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LAGGING GOVERNMENT SALARIES SPUR NCI TURNOVER AMONG SENIOR STAFF, THREATEN CANCER PROGRAM

Turnover among senior NCI staff members and the inability to recruit scientists from universities is a major threat to the cancer program and the problem appears to be accelerating, according to a background paper prepared by the institute.

The paper noted that during the past year, directors of three of the five NCI divisions have left to accept positions with universities or cancer centers. Also, the position of clinical director has been twice vacated during the year, and the associate director for cancer centers and program director for molecular control have moved on.

"Non-competitive salaries appear to be the major factor" in the turnover, the paper said, although noting that desire for career advancement and fringe benefits such as free or low cost university education for children of the departed staff members are also important considerations.

(Continued to page 2)

In Brief

ACCC TO BID ON OVARIAN CANCER TREATMENT RFP; COMMUNITY MDs HANDLE 90% OF OVARIAN PATIENTS

THE ASSN. of Community Cancer Centers will bid, as an organization, on an NCI RFP for therapy of patients with ovarian carcinoma (RFP CM-67026). Charles Cobau of the Toledo Cancer Interest Group, will be the principal investigator if ACCC gets the contract. The ACCC executive committee decided to submit a proposal after a survey of the membership indicated the members together treated a substantial number of ovarian cancer patients every year, probably more than any single institution or other organization. Coincidentally, Div. of Cancer Treatment Director Vincent DeVita commented recently that only 10% of ovarian cancer patients are going into clinical studies. "The other 90% are being handled by community physicians, and handled very well according to the state of the art," DeVita said. "But we should be able to improve what they're doing" (by bringing more of those patients into clinical research). ACCC is working on the first year of a three-year planning grant from the Div. of Cancer Control & Rehabilitation, to plan for establishing clinical investigation programs at the community level to be performed in cooperation with the major cancer centers. The grant is worth $95,000 the first year, $250,000 each for the second and third years. ACCC President James Donovan and Cobau are co-PIs of the grant. . . . "TREATMENT AND Survival Patterns for Black and White Cancer Patients," a publication which cites generally lower survival rates among black patients as compared to whites, is available from NCI. Single copies may be obtained free of the Office of Cancer Communications, NCI, Bethesda, Md. 20014. Multiple copies can be ordered from the USGPO, Washington, D.C. 20402, for 75 cents each.

SALARIES RANGING UP TO $90,000 INHIBIT NCI RECRUITING EFFORTS

(Continued from page 1)

In the six cases cited above, each former NCI staff member received a salary ranging from $50,000 to $70,000 in his new job. Government salaries are frozen at $36,000, although there are exceptions.

Some of those exceptions, incidentally, create the unusual situation in which 65 NCI medical officers receive more than their boss, Director Frank Rauscher. They are uniformed officers of the Public Health Service and are entitled to variable incentive pay designed to attract MDs to the service. Rauscher is a PhD, not an MD, and does not qualify for the extra pay.

With the freeze of government executive salaries at $36,000, in effect since 1969, another 80 NCI staff members have bumped up against the limit and thus get the same pay as Rauscher.

"NCI has succeeded in filling the above cited vacancies primarily through promotion of existing staff," the paper said. "To date highly qualified staff have been placed in these positions. But the normal course for filling senior level investigator and branch chief positions, who form the pool for internal promotion, is through recruitment of department chairmen and professors from universities. The increasing gap between federal salaries and university salaries will inevitably dry up this recruitment source."

The paper quoted an NIH survey of seven universities and research institutions receiving NIH grants. The survey revealed that principal investigators receive from $38,000 to $90,000 with an average salary of $54,000.

It also referred to a 1974 faculty salary study by the American Assn. of Medical Colleges which revealed that base salaries for department chairmen average $49,700; professors are paid an average of $39,000; chairmen of anesthesiology, pathology and radiology departments receive $49–55,000; and professors in those departments average $40–43,000.

