Infrastructure Support and Pilot Tissue Collection for the CARET Biorepository

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1. OVERVIEW

The Carotene and Retinol Efficacy Trial (CARET) was a randomized, double-blind, placebo-controlled trial of the cancer prevention efficacy and safety of a daily combination of 30 mg β-carotene and 25,000 IU retinyl palmitate in 18,314 persons at high risk for lung cancer, founded by Drs. Gilbert Omenn, Gary Goodman, and Mark Thornquist. Two populations were enrolled in this trial: 4,060 men with extensive occupational exposure to asbestos, and 7,965 men and 6,289 women with at least 20 pack-years of cigarette smoking history, the most identifiable high-risk populations for lung cancer. The CARET intervention was halted in January 1996, 21 months ahead of schedule, with the twin conclusions of no benefit and substantial evidence of harm on both lung cancer incidence and total mortality. After the intervention ended, participants were followed with updated lung cancer incidence and cardiovascular disease mortality findings published in 2004. In a biorepository support UM1 grant (2013-2018) provided funds for the passive follow-up of CARET participants through 2012/2013 and the collection of supplemental clinical and laboratory data.

During the active intervention phase of CARET, serum, plasma, whole blood, and lung tissue specimens were collected. These biospecimens comprise the CARET Biorepository, an invaluable legacy of the parent trial. Although 5-10% of lung cancers occur in those without extensive tobacco abuse, cigarette smokers, the population recruited to CARET, represent the largest identifiable population at risk for lung cancer. Other cancers and disease endpoints have also developed in this large population, both tobacco-related and unrelated. Hence, the CARET Biorepository is an excellent resource for investigators of both lung cancer and cancers of other primary sites, such as cancers of the prostate, breast, bladder and colon. It is important that this resource continues to be available to researchers for hypothesis-driven studies. In 2007, when our original NIH CARET support ended, there was no NIH funding mechanism for continued biorepository support. Dr. Goodman lobbied governmental organizations and published an editorial in Cancer Epidemiology Biomarkers & Prevention on the critical need for a grant mechanism to provide support for the many biorepositories that have been created during the conduct of NCI-sponsored clinical intervention trials. The funds expended to initiate, conduct, and complete these trials, and collect their allied biospecimens, is many times the amount needed to maintain their heritage biorepositories.

In 2013, we were awarded a 5-year biorepository support grant (5UM1CA167462) which in part continued funding to staff the CARET Biorepository and allowed us to continue to participate in both funded investigator-initiated studies as well as provide requested material to those investigators that do not have funds to cover our costs. During these 5 years, we improved the biorepository database by extending participant follow-up to 2012/2013 for cancer, death, and cause of death via public databases, and also abstracted from participants' charts additional dietary, laboratory, and clinical data. Extent of disease is important in biomarker research and development. Using the extensive medical records collected at the time of endpoint determination, we have completed cancer staging at diagnosis for participants with lung, prostate, breast and colon cancers, the four most common CARET cancer endpoints.

We have now been approved for an additional 5 years of funding (U01CA167462). Because of the limited objectives and funding available to this continuing application, we proposed new initiatives as pilot investigations. Genetic analysis of both the tumor and host can potentially have a significant impact in cancer prevention, early diagnosis, prognosis, and treatment. Investigators accessing the CARET biorepository have requested resected or biopsied tumor tissue from both living and no longer living CARET participants. Currently our biorepository has only a small sample of these tissues. In this grant cycle, we will pilot collection of tissue from CARET participants diagnosed with lung cancer after 2003.

2. SPECIFIC AIMS

Our Specific Aims are:

1) Maintain and support the CARET Biorepository, database, and website to allow researchers' easy access to CARET biologic samples and data and contribute to and collaborate in their research;
2) Pilot procedures to obtain updated signed releases of medical records and consent for the utilization of biologic material in the CARET biorepositories consistent with recent developments on obtaining consent for broad research purposes and data sharing;
3) Pilot the collection of diagnostic lung cancer biopsy/surgical specimens from Washington State CARET participants diagnosed after 2003.

3. RESEARCH STRATEGY

3.A. COHORT OVERVIEW

3.A.1. Background and Experience.

Lung cancer is a highly lethal disease and a major public health problem. It has been estimated that in 2017 the US will report approximately 222,500 new cases of lung cancer and 155,870 deaths exceeding the combined total for breast, prostate and colon cancers.[1-3] Lung cancer is also one of the few diseases with a well-defined risk factor: inhalation of tobacco smoke. While tobacco use has become less common over the past 25 years, approximately 20% of American adults still currently use tobacco and 20% are former smokers. Although the percentage of current smokers has decreased, former smokers continue to be at elevated risk. The majority of Americans who now develop lung cancer are former smokers.[4, 5] Thus, even if cigarette smoking could be eliminated as an environmental carcinogen, lung cancer would remain a problem for the foreseeable future. Asbestos exposure is also a risk factor for lung cancer. Although current occupational asbestos exposure is virtually eliminated in the US, much asbestos remains in older buildings, including residential dwellings. Like tobacco exposure, when asbestos exposure is eliminated, risk for lung cancer and mesothelioma would continue for some time to come.

Over the past 20-30 years it has been accepted that cancer is the result of stepwise accumulation of multiple genetic and epigenetic changes that results in a cell with the properties we define as cancer.[6] Along with this understanding, there has been a parallel acceptance of the concept of chemoprevention, the use of agents to prevent, arrest, or reverse these genetic and epigenetic changes and thus prevent or delay the development of clinical cancers. [7] Based on epidemiologic, *in vivo*, and *in vitro* studies, dietary micronutrients (including β-carotene and vitamin A) with their presumed safety were some of the first agents to attract wide interest as potential prevention agents[8-11] especially in lung cancer.

The Carotene and Retinol Efficacy Trial (CARET) was one of several trials started in the early 1980s to assess the chemopreventive efficacy and safety of β-carotene and vitamin A.[12-15] Two high-risk groups were eligible: male and female heavy smokers age 50-69 years who had a history of at least 20 pack-years of cigarette smoking and who were either current smokers or had quit within six years prior to enrollment, and male workers age 45-69 years who had first exposure to asbestos on the job at least 15 years prior to enrollment and either chest radiographs positive for changes compatible with asbestos exposure according to the International Labour Organization (ILO) criteria or employment in one of ten high-risk trades for at least 5 years at least 10 years before enrollment.[16, 17] Asbestos workers were either current smokers or had quit smoking within 15 years prior to enrollment. At the time of enrollment, 66% of the CARET heavy smoker population and 38% of the asbestos-exposed population were current smokers.

Recruitment of smokers was via the mailing of recruitment information to age-selected populations including American Association of Retired Persons (AARP) members and subscribers of local health insurance companies. Recruitment of asbestos-exposed participants was through local high-risk union member lists and through primary care and occupational health clinics. Although recruitment and enrollment was voluntary and only those showing interest joined the trial, our population-based recruitment makes CARET findings (and the use of the biorepository) generalizable to all cigarette smoking populations. Table 1 illustrates final recruitment by study center location.

Table 1. Participants randomized by study center

	Baltimore MD	New Haven CT	Irvine CA	Portland OR	San Francisco CA	Seattle WA	Seattle Pilot	Totals

Asbestos-Exposed	813	1,024	----	308	854	245	816	4,060
Heavy Smokers	9	18	4,224	4,257	12	4,705	1,029	14,254
Totals	822	1,042	4,224	4,565	866	4,950	1,845	18,314

The design of CARET projected active intervention until late 1997, encompassing 110,000 person-years of follow-up for the 18,314 randomized participants.[18] In January 1994, the Alpha-Tocopherol Beta-Carotene (ATBC) trial, testing β-carotene and alpha-tocopherol in a 2x2 factorial design in 29,133 male smokers, reported an unexpected 18% increase in the incidence of lung cancer and an 8% increase in death in those participants randomized to 20 mg/day β-carotene. These findings resulted in a review and a decision for closer monitoring of all trials using β-carotene, and, in January 1996, the CARET intervention was halted, 21 months ahead of schedule (published in the *New England Journal of Medicine* in January 1996[19]). At the time intervention was ended, the relative risk estimates from Cox regression models of active intervention to placebo group were 1.28 (95% nominal CI 1.04-1.57) for lung cancer incidence, 1.17 (95% CI 1.03-1.33) for all-cause mortality, and 1.26 (95% CI 0.99-1.61) for mortality from cardiovascular causes.[19, 20] It was concluded that although CARET's pre-specified stopping boundaries had not been reached, CARET's data, in conjunction with the published findings of the ATBC trial, provided definitive evidence of no benefit and substantial evidence of harmful effect of the intervention on both lung cancer incidence and total mortality. When CARET stopped the intervention in January 1996, participants were asked to return for an end of trial visit. At that time, additional data and blood were collected, and consent was sought for continued follow-up. Nearly 99% of CARET participants completed this visit with 98% consenting to continued follow-up. Participants were contacted annually by either telephone or mailed questionnaire and, if there was a self-report of cancer, endpoint material was collected. Participant follow-up ended in June 2005 and the NIH funding for the clinical trial ended in June 2007. Results of the first six years of post-intervention follow-up (1996 – 2001) were published in JNCI finding that the adverse cardiovascular effects rapidly disappeared, but the adverse effects in lung cancer incidence slowly approached placebo levels.[21] During the previous Biorepository support grant funding period (2013-2018), cancer and death outcome ascertainment was extended through 2013 via linkage with state cancer registries and the National Death Index (NDI). An additional 1,015 cases of lung cancer were identified in CARET participants by the cancer and death registry linkages, bringing the total number of lung cancers in the CARET population to 2,460.

3.A.2. CARET Study Activities and Procedures (1983-2007)

Recruitment Strategy. Study centers presented the objectives of CARET and proposed procedures to potential source organizations and, on their approval, recruitment packets were mailed to their age-selected membership rolls. Potential participants responded by returning interest/eligibility surveys. Study centers conducted screening eligibility phone calls, First Visits to determine eligibility and distribute placebo run-in capsules, and Second Visits to confirm eligibility and capsule consumption adherence and to perform randomization. Randomization to intervention was done by the Coordinating Center.

Participant characteristics. Table 2 represents the baseline risk factors in the two high-risk groups.

