. Clinical information and details of follow-up came from data routinely collected by the institutions' cancer registries. Coded data are maintained centrally in a single database. A subset of the data may be searched on the World Wide Web to determine the availability of cases with specified characteristics. The material collected by this Cooperative Breast Cancer Tissue Resource is generally representative of breast cancer diagnosed in community hospital settings in the United States. Seventy-two percent of the living cases have been followed for at least 5 years, and follow-up status is updated regularly. Interested laboratory investigators may apply to the Resource for the use of these tissues. This Resource is proving valuable to laboratory investigators who require large numbers of specimens for validation studies of prognostic markers of breast cancer.

Received 10/31/00; revised 4/6/01; accepted 4/16/01.

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<sup>1</sup> Supported in part by Grants 5U01-CA62772, 5U01-CA62773, 5U01-CA62779, and 5U01-CA62938 from the National Cancer Institute.

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## Introduction

The prognosis for a woman with breast cancer depends on many factors, not the least of which is the underlying biology of her cancer. Resected breast cancers may be characterized and prognosis estimated by spread to lymph nodes and by such tumor characteristics as histological and nuclear grade, receptor status, and size of the primary tumor (1–5). Nonetheless, cancers that appear to have been completely removed by surgery and which have “favorable” tumor characteristics may yet metastasize, whereas other, very malignant-appearing tumors are cured by the initial treatment.

Although many markers of prognosis have been described and characterized, attempted validation studies have been hampered by small sample size with limited statistical power (6, 7). Experiments may have used “convenience samples” of uncertain generalizability or selection bias or may have been hampered by missing clinical or therapeutic information and short periods of follow-up.

Laboratory techniques in the past often required fresh tissue for analysis. In today's laboratories there exist new techniques that can take advantage of archived, paraffin-embedded tissues and the long follow-up available on those patients from whom the samples were originally obtained in years previous. The National Cancer Institute has responded to these changes in technology by funding the CBCTR.<sup>3</sup> This is a publicly available supply of archival breast cancer specimens coupled with clinical, pathological and follow-up data to be used primarily in validation studies of prognostic markers. The material has been characterized by CBCTR pathologists according to a common syllabus and is linked to a database that contains coded clinical and follow-up information from institutional cancer registries.

## Materials and Methods

**Organization of the CBCTR.** Four institutions comprise the CBCTR: Fox Chase Cancer Center, Kaiser Permanente Northwest Region, Jackson Memorial Hospital-University of Miami, and Washington University Hospitals. Although each institution is different in its local setting, each possesses large numbers of archival breast cancer specimens linked to diagnostic and follow-up information. The specimens collected at Fox Chase come from a network of pathology departments at 11 community hospitals in a geographic area extending from Philadelphia and its immediate suburbs to central New Jersey. Kaiser Permanente cases represent all incident breast cancers of women members of the Kaiser Foundation Health Plan in the

<sup>3</sup> The abbreviations used are: CBCTR, Cooperative Breast Cancer Tissue Resource; SEER, Surveillance, Epidemiology, and End Results; TNM, Tumor-Node-Metastasis; IMS, Information Management Services; IRB, Institutional Review Board; REP, Research Evaluation Panel.

Portland, Oregon metropolitan area from 1970 to 1995. The cases collected by Jackson Memorial Hospital similarly include all breast cancers diagnosed at their institution, a large city hospital with many indigent patients, from 1975 to 1995. The material from Washington University comes from five hospitals in the St. Louis metropolitan area, each hospital serving a slightly different population. Although each of the four CBCTR institutions gathered a group of cases that reflect its own community, the combination of the four different sites has produced a mix of cases for the CBCTR as a whole that appears generally comparable with incident cases described by the SEER program (8).

The CBCTR has been designed as a "virtual tissue bank": the Resource's pathological specimens remain at each of the four participating institutions but the database of coded information about each case is housed and managed at a central site. Specimens are identified at each of the four sites as reserved for the CBCTR and are not to be used for other purposes. Each site has submitted to a central database coded information about the case sufficient to describe the case's essential features. This information has been combined into a database that allows, on the one hand, the analyses reported in this paper and, on the other, a targeted search for pathological material by interested investigators.