"This salary gap constitutes a clear and present danger to our ability to recruit and retain the senior scientific executives needed to plan, administer and monitor the National Cancer Program," the paper said.

The paper on the salary problem was accompanied by other background papers on cancer research achievements and NCI's response to congressional mandates under the National Cancer Act and appropriations acts. These were prepared in response to inquiries from members of Congress and others who have felt the need to develop some defense against critics of the cancer program.

Extramural research achievements noted in the paper referred mostly to treatment advances:

★ The study at St. Jude's by Joseph Simone in which more than 50% of children with acute lymphocytic leukemia were alive and without evidence of disease more than five years after starting treatment with a combination of anticancer drugs and radiation.

★ Bernard Fisher's National Surgical Adjuvant Breast Project cooperative group program, in which the rate of recurrence of breast cancer was reduced significantly in preliminary trials in patients treated after surgery with L-PAM.

★ The NCI-supported studies using adriamycin for use alone and in combination with other treatment modalities against cancers of connective tissue, advanced breast cancer, lung cancer, lymphomas, acute leukemias, childhood cancers, and cancers of the ovary, bladder and thyroid.

★ Advances in treatment of Wilms' tumor through combined modalities including surgery, radiotherapy, and actinomycin D and vincristine. The National Wilms' Tumor Study Group, headed by Giulio D'Angio, found that the combined therapy had achieved a two-year survival rate of about 80%, and, when early stages of the disease can be treated, a two-year survival rate of almost 100%.

★ Use of anticancer drugs after surgery to prevent recurrence of osteogenic sarcoma in studies supported by NCI at several institutions. Patients remained free of disease for up to two years after surgery and treatment with adriamycin or high doses of methotrexate combined with citrovorum factor.

★ First synthesis of an artificial and potentially functioning gene by an NCI grantee, Gobind Khorana of MIT.

★ The combination of physical examination and x-ray mammography in breast cancer screening in which earlier detection helped decrease deaths by one-third over a five-year followup period.

★ Studies by John Frost and Bernard Marsh of Johns Hopkins in developing the ability to detect lung cancer through sputum cytology, combined with scanning of lung passages with a flexible fiberoptic bronchoscope. Followup studies using those techniques, in which Robert Fontana of Mayo is participating, are attempting to determine if earlier detection will improve treatment results.

★ The test developed by Elwood Jensen at the Univ. of Chicago for predicting the response of advanced breast cancer to hormone therapy.

★ The finding that daughters of women who had taken DES during pregnancy sometimes developed clear cell adenocarcinoma in the vaginal or cervical regions.

Intramural programs and progress included in the paper:

• Compilation of cancer death rates for each of the 3,056 counties in the 48 contiguous states and D.C.

• Use of combination chemotherapy to improve chances for disease free survival and cure in patients with advanced diffuse histiocytic lymphoma, reported by Div. of Cancer Treatment Director Vincent DeVita and his associates. Ten of 27 patients with

advanced disease achieved a complete disappearance of symptoms for two to nine years after treatment with a four-drug combination called MOPP—mustargen, oncovin, procarbazine and prednisone.

• Isolation of a candidate human virus from the leukemic cells of a 61-year-old woman with acute myelogenous leukemia by Robert Gallo and Robert Gallagher.

• Studies by DeVita and colleagues in which they achieved complete disappearance of symptoms of advanced, recurrent breast cancer in seven of 25 patients with a four-drug combination of cytoxan, methotrexate, 5-FU and prednisone, and a partial response in another 10.

• Discovery by Peter Mora and coworkers that cancer-causing viruses may act on the surface membranes of cells to change cell susceptibility to the body's immunological defense system.

• Development of a more rapid method to screen chemicals for carcinogenic activity using hamster embryo cells.

• Improvement of survival rates in Hodgkin's disease with supervoltage x-irradiation to diagnosed disease sites plus prophylactic radiation to uninvolved areas with a high potential for disease extension.

• Development of a four drug regimen for combination treatment of advanced Hodgkin's disease—prednisone, procarbazine, vincristine and either nitrogen mustard or cyclophosphamide.