Table 2. Risk factors among the 18,314 participants at baseline[1]

Characteristic	Workers Exposed to Asbestos		Heavy Smokers	
	Active Treatment	Placebo	Active Treatment	Placebo
No. randomized	2044	2016	7376[2]	6878[2]
Age – year	57±7	57±7	58±5	58±5
Female sex – no. (%)	0	0	3208 (43)	3081 (45)
Race or ethnic group – no. (%)				
White	1805 (88)	1775 (88)	7000 (95)	6487 (94)
Black	152 (7)	153 (8)	103 (1)	122 (2)
Hispanic	36 (2)	43 (2)	101 (1)	95 (1)
Other or unknown	51 (2)	45 (2)	172 (2)	174 (3)
Smoking status – no. (%)				
Never smoked	69 (3)	64 (3)	0	0
Former smoker	1194 (58)	1176 (58)	2474 (34)	2332 (34)
Current smoker	781 (38)	776 (39)	4902 (66)	4546 (66)
Cigarettes smoked/day				
Former smokers	25±12	25±12	28±11	28±11
Current smokers	24±10	25±10	24±9	24±8
Pack-years of smoking[3]	43±24	42±24	50±21	49±20
Years since quitting smoking[4]	10±8	10±8	3±2	3±2

[1] Plus-minus values are means±SD. Because of rounding, not all columns total 100 percent.

[2] The imbalance in the numbers is due to the assignment of three pilot participants to active treatment for every one assigned to placebo (773 to active treatment vs. 256 to placebo).

[3] Only former and current smokers were included.

[4] Only former smokers were included.

Contact schedule. In the first year after randomization, participants were contacted four times, twice by telephone (at 3 and 9 months) and twice by study center visits (at 6 and 12 months). In subsequent years, participants were contacted twice by telephone (at 4 and 8 months past the randomization anniversary date) and had an annual visit at the study center. Since adverse effects were likely to depend on the length of exposure to the study vitamins, side effects, if any, were anticipated to appear first in the original Seattle pilot populations, termed CARET's "Vanguard" cohort. The Vanguard cohort was more closely monitored with every three months alternating telephone calls and study center visits. After the intervention ended, participants were contacted annually.

Smoking cessation. At each visit after randomization, study center interviewers encouraged current smokers to quit smoking and former smokers to maintain smoking cessation. Smoking cessation packets were distributed to current smokers who expressed an interest in quitting smoking. During the intervention phase of CARET, the percentage of current smokers declined by 3 percentage points per year in the current smokers and 1.5 percentage points per year in the asbestos-exposed population.

Data management and collection. CARET collected extensive data that can be used in conjunction with the CARET Biorepository in studies of cancers and other diseases. Data collected included:

- At baseline (1985 - 1994): Lifetime smoking history, lifetime medical conditions checklist, family cancer history, personal cancer history, occupational history, chest X-Ray review (for asbestos-exposed participants), demographics, laboratory chemistry profile.
- Every contact (1985 - 2005): Updated smoking history, vital status/death certificates, cancer incidence/path reports, symptoms and signs potentially related to the study vitamins (through 1997 only)
- Every visit (1985 - 1997): Personal use of dietary supplements, study adherence, cataract incidence (1994 – 97), updated medical conditions checklist, height, weight, blood pressure.
- Every two years (1985 - 1997): Food frequency questionnaire, spirometry (asbestos-exposed only)
- Post-intervention, active follow-up (1996 - 2005): Physical activity (1996 - 1997), incidence of bone fractures

and use of NSAIDS (2000-2003)

- Post-Intervention passive follow-up (2005 - 2013): cancer incidence and vital status/cause of death from linkages with state cancer registries and the NDI

All data collection forms are processed and stored at the Coordinating Center in individual participant charts, excluding Portland Study Center charts. Quality control and quality assessment methods included detailed study procedures and data collection guidelines; two-pass key-entry and verification of data; computerized edit checks; and routine feedback and quality control reports. Annual quality assurance site visits were conducted by the Coordinating Center and findings reported to the Steering Committee and the NCI.

Endpoint data collection and adjudication. Prior to October 2003, we collected medical records and pathology reports. Members of the Endpoints Review Committee (prior to 1998) or the CARET Endpoints Specialist (1998-2003) reviewed and adjudicated every endpoint, according to a detailed protocol. In October 2003, we piloted the accuracy of self-reported cases of cancer and we discontinued collection and review of pathology reports, making several modifications to the mailed questionnaire to help differentiate new primary cancers from recurrent, metastatic, and benign diseases.

3.A.3. The CARET Biorepository, including Accomplishments during the Previous Funding Period (2013-2018)

In 2012, we applied for the NIH biorepository support grant and received an award in March 2013. We will now discus the aims of that grant and our accomplishments. The specific aims of that application were:

1) Maintain and support the CARET Biorepository and database to contribute to and collaborate in research.

The current contents of the CARET Biorepository have been updated and are shown in Section 3.A.4. This section will discuss the maintenance and support during the grant period 2013-2018. The CARET serum, plasma, and DNA Biorepository consists of 16 freezers, which we monitor on a weekly basis to ensure specimen integrity. Routine maintenance alongside the gradual replacement of older models with newer, more efficient freezers ensures the long-term stability of the biorepository. The biorepository database is regularly updated, including tracking sample amounts and freeze-thaw status. Established QC monitoring procedures are followed, and backup of electronic files is performed routinely. Most of the ongoing maintenance and support procedures we detail in our proposed specific aims (Section 3.B.1) are procedures that have been ongoing during the 2013-2018 grant period.

The CARET website allows users access to CARET background and study design, publications to date, specimen availability summaries, cancer incidence and mortality among the CARET participants, tools for customized searches of the biorepository, and instructions for accessing specimens and data. As samples are used for approved studies, the biorepository contents area is updated regularly on the website.

We have developed policies and procedures for interested investigators to follow when requesting samples from the CARET Biorepository. Since 2018, the CARET Core Leadership Group (CLG) reviews new collaborative studies proposing to use CARET samples and/or data. The CLG reviews and evaluates the scientific merit of collaborative study proposals, while also considering the impact on the CARET repository. If additional expertise is needed, the proposal is routed to the Scientific Review Committee (SRC) for input before a final decision is made.

These policies have been very successful in developing collaborative research projects. As a result of our efforts to maintain the CARET Biorepository and database, we have collaborated with investigators in the United States and around the world. This has been a strong point of the CARET Biorepository; we are truly a resource to investigators worldwide and not just a resource for “in house” investigators

Because the CARET population is at high risk for many disease endpoints, CARET ancillary studies have focused on both cancer (primarily lung, prostate, breast, colon, and pancreas) and chronic lung diseases (asbestosis, tobacco-associated or idiopathic). Section 6 lists parent projects of CARET collaborations to which specimens and/or data have been released.. The CARET investigators always carefully consider this aspect of a study before supplying samples, balancing the difficult-to-replace nature of the sample, the volume requested, the importance of the hypothesis being tested, and the strength of the preliminary data in the application.

2) Extend the CARET database and online accessibility to include participant use of micronutrient, mineral, and vitamin supplements; baseline laboratory values; and stage at diagnosis of lung, prostate, breast and colon cancer cases.

During the active CARET intervention, data were collected on dietary supplements used by participants at all visits. Per the CARET protocol, dietary information specifically solicited for inclusion in the database was restricted to total daily intake of beta-carotene and vitamins A and E, along with a single indicator for use of supplements of any type (coded as yes/no). Information about specific brands and types of dietary supplements was captured on the data collection instrument by open-ended text fields completed by study center interviewers. These dietary supplement data were not previously entered into the CARET database. In this cycle of the grant funding, we first developed procedures to pull charts, followed by coding and data entry of the supplement data. Forms from all visits at which supplemental vitamin use was reported were targeted for review. At each stage, QC procedures were implemented and applied. Two-pass key-entry, with range checks and manual review of discrepancies, was used to ensure accuracy. QC reports were generated to capture missing records. Coding procedures were established to classify the text responses to supplement type categories. Dr. Neuhouser and Mr. Barnett worked together closely to establish these categories to prevent overlap, redundancy, and to decrease a risk of double-counting. Because text entries used for a given supplement varied over time and by interviewer, electronic coding rules were developed to capture the various descriptions used for a particular supplement (e.g., “C”, “Vit C”, “V-C” for vitamin C usage). At the end of this process, we will have usable variables on categories of multivitamins (with or without minerals), stress supplements, antioxidant mixtures, B-complex mixtures, other specialty mixtures and single supplements such as calcium, vitamin D and vitamin E.

Participant charts were also reviewed to capture over 20 laboratory measures that had not been entered previously (see Table 3). A baseline, full blood laboratory panel was performed routinely for participants at the Seattle and San Francisco centers, which combined to enroll about 40% of CARET participants. In addition, post-baseline laboratory measurements were conducted annually for the Seattle pilot population (10% of the cohort). Key-entry during the active trial was limited to measures potentially related to toxicity of the intervention (primarily liver function tests). Key-entry and QC procedures were similar to those used for the dietary supplement information, although to increase efficiency single-pass key entry was adopted in 2016 after observing discrepancy rates of less than 1% in the double key-entry of laboratory data.

These new data elements are of substantial benefit to the CARET database. In addition to informing outside investigators of these new data enhancements, CARET investigators (e.g., Drs. Neuhouser and Goodman) have several planned manuscripts using both the new dietary supplement and the laboratory data. Some of these planned manuscripts include: 1) associations between supplemental iron and colorectal cancer risk and laboratory measures of iron (e.g., ferritin) and colorectal cancer risk; 2) associations between use of multiple dietary supplements (e.g., multivitamins, antioxidant mixtures, single supplements) and total cancer plus site-specific cancers (lung, prostate, colon, breast); 3) associations between supplemental vitamin D and breast cancer risk. Other laboratory measurement based manuscripts will include associations of albumin (as a measure of overall nutritional status) and total and site-specific cancer risk and associations of total LDL-cholesterol and HDL-cholesterol with total and site-specific cancer risk, and uric acid and cardiovascular disease risk.

Table 3. Additional laboratory measures coded from charts of Seattle (N = 6,795) and San Francisco (N = 866) participants[1]

Albumin	Calcium	Cholesterol,	GGT	LDH	SGOT	Uric
Alk	Chlorides	LDL	Globulin	Phosphorous	SGPT	Acid
Phos	Cholesterol, tot	Cholesterol,	Glucose	Potassium	Sodium	
Bilirubin	Cholesterol,	VLDL[3]	Iron[3]	Protein	Triglyceride	

BUN	HDL	Creatinine CO2[2] Ferritin[2]	Iron binding capacity[3]

[1]Baseline measurements available for all Seattle and San Francisco participants; annual post-baseline measurements available for the Seattle pilot population (N=1,845)
[2]Tested routinely for Seattle participants only
[3]Tested routinely for San Francisco participants only

In total, approximately 50,000 dietary supplement and laboratory measurement forms were targeted from among nearly 14,000 participant charts. Excluded were charts of Portland Study Center participants, as these charts were archived at Kaiser Permanente Center for Health Research (Portland, OR) and are not available to us. To date key-entry has been completed for 82% of targeted forms, including all laboratory reports. The remaining forms with supplement information will be completed by the end of the current grant period.