**Nature of the Specimens.** Each of the four sites identified cases of primary breast cancer, mostly from the years 1980 to 1993, for which it possessed archival specimens, diagnostic slides, and follow-up data. The specimens were cataloged at each institution and examined by pathologist investigators to assess their integrity, the presence or absence of cancerous and noncancerous tissue in each block, and availability for use in the Resource. Specimens were placed in designated locations at each site and clearly identified as part of the Resource and not to be used for any other purpose with the exception of patient care. Each site retained a single block for diagnostic purposes and excluded a small number of originally identified cases from the Resource because of lack of pathological material.

There are currently 9308 specimens in the CBCTR. Each institution has contributed between 1613 and 2823 cases. The Resource principal investigators determined that this constituted a sufficient number of cases to meet the needs identified by requests and therefore have stopped accrual.

**Pathological Review.** Before inclusion in the Resource, each institution's pathologist reviewed the histology of the specimen using a syllabus based on the Armed Forces Institute of Pathology fascicle (9) and modified for that purpose by the CBCTR. The pathologists subtyped each cancer, confirmed staging information (tumor size, nodal status, and invasion of adjacent anatomical structures), and inventoried the archived blocks. Their review was incorporated into the data included in the CBCTR database described below.

Resource pathologists performed reliability and validity checks on each other's specimens every 6 months for 4 years as part of a program of continuing quality review of the Resource. Reviews included reevaluation of randomly selected specimens at each site and joint examination of a common group of specimens to assure consistent interpretation of material.

**Clinical Information.** All cases to be accessioned to the Resource were diagnosed and treated at hospitals participating in the accreditation program of the Commission on Cancer of

the American College of Surgeons. The dataset maintained by the cancer registries of these hospitals included considerable data about the clinical/pathological stage of the breast cancer, the initial treatment course, and subsequent follow-up. We have included a significant part of this dataset in the record of each CBCTR case. This material has also been subjected to quality assurance audits at each institution both by local staff and visiting members of the CBCTR at the quality review visits noted above.

An essential feature of the CBCTR is the ability to link coded clinical data to the pathological specimen. Cases that could not be so linked because they lacked cancer registry data or staging information have been excluded from the CBCTR.

**Variables Collected by the CBCTR.** The dataset collected by the CBCTR derives from several sources and is divided into logical categories as shown in Table 1. The case identifiers allow for the linkage of data from the local cancer registry and the pathology department. The individual cancer registries have generated follow-up data so that patient confidentiality is preserved. The Race and Hispanic Origin entries follow the general classification scheme described in the NIH Guidelines. Staging information uses the TNM classification from the cancer registry files previously documented by the hospital cancer registrars through review of medical records, operative and pathology reports, and discussions with responsible physicians (10).

The institution's pathologist usually measured the size of the primary lesion, recorded here as its largest diameter, at the time of initial processing of the specimen. If after biopsy there was a subsequent mastectomy, the CBCTR pathologist estimated the largest diameter of the primary breast cancer from review of all reports, blocks and slides. In the majority of cases, this estimate corresponded to dimensions recorded at the initial inspection and measurement of the gross specimen. For smaller lesions, and those not clearly evident on gross inspection, the measurement came from microscopic review.

The CBCTR pathologists classified the specimens into those containing invasive, *in situ*, or both types of cancer. For each case of invasive breast cancer, CBCTR pathologists recorded the most prominent and the next most prominent histological type, and for each case of *in situ* breast cancer, the presence or absence of ductal or lobular elements. The review also included an estimate of the amount of malignant tumor present in each block and the number of such blocks available for the CBCTR. Finally, pathologists have recorded the amount and nature of nonmalignant tissue available for each CBCTR case.

We have included a variable to indicate whether estrogen and progesterone receptor determinations were done at the time of diagnosis, but we have not included the actual value nor whether the cancer was considered "positive" or "negative." This decision was necessary in view of the great variability of such values and interpretations among institutions over the nearly 20 years spanned by the CBCTR cases. Investigators who need such values for their work may elect to perform their own immunohistochemical receptor determinations on the pathological material that they receive from the CBCTR. If they require the values from the historical record, they may request this information.