• Discovery that metabolism of the chemical cyclic adenosine monophosphate appears to be disrupted when laboratory grown cells are made cancerous by infection with cancer-causing viruses. This study suggested that cyclic AMP may be associated with control of cell movement and growth, both of which become deranged when cells become cancerous.

• Determination that patterns of cancer occurrence are changing, probably as a result of environmental factors and individual behavior patterns, according to data from the Third National Cancer Survey, a study of seven metropolitan areas and two entire states.

CONTRACT AWARDS

Title: In vitro sensitization of human lymphocytes
Contractor: Weizmann Institute of Science, Rehovot, Israel, $69,081.

Title: Mechanisms by which tumors avoid destruction by the immune system
Contractor: Univ. of Hawaii, $69,877.

Title: Vaginal-cervical cell sample sources by cytology automation
Contractor: State Univ. of New York, $25,511.

REPORTS ON NUTRITION AND CANCER SHOW NEED FOR MORE CLINICAL STUDIES

Reports on various relationships of diet and nutrition to the etiology and treatment of cancer were presented at the initial meeting of the Diet, Nutrition & Cancer Program Advisory Committee, and at a workshop held previously. Some of those reports appeared in ***The Cancer Letter*** last week; others follow here.

Joseph Bertino, Yale, discussed selection nutrient depletion during therapy.

"Selective dietary depletion of asparagine, isoleucine, methionine, phenylalanine, and histidine has been associated with partial tumor regression in experimental tumors," Bertino said. "However, these diets usually become unpalatable for the patient and are discontinued. Enzymatic depletion, as via asparaginase to decrease serum asparagine levels, has resulted in 50 to 60% complete, but transent, regressions in patients with acute lymphocytic leukemia. Since normal tissues do not depend upon exogenous asparagine for survival, this type of therapy is without toxicity to normal tissues, except for the allergic reactions this foreign protein stimulates. Enzymatic methionine depletion may also be of value, and one such enzyme has caused tumor regression in experimental animals bearing the Walker 256 carcinoma. Several reports indicate that tumor cells, but not normal cells in culture, may require methionine for growth.

"Vitamin depletion therapy has also been attempted to produce tumor regression, but again the liquid deficiency diets are extremely difficult for these sick patients to tolerate over the weeks and months required. Deficiencies of folic acid, vitamin B-12, riboflavin, and vitamin B-6 have all been reported to cause tumor regression in experimental animals, and folic acid deficiency and riboflavin deficiency with galactoflavin, a weak antagonist, have been reported to cause regression of certain tumors in man. In this laboratory, a folate-cleaving enzyme, carboxypeptidase G_1, has been isolated and is now undergoing clinical trial."

Sarah Donaldson, Stanford, reporting on the relationship of diet and nutrition to radiation therapy, said that symptoms resulting from radiation may create direct or indirect problems, either acute, occurring during therapy, or chronic, following therapy.

"Those symptoms which occur during therapy are often reversible," Donaldson said. "The post-therapy symptoms which indirectly create severe nutritional problems are often associated with severe sequelae and usually are dose-related. There is very little information available regarding possible therapeutic approaches for those conditions, and specifically very little information is available related to nutritional and dietary treatment. Radiation therapists carry a general armamentarium of therapies used to reverse symptoms related to radiation injury. With respect to nutritional management, specific diet may be prescribed to relieve the symptoms created by the treatment. There has, however, been very little attention given to nutritional therapy used before the initiation of radiation therapy; very little attention given to

nutritional therapy used prophylactically; and very little attention directed toward nutrition used specifically for the purpose of reversing radiation injury.

Donaldson discussed dietary management as a specific treatment of radiation injury, and reported on a study at the Institut Gustave-Roussy in France. In this study, 44 children received whole abdominal radiation as part of the treatment for their malignant disease. Ages ranged from 6 months to 16 years at the time of radiation. The diagnoses included non-Hodgkin's lymphoma, Wilm's tumor, malignant ovarian teratoma, and retroperitoneal rhabdomyosarcoma. All patients had extensive tumor which required full abdominal-pelvic radiation fields to cover the known disease.