During the current funding period, we have completed the American Joint Committee on Cancer (AJCC) staging of incident cases that were diagnosed during active follow-up at which time medical record including surgical and pathology reports were available. Staging has been completed for lung, prostate, breast and colorectal cancer (Table 4). Case documents were reviewed by a single reviewer (Dr. Goodman) and were staged by AJCC criteria using both the TNM and stage criteria. Because requests for medical records for endpoint confirmation ended in October 2003, staging is only available on CARET participants diagnosed prior to that date. However, as part the information we received from the state registries on cancer incidence and survival, we also obtained staging information and are in the process of reviewing and adding that data to the CARET database. These findings have also been added to the CARET website.

Table 4. AJCC stage of CARET lung, prostate, breast, and colorectal cancer, for case diagnoses reported and adjudicated during active participant follow up (1985 – 2005)

		AJCC stage of disease[1]				
Cancer type	**N**	**0**	**I**	**II**	**III**	**IV**
Lung	1,079	1	220	94	286	478
Prostate	721	---	6	554	100	61
Breast	319	46	165	89	10	9
Colorectal	209	27	42	57	44	39

[1]AJCC 6th (prostate, breast) or 7th edition classification (lung, colorectal)

3) Extend CARET follow-up with cancers, deaths, and causes of death via public registry searches.

As part of our previous grant (2013-2018), state cancer registry and National Death Index (NDI) linkages were conducted in 2015 to extend follow up for endpoints. NDI linkage was complete through 2013; state cancer registry linkage was through 2012 for WA and CA, and through 2013 for CT. Cancer registries of the five states in which CARET enrollments occurred were targeted for the linkage, with approval obtained for three registries: California Cancer Registry, Connecticut Tumor Registry, and Washington State Cancer Registry. Regulatory guidelines in Maryland and Oregon at present prohibit access to cancer registry data for the aims of the previous CARET grant. Of the 18,314 total CARET participants, 12,927 (71%) were enrolled by a study center located in CA, CT, or WA; and another 1,109 (6%) enrolled by other study centers had a history of residence in one of the three states. In total, records from 14,036 (77%) participants were included in the cancer registry linkages. Probabilistic software was used to match CARET records to cancer registry records based on data elements common to both repositories, including full social security number, name, sex, race, and date of birth (which are complete for 99% of CARET participants). Linkage results were classified as matches to previously reported CARET endpoints or new endpoints based on degree of matching between common data elements (e.g., date of diagnosis, cancer site, and histologic type) and manual review of pathology reports and other medical records collected during active follow up. The registry data were also used to adjudicate cases closed previously based on self-report only.

NDI linkage was performed to ascertain vital status and underlying cause of death on a total of 13,830 participants who were alive at the end of active follow-up or for whom report of death had not been confirmed by death certificate. Matches were determined on the basis of the NDI probabilistic score and classification group assignment, electronic evaluation of CARET data elements not incorporated in the NDI algorithms (e.g., date of last contact), and manual review of records. Discrepancies in cause of death and cancer diagnoses between NDI and cancer registry records were reviewed as part of the adjudication process.

3.A.4. The CARET Biorepository, Current Contents

With our recent linkage to cancer and death registries to extend follow-up through 2013, the CARET repository now includes 2,460 participants with lung cancer, 1,256 with prostate cancer, 606 with breast cancer, 541 with bladder cancer, 512 with colorectal cancer, and 2,557 with other cancers. CARET is one of the few trials that has prospectively collected serial serum, plasma, whole blood, blood spots (for DNA), and lung cancer tumor specimens, as well as smoking history and serial food frequency questionnaires (in some individuals for up to 12 years) on male and female smokers and male asbestos-exposed workers. This wealth of information in 18,314 individuals selected because of their increased risk for lung cancer makes the CARET Biorepository a special resource for lung cancer researchers. Although CARET enrolled only current and ex-tobacco smokers, the incidence of many other cancers was similar to a non-smoking population allowing the repository to also serve as an excellent resource for these non-tobacco-related cancers. Prospectively collected serial serum and plasma, and DNA from these individuals with cancer and appropriate controls will be a resource to study the molecular, genetic, and nutritional epidemiology of cancer in both men and women. The prospective collection of serial pre-diagnostic samples is ideal and necessary for discovery and confirmatory studies of biomarkers of cancer development and prognosis.[25]

Blood specimens CARET participants provided blood at their pre-randomization, baseline visit and at every even-numbered annual visit; Vanguard participants (the Seattle pilot) provided blood annually. CARET used standardized procedures for the collection, processing, and shipment of specimens at each study center by trained and certified personnel. In brief, forty milliliters of blood were collected at each draw, aliquoted into four 2 ml vials and stored at -70°C. During the first year, ten milliliters of anticoagulated (heparin) blood were processed and plasma was stored in two 2 mL vials. Plasma collection was discontinued in 1990. CARET participants were not required to fast before blood draw; the elapsed time from the most recent meal was recorded. Beginning in February 1994, we made a one-time collection of two 1.8 mL aliquots of whole blood and a blood spot card (4 spots/card) for DNA analysis.

Quality control steps included prompt processing after blood draw, usage of tourniquet, protection from light, use of refrigerated centrifugation and documentation of the process. A thorough audit of the specimen bank was completed in September 2000. The audit included all specimens collected from participants who were deceased or had been diagnosed with any CARET cancer endpoint, together with a 10% sample of specimens from living, cancer-free participants. Approximately 120,000 specimens were audited. We continue to routinely conduct quality assurance on CARET samples, confirming vial location and physical status.

Table 5. CARET Specimen Bank. Number of participants with samples available (as of February 2017)

		Pre-Randomization		Post-Randomization		
Classification*	**N**	**Serum**	**Plasma**	**Serum**	**Plasma**	**Whole Blood (DNA)**
Lung	2,460	2,403	634	1,976	261	1,589
Prostate	1,256	1,231	367	1,086	180	937
Breast	606	601	149	481	57	418
Bladder	541	530	139	476	64	417
Colorectal	512	501	148	426	53	359
Head & Neck	312	300	69	243	37	210
Melanoma	311	303	87	264	39	239
Lymphoma	232	225	61	196	24	168
Pancreas	209	206	53	168	23	133
Kidney	196	194	45	160	22	131
Esophagus	179	177	49	139	20	112
Leukemia	152	150	38	122	15	100
Stomach	89	88	22	70	9	57
Mesothelioma	84	83	43	77	30	53
Liver	78	75	20	66	8	53
Myeloma	70	69	26	59	11	46
Brain	70	68	15	53	4	45
Ovary	62	61	16	49	4	43
Uterus	40	40	8	30	1	26
Other cancers	782	761	205	640	100	541

Cancer free	11,541	11,278	2,550	9,296	945	7,993
All participants	18,314	17,912	4,316	14,834	1,701	12,599

* Participants may be in more than one classification

		Pre-Randomization		Post-Randomization		
Cause of Death	**N**	**Serum**	**Plasma**	**Serum**	**Plasma**	**Whole Blood**
Lung Cancer	1,974	1,931	506	1,577	204	1,238
Other Cancers	1,816	1,783	472	1,444	202	1,187
CVD, ASCHD	1,493	1,450	414	1,157	182	907
CVD. ASCVD	792	771	276	642	136	502
CVD, cerebrovascular	384	379	124	318	49	266
CVD, other	129	127	46	110	21	92
COPD	1,295	1,261	342	1,032	129	841
Other causes	1,994	1,950	586	1,637	251	1,331
Alive at end of follow-up	8,437	8,260	1,550	6,917	527	6,235
All participants	18,314	17,912	4,316	14,834	1,701	12,599

* Participants are represented no more than once within each cancer type, but may be counted in more than one type.
* Serum collection at baseline, biennially during the intervention phase, and at the end of intervention.
* Whole blood collected at a single time in 1994-96 (whole blood is in spot cards and 1.8 mi vials).
* Aliquots of DNA extracted from whole blood are also available for lung and prostate cancer cases (and a matched set of controls) from whom whole blood was collected.

Table 5 shows the number of participants with blood samples available by the timing from randomization for serum/plasma sample, by cancer endpoint, and cause of death endpoint. In most cases, each participant has multiple serum vials available from each of several post-randomization time points.

Volume of samples for future studies. The contents of the CARET Biorepository are dynamic. As shown in Section 6 samples have been provided to many studies, all requesting different types of samples (DNA, serum, plasma) with different volumes, and participant demographic characteristics. For each proposed study, we negotiate with the investigator to minimize the volume of sample requested. If for any reason the recipient does not use the entire specimen provided, the remainder is returned and restored in the CARET Biorepository. The biorepository database is updated with each study to reflect the change in volume of available specimen and any change in the number of thaw/refreeze cycles. Currently most studies utilizing DNA request 2-5 µg with many less so. Serum and plasma requests are usually 100 µl or less. An updated analysis of the bank is shown in Table 6. As shown, the CARET Biorepository continues to be a rich source for investigators, for example, only 19 (< 1%) lung cancer cases have no serum remaining.

Table 6. Number of participants by cancer status and quantity of DNA and serum available in CARET Biorepository (as of February 2017)

	Cancer Site							
	Lung	Prostate	Breast	Bladder	Colorectal	Other[1]	Cancer free	Total ppts
Total N	2,460	1,256	606	541	512	2,557	11,541	18,314
DNA[2]								
>20 µg	1,541	925	415	409	353	1,727	7,916	12,434
5 – 20 µg	36	9	3	8	5	19	58	129
<5 µg	12	3	0	0	1	7	19	36
None	871	319	188	124	153	804	3,548	5,715
Serum								
All time points combined								
5 + mL	2,241	1,093	586	526	490	2,453	11,172	17,608
3 – 4 mL	194	120	16	12	15	69	246	504

1 – 2 mL	5	35	1	1	5	18	54	94
< 1 mL	1	0	0	0	0	1	3	4
None	19	8	3	2	2	16	66	104

	Cancer Site							
	Lung	Prostate	Breast	Bladder	Colorectal	Other[1]	Cancer free	Total ppts
Collected ≤ 2 years prior to dx								
5 + mL	411	264	173	137	118	596		
3 – 4 mL	184	146	21	15	29	65		
1 – 2 mL	10	26	5	1	5	14		
< 1 mL	0	1	1	0	2	1		
None	1,855	819	406	388	358	1,881		
Collected > 2 years prior to dx								
5 + mL	2,071	951	510	484	431	2,226		
3 – 4 mL	173	103	12	10	19	59		
1 – 2 mL	8	63	0	3	4	16		
< 1 mL	1	0	1	0	0	2		
None	207	139	83	44	58	254		
Three or more serial samples collected prior to dx	1,421	746	319	321	282	1,441	6,838	10,988

[1] See Table 5 for listing of other cancer types and number of cases accrued.

[2] Consists of previously extracted DNA or whole blood samples. A one-time collection of whole blood was initiated in 1994 and completed on about 69% of the study population. For the tabulation, it is assumed whole blood samples (stored as 1.8ul aliquots) which have not yet been extracted will yield > 20 µg of DNA, as has been our experience to date. Not included in estimate is DNA potentially available from dried blood spots and serum samples.