Table 1 List of variables in the CBCTR database

Demographic and initial treatment variables	
Case identifier	
Sequence of breast cancer(s)	
Race	
Hispanic origin	
Gender	
Birthdate	
Age at diagnosis	
Date of diagnosis	
Laterality	
Contralateral breast tumor (Y/N)	
Nodes examined	
Nodes positive	
Type of distant metastases at diagnosis	
TNM stage	
Radiation therapy (Y/N)	
Chemotherapy (Y/N)	
Hormone therapy (Y/N)	
Immunotherapy (Y/N)	
Other therapy (Y/N)	
Estrogen receptor (Y/N)	
Progesterone receptor (Y/N)	
Follow-up variables	
Date of 1st recurrence	
Ipsilateral breast recurrence (Y/N)	
Type/Site of 1st non-breast recurrence	
Distant sites of 1st recurrence	
Vital status	
Date last known alive	
Date of death	
Cancer status at death	
Date last verified recurrence-free	
Variables assessed by reviewing pathologist	
Invasive cancer present? (Y/N)	
Most prominent invasive cancer histology	
2nd most prominent invasive cancer histology	
Size of invasive cancer (in cm)	
Size from gross inspection? (Y/N)	
Multifocal disease (Y/N)	
CIS <sup>a</sup> present? (Y/N)	
Ductal CIS present? (Y/N)	
Lobular CIS present? (Y/N)	
Tissue resource housekeeping variables	
No. blocks with invasive cancer $\leq$ 0.5 cm	
No. blocks with invasive cancer $>$ 0.5 cm	
No. blocks with CIS $\leq$ 0.5 cm	
No. blocks with CIS $>$ 0.5 cm	
No. normal breast blocks	
No. normal muscle blocks	
No. normal skin blocks	
No. normal fat blocks	
Is needle biopsy specimen available? (Y/N)	
No. blocks containing positive nodes only	
No. blocks containing negative nodes only	
No. blocks containing mixed positive/negative nodes	
No. blocks containing nodes, not otherwise specified	
Other comments	

<sup>a</sup> Y/N, yes/no.<sup>b</sup> CIS, carcinoma *in situ*.

Treatment information is limited to Yes/No answers concerning any radiation therapy, chemotherapy, hormonal therapy, or immunotherapy delivered as part of the initial course of treatment. This is the limit of reliable treatment information in most cancer registries. We have also not included information about the specific type of surgery performed (lumpectomy,

modified radical mastectomy, etc.) because the accurate recording of such information at local cancer registries varies considerably. Accurate information about surgery requires review of the medical record, and this was beyond the scope of the initial effort of the Resource.

We have included information about the date and type of breast cancer recurrence and the date of death. The data specify the general category of recurrence (in-breast, local, regional, and distant) as well as the recorded organs of involvement for women with distant spread. To calculate length of observation, we have used cancer registry data from each Resource noting the date of last contact as well as the cancer and vital status. This has allowed calculation of survival for all cases enrolled in the Resource and of length of follow-up for living cases and time to death for those who died.

**Protection of Confidentiality of Patient Data.** Each of the four sites maintains its own database of specimens and clinical and follow-up information in a secure setting. Coded data are transmitted electronically to the central database at IMS, and elements of the data are incorporated into the public database as described below. Before transmission of the data, each site assigns a new unique identifier, the CBCTR ID, to IMS. The central database has access only to the CBCTR ID; the local site retains the only linkage between the CBCTR ID and any local identifiers. This procedure prevents identification of any individual case by the central database. When specimens are distributed, they are identified solely by the CBCTR ID.

**Review by IRB.** This project received full board review by IRB's at each of the four sites before the initial award and annually since then. In particular, the IRB's examined the protections to patient confidentiality at each site and the barriers erected between the four sites and the central database and between the CBCTR and the investigators using tissue specimens. Each IRB determined that, under the Common Rule,<sup>4</sup> the research supported by this project represented only minimal risk to the human subjects whose breast cancer tissue had been used to construct the CBCTR and that informed consent was not required to process and send out specimens to other investigators. Subsequently, the National Bioethics Advisory Commission and the National Cancer Institute have issued reports concerning confidentiality and consent issues for archived specimens (11).<sup>5</sup> These reports endorse the procedures that have been followed by the CBCTR for the resource as currently constituted. Should the CBCTR elect to add to its collection, particularly if it were to collect fresh tissue, the sites would likely choose to obtain informed consent at the time of surgery.