Over the 11-year period of this retrospective study, the treatment techniques varied greatly with the diagnosis, stage, and extent of the disease and the age of the child. Radiation, designed to cover the entire peritoneal cavity, was given by anterior and posterior abdominal-pelvic portals extending from the diaphragm to the floor of the pelvis. Of the 44 patients, 42 were treated with Cobalt-60 teletherapy, the remaining two being treated with 200 kv X-ray. The doses delivered varied depending on the diagnosis, stage, and extent of tumor and the age of the child. The dose rate was quite uniform at 800 rads per week.

In 25 of the 44 children (57%), chemotherapy was given concomitantly or within one month preceding the whole abdominal irradiation.

An analysis of the frequency of the intestinal reactions occurring during the course of radiation revealed that 31 (70%) had acute radiation enteritis. In 13 of these cases (30%), the symptoms were severe, with repeated nausea and vomiting requiring careful medical evaluation and supportive therapy in terms of fluid and electrolyte balance. In 24 of the 44 children (55%), there was weight loss. Five of the 44 children (11%) developed symptoms of delayed reactions, which, in each case, presented as nausea and vomiting, with a distended abdomen and with symptoms suggestive of small bowel obstruction. In four of the five cases, abdominal laparotomy was performed, revealing extensive adhesions and fibrosis responsible for the bowel obstruction but no evidence of tumor. In none of the cases was a definitive decompressive procedure performed.

All patients who developed severe delayed radiation enteritis were treated with a specific dietary regimen which was free of gluten, milk, milk products and lactose, and was low in fat and low in residue. The diet was given in fractionated feedings, 6 to 8 feedings per day for children of more than two years of age, and 8 to 12 feedings per day for children of less than two years of age, with infants treated by continuous drip via nasogastric tube with aid of a pump.

The rationale for the diet was that the histological findings showed a picture similar to that seen in malabsorption from other causes. The diet was made free of gluten, free of protein, and free of lactose because of the subtotal villus atrophy. The fat was limited because of the marked lymphangiectasis. The residue was limited to avoid further mechanical obstruction. The response to the diet was dramatic. All five children are surviving and doing well without relapse and without recurrent episodes of obstruction. The diet is well tolerated. In each case, the follow-up X-rays and small bowel biopsies have returned to normal. There is no question that this diet is therapeutically effective, Donaldson said.

At the Institut Gustave-Roussy, there is now under way a study in which the specific diet is initiated at the beginning of radiation therapy in all patients undergoing whole abdominal or hemi-abdominal radiation. Over the past 1½ years, since the initiation of this prophylactic dietary management, there have been no cases of early severe radiation enteritis and no cases of delayed radiation enteritis. Such a response encourages further clinical studies to dietary management. An important clinical study to undertake is one designed to examine the clinical-pathological effect of well-controlled nutritional management on radiation injury. Such a clinical trial should include surgically staged patients who will receive uniform small bowel irradiation and in whom systematic laboratory studies for malabsorption and gastrointestinal function would be performed. Pretreatment, midtreatment, and interval follow-up X-rays should be performed, coinciding with the timing of small bowel biopsies. Patients would be randomized to receive conventional supportive treatment or conventional supportive treatment plus a specific dietary therapy. Such a clinical-pa thological study is currently under way at Stanford Univ. Medical Center and will be important in determining the effects of nutrition and dietary management on radiation injury, Donaldson concluded.

Joan Bull, of NCI's Div. of Cancer Treatment, discussed the relationship of nutrition and chemotherapy. The central problem in chemotherapy as well as radiotherapy, she said, is that it requires the use of toxic agents against the tumor that also are toxic against normal tissue. Tumor cells frequently are more sensitive to these agents than normal cells, and nutrition may play a role in increasing tumor susceptibility while decreasing host susceptibility, she said.

