

AD _____

GRANT NO: DAMD17-94-J-4206

TITLE: A Follow-up of a National Cohort of Breast Disease -
Factors Affecting the Development of Breast Cancer

PRINCIPAL INVESTIGATOR(S): Baruch Modan, M.D.

CONTRACTING ORGANIZATION: Chaim Sheba Medical Center
Tel Hashomer 52621 Israel

REPORT DATE: September 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, 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.

19960819 004

REPORT DOCUMENTATION PAGE

Form Approved
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 September 1995	3. REPORT TYPE AND DATES COVERED Annual (9/1/94 - 8/31/95)	
4. TITLE AND SUBTITLE A Follow-up of a National Cohort of Breast Disease - Factors Affecting the Development of Breast Cancer			5. FUNDING NUMBERS DAMD17-94-J-4206	
6. AUTHOR(S) Baruch Modan, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Chaim Sheba Medical Center Tel Hashomer 52621 Israel			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT <p>In 1979-80 we collected and re-examined all breast biopsies performed in Israel by a single pathologist (Dr. M. Black) in New York, using his prognostic grading system, nuclear differentiation and Lymphocyte Reticular Endotelial (LRE) response for benign breast diseases (BBD). The complete cohort consisted of about 3500 women. By September 1995, 460 women were traced and 349 of them were interviewed. Preliminary data show that about 42% of these women went through a second biopsy and 22% went through >2 biopsies. The latter pathological slides were sent to Dr. Black in the U.S. for re-evaluation. First follow-up for morbidity and mortality was done by linkage of our file with that of the Cancer Registry 2.2% of women with normotypic (grade 1), 3.3% of hyperplastic (grade 2), and 9% of atypic, precancerous mastopathy (grade 3-4) developed breast cancer (BC). Mortality of the cancer patients in the cohort was 38% for in-situ BC and for 67.2% invasive BC. A second stage of this study i.e. a nested case control study of the BBD cohort, using a questionnaire with complete hormonal and parity history as well as personal and family history as well as personal and family history of benign and malignant BC, physical activity and alcohol drinking habits, is on the way.</p>				
14. SUBJECT TERMS breast cancer; epidemiology; carcinogenesis, tumors			15. NUMBER OF PAGES 16	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

GENERAL INSTRUCTIONS FOR COMPLETING SF 298

The Report Documentation Page (RDP) is used in announcing and cataloging reports. It is important that this information be consistent with the rest of the report, particularly the cover and title page. Instructions for filling in each block of the form follow. It is important to *stay within the lines* to meet *optical scanning requirements*.

Block 1. Agency Use Only (Leave blank).

Block 2. Report Date. Full publication date including day, month, and year, if available (e.g. 1 Jan 88). Must cite at least the year.

Block 3. Type of Report and Dates Covered. State whether report is interim, final, etc. If applicable, enter inclusive report dates (e.g. 10 Jun 87 - 30 Jun 88).

Block 4. Title and Subtitle. A title is taken from the part of the report that provides the most meaningful and complete information. When a report is prepared in more than one volume, repeat the primary title, add volume number, and include subtitle for the specific volume. On classified documents enter the title classification in parentheses.

Block 5. Funding Numbers. To include contract and grant numbers; may include program element number(s), project number(s), task number(s), and work unit number(s). Use the following labels:

C - Contract	PR - Project
G - Grant	TA - Task
PE - Program Element	WU - Work Unit Accession No.

Block 6. Author(s). Name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. If editor or compiler, this should follow the name(s).

Block 7. Performing Organization Name(s) and Address(es). Self-explanatory.

Block 8. Performing Organization Report Number. Enter the unique alphanumeric report number(s) assigned by the organization performing the report.

Block 9. Sponsoring/Monitoring Agency Name(s) and Address(es). Self-explanatory.

Block 10. Sponsoring/Monitoring Agency Report Number. (If known)

Block 11. Supplementary Notes. Enter information not included elsewhere such as: Prepared in cooperation with...; Trans. of...; To be published in... When a report is revised, include a statement whether the new report supersedes or supplements the older report.