**Application Procedures and Quality Control of Specimens Provided.** The CBCTR has a site on the World Wide Web.<sup>6</sup> The site contains a searchable database of the Resource, instructions on its use and how to apply for specimens. The

<sup>4</sup> 45 CFR 46.101 (b)(4): Code of Federal Regulations, National Archives and Records Administration. Internet address: <http://www.access.gpo.gov/nara/cfr/index.html>.

<sup>5</sup> Confidentiality, Data Security and Cancer Research: Report of a Workshop. National Cancer Institute. Internet address: <http://www.nci.nih.gov/scienceresources/announcements/confidentialityreport.pdf>.

<sup>6</sup> Internet address: <http://www-cbctr.ims.nci.nih.gov/>.

Table 2 Number of cases in the CBCTR by size and invasive/noninvasive cancer

	No. of cases
Invasive	
≤0.5 cm	414
0.6–1.0 cm	1412
1.1–2.0 cm	3196
2.1–5.0 cm	2822
>5.0 cm	467
Unknown	184
Noninvasive	813
Total	9308

intent of the public database is to allow investigators to determine whether the Resource contains the requisite numbers of particular categories of pathological material needed to support their research. Investigators' Letters of Intent are first reviewed at the central database to assess whether the CBCTR can meet the specific needs of the proposed project. The study is then reviewed by the REP, a group of senior scientists convened by the National Cancer Institute representing a range of disciplines in the field of breast cancer research. Each application is reviewed for scientific merit, statistical design, technical approach, and feasibility of the work proposed. Applications recommended by the REP are then reviewed by the Coordinating Committee of the CBCTR to set priorities for the use of this nonrenewable resource.

After approval by both the REP and the Coordinating Committee, IMS compiles a list of specimens from the centrally maintained database that meet the criteria specified in the application. Each of the four CBCTR sites receives a list of their cases and proceeds to assemble the requisite samples.

The blocks are cut according to specifications provided by the requestor and commonly include a number of tissue sections of appropriate thickness or slides prepared in a particular manner from each block. Resource pathologists at each site examine the slides that are actually being sent as well as parallel sections to assure that they include representative sections of cancer and noncancer tissue requested by the laboratory researcher. Entire blocks or larger pieces of tissue have not been provided.

Clinical information is also included for each case in a separate computer file. Investigators are given the option to complete their laboratory investigations first and subsequently receive coded clinical data or, alternatively, to obtain both the specimens and the data at the same time. The fee schedule for provision of tissue and data appears on the Web site at the address noted.<sup>6</sup> Charges defray the costs of tissue preparation, data collection, and shipping.

## Results

There are over 9300 cases of breast cancer currently in the CBCTR. The CBCTR requires that each case have pathological material available for eventual distribution to other investigators. This requirement would be expected to bias the cases within the Resource toward larger primary breast cancers. Nonetheless, as seen in Table 2, the Resource includes 1826 cases (19.6% of the total) that were <1 cm in diameter. The 184 cases with no size of tumor noted (only 2% of the cases in the

Table 3 Principal histology of breast cancers in the CBCTR

	No.	%
DCIS	827	9%
Ductal NOS	7074	76%
Tubular	177	2%
Papillary	57	1%
Mucinous	208	2%
Medullary	85	1%
Cribiform	52	1%
Adenoid Cystic	8	0%
Lobular	660	7%
Mixed Ductal/Lobular	105	1%
Other	55	1%
Total	9308	

CBCTR) are specimens from a mixture of breast cancers. Some are from women who presented with metastatic breast cancer. The remaining cases include cases with notations of T stage but no size measurement recorded in the database and a few cases with notations of nodal and metastatic stage (N and M) but absent data concerning primary tumor size (T stage).

The pathological diagnoses assigned to specimens derive from an independent review of each case by the CBCTR pathologists. The criteria used to assign principal and secondary diagnoses to each case reflect criteria described in a pathology manual prepared by the members of the Resource expressly for this purpose. The distribution of histologies of the CBCTR cases appears in Table 3 and mirrors what one would expect in a sample of unselected breast cancers. The relationship between primary and secondary histological types is shown in Table 4 only for invasive breast cancers. Eight thousand four hundred and forty-six cases have only a single histological type in the specimen, but there are 862 cases of two histologies, most commonly ductal together with lobular and ductal together with any other type.