Bull commented on one study that showed with patients who were either at ideal weight or no more than 10% underweight, 55% responded to chemotherapy, while among the underweight patients, only 28% responded.

Charles Moertel, Mayo, also reported on nutrition and chemotherapy at the workshop.

"Although it is an appealing presumption that improved nutrition will improve the effect of cancer chemotherapy, it must be emphasized that such a theory has very little factual support," Moertel said. "I was very reluctant to select clinical examples of the

relationship between nutrition and cancer for fear that I might imply dogma that really has no foundation in scientifically acceptable data. Certainly, it is possible to select our patients with poor nutrition who did very badly with chemotherapy to the point of drug-related death or patients with excellent nutrition who had excellent clinical responses to chemotherapy. On the other hand, it is also possible to find examples of patients with initially poor nutrition who had remarkably good responses and patients with good nutrition who had remarkably poor responses, but would these same patients have had these same chemotherapeutic responses irrespective of their nutritional status? That question becomes very difficult to answer."

Moertel cited studies in which 5—FU plus radiotherapy was used to treat carcinomas of the stomach, pancreas or large bowel. It was found that there was no significant correlation between nutritional status and 5-FU toxicity, he said.

"Although the results are disappointing from the standpoint of any nutritional correlation, it must be borne in mind that 5-FU used alone is a very ineffective chemotherapeutic approach to gastrointestinal carcinoma; therefore, these same nutrtional parameters were looked at in relationship to more recent results with drug combinations that have proved significantly superior to standard 5-FU therapy. Again, there was no relationship between pretreatment nutritional status and toxicity. There was, however, a striking and statistically significant relationship between nutritional status and therapeutic results. Those patients with pretreatment nutritional symptoms or those with a pretreatment weight 10% or more below ideal weight both had response rates which were essentially half of those recorded for patients in presumably better nutritional condition. Although the cause and effect relationship remains to be proved, there is sufficient suggestive evidence here to justify more vigorous research on the relationship between chemotherapy and nutrition. . . .

"Although the evidence that has been collected is fragmentary, there does seem to be some basis for the thesis that improved nutrition may improve the response to chemotherapy for advanced gastrointestinal cancer. In the past, the accomplishments of chemotherapy for gastrointestinal cancer were so meager that vigorous efforts to improve nutrition were difficult to justify. Within the past two years, however, substantial improvements in response rates have been recorded with combination drug regimens, now reaching the 30 to 50% range and with some evidence of improved survivorship. With these advances, and with increased attention being directed towards surgical adjuvant chemotherapy approaches with the intent of increasing cure rate, it now seems mandatory that far greater effort be expended to optimize nutrition in the patient subjected to cytotoxic drug regimens," Moertel concluded.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CB-64010-35

Title: *Standard protocol for evaluation of imaging techniques in cancer diagnosis*

Deadline: *Oct. 30*

NCI is interested in establishing a contract for developing a general protocol for the unbiased and properly controlled comparison and evaluation of imaging techniques utilized in cancer diagnosis and to apply that protocol to image data bases that will be obtained for the Div. of Cancer Biology & Diagnosis by other contractors. These imaging data at this point include: (1) Conventional mammograms and xeroradiograms of the same patients and (2) Digitized computerized brain tomographs, radionuclide scans and conventional roetgenographs of the same patients.

Emphasis should be placed on protocols that will compare the medical efficacy and overall cost-effectiveness of different imaging techniques for detection, diagnosis and localization of early (small) cancer lesions. It is expected that clinical application of such a protocol may improve both the medical efficacy and paramedical cost-benefit of cancer diagnosis by imaging techniques either currently in use or under development. In particular, it is expected that diagnostic accuracy may be enhanced by these efforts and that, where radiation is involved in the method, reduction in radiation dosage to the patient may also be achieved.