Tissue specimens. Tissue from cases of lung cancer, mesothelioma, and cancers of unknown primary was retained at the CARET Coordinating Center beginning in September 1999. These formalin-fixed paraffin-embedded (FFPE) blocks and slides are stored onsite at room temperature following a standard protocol. Prior to September 1999, tissue specimens requested for CARET's centralized review process were returned to their originating institutions after the review process was complete.

The CARET tumor bank consists primarily of slides and FFPE blocks (Table 7) from CARET participants who developed lung cancer. All tumor tissue in CARET was collected retrospectively so fresh frozen tissue is not available. Because investigators have requested cancer tissue on CARET participants, we plan to conduct a pilot in the next funding period to acquire additional FFPE samples on lung cancer cases diagnosed after 2003.

Table 7. CARET tissue specimens

	Total[1] Lung Cancer Cases	**FFPE Blocks**				**Slides (Unstained)**			
		Lung Origin		Other Origin		Lung Origin		Other Origin	
Procedure		Tumor	Normal	Tumor	Normal	Tumor	Normal	Tumor	Normal
Cytology									
Bronchial washings/ brushings	94	17	8			61 (5)	36 (4)		
Fine needle aspirate	94	28	4			76 (11)	12 (1)		1 (0)
Pleural Effusion	19	6	1		1	12 (2)			2 (0)
Biopsy									
Lung biopsy	247	111	19			173 (31)	33 (4)		

Liver biopsy	20			9	1			15 (4)	2 (0)
Lymph node biopsy	90			30	20	1 (0)		40 (10)	35 (1)
Resection									
Wedge resection	35	17	5			25 (13)	8 (1)		
Lobectomy	108	61	36			64 (26)	38 (12)		
Pneumonectomy	14	7	5		1	10 (3)	6 (1)		1 (0)
Other	79	5	2	23	4	10 (3)	5 (1)	43 (10)	10 (2)
Total Lung CA Cases	570	223	71	61	26	350 (80)	116 (23)	97 (24)	47 (3)
Total Specimens Banked	3,622	441	142	111	68	1,717 (656)	536 (176)	428 (189)	179 (13)

[1] Participants are represented no more than once in the count in each cell (procedure and specimen type). However, a participant may be counted in more than one cell.

3.A.5. Aspects of the CARET biorepository that set it apart from other biorepositories

CARET participants are an ideal population to study the biology of lung cancer. The recruited populations are those that are at high risk for lung cancer. One of the challenges in finding early detection biomarkers for lung cancer is ensuring that the putative markers are not just markers of tobacco use or tobacco-induced lung injury. With our 2,460 lung cancer cases and our median 20 years of follow-up, CARET is the ideal population to test potential biomarkers for their ability to distinguish those with lung cancer from those without lung cancer who have matched smoking history. CARET is one of the few studies that has prospectively collected pre-randomization as well as serial post-randomization and pre-diagnostic serum samples in this high-risk population. We have collected demographics, diet, and other risk factors on the entire population so investigators can match the lung cancer (or other primary cancer) group with the cancer-free controls. These samples will allow the study of early biomarkers of cancer controlling for important confounding variables. The extremely valuable serial pre-diagnostic samples will allow the investigation of the time course and temporal development of these markers for the early detection of cancer.

CARET randomized 6,289 women. Based on follow-up through 2013, 860 lung cancers, 606 breast cancers, and 131 colorectal cancers have developed in this population. This bank represents one of the largest prospectively collected specimen banks of women smokers with lung cancer and controls that have serial pre-diagnostic serum samples.

CARET randomized 4,060 male asbestos workers, a group that is at high risk for both lung cancer and pleural mesothelioma. Although the occupational exposure to asbestos use has decreased dramatically in this country, 33 countries have quintupled their asbestos use but have not reported mesothelioma deaths.[26] In addition, there is extensive existing asbestos in many US buildings (the former NYC World Trade Center for example) and areas (such as Libby, Montana) where asbestos mining has taken place which still expose large numbers of individuals to asbestos. The age-adjusted mortality for mesothelioma is increasing in both Europe and Japan with over 92,000 world-wide deaths reported from 1994-2008.[26] Thus, asbestos exposure remains a problem in the less-developed world[27] as well as the developed world.

In addition, similar to what is seen in former cigarette smokers, those exposed to asbestos remain at high risk for malignancy long after exposure ends. Like tobacco exposure, even if continued asbestos exposure can be eliminated, lung cancer and mesothelioma will remain a problem for the foreseeable future in the exposed population. CARET has one of the largest biorepository for asbestos-exposed individuals and will continue to be a resource for studying asbestos-related mesothelioma as well as asbestos-related lung diseases.

<u>Why Is It Important to Maintain CARET Biospecimen and Data Repository?</u>

First, CARET has served and continues to serve as a resource for the scientific community for the testing of numerous hypotheses to enhance our understanding of cancers and its prevention. This is evidenced by the many funded studies and pending studies that CARET has been supporting, as well as many international pooled analyses on genetic and environmental factors that may impact the incidence and mortality of cancers. Examples of such include numerous past and ongoing collaboration projects with investigators in the International Lung Cancer Consortium (ILCCO)[28-38] and the collaboration with the Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborating Group.[39, 40] Because of the size of the CARET

study and its meticulously collected prospective information on its study participants and serially collected biospecimens, CARET not only adds to the study power of the studies it contributes to, it also adds to the quality of the information, thus the credibility of results. The availability of the prospectively collected biannual samples also put CARET in a unique position to allow investigations into time course of disease occurrence. CARET now has outcome information on 2,460 lung, 1,256 prostate, 512 colorectal, and 606 female breast cancer cases. This effort has positioned CARET to contribute to studies that aimed at the evaluation of factors that may be related to survival from these cancers.

Second, some scientific questions related to cancers that take many years to develop can only be answered with studies that not only have biological specimens that are collected at baseline but also have an extended follow up on the study participants. The importance of studies like CARET can be illustrated in the following example. Several years ago, in order to examine the potential role of circulating fatty acids in the etiology of prostate cancer, a meta-analysis was conducted using data obtained in seven nested case-control studies.[41] Little or no association was seen for blood levels either of mono-unsaturated fatty acids or poly-unsaturated fatty acids. However, in the seven studies the mean duration between blood draw and cancer diagnosis was just five years. Given that factors bearing on the occurrence of prostate cancer could be acting at points in time well before the most recent five years, the impact of circulating fatty acids on risk could be underestimated even in studies with prospective specimen collection. In an effort to address this issue, Yang et al. [42] took advantage of the very long follow-up of participants in the large Physicians' Health Study - for 172 cases of prostate cancer, baseline blood samples had been obtained more than 10 years prior to diagnosis. The results of their nested case-control study were striking: whereas the interquartile relative risk of prostate cancer in relation to levels of mono-unsaturated fatty acids was but 1.03 (95% CI 0.86-1.25) for cases diagnosed within 10 years of blood draw, the corresponding relative risk for cases diagnosed 10 or more years after blood draw was 1.69 (95% CI 1.21-2.34). A similar difference over time was seen for levels of poly-unsaturated fatty acids, with an interquartile relative risk of 0.95 (95% CI 0.78-1.15) during the first 10 years following blood draw and 0.59 (95% CI 0.42-0.83) afterwards. If confirmed in other cohorts with long-term follow-up, these data provide a strong argument that a substantial association between serum levels of fatty acids and prostate cancer occurrence exists – positive for mono-unsaturated fatty acids, inverse for poly-unsaturated fatty acids - but that the action of those molecules (or others with which they are correlated) takes place years before the cancer is clinically evident. They argue that in the absence of studies such as CARET – in which there has been lengthy follow-up of participants after blood samples (and/or other biological samples) have been obtained - associations such as this one would be completely missed.

Points to consider: Generalizability

Except for a handful of participants in the asbestos-exposed pilot, all participants in CARET were current or former tobacco smokers. Investigators examining lung cancer in "never smokers" will not consider CARET an appropriate source except as a comparator group. Other tobacco-related cancers (bladder, kidney, head & neck, etc.) also occurred in CARET in large numbers. The CARET population is also ideal for studies of these cancers. Because studies of these cancers in non-smokers exist, comparisons can be made to the CARET population to determine if there are differences in the cancers that occur in the smoking CARET population and populations of never smokers.

The CARET population developed the expected number of common non-tobacco-related cancers such as prostate, breast and colon. Investigators utilizing the CARET Biorepository to study these cancers will need to consider that the CARET population consists of current and ex-tobacco smokers and the findings in this population may differ from the never-smoking population. It is important to note, however, that investigators using the CARET database and biorepository in this cycle of funding have not expressed any concern or hesitation about CARET's low number of never-smokers.

Points to consider: Active intervention vs. placebo

The CARET intervention increased the incidence of both lung cancer and CVD deaths. Our analyses have found no statistical evidence that the CARET intervention altered the incidence of the eight other cancers analyzed (bladder, breast, colorectal, head and neck, leukemia, lymphoma, mesothelioma, and prostate).[20] For lung cancer and CVD mortality, the effect of the intervention must be considered when selecting samples for studies of these endpoints. For other endpoints not affected by the intervention, depending on an investigator's study objectives a decision must be made whether to study specimens from only participants on the placebo arm or to also accept specimens from those randomized to the active intervention. Many investigators have chosen to study samples only from the population on placebo arm (micronutrient studies),

while other have chosen samples from participants on both the active and placebo arms (genetic risk factor studies). If selecting samples from both arms, the large sample size of CARET usually allows the investigator to compare placebo/active arms to determine if there is an effect of the intervention on their study endpoint and to include intervention arm as a covariate in the analysis.

Points to consider: Funding issues

Prior to the availability of this biorepository support grant, we supported the biorepository infrastructure and personnel with small grants from individual investigators requesting samples, involvement as named investigators on NIH funded grants, and funding from our parent institution, Fred Hutchinson Cancer Center. To buttress these sources of funding, we initiated a fee-for-service schedule. This system charges investigators a sample acquisition fee that is based on the type of sample requested, the manipulation needed (e.g., aliquoting or DNA extraction), the number of samples requested, the programming effort required to perform sample selection to meet study requirements (e.g., matching on risk factors, case/control ratios, use of longitudinal specimens), and academic or commercial affiliation.

Continuation of this biorepository support grant will allow us to continue to contribute samples to some approved studies that do not have independent funding available. Many pilot studies request fewer than 100 samples. As a specific example, we are members of the International Lung Cancer Consortium (ILCCO) and have participated in many of their non-funded studies. CARET has a large sample size, and the range and completeness of the demographic information we have collected make CARET a valuable contributor to these ILCCO studies. In fact, contributing to such large population-based studies is our core mission.