Comparisons between the CBCTR cases and those reported in SEER address the representativeness of the CBCTR collection. Fig. 1 indicates that the age at diagnosis of breast cancer cases in the CBCTR closely follows the distribution reported by the State of Connecticut Registry (12) and other SEER programs (8).

Staging information was available on 86% of the cases. The CBCTR reports stage both by the individual components of the TNM system and by consideration of each component to derive a single summary stage, as outlined in the Staging Manual of the American Joint Commission (9). The distribution of cases (Table 5) represents the cases diagnosed and treated at the four cooperating sites. For comparison, the distribution by stage from SEER (8) reflects the overall pattern of incident breast cancers in the United States. The year 1990 represents the approximate midpoint of specimen collection, with approximately equal numbers of cases diagnosed both before and after that date. Table 5 shows that the SEER cases are of a lower stage than cases in the CBCTR, particularly when one includes ductal carcinoma *in situ* (DCIS) and Stage 1 cases. Nearly 50% of the cases in SEER are DCIS or Stage 1, whereas only 39% of CBCTR cases fall into these categories. Similarly, 47% of CBCTR cases are of stages II–IV in comparison to 40% for SEER.

Table 4 Primary and secondary histology of specimens in the CBCTR

1 <sup>0</sup> Histology	2 <sup>0</sup> Histology											Total
	Ductal	Tubular	Papillary	Mucinous	Medullary	Cribiform	Adenoid/Cystic	Lobular	Mixed	Other	None	
Ductal	10	123	17	90	31	67	2	135	8	168	6423	7074
Tubular	24					8				4	141	177
Papillary	8					2				1	46	57
Mucinous	25		1			1				1	180	208
Medullary	6										79	85
Cribiform	18	2	1	3				1		1	26	52
Adenoid/Cystic	1										7	8
Lobular	73	6				1				11	569	660
Mixed D/L				2					2		101	105
Other	6	2									47	55
Total	171	133	19	95	31	79	2	136	10	186	7619	8481

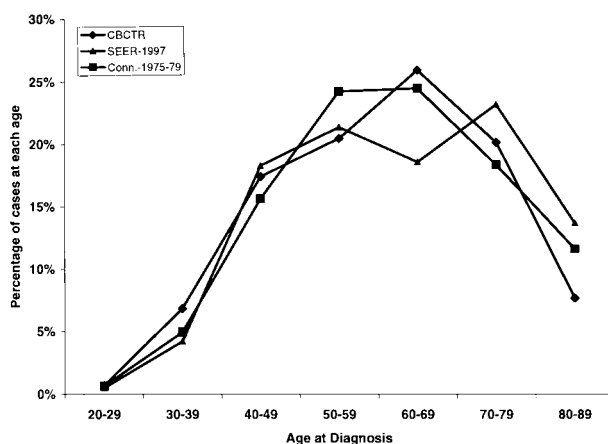


Fig. 1 Age-distribution of breast cancers in CBCTR, SEER, and Connecticut.

Fourteen percent of CBCTR cases are of unknown stage, whereas only 9% of SEER cases fall into this category. This seemingly large difference likely represents the reluctance of cancer registrars at the CBCTR cooperating hospitals to declare a summary stage when one of the elements of the TNM classification has not been explicitly specified. Indeed, 1095 of the 1263 cases of unknown stage have adequate information on T and M stage for coding, as shown in Table 5, but have not undergone a node dissection and therefore have been coded "NX." In other settings, registrars may have included clinical (and not only pathological) evaluation of nodal status in such settings and likely coded many of these women as N0. Similarly, of the 1095 NX patients, M stage was known in 991 and unknown in only 104.

There is some variation in the T stage by institution (Table 6), which reflects the mix of breast cancer patients seen in the different settings represented by the four sites. The principal differences lie in the proportion of T1 (36–60%) and T2 (24–34%) lesions. There exist only small differences at the higher stages, but the numbers from any one site are quite small. The smallest variation appears in the noninvasive breast cancers, probably indicating the lack of major screening efforts at any of

Table 5 Stage of primary breast cancer as compared to SEER

Summary stage	CBCTR (n)	CBCTR (%)	SEER-1990 <sup>a</sup> (%)
DCIS	801	8	13
Stage I	2859	31	37
Stage IIA	2182	23	20
Stage IIB	1187	13	10
Stage III	576	6	5
Stage IV	440	5	5
Invasive, stage unknown <sup>b</sup>	1263	14	9
Total in CBCTR	9308		

<sup>a</sup> Ref. 8.