Contract Specialist: Cathy Baker
Biology & Diagnosis
301-496-5565

RFP NCI-CB-64012-35

Title: *Development and evaluation of radioisotopic surface markers and detectors to be used in endoscopic techniques*

Deadline: *Oct. 30*

NCI is interested in establishing a contract to develop a procedure for earlier tumor detection on mucosal surface such as the large intestine or the lung by means of improved detection procedures to

be used with endoscopic examination.
Contract Specialist: Cathy Baker
Biology & Diagnosis
301-496-5565

Brief summaries of the following RFPs appeared in previous issues of ***The Cancer Letter****. More complete information on the work to be performed under each proposed contract follows:*

RFP NCI-CB-63932-39

Title: *Radioimmunoassay of immunoglobulin molecules*

Deadline: *Sept. 30*

A series of studies has been initiated at NCI to define the factors controlling the differentiation of lymphocytes into immunoglobulin synthesizing and secreting cells. The technique developed in these studies is being utilized to study the physiological factors controlling this differentiative process and to define defects in patients with primary immunodeficiency diseases and a high incidence of malignancy or with chronic lymphocytic leukemia, multiple myeoloma or macroglobulinemia of Waldenstrom. The technique requires the quantitation of the different classes of immunoglobulins in the culture supernatants by double antibody radioimmunoassay procedures.

The contractor will be expected to perform 5,000 determinations in duplicate of IgG, IgA, IgN, IgD or IgL by double antibody radioimmunoassay yearly by procedures defined by the project officer. The procedures to be followed have been described in detail previously (*Lancet* 2:609-613, 1974). Since standard curves, quality controls and periodic evaluation of the assay are required this part of the work will require processing of 15,000 individual tubes annually. The contractor will be required to log in samples, to radioiodinate the serum proteins, to perform double antibody assays and to analyze the data using the Rodbard program or its equivalent.

NCI will provide all of the purified antigens, standard displacers, first antibody system (i.e. rabbit antibody to each class of immunoglobulin) and second antibody system (antibody to rabbit IgG). The samples to be assayed will be submitted in one to two ml volumes in one dram vials in a form that can be directly used with an automatic pipeting station for performance of the radioimmunoassay.

The contractor must be located within 1 hour drive of the NIH and will be required to pick up samples from NIH twice a week. The contractor should have facilities for storage of the frozen samples until the assays are performed. The contractor will complete the assays within two weeks of submission of the samples.

Contract Specialist: Thompkins Weaver
Biology & Diagnosis
301-496-5565

RFP NCI-CB-64000-34

Title: *Studies and investigations on endocrine therapy plus chemotherapy in patients with breast cancer*

Deadline: *Dec. 1*

The Breast Cancer Task Force desires to evaluate the use of chemotherapy combined concurrently or sequentially with hormone manipulation in patients with advanced breast cancer. Hormonal manipulative therapies include surgical removal of endocrine organs, the administration of hormonal agents, and the administration of hormone antagonists.

The contractor shall furnish all necessary personnel, labor, patients, facilities, equipment, materials and supplies required to conduct a controlled clinical study designed to meet the objective. At least 50 patients per year are to be admitted to the study. Each patient will have a microscopically confirmed diagnosis of carcinoma of the breast. The carcinoma will be in an advanced stage; i.e., either recurrent after treatment of the primary carcinoma or such extensive primary cancer that local therapy is not feasible. The carcinoma will be in a progressive state and objectively measurable lesions will be present.

Specifically, the contractor should submit a proposal which will include a clinical protocol that assures:

1. That the patients admitted to the study have recurrence of their breast cancer or have primary disease beyond the possibility of surgical or radiotherapeutic cure.
2. That the disease will be clinically staged.
3. That objectively measurable lesions are present.
4. That pretreatment laboratory and roentgenographic studies will be adequate and that follow-up studies will be performed at regular intervals.
5. That the patients are initially stratified for disease site and hormonal status.
6. That the treatment programs will be agreed upon by the principal investigator and the project officer.
7. That the response to treatment will be evaluated by the following parameters—objective remission or progression of the cancer, toxicity, duration of disease remission, and survival.
8. That all institutional, NCI, and federal regulations concerning safety from research risks, informed consent and peer judgment will be fulfilled.
9. In addition the proposer should indicate a willingness to offer clinical records for peer review; and participate in sending tumor tissue and other materials to core laboratories (e.g. estrogen receptor, and biologic marker assays).