Points to Consider: Research Collaborations

The CARET Biorepository has been successful in providing biospecimens to scientists worldwide and has been very productive in published manuscripts. During active intervention, CARET was funded to prospectively analyze serum concentrations of β-carotene and other carotenoids, vitamin A-related micronutrients, and liver enzymes in a subset of participants. The CARET investigators completed these analyses during the funding period of 1988-2007. Thirty-four manuscripts were published exploring the relationship between lung cancer and various risk factors. We have also collaborated on numerous manuscripts examining biomarkers for the early detection of lung cancer and germline genetic risk factors for lung cancer during the current grant period (2013-2018). Since 2013, CARET has been collaborators in 23 publications and has 93 current studies (see accomplishments during the current grant period section 3.A.3).

It has been the philosophy and goal of CARET investigators that the biorepository specimens and associated data should be used for the optimal advancement of science and be available to any investigator with a well-justified hypothesis. With this goal in mind, we have tried to make the CARET Biorepository an “open access” repository and available to all. To aid in this open access philosophy we have been innovative and established and continually update the CARET website to allow web access to our biorepository and database. Systems are in place to allow any investigator to search the database and submit a proposal to access CARET samples. Projects are peer-reviewed and those approved are given access to samples. We have also encouraged outside collaboration by our membership in the NCI Cohort Consortium, ILCCO, and by our placing links to our repository on collaborative websites such as those from the NCI Epidemiology and Genetics Research Program and the Early Detection Research Network. The open access of the CARET Biorepository has been a strongpoint. A review of our completed and ongoing projects illustrates that we have worked with investigators nationally and globally in providing samples and data for collaborative projects.

Points to consider: The CARET website

The innovative CARET website includes extensive details of ongoing and completed projects using CARET specimens and data, including a complete bibliography of published research, abstracts of ongoing studies, and descriptions of pilots and other as yet unpublished exploratory studies, all organized by disease outcome of interest and category of research (e.g., dietary studies or genetic analyses). The heart of the site allows investigators to access and search the CARET Biorepository Database for the existence of samples with demographics specified by their study. Users can specify participant characteristics (e.g., age ranges or smoking histories), primary outcomes of interest (cancer incidence or causes of mortality) and, since CARET has serial biological samples collected prior to a cancer endpoint, timing of specimen collection with respect to disease event. The primary outcomes page provides a table of the numbers of CARET participants with specimens at the desired endpoint(s) times. Users can drill down on the cell entries in the table to see 30 data elements for each individual study participant meeting the search query. The website has been designed to enable most users to determine if the CARET Biorepository has specimens that meet their study needs.

Finally, the website provides details on the process of requesting CARET specimens, including forms to complete and CARET contact information.

3.B. INFRASTRUCTURE DESIGN AND RESEARCH PROGRAM

3.B.1. Core Infrastructure Activities

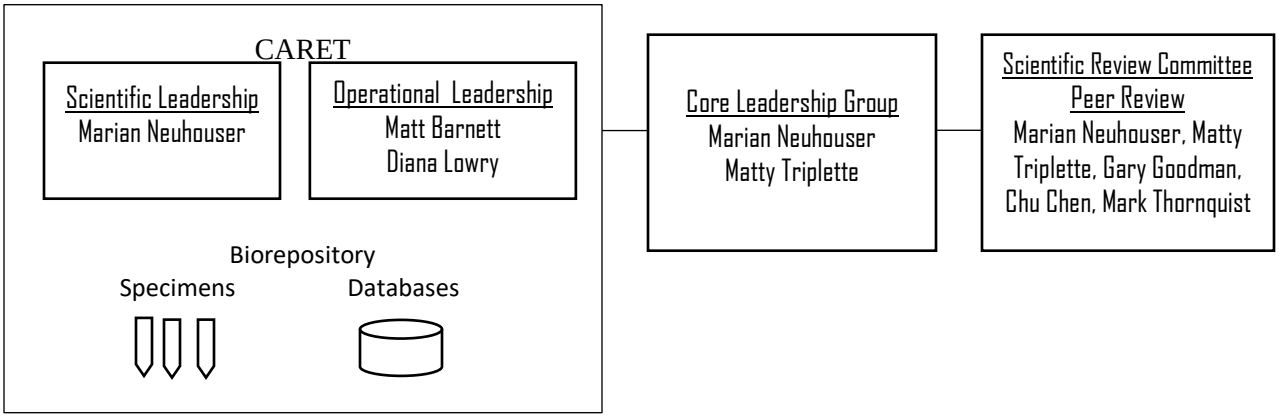
The specific aims of this application are:

1) Maintain and support the CARET Biorepository, database and website to allow researchers' easy access to CARET biologic samples and data and contribute to and collaborate in their research,
2) Pilot procedures to obtain updated signed releases of medical records and consent for the utilization of biologic material in the CARET biorepositories consistent with recent developments on obtaining consent for broad research purposes and data sharing, and
3) Pilot the collection of lung cancer biopsy/surgical specimens from Washington state CARET participants diagnosed after 2003.

We will first discuss CARET's organizational structure and scientific components and then our approach to the proposed specific aims.

Organizational structure. Figure 1 represents the CARET organizational structure. The CARET Coordinating Center, located at the FRED HUTCHINSON CANCER CENTER in Seattle, Washington, continues to be responsible for directing the CARET Biorepository. Scientists and staff at the CARET Coordinating Center work with the Core Leadership Group (CLG) and the Scientific Review Committee (SRC) to oversee activities related to CARET's specimen biorepository and scientific database. Many of the original CARET investigators have retired or have changed their career focus. In this application, we have streamlined the CLG and added new SRC members with complementary expertise. Drs. Marian Neuhouser (nutritional epidemiology), and Matty Triplette (pulmonary medicine) make-up the CLG and Drs. Marian Neuhouser (nutritional epidemiology), Matty Triplette (pulmonary medicine), Gary Goodman (medical oncology), Mark Thornquist (biostatistics), and Chu Chen (molecular epidemiology, genomics, transcriptomics, and clinical chemistry)) make-up the SRC. Mr. Matt Barnett, Coordinating Center and Analytic Section Manager, oversees all operational activities of CARET, processes and coordinates the development of collaborative studies, manages the extensive CARET Biorepository and associated scientific databases, develops and conducts routine quality assurance, and coordinates and performs CARET analysis functions, including data management and analytic support for progress reports, publications, collaborative studies using CARET data and/or specimens, and ad hoc analyses.

Figure 1. CARET organizational chart



CARET collaborators are from the global scientific community. This includes any scientist who has been approved to use CARET biospecimens and/or associated scientific data, consortia which influence policies and direction of cancer research (e.g., NCI Cohort Consortium), large consortia (e.g., EDRN and ILCCO), and pharmaceutical/industry scientists. We demonstrate the impact CARET has on the global scientific community and how important it is to work in partnership with the scientific community.

CARET uses FRED HUTCHINSON CANCER CENTER's Specimen Processing Laboratory to prepare sample aliquots prior to shipment. CARET uses other FRED HUTCHINSON CANCER CENTER Shared Resources as

needed; of particular value is the Lost to Follow-Up Tracking Service to find participants who have been lost to follow-up if a particular study using CARET's biorepository needs additional data not in CARET's database or charts.

All CARET data are stored securely behind firewalls on SAS and SQL servers hosted and managed by CARET Coordinating Center and FRED HUTCHINSON CANCER CENTER jointly. Access to CARET data must be approved by the Coordination Center investigators and those with access are limited to Coordination Center statistical staff who work with internal and external investigators on ancillary studies. Participant source documentation such as the data collection charts/forms are stored in securely locked rooms accessible only by approved CARET staff. All data summarized and presented through the CARET public portal are completely de-identified such that participant identities cannot be revealed.

Specific Aim 1) Maintain and support the CARET Biorepository, database and website to allow researchers' easy access to CARET biologic samples and data and contribute to and collaborate in their research

CARET biospecimen storage maintenance, replacement, and quality control. The contents of the biorepository change over time as specimens are withdrawn for use and residual specimens, usually aliquoted into smaller vials, are returned and restored. As a result of downsizing of original specimens, the number of specimen vials in the bank has actually increased since the end of active CARET follow-up. CARET staff is responsible for ensuring the specimen database remains up-to-date and reflects all transfers of specimens out of and into the specimen bank. See Tables 5 and 6, CARET Biorepository and Table 7, CARET Tissue Summary Report in Section 3.A.4 for the number of biospecimens available.

Serum, plasma, blood and DNA specimens are stored at -70° C in 18 CARET freezers at the FRED HUTCHINSON CANCER CENTER. All freezers are equipped with a seven-day temperature recorder, which is monitored daily by CARET staff. Freezers are connected to an alarm system through the FRED HUTCHINSON CANCER CENTER security system that is activated when a freezer's temperature rises 10 degrees above the -70° C set point. There is also a backup generator in case of power failure. Emergency procedures for responding and handling specimens in the event of freezer failure are posted, and CARET staff with primary and backup responsibility receive regular training on these procedures. CARET specimens from a specific blood draw are split between multiple freezers so that not all of a participant's specimens from a blood draw are compromised if one freezer fails. Tissue specimens are stored securely onsite at room temperature in locked file cabinets that have a separate hanging file for each participant's samples and corresponding paperwork. The slides are in plastic, slotted containers that are sealed in plastic, zip lock bags. The paraffin blocks are also sealed in plastic, zip lock bags. Quality control checks, consisting of file location, specimen identification number verification, and specimen condition, are performed quarterly.

The CARET website. The CARET website is an important conduit for investigators to learn about CARET and the availability of samples that could advance their research. Maintenance and updating of this site is a critical aspect of CARET infrastructure support. Maintenance of the CARET website includes updating collaborative study descriptions, publications, and specimen search datasets. The specimen data accessed by the website search function comprise a separate, condensed subset of data from the CARET central database. Therefore, when updates are made to the CARET central database's specimen bank, they must be followed by data updates to the website's condensed representation of the specimen bank. Maintenance also includes the monitoring and updating of the website and database server hardware, software, and content. (See Appendix 7)

Collaborative Research. CARET usually receives proposals (Appendix 1) requesting to access samples or data from the CARET Biorepository from investigators via the website or email. CARET accepts requests for specimens and/or data at any time, rather than at set application dates.