<sup>b</sup> N = 1263; N0 = 116; N1 = 50; N2 = 1; N3 = 1; NX = 1095; (T1 = 774; T2 = 267; T3 = 37; T4 = 17); (M0 = 991; MX = 104).

the sites during the period when most specimens were being collected for this Resource.

There is a hint of "stage shift" during the 24 years (1974–1997) of specimen collection. (Table 7). Thus, cases selected from the earlier period of specimen collection tend to be somewhat larger on average than more recent cases. The differences noted are confined to T1 and T2 lesions, because the number of T3 and T4 breast cancer specimens in the CBCTR is relatively small. Increased mammographic screening occurred after 1990, and the number of noninvasive breast cancers (Tis) form a larger percentage of the Resource in recent times.

The pattern of death of CBCTR cases is shown in Fig. 2, drawn from an actuarial, life table analysis of all cases, both alive and dead, in the Resource. These women were diagnosed between 1974–1997. The 5-year survival is 75% and the 10-year survival is 56%. The SEER 5-year survival for cases diagnosed 1989–1995 (a somewhat more contemporary group than found in the CBCTR) was 84.7%. No comparable figure is given for 10-year survival of the 1989–1995 cohort, but for SEER cases diagnosed in 1985, 10-year survival was 68.5% (8).

The CBCTR has distributed tissue to a number of investigators. Studies have included investigations of markers of several types. Examples of studies that have used CBCTR specimens are outlined in Table 8. Immunohistochemistry has been the principal analytic method used, but one investigator was able

Table 6 T stage by institution—All cases

	TIS	T0	T1	T2	T3	T4	TX	
Institution 1	252 9%		1494 53%	868 31%	73 3%	136 5%		2823
Institution 2	141 6%	38 2%	1494 60%	594 24%	62 2%	79 3%	75 3%	2483
Institution 3	143 9%	8 0.5%	579 36%	554 34%	135 8%	134 8%	60 4%	1613
Institution 4	231 10%		1386 58%	664 28%	102 4%	6 0.3%		2389
Total								9308

Table 7 T stage by year of diagnosis

	T0	T1	T2	T3	T4	TIS	TX	N
1974–1979	1%	55%	34%	5%	2%	2%	1%	617
1980–1984	1%	42%	35%	7%	7%	4%	5%	1247
1985–1989	1%	53%	29%	4%	4%	8%	1%	3570
1990–1994	0%	57%	25%	3%	3%	11%	1%	3625
1995–1997	0%	46%	36%	4%	4%	10%	1%	249
Total								9308

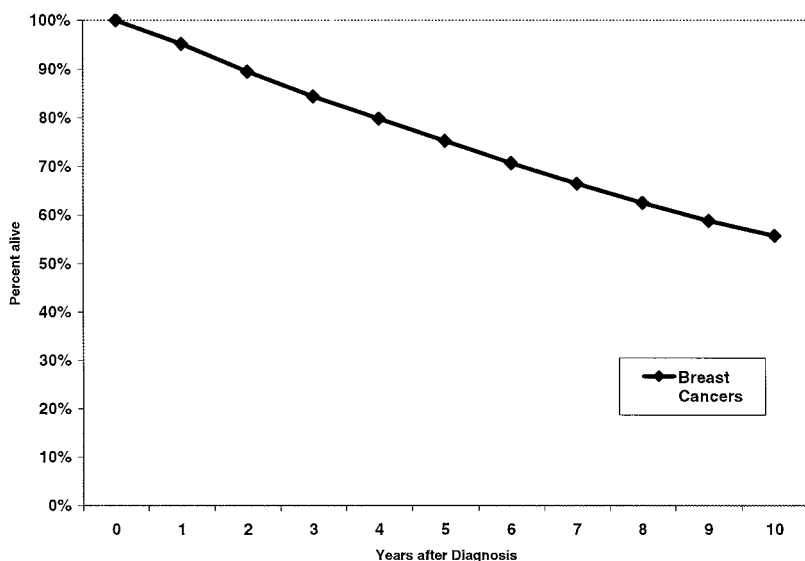


Fig. 2 Survival of breast cancers in CBCTR.

to extract DNA and perform PCR on the archival material provided.