Contract Specialist: Elizabeth Abbott
Biology & Diagnosis
301-496-5565

RFP NCI-CB-63999-34

Title: *Studies of breast cancer incidence in populations exposed to repeated mammography*

Deadline: *Dec. 20*

NCI is interested in soliciting proposals from organizations having access to female populations that have had breast mammography on a regular basis for over 20 years. The primary objective is to determine the occurrence as well as the present incidence of breast cancer in these populations for comparison with the occurrence and present incidence in similar control groups.

The increased usage of mammography in large scale screening projects designed for the early detection of breast cancer with follow-up examinations has resulted in much concern regarding possible radiation hazards. There are several reports showing that ionizing radiation in sufficient quantity can result in an incidence of breast cancer higher than that found in comparable nonirradiated populations.

Deduction of risk estimates made from these studies was based on data drawn from three populations: (a) women with tuberculosis undergoing multiple fluoroscopic examinations for performance of artificial pneumothorax, (b) women treated with x-irradiation for acute postpartum mastitis and (c) female survivors of the atomic bombings of Hiroshima and Nagasaki. However, there were a number of possibly unwarranted assumptions made in these studies in estimation of risk.

The contractor shall:

1. Define the study cohort at onset of study stating reasons for mammography, age distribution and distributions of breast cancer risk factors and their influence on the occurrence of breast cancer. (Onset refers to the time 20 years or more ago when mammography was begun.)

2. Adequately define the control population, stating age distribution and distributions of breast cancer risk factors.

3. Have records of the known status of patients over the years of follow-up including the occurrence of cancer of the breast. For the study cohort, the records should also include type of mammographic equipment, radiation dosages and frequency of examination over the entire period of observation. For the control group, the records should also include the amount of mammography over the entire period, to the extent that this can be determined.

4. Maintain records of patients for whom follow-up is not available and for whom additional follow-up procedures must be instituted.

5. State what methods of follow-up are to be utilized, the investigator's experience with the method and what resources will be needed.

6. Have available biostatistical support to indicate that the population size is large enough to reach valid statistical conclusions.

7. Indicate biostatistical resources and manner of data analysis, including possible differences or biases between study and control groups and how adjustments for these biases will be made in the analysis.

Contract Specialist: Elizabeth Abbott
Biology & Diagnosis
301-496-5565

RFP NCI-CB-63997-34

Title: *Epidemiologic characteristics of medullary and lobular breast cancer*

Deadline: *Dec. 20*

These studies should compare risk factors for the less common defined morphologic types, such as lobular and medullary cancers with the more common infiltrating ductal type which comprises approximately 80% of breast cancers in the United States.

A number of reports suggest that breast cancer is a heterogenous disease. There seem to be differences between pre-menopausal and post-menopausal breast cancer (1) between familial and non-familial breast cancer, (2) and between cancer with and without estrogen receptors (3). However, the fact that these sub-entities are not clearly separated at the present time, may be resulting in a dilution effect, blurring the search for etiologic factors.

Preliminary epidemiologic data suggests that the less common types of breast cancer have some characteristics of their own. Some international comparisons suggest that the relative frequency of these types is higher in Japan than in the United States and Europe. Medullary and colloid carcinomas have been reported to be more frequent in blacks than in white. Although lobular and medullary breast cancers are relatively rare, it is conceivable they may fit into epidemiologically definable patterns. It is also possible that skilled analysis of epidemiologic data may point to sub-groups with histologic features in common which cut across currently accepted boundaries, but which may help to define the histology of breast carcinoma in a more epidemiologically relevant way.