Block 12a. Distribution/Availability Statement. Denotes public availability or limitations. Cite any availability to the public. Enter additional limitations or special markings in all capitals (e.g. NOFORN, REL, ITAR).

DOD - See DoDD 5230.24, "Distribution Statements on Technical Documents."

DOE - See authorities.

NASA - See Handbook NHB 2200.2.

NTIS - Leave blank.

Block 12b. Distribution Code.

DOD - Leave blank.

DOE - Enter DOE distribution categories from the Standard Distribution for Unclassified Scientific and Technical Reports.

NASA - Leave blank.

NTIS - Leave blank.

Block 13. Abstract. Include a brief (*Maximum 200 words*) factual summary of the most significant information contained in the report.

Block 14. Subject Terms. Keywords or phrases identifying major subjects in the report.

Block 15. Number of Pages. Enter the total number of pages.

Block 16. Price Code. Enter appropriate price code (*NTIS only*).

Blocks 17. - 19. Security Classifications. Self-explanatory. Enter U.S. Security Classification in accordance with U.S. Security Regulations (i.e., UNCLASSIFIED). If form contains classified information, stamp classification on the top and bottom of the page.

Block 20. Limitation of Abstract. This block must be completed to assign a limitation to the abstract. Enter either UL (unlimited) or SAR (same as report). An entry in this block is necessary if the abstract is to be limited. If blank, the abstract is assumed to be unlimited.

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).

____ 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.



PI - Signature

Date

TABLE OF CONTENTS

	PAGE
Table of Contents	3
Study Purpose	4-6
Technical Objectives	6-7
Work Progress and Preliminary Results	7-9
Future plans	9-10
Tables	11-14

STUDY PURPOSE

Background

This study offers a unique opportunity to evaluate the course of development of the whole range of benign and malignant breast diseases diagnosed in a national incidence study conducted fifteen years ago, in relation to a histologic type and selected risk factors, in women belonging to distinct ethnic groups who also differ in their BC incidence.

In Black's BBD prognostic system the essential feature of Black-Chabon grading system is based on a score of 1 to 5 describing a degree of ductal atypia. Normotypic lesions included those classified as normoplastic (Grade 1) and hyperplastic (Grade 2). The normoplastic lesions included those conventionally categorized as cystic changes, stromal fibrosis, duct ectasia, and normal-appearing breast parenchyma. The hyperplastic lesions included those conventionally classified as intraductal papillomas, papillomatosis, adenosis, and duct hyperplasia without atypia. The term benign proliferative mastopathy was ascribed to the preceding group of conditions with duct Grades 1 to 4. Minimal, moderate and marked degrees of ductal and/or lobular atypia were graded as 3-5, respectively. A grading of 5 essentially coincides with the traditional category of *Ca in situ*, while Grades 3 and 4 are sometimes diagnoses as *Ca in situ*.

The evolution of BC from normal tissue to malignancy has a long natural history which may be a multistage process that proceeds through duct cell hyperproliferation to atypia, *in situ* growth, and malignant transformation. This tumorigenesis model may be associated with several genetic, hormonal and

reproductive factors that may act to depress, or enhance, the final outcome in this dynamic continuum.

The Israeli National Population Registry maintains a registry of all citizens and permanent residents in Israel. The registry includes first and second names; father's first name, I.D. number; sex; date of birth; country of origin; year of immigration; marital status; address; vital status; and date, place and cause of death, where applicable. Each Israeli citizen and each permanent resident, has a unique nine-digit National I.D. number which cannot be assigned to anyone else. This number is used for many purposes and facilitates record linkage. The Israel National Population Registry is updated on a routine basis for births, deaths, and in- and out-migration, and is corrected by linkage with census data.

Israeli population is characterized by its marked ethnic diversity and varying incidence of BC risk which parallels racial black/white differences in the U.S. Follow-up for morbidity and mortality can easily be done due to the possibility of linkage of the original epidemiological data with the Cancer Registry using a unique I.D. number, identifying all Israel citizens.

Our study will allow identification of factors (reproductive, hormonal, family history, etc.) affecting BC onset. The temporal influence of these recognized risk factors associated with breast events will be investigated in a gradient of pathological subgroups (normotypic, hyperplastic, atypic, in situ) and BC incidence.