**Discussion**

The CBCTR is a publicly available collection of paraffin-embedded tissue blocks, coupled with pathological, clinical, and outcome data. It is a “virtual tissue bank,” because the pathological material remains at the contributing local site yet is retrievable for investigators seeking material for studies of prognostic markers in breast cancer. A central database of coded information has been constructed, and a subset of the database has been placed on the World Wide Web to allow detailed categorical searches by individuals seeking this material for their studies.

The description of the Resource in this paper demonstrates that the accessioned cases generally reflect breast cancer as diagnosed and treated in the community, with a few potentially important differences. The cases tend to be younger and have somewhat more advanced disease than women reported by SEER. This combination of poorer prognostic factors is reflected in an increased mortality, as shown by a median survival that is some 5–10% less than the SEER population. Whether this degree of poorer prognosis will affect the validity of marker studies is uncertain. We believe it is unlikely to be detrimental to such studies for at least two reasons: (a) the effect described is relatively small; and (b) investigators may, if they so choose, design their study to examine a sample of specimens that more closely mirrors a less advanced risk group. There are sufficient

Table 8 Studies performed with tissue from the CBCTR

Research study design	No. of cases	No. of sections	Laboratory technique
Detection of mouse mammary tumor virus particles	140	700	PCR, DNA hybridization
Expression of insulin-like growth factor receptors	400	2400	Immunohistochemistry
Concordance of new proposed commercial HER2 test with research test	1200	8765	Immunohistochemistry
Detection of markers for poor prognosis in untreated node positive patients	367	2936	Immunohistochemistry

numbers of cases available to make practicable any reasonable selection process.

Cases entered in the Resource must have been large enough to allow for extra material in the tissue block for analyses beyond just routine histological examination. Cases that were very small, for example those diagnosed by mammography as performed today, do not appear in CBCTR files, though there are over 1800 cases of 1 cm or less in diameter at diagnosis, indicating that some screen-detected cancers have been included. The tissue available on such cases is necessarily limited to that present in the surgical block and may only be available for a few studies.

The follow-up information in the Resource has been extensively evaluated at each of the semiannual meetings of the Coordinating Committee and at the quality assessments undertaken at each site as part of routine operations. Data concerning the initial diagnosis and treatment has been found to be quite accurate. Similarly, notation of signal dates (diagnosis and death in particular) is very reliable. The deficiencies that exist in the data reflect the known weaknesses of cancer registries. These include: (a) the lack of outpatient treatment data, because these registries are all hospital-based; and (b) inconsistent notation and inadequate description of the development of metastases and their treatment. For these reasons some investigators have relied on "death" as a well-defined end point or explicit statements regarding treatment or recurrence status.

The Resource was particularly designed to support validation studies of markers believed to be of prognostic importance. Such studies require large numbers of specimens, accurate clinical and pathological material, and extended follow-up. Although the material and data cataloged for the CBCTR is extensive, more clinical and pathological data can sometimes be obtained if requested. Obtaining additional data may require additional examination of medical records or more extensive pathological review, both of which may be arranged on a collaborative basis.

The CBCTR represents a valuable resource for laboratory investigators who seek large numbers of archival specimens accessioned and evaluated uniformly by a single protocol and linked to extensive clinical and outcome data. Interested individuals using the World Wide Web can readily access the catalogue of available material. Searches of this catalogue not only verify that the material is representative of breast cancer, but that ample numbers of specimens are available for study.

## Acknowledgments

Many individuals collaborated in the development and construction of the CBCTR. We acknowledge the following contributors at the several sites for their efforts: Kaiser Permanente Northwest Region, Portland, OR: Neal Olson, Bradley Brown, Barbara Armstrong, Michael Allison, Mina Monroe, Lois Drew, and Beverly Battaglia; Fox Chase, Philadelphia, PA: Irma Russo, Eric Schulz, Paulo Tahin, and Darcy Quillen; University of Miami, Miami, FL: Edward Trapido, Ruth Soto, and Luz Arias; Washington University, St. Louis, MO: John Meyer, Helen Marshall, William Dilley, and Cynthia Helms; National Cancer Institute, Bethesda, MD: Lisa McShane; and Information Management Services, Bethesda, MD: Sherrill Long, Kevin Meagher, Winnie Ricker, and Jim Rovon.

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