The contractor shall carry out a study of the epidemiological characteristics of medullary and lobular breast cancer. The following aspects should be included:

1. Studies may be conducted within established high or low risk populations or across socio-cultural groups with different risk levels.

2. Numbers of cases and controls in each group must be sufficiently large so that the epidemiological characteristics can be defined with precision and valid comparisons made between them.

3. Respondents must indicate their source of cases and anticipated numbers with each histologic type.

4. Source of controls should also be well defined.

5. Information to be obtained on cases and controls must be included

6. Respondents must identify the morphologic criteria it is planning to use in defining each type of breast cancer and the methods by means of which each type will be subsequently reviewed and defined.

Contract Specialist: Elizabeth Abbott
Biology & Diagnosis
301-496-5565

RFP NCI-CB-63996-34

Title: *Definition of epidemiologic characteristics of pre- and post-menopausal breast cancer*
Deadline: *Dec. 20*

The major objective is to determine whether breast cancer developing in women prior to the menopause has a similar spectrum of risk factors as breast cancer developing in women following a natural menopause.

A number of studies have indicated that breast cancer is not one disease with a single or uniform etiology. Studies have suggested that the disease occurring in pre-menopausal women is characterized by a greater concentration of cases with a familial or genetic onset, with more frequent multicentricity and with a possibly different distribution of histologic types than the disease occurring in post-menopausal women. Other studies have suggested there may be a difference in the extent to which age at first birth, height and weight may operate as risk factors in pre- and post-menopausal women and it is possible that some of these factors operate as indicators of nutrtional effects. Differences in the excretion of urinary steroids also suggests endocrine effects.

The contractor shall carry out a study defining the epidemiologic characteristics of pre- and post-menopausal breast cancer. The following aspects should be included:

1. Studies may be retrospective (case-control) or prospective (cohort) but should encompass a sufficiently large population, such that the epidemiological characteristics in both groups may be defined with precision.

2. Studies may be conducted within established high or low risk populations or across socio-cultural groups with different risk levels.

3. The source of patients, also the anticipated number of patients within each group of interest should be indicated.

4. Information to be obtained on each study case should also be indicated.

5. Respondents must also identify the source of their controls.

6. Methods for obtaining data of risk factors from cases and controls should be well defined.

7. Manner of analysis of data and nature of biostatistical support should be provided.

Contract Specialist: Elizabeth Abbott
Biology & Diagnosis
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RFP NCI-CB-63995-34

Title: *Epidemiology of non-invasive breast disease*
Deadline: *Dec. 20*

It is evident from clinical and experimental studies of neoplastic development that the evolution of a malignancy is a multistep process. Several breast lesions have been suggested to be associated with increased incidence of breast cancer. These include: Chronic mastitis, fibrocystic disease, ductal hyperplasia, and ductal atypia.

If any of these lesions is in fact a precursor lesion to breast cancer, it may be associated with the same "risk factors" as breast cancer. However, the extent to which risk factors for subentities of benign breast disease are similar to those for breast cancer is unknown.

Further knowledge of the epidemiology of precursor lesions would aid in understanding invasive breast cancer and might provide means to identify women at high breast cancer risk for follow-up observation or treatment, and for relatively rapid evaluation of prevention measures for invasive breast cancer by observation of the effects of preventive measures on the development of precursor lesions, which might be identifiable years before the appearance of clinical breast cancer.

The contractor shall carry out studies of the epidemiology of non-invasive breast disease with attention to the following aspects:

1. Studies should encompass large enough populations, so that epidemiologic characteristics may be defined with precision and statistically valid comparisons made.

2. Studies may be conducted within established high or low risk populations or across socio-cultural groups with different risk levels.

3. Source of study cases and controls, anticipated numbers, information to be obtained on each and methods for obtaining this information should be included.

4. A reproducible classification of types of benign breast disease should be demonstrated and utilized.

5. The biostatistical support and proposed methods for data analysis should be described in detail.

Contract Specialist: Elizabeth Abbott
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The Cancer Newsletter—*Editor* JERRY D. BOYD

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