The study is based on a fifteen-year follow-up of the cohort of 3500 women diagnosed nationwide for benign and malignant breast lesions, between July 1979 and June 1980. A particular feature of the study population is that it stems from a single community but comprises subgroups with varying BC incidence; high risk women born in Europe, America and Israel, and low risk women originating from the

Middle East and North Africa. The age-adjusted incidence rates of these groups in the late 1980's were 87.0 and 57.2 per 100,000 respectively, a gradient similar to the one observed between US whites and blacks.

Significance

This study offers a unique opportunity to evaluate the progression of benign and malignant breast disease on a whole community base population.

Results will contribute to shedding light in respect to the role of BBD in general and its specific histologic types in BC causation, taking into account interactions with main hormonal and demographic risk factors.

TECHNICAL OBJECTIVES

The specific aims are:

1. To assess morbidity patterns in a nationwide cohort of women with breast lesions by histopathological type and by ethnic origin.
2. To compare the prognostic value of Black-Chabon atypia-based grading system of BBD to the "traditional" histopathologic diagnosis, as predictors for progression from benign to malignant breast lesions.
3. To evaluate the prognostic significance of selected specific characteristics of breast neoplasms by clinical stage (TNM): histopathology; laterality of sequential neoplastic events; angiogenesis; degree of nuclear differentiation of the tumor cells (expressed as nuclear grade (NG)); and cell mediated immunity to autologous cancer cells (as manifested by microscopically demonstrable lymphoreticuloendothelial (LRE) response).
4. To evaluate the role of selected hormonal and other factors, on the course of progression from benign to malignant breast lesions.

5. To assess the role of demographic and medical characteristics on the development of a second BC.
6. To establish a national datafile for subsequent long-term follow-up of this population.

Questionnaire

All patients are interviewed in their homes by means of a standard structured questionnaire in Hebrew containing items on the following list of subjects.

Demographic information:

Name, birth date, marital status, year of immigration, country of origin, education, profession, working place, working exposure.

Smoking history; Drinking habits; Weight: adult life (now; age 18); Height.

Menstrual history: Reproductive history, parity
Hormone intake: OC

Sterility treatment and other:

Medical history: surgery, genitry tract morbidity
Radiation treatment

Diagnostic x-ray:

Mammographies in particular

Drugs taken for at least three consecutive months

Family history of breast cancer; breast diseases; genitry cancer; other cancers

Physical activity; No. of active hours versus passive daily hours

WORK PROGRESS AND PRELIMINARY RESULTS

There was a late start of the study due to a delay in transfer of funds.

Consequently the actual study months do not correspond to the original work flow.

Table 1 presents the study cohort by main diagnosis, representing all women going through breast biopsy in Israel during one year period (6.1.79 - 7.1.80)

(Appendix), and identified 15 years later. The source of the demographic information

collected at time of first identification of cases consisted of the pathological records, which in many cases were found to be incomplete. During the last year completion of demographic information was done by tracing and identifying medical records in all hospitals in Israel. Our file was then linked to the Population Registry to further update addresses and vital status (complete name and address, year of birth, father's name and place of birth) to validate identification. As can be observed, 229 cases (8.4%) were not identified and we continue the tracing process individually. Unidentified women were found not to belong to one specific type of benign breast disease but are rather distributed similarly among the various diagnostic categories (9.5 in precancerous breast diseases and 9% in the normotypic benign breast disease and 8.3 in the invasive carcinoma patients).

Biological relationships between invasive breast carcinoma and non-invasive lesions have been obscured by the tendency to categorize most benign parenchymal lesions (excluding fibroadenoma) as fibrocystic disease, in spite of distinct differences in their proliferative and atypical characteristics.

Dissatisfaction with the prognostic value of traditional pathological categorization of BBD has led to the development characterization of BBD based on proliferation and atypical degree of changes of defined segments of the mammary duct system.

Table 2 shows results of 12 years BC morbidity follow-up. The prognostic value of Black-Chabon grading system of benign breast diseases was confirmed in findings in our cohort. An increased risk for breast cancer with increased grading was observed: from 2.2% in the normotypic normoplastic type of BBD (grade 1) to 9.0% in atypic precancerous mastopathy (grade 3).