Step 1: Review of proposals, The CLG and, if necessary, SRC. CARET has a formal process for submitting and reviewing proposals. Investigators are asked to submit a maximum 7-page scientific proposal addressing specific aims, background and significance, preliminary results (if available), and experimental methods and design. The design and methods section describe the study population (e.g., inclusion/exclusion criteria, case-control matching criteria), data and specimens being requested, laboratory methods, and statistical analyses and power calculations, as appropriate. A protocol template is provided to investigators through the CARET website. When a CARET application is received, the CLG (Drs. Neuhouser and Triplette) and CARET staff perform an initial review for scientific design quality, evaluate whether the proposal fits the CARET policy criteria for the use of the CARET samples, and assess the completeness of information such as sample size,

specimen volume needed, and data variables requested. If the CLG has the expertise needed to review and approve, they do so. If additional expertise is needed, then the proposal is sent to the SRC for input. If deficiencies are found in the application, the CARET investigators and staff provide feedback to the applicant. If SRC is involved, then the application is sent electronically to the SRC for their review along with a report showing the impact of the study on the biorepository. If the proposed area of study is not consistent with any of the SRC investigators' expertise, an independent outside reviewer may be suggested as the primary reviewer. (See Appendices 1, 2, 3 & 4)

The SRC members are given a two-week deadline to respond. The responses are tracked by CARET staff. If the SRC has concerns with the proposal, conference calls among the CLG/SRC or between the CLG/SRC and the applicant will be conducted to discuss issues. Once an application is approved, CARET staff communicates to the proposing investigator.

After a project is approved, CARET staff assess the workload and the potential need for additional funding. Some studies can be fully supported by CARET (through our biorepository support grant) while other with a large sample size and a need for biostatistical support may require additional funding. The study investigator will be contacted and given a proposed budget. In many cases, support is obtained from the investigator's institution or as part of a proposed NIH grant application. Studies are pending until financial support is approved.

Administrative tasks subsequent to approval of the proposal. Procedures followed are dependent on the data sharing mechanism.

Specimens or data provided from the CARET repository directly. The proposing investigator submits the approved proposal to his/her Institutional Review Board (IRB), and the CARET staff prepares and submits the application to the FRED HUTCHINSON CANCER CENTER IRB for review.

CARET staff will notify the investigator of IRB approval and give permission to proceed with the study. Prior to the selection and shipment of samples, the following documents must be completed:

- Confidentiality agreement, in which the investigator assures that data and specimens received will be kept confidential, in accordance with the FRED HUTCHINSON CANCER CENTER institutional policy and the consents signed by the CARET participants (Appendix 3)
- A CARET Certificate of Privilege, which is an agreement signed by the investigator that lists the assays that s/he is approved to perform, confirms that the investigator is responsible for notifying CARET of any changes to the protocol, and that all changes to the protocol (such as addition of new laboratory measures) must have prior approval from the CARET SRC and all participating IRBs before they can be implemented. (Appendix 2)
- A CARET Material Transfer Agreement, between FRED HUTCHINSON CANCER CENTER and the investigator's institution if appropriate. (Appendix 4)
- A CARET Data Use Agreement, between FRED HUTCHINSON CANCER CENTER and the investigator's institution if appropriate. (Appendix 4)

Once a proposal is approved, an abstract of the study is posted on the CARET website. Doing so helps ensure that CARET does not receive proposals with significant overlap with ongoing approved studies.

Data provided by a collaborating, external repository: CARET has provided data directly, following the procedures above, to projects that acquired data from multiple studies for pooled analyses. The following projects have since created external repositories of the pooled data for access by consortium members and collaborators through established procedures:

- The International Lung Cancer Consortium (ILCCO) repository; housed at the Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Protocol ID 0A, Dr. Rayjean Hung, Mt. Sinai
- The Transdisciplinary Research in Cancer of the Lung (TRICL) repository; housed at Dartmouth College, Protocol ID 0B, Dr. Olga Gorlova, Dartmouth
- The Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL); housed at Baylor College of Medicine, Protocol ID 0C, Dr. Chris Amos, Baylor
- The Pooling Project of Prospective Studies of Diet and Cancer (DCPP); housed at Harvard, Protocol ID 0D, Dr. Stephanie Smith-Warner
- The Lung Cancer Cohort Consortium (LC3), housed at the International Agency for Research on Cancer (IARC), Protocol ID 0E, Dr. Hilary Robbins, IARC

For each of these repositories, CARET has a standing Data Use Agreement (DUA) in place with the individual institution/investigator charged as gatekeeper to their respective repository. We do not submit a new study application to the FRED HUTCHINSON CANCER CENTER IRB for review because they are receiving the data from the external repository and not from CARET directly.

For proposed studies using an external biorepository, the application is provided to CARET by the outside repository. CARET investigators review the proposal to determine whether or not to participate.

Step 2: Pilot study. At the discretion of the CLG, investigators submitting a proposal based on promising results completed on non-CARET biospecimens may be asked to conduct a blinded pilot study with small numbers of CARET specimens. The purpose of the pilot is to determine whether the marker can be measured successfully in CARET specimens; the manner of CARET's sample collection, processing, and storage (particularly length of storage time) may compromise the ability to assay the specimens for the proposed marker. In addition, the pilot study may demonstrate that the preliminary data are overly optimistic; a common problem in biomarker research in which early discovery work is conducted using convenience samples. Performing a pilot helps to identify early with minimal specimen use those assays that are not good uses of CARET specimens.

Typically, these small blinded pilot studies include 10-20 samples from participants with the planned study endpoint (such as participants who developed lung cancer) and an equal number of matched controls. The number of cases and controls is determined by the measurement characteristics of the planned assay(s). After the assay has been performed, the data are returned to the CARET where they are analyzed by the CARET statistician. Analyses examine whether there is some evidence that the distribution of the analyte differs between cases and controls. The summary of the analysis results is provided to the proposing investigator and to the CLG/SRC. If the pilot study is encouraging, the investigator moves to a full-scale study.

Step 3: Full-scale study conduct. CARET's activities in supporting approved studies are generally much more involved than simply pulling a set of specimens and shipping them to an investigator.

Identification of samples. While a detailed protocol is required for any proposed study to be approved, a number of refinements are necessary prior to delivery of specimens and/or participant data. For example, all approved proposals include a list of eligibility and case-control matching criteria, but often this description will be in general terms and will require clarification. A common situation is that "smoking history" is listed as a matching criterion; the investigator must establish exactly which variable(s) assessed at which time(s) (e.g. pre-randomization, time of collection of the specimen being analyzed) should be used to define smoking history, as extensive smoking data are available in the CARET database (e.g., pack-years, years since quit smoking, smoking intensity, etc. all at multiple times). In addition, investigators frequently have not realized that asbestos-exposed workers were also recruited in CARET. The investigators may also choose to study only participants randomized to the placebo arm if there is evidence that the active intervention may affect their experimental endpoint.

Specimen pull lists. The CARET statistician consults with the study investigator to determine requirements for ordering of samples within the pull. In some instances, only a simple random ordering may be necessary; others might require cases and their matched controls be assigned positions following a detailed randomization scheme. Once selection and ordering criteria have been established, the statistician submits a dataset with information necessary for the pull (sample ID numbers, pull list ordering assignments, etc.) and any supporting documentation to the CARET programmer. The programmer creates a Project Request (PR) to document the programming steps to generate a pull list.

Associated data. CARET has a rich database as described in 3.A.3 - Important aspects of the CARET specimen bank. As typical in large cohort studies with extended follow-up, data collection protocols and instruments differed somewhat among subpopulations and over the course of follow-up spanning a total of 20 years. These differences add to the complexity of identification of the appropriate set of data.

Our experience is that data needs are ideally addressed in two phases. During protocol development and review, we consult with the investigator to ensure that data are available and suitable to address the scientific questions posed. Only once it is confirmed that the CARET data are appropriate for the proposed study would the protocol go on for formal review by the CLG/SRC. Finer details for the data request will be addressed after the study is approved and prior to the creation of the dataset to be used for statistical analysis.

Data provided to individual research projects and to the external data repositories include de-identified genomic information and other data derived from specimen analysis, as well as CARET database elements including cancer and death outcome information, health history, demographics, food and nutrient intake data,

and disease risk factors. If data beyond those listed are to be provided, CARET submits a protocol modification for internal IRB review.

Specimen handling. Handling of CARET specimens follows an existing and well established protocol. Quality control and assurance measures are implemented throughout the process.
Most CARET specimens are stored as collected originally, in 1.8 mL or 0.5 mL aliquots. Our experience has been that most studies using serum or plasma require only about 50-100 µL for their assays. A total of 20-40 µg of DNA can be extracted from 1.8 mL of whole blood, but studies accessing these samples typically need no more than 2-5 µg and often much less. To minimize thaw-refreeze cycles for specimens, it is our practice when pulling original vials for analysis to thaw them, extract the quantity requested by the study, and then to aliquot the residual serum/plasma specimens into 110 µL (up to four total) and 250 µL aliquots for refreezing; for DNA specimens, aliquots of 1-5 µg are typically created. The downsized aliquots are available for future studies, to avoid additional thaws (or the added expense for additional aliquoting).
We utilize FRED HUTCHINSON CANCER CENTER's Specimen Processing Lab (SPL) for aliquot creation. For each shipment, we prepare a document detailing the aliquot creation specifications for the given study. To protect participant confidentiality and study integrity, participant identifiers and endpoint status are never included with the specimen shipment. Pull lists and vials are labeled with unique sample identification numbers, which are used by CARET staff to link specimens and assay results to other participant data for statistical analysis.
Downsized specimens must be stored back in CARET freezers. The CARET programmer creates a specimen restore list for the samples, assigning a freezer/box/position number for each aliquot. Samples are stored in their assigned position, and the programmer then updates the database to reflect the location information. The database is also updated with available specimen characteristic data (e.g., volume, yield, concentration, and the number of thaw-refreeze cycles).
Step 4: Data receipt, analysis, and publication. The role of CARET staff in the management and analysis of data will vary. Some studies will have their own database managers and statisticians and will rely on CARET staff for delivery of specimens and participant characteristic data only. In this situation, after the laboratory data have been returned to CARET and merged with participant data, CARET staff members will serve only as collaborators during analysis.
If requested by the study investigator, CARET statisticians perform statistical analyses following the analysis plan provided in the study protocol. Results are summarized in tables and graphs for review with study investigators. Secondary and ad-hoc analyses are performed as appropriate. If statistical analyses are to be performed by the study's own statistician, CARET statisticians provide consultation as needed. CARET statisticians share their knowledge of the CARET protocol and database to ensure analytic approaches and variable usage are appropriate.
The release of data unblinded to study outcome is negotiated with CARET investigators and study statisticians. Investigators are not unblinded until laboratory assays have been completed and the data have been transmitted to the CARET Coordinating Center. If CARET statisticians are responsible for data analysis the investigators are not unblinded.
CARET investigators are represented as appropriate in publications using CARET data and/or specimens. Authorship specifics are negotiated in advance independently for each study. All manuscripts are reviewed to ensure CARET study details and data are represented accurately and appropriately. Publication citations are provided on the CARET website.

Specific Aim 2) Pilot procedures to obtain updated signed releases of medical records and consent for the utilization of biologic material in the CARET biorepositories consistent with recent developments on obtaining consent for broad research purposes and data sharing

Analyses of tumor tissues has been an area of intense interest among individuals seeking to use CARET specimens, including the NCI Cohort Consortium, the Harvard Pooling Project, and the OncoArray investigators. However, CARET has retained tissue samples from only a very small subset of CARET lung cancer cases, limiting the ability of CARET to contribute to such studies. In addition, scientists have approached CARET several times requesting data on treatments received by CARET participants after lung cancer diagnosis, for example to study genetic determinants of response to treatment. CARET has data only on initial treatment received by participants, with no longitudinal data on the response to that treatment or any subsequent treatment. In this application, we will perform a pilot to test our ability to expand the CARET data

and specimen repository by obtaining tumor tissue specimens and more extensive treatment data from CARET participants in Washington State who were diagnosed with lung cancer after 2003.
This pilot will involve the following steps:

1. Identification of CARET participants at the Seattle Study Center with a lung cancer diagnosis after 2003 (done)
2. For those participants who are deceased, approaching our Institutional Review Board (IRB) for approval for a waiver of a signed release of medical records in order to request medical records from the treating hospitals.
3. Using the FRED HUTCHINSON CANCER CENTER Lost to Follow-Up Tracking Service to locate living CARET participants in the target subset and the Cancer Surveillance System (the local SEER Cancer Registry) housed at FRED HUTCHINSON CANCER CENTER to identify hospitals where CARET participants in the target subset received treatment. At this time, we will also use the Lost to Follow-Up Tracking Service (LFUTS) to locate a subset of CARET participants from the Seattle Study Center not known to be deceased and with no known lung cancer diagnosis in order to evaluate our ability to obtain new consent meeting more up-to-date standards for informed consent particularly relevant to data sharing.
4. Contacting living CARET participants in the target subgroup with requests to sign new informed consents and (for those with cancer diagnoses) new releases of medical records and information on where they received treatment.

We will also track success rate in obtaining new signed consents from participants without a lung cancer diagnosis. We will use the information to decide whether expanding the effort to participants at other CARET Study Centers may be worthwhile; if so, we will seek additional funding for an expansion to the greater CARET study population.
Procedures for this pilot are as follows:
Step 1. We have identified 457 CARET participants from the Seattle Study Center with a lung cancer diagnosis after 2003, of which 393 are known to be deceased.
Step 2. We will approach our IRB with a request to waive the requirement of release of medical information for deceased CARET participants. In the State of Washington, where most of the Seattle Study Center participants resided, deceased individuals retain privacy rights, so in order to obtain medical records we will need either a signed release of medical records or documentation of an IRB-approved waiver of this requirement. To obtain a waiver, it will be necessary, among other requirements, to demonstrate that the research could not practicably be carried out without the waiver. For this project, the research could not practicably be carried out since CARET does not have information on participants' legal next-of-kin who would be the only person with the legal right to sign the release, and it would be prohibitively difficult to identify and locate the legal next-of-kin. CARET has been successful in obtaining waivers for deceased participants in other contexts and anticipates no issues in obtaining a waiver for this purpose. If CARET does not receive a waiver, then we will conduct the pilot using only living participants, recognizing the resulting limitation on the interpretation of data that would result from obtaining medical records only from participants who remain alive.
Step 3. FRED HUTCHINSON CANCER CENTER has established the LFUTS as part of the Collaborative Data Services (CDS) resource. CDS has provided tracking services to 13 studies in the last five years. They have access to unlisted telephone numbers and cell phone information from a database of over 400 million unique, non-published telephone listings, have extensive address histories, and can provide vital status updates via Social Security. CDS is budgeted in this application to perform tracking service for 64 lung cancer cases and 64 participants with no known lung cancer diagnosis from the CARET Seattle Study Center.
The Cancer Surveillance System (CSS) maintains population-based data on cancer incidence and survival as part of NCI's Surveillance, Epidemiology, and End Results (SEER) program. The catchment area of CSS includes 13 counties in western Washington State, where a large majority of the CARET participants in Washington State have their residence. Since 1992, Washington State law requires all cancer diagnoses be reported and CSS is designated as the contractor responsible for receiving abstracts on cancer cases from health care facilities in the CSS reporting region. CSS maintains individual-level data on incidence, treatment, follow-up, and survival of all newly diagnosed cancer cases (except non-melanoma skin cancers) together with information on where medical care is received. CSS is budgeted in this grant to perform linkages on all CARET participants and provide data for all cancers reported in their registry.
We will use the CSS to identify the hospitals where the tumor blocks are kept, both for the deceased and living study participants. CSS data on name, SSN, date of birth, and race allows linkage to CARET participants; CSS

also has address information abstracted from medical records, Department of License records, and Voter Registration records. Its information on treatment hospital, medical record number, pathology record number, surgeon's name, follow-up physician's name allows us to identify from which facility we should request the archival tumor blocks. In this pilot, we also plan to abstract treatment information on surgery, radiation therapy (Y/N) and chemotherapy (Y/N, chemo agents used) from the CSS appended pathology reports.

Step 4. CARET participants were recruited and consented between 1985 and 1994. The initial consent obtained from participants during this period lacked many elements included in more modern consent forms, including descriptions of the frequency and types of specimen collection and whether participants were willing to allow their data or specimens to be shared with investigators outside of CARET. Between 1994 and 1997, CARET conducted a one-time collection of whole blood for DNA analysis. The consent form for this activity had limitations with regard to data sharing; specifically, it allowed data and specimens to be shared only with "CARET investigators", and it did not discuss the risks of re-identification possible from genome-wide analyses. These limitations have in turn created issues for the broad sharing of CARET genomic data. Thus, the federally mandated deposition of the CARET portion of the OncoArray data from the International Lung Cancer Consortium into the Database of Genotypes and Phenotypes (dbGaP) currently imposes limitation on individuals wanting to access the data. They first have to obtain permission from the CARET Steering Committee in order to become a CARET investigator. This limitation makes it less likely that the data will be used, and also carries the risk that dbGaP may release the data without this permission (since that is not the usual operating procedure), contravening the agreement under which the data were deposited.

In this pilot, we will develop a new consent form (Appendix 10) for participants that will include language for general data sharing, broad specimen analysis including DNA and genome-wide analysis, and deposition of de-identified data into public databases such as dbGaP, including discussion of the risks of re-identification inherent in such databases. FRED HUTCHINSON CANCER CENTER has developed standard language that cover data sharing and the issues related to genome-wide analyses to facilitate development of the required consent.

For this pilot, we target the 64 participants at the Seattle Study Center who have had a lung cancer diagnosis and are not known to be deceased, and an equal number of participants randomly chosen from Seattle Study Center participants who are not known to be deceased and are not known to have lung cancer (although they could have other cancers). Once located, participants will be initially approached with a mailing from the CARET Principal Investigator (PI). The mailing will include a letter signed by PI reminding participants of their involvement in CARET, describing some of the findings of CARET and the uses to date of CARET data and specimens to advance science, and introducing the new consent form (Appendix 8 and 9). The mailing will also include a copy of the new consent and a release of medical records (Appendix 11) if appropriate, together with a stamped return envelope. All participants with known lung cancer diagnosis will receive the release of medical information; participants selected in the group with no known lung cancer diagnosis may have a cancer diagnosis in another organ and, if so, will also receive the medical release form. Participants will be asked to return the consent and medical release even if they do not agree to sign them. Three weeks after the initial mailing, participants who have not responded to the mailing will be contacted by mailing again, with a new letter from the CARET PI, consent form, release of medical records, and return envelope. Participants who do not respond to the second mailing after three weeks will be contacted by telephone to determine if they are willing to sign the updated consent and release of medical records (if appropriate) – See Appendix 13. CARET staff will conduct up to six calls to the participant at various times of the day and will leave a message requesting a return call if we receive voice mail. The message will be non-disclosing of the role the individual played in research in order to protect her/his confidentiality. Participants who do not respond by the sixth call will be considered to be non-responsive and not approached any further. Any participant who refuses contact will have further follow-up halted.

We will track response rate to these efforts to contact participants by category of contact type—first mailing, second mailing, telephone call. We will also track the cost (staff time, materials) for each category to determine the cost per yield as data in determining whether to seek further funding to expand the collection of new consents and releases of medical information to the larger CARET cohort.

Specific Aim 3) Pilot the collection of lung cancer biopsy/surgical specimens from Washington state CARET participants diagnosed after 2003

Because of the heterogeneous nature of cancer, accurate molecular subtyping is critical for the development of targeted therapy that can enable the practice of personalized medicine. With the improved molecular

technologies available, it is now possible to conduct molecular subtyping to subcategorize many tumors and to identify the presence of specific mutations or other molecular alterations in the tumor to inform personalized treatment and/or to predict prognosis. Along these lines, investigators at Univ. of Texas Southwestern Medical Center and the Univ. of Texas MD Anderson Cancer Center developed and validated a 62-gene classifier to distinguish lung squamous cell carcinoma (LUSC) from lung adenocarcinoma (LUAC) and from nonmalignant lung.[43] Others have also developed gene signatures for the prediction of prognosis for various histologic types of lung cancer. While overall prognosis of stage I non-small cell lung cancer (NSCLC) patients is generally favorable, up to 40% of these patients will develop recurrence and metastatic disease within 5 years after surgery. An Italian group has developed and validated a 10-gene signature that can be tested using FFPE samples for the prognosis of stage 1 LUAC patients. A ridge-penalized Cox regression model was used to generate a continuous risk score on 351 LUAC patients based on the expression data of the 10-gene signature. Patients were divided into high- vs. low-risk groups using the median as a cut-off. The risk of death was significantly higher for the high-risk group. The 3-year overall survival was 84.2% (95% CI 78.7-89.7) for patients in the high-risk group and 95.6% (95% CI 92.4-98.8) in the low-risk group.[44] Their investigation using the Cancer Genome Atlas (TCGA) data to gain molecular insights into the high risk subgroup has led to the conclusion that the high risk stage I tumors represent a distinct subgroup that share genetic characteristics with more advanced lung cancer, including mutation rate that is comparable to that of stage II-IV tumors, and a copy number variation rate that is higher than lung tumors of all other stages. For predicting survival of lung cancer patients, in addition to this 10-gene signature for LUAC, there is a 7-microRNA signature for lung LUSC based on RNASeq data on 447 LUSC patients in TCGA,[45] an 8-microRNA signature for LUAC based on RNASeq data on 372 LUAC patients in TCGA.[46] CARET, with its large sample size, long-term follow-ups spanning a total of 20 years, and extensive data on risk factors and demographic characteristics is in a position to contribute to the study of clinical outcomes based on cancer molecular subtypes and molecular alterations in the tumors.

We believe that CARET has the potential to be a resource for the studies of ETIOLOGIC factors for cancer molecular subtypes, since rich information on personal characteristics such age, sex, BMI, life style characteristics, diet/nutrient intake (including many nutritional biomarkers), clinical characteristics, etc., has already been carefully collected on its study participants. Our pilot project to collect tumor tissue from CARET participants diagnosed with lung cancer after 2003 will help to determine if adequate number of patients' specimens can be collected from the CARET lung cancer population to make these studies possible.