We evaluated the frequency of subsequent BBD in a subgroup of 250 BBD women interviewed (table 3) and found that 64% of the women went through at least one additional biopsy, 42% had two biopsies, while 22% had three or more. All pathological slides of these biopsies are being reassessed by Dr. Black and the BBD history status by highest grade through life will be rechecked against BC morbidity in further follow-ups, before the end of the study period.

Table 4 shows the interview status of the nested case control study. By 1.6.95 we completed 349 interviews and a similar number is in process in the field. Response was 77.5%. Non response was mostly due to incorrect address and therefore should not be considered final. Non response by type of diagnosis shows a similar distribution among all types of diseases.

DISCUSSION

As can be observed from Table 2, 9% of BBD graded 3-4, developed breast cancer as compared to 2.2% in grade 1 BBD (normotypic normoplastic) while grade 2 has an in-between risk (3.3%). Using conventional diagnostic nomenclature fibrocystic BBD grade 2-3-4 would have just distributed among fibrocystic diseases.

Future plans

Breast cancer cohort - Follow-up of BC patients includes abstracting medical information from the oncological records in all hospitals in Israel. About 50% of these were identified. During the next year completion of BC follow-up will be done, and a special effort will be made to identify records on the basis of a personal, nationwide search.

Nested case control study - Interviews will be completed, and on line data entering will continue. A double check of case identification will be done by going back to unidentified cases by a second interviewer and, if needed, a special professional

tracer will be employed. Data analysis of familial BC and familial BBD is being considered for the next year.

Direct and inferential evidence indicates that the precursor to invasive progression is impeded by cell-mediated immunity to a particular immunogen that is characteristically expressed in the preinvasive phase of mammary carcinogenesis.

Evaluation of this component, LRE, response to the tumor was made in our cohort and will also be analyzed as marker for further BC morbidity. Within grade 2 and 3 there are many cases (67%) that were designed traditionally as fibrocystic disease.

Shipping of all pathological slides to N.Y will start next year. Dr. Black's visit to Israel is due November for special counselling and review of original pathological slides.

Table 1
Study cohort by main Black's diagnostic category
and current status

Diagnostic Category (1979-80)	Total Cohort (1979-80) n	Total Cohort Identified* (1995) n
Total BBD	2728**	2499
Normotypic/ hyperplastic (Grade 1-2)	2521	2303
Atypic, precancerous (Grade 3-4)	132	126
In situ (Grade 5)	75	70
Invasive	992	828

* *By Population Registry only (not home identification) for mortality and demographic information only (does not include non-responders)*

** *For about 10% of cases no review was done by Dr. Black, the complete cohort includes these women as well, with their histopathology by local pathologist*

PRELIMINARY DATA

Table 2

Number and percent of breast cancer (BC) in the BBD cohort,
 diagnosed by Black, and BC morbidity
 after 12 years of follow-up by category

Type of disease BBD (1979-80)	Total No. in the cohort* n	BC (year 1991)	
		n	%
Normotypic-Normoplastic (Grade 1)	991	22	2.2
Normotypic-Hyperplastic (Grade 2)	932	32	3.3
Atypic precancerous mastopathy (Grade 3-4)	132	12	9.1
In situ Ca. (Grade 5)	62	3	4.8
Total	2117	79	3.1

* *total includes only women for whom all demographic characteristics were ascertained and were diagnosed originally by Dr. Black*

PRELIMINARY DATA

Table 3

BBD COHORT SUBSAMPLE
(n=250 interviews)

Frequency distribution of repeated breast biopsies

No. of Breast Biopsies	Total	
	n	%
1	90*	36
2	105	42
3	36	14.4
≥4	19	7.6
Total	250	100

** no additional biopsy*

Table 4

Distribution of population by interview status and cause of non-response

Total cohort	Interviewed		In process*		Non-response					
					Refused		Not identified		Other reasons	
					n	%	n	%	n	%
2400	349	77.6	450	100	27	6	39	8.7	35	7.8

* *traced population of the nested case-control study until 8.1.95*