This pilot will involve the following steps:

1. Contacting the relevant medical providers (Appendix 12) with the new signed releases of medical records or the IRB approval of waiver of release of medical records to request tumor specimens and medical records. Based on the experience of WHI LILAC study in acquiring tumor blocks of consented study participants from diagnostic hospitals, we will assume a 50-60% success rate of our requests for tumor blocks. Thus, we plan to request blocks of 200 study participants with the anticipation of receiving tumor blocks from ~100 lung cancer cases. The requests would include all those alive cases who have given consent in Specific Aim 2, with the remainders coming from the deceased lung cancer cases under IRB approved waiver of consent.
2. Coding the received medical record data into the CARET database and adding acquired tissue specimens to the CARET specimen bank.

We will track success rate in the pilot in receiving tissue and data, separately for living participants (from whom we receive signed releases) and deceased participants (for whom we will rely on the IRB waiver).

<u>Procedures for this pilot are as follows:</u>

<u>Step 1</u>. CARET staff will contact relevant medical facilities where CARET participants received treatment, requesting copies of medical records and tumor tissue samples if available. Letters to the medical facilities will include copies of the signed release of medical records or (if approved by the IRB) notification that the IRB has waived the requirement for release of medical records for deceased participants. Our experience is that it may take multiple letters to a facility before a response is received. We will track the cost (primarily staff time) to obtain the specimens and data to determine the cost per yield of the effort to obtain data and specimens.

<u>Step 2</u>. The received specimens will be labeled using the CARET specimen numbering system. Specimen IDs are assigned randomly so that it is not possible to tell that two specimens come from the same participant. The link between specimen ID and the corresponding participant ID exists solely in the CARET database. Using specimen IDs that are independent of participant IDs is important to maintain blinding when specimens are

shared; a researcher who has been unblinded after performing an analysis on one set of specimens would remain blinded if conducting an analysis on a new set of specimens.
The medical records will have their data abstracted. CARET has existing data abstraction forms for endpoints that will be used to abstract details on the cancer, such as stage, grade, histology, date of diagnosis, and survival. CARET staff will develop a new form to abstract treatment information, adapting forms from the Women's Health Initiative. The data abstraction will be performed by CARET's data abstraction staff and the results reviewed by Dr. Goodman. Once approved, the data will be incorporated into the CARET database.
The CARET specimen bank is accessible online with tools to allow outside individuals to identify specimens of possible use for their research. The website accesses the CARET database directly, so information on participants added from this pilot effort are automatically reflected in the online CARET tools, ensuring that outside investigators have access to the most up-to-date information about CARET participants and their available samples.
The proposed pilot project assesses the feasibility of obtaining hospital diagnostic archival biopsy/surgical specimens from CARET lung cancer cases who were residents of, and had received biopsy and/or surgery at, western Washington hospitals following their diagnosis.
If the approach described above proves to be successful, in a separate proposal we would seek funds to conduct a similar pilot in California, since CARET had study centers at Univ. of California at San Francisco and Univ. of California at Irvine, as the cases identified by those centers resided in areas covered by a SEER Registry.
The archival samples obtained through this pilot investigation will be stored in a limited access, highly secure and temperature-controlled room.

3.B.2. Broad Research Agenda

The CARET Biorepository is a valuable national resource for population-based studies of the major human cancers. Because of the extensive content of our demographic/disease/specimen-linked database and the fact that the CARET Biorepository is one of the few that has prospective pre-diagnostic serum samples, our studies have focused on biomarkers for the early detection of cancer. The availability of DNA in a large part of our population and controls matched for important covariates has led to studies examining genetic factors of cancer risk and prognosis. The availability of comprehensive dietary questionnaires and serum micronutrients results has allowed investigations of the diet/micronutrient/genetic/cancer association. As methodological techniques improve, requiring smaller amount of biospecimens we expect more of these types of studies and the request for CARET samples to grow.
Our research agenda over the next 5 years will be to continue to work with investigators whose studies require the type of biospecimens and data that are available in the CARET Biorepository. We will encourage investigators to develop methods that require small sample volumes since the amount of DNA and serum within the repository are finite. We will reach out to new investigators previously unfamiliar with the rich contents of the repository. We have also encouraged outside collaboration by our membership in the NCI Cohort Consortium, the International Lung Cancer Consortium, and by our placing links to our repository on collaborative websites such as those from the NCI Epidemiology and Genetics Research Program and the Early Detection Research Network. The open access of the CARET Biorepository has been a strongpoint. A review of our completed and ongoing projects illustrates that we have worked with investigators nationally and internationally in providing samples for collaborative projects. We have had early discussion with investigators planning to submit a mesothelioma SPORE and will continue to establish more links with the environmental health/asbestosis community.

3.C. LEADERSHIP AND ADMINISTRATIVE CORE

3.C.1. Scientific Leadership

Marian Neuhouser, Ph.D., is a Full Professor in the Cancer Prevention Program, Division of Public Health Sciences at the Fred Hutchinson Cancer Center. She is also an Affiliate Professor in the Department of Epidemiology and a Core Faculty Member of the Graduate Program in Nutritional Sciences, both at the University of Washington. She has been collaborating with Dr. Goodman since her arrival at the Fred Hutchinson Cancer Center in 1997. She was Principal Investigator of R01 CA 0976789, Diet and Genetic Risk for Prostate Cancer, and Co-PI of R03 CA 89734, Diet and Genetic Risk for Lung Cancer; both of these studies used CARET data and specimens. One of the publications from these studies demonstrated that use of both dietary supplements and the CARET intervention vitamins increased the risk of aggressive prostate cancer.[47] In the current funding cycle we have coded and data entered the dietary supplement data from

CARET and manuscripts will be underway very soon to further this line of inquiry. In addition, Dr. Neuhouser has been the primary scientific contact with the Harvard Pooling Project Studies of diet and cancer risk. This collaboration has been very successful and has generated numerous highly cited publications. One of her doctoral students in Epidemiology at the University of Washing used the CARET database for his doctoral dissertation research.[22, 48] Dr. Neuhouser is extremely familiar with the CARET data operations systems, biostatistical support and the biorepository. In this cycle of funding she will continue to be the lead investigator on dietary related studies, including those using nutritional biomarkers, she will continue to be the liaison with the nutrition-related pooling project studies with both Harvard and the Oxford Collaborative Group and she will lead manuscripts using the new data to be collected. Of particular interest and relevance in this cycle will be understanding whether body weight or nutritional status predicts response to lung cancer treatments.
Matthew (Matty) Triplette, M.D., M.P.H., is an Associate Professor in Pulmonary and Critical Care Medicine at the University of Washington and recently received a Joint Appointment in the Cancer Prevention Program (led by PI Dr. Neuhouser) Division of Public Health Sciences at Fred Hutch. Dr. Triplette's research focus is on lung cancer screening and lung cancer prevention. Dr Triplette recently became involved in CARET and is now the Fred Hutch site PI of a CARET ancillary study leveraging data and biospecimens that will create a biomarker panel for lung cancer screening and outcomes. Dr. Triplette will provide expertise on lung cancer incidence and mortality for all CARET collaborative studies.
Delegating leadership responsibility. Dr. Neuhouser is responsible for the scientific conduct of policies and procedures and use of the biorepository and associated database. If Dr. Neuhouser is unable to exercise those responsibilities, Dr. Triplette, , Co-Investigator, will assume that role.
CARET Core Leadership Group. The CARET Core Leadership Group (CLG) will consist of CARET investigators and co-investigators. This committee is charged with reviewing study proposals requesting the use of CARET specimens and/or data. The CLG has the responsibility to review and evaluate the scientific merit of collaborative study proposals, while also considering the impact on the CARET repository. Drs. Neuhouser and Triplette make-up the CLG. If the CLG lacks the expertise needed to conduct a thorough review, then the proposal is reviewed by the CARET Scientific Review Committee (SRC). SRC membership includes Drs. Marian Neuhouser, Matty Triplette, Gary Goodman, Mark Thornquist, and Chu Chen...

3.C.2. Administration and Operations

Key staff have been involved in CARET for extensive time periods ranging from 18 to 35 years. They bring critical historical history and knowledge of CARET science and operations, as well as developed working efficiencies. Because of this, we have been able to minimize the number of staff members being requested for this proposal. The staff members described below will work on all specific aims of this proposal.
Matt Barnett, MS, has been with CARET since 1992 and is responsible for overall coordination and providing statistical and data management support for all CARET studies, including collaborative studies using CARET data and/or specimens. Mr. Barnett is responsible for coordinating and performing analysis functions, including analytic support for progress reports, publications, and ad hoc analyses. Mr. Barnett has provided statistical support for over 60 collaborative studies that have utilized the CARET Biorepository and contributed to 47 CARET publications and presentations.

Table 8. Timeline of Activities

	Year 1		Year 2		Year 3		Year 4		Year 5	
	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half
Maintain and support the CARET Biorepository and database to contribute to and collaborate in research										
Perform overall management and coordination	x	x	x	x	x	x	x	x	x	x
Maintain and update biospecimen, clinical, and research databases and perform routine quality assurance			x		x		x		x	x

	Year 1		Year 2		Year 3		Year 4		Year 5	
	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half
Monitor freezer temperatures and back-up systems, remove excess ice from freezers, respond to freezer failures, and replace failed freezers	x	x	x	x	x	x	x	x	x	x
Perform quality control and consolidate the CARET biospecimens	x	x	x	x	x	x	x	x	x	x
Update CARET website and associated website databases, including publications and updating specimen data for searching	x	x	x	x	x	x	x	x	x	x
Support a limited number of studies that do not have funding with emphasis on large pooling collaborators	x	x	x	x	x	x	x	x	x	x
Process new applications to use CARET samples										
Perform scientific and administrative review of proposals for completeness, study design quality, and impact on the CARET Biorepository.	x	x	x	x	x	x	x	x	x	x
Provide front-end consultation on collaborative study proposals	x	x	x	x	x	x	x	x	x	x
Coordinate IRB approvals	x	x	x	x	x	x	x	x	x	x
Draft and obtain documentation (Confidentiality Agreement, Certificate of Privilege, Material Transfer Agreement, Data Use Agreement)	x	x	x	x	x	x	x	x	x	x
Negotiate and confirm funding source for specimens and work outside of infrastructure activities	x	x	x	x	x	x	x	x	x	x
Coordinate collaborative study application process with the Scientific Review Committee	x	x	x	x	x	x	x	x	x	x
Support approved CARET collaborative studies	x	x	x	x	x	x	x	x	x	x
Communicate with investigators on their study needs, sample size, volume, data variables, etc.	x	x	x	x	x	x	x	x	x	x
Develop statistical and analytical methods and provide statistical support	x	x	x	x	x	x	x	x	x	x
Identify specimen to match study criteria and create specimen pull lists	x	x	x	x	x	x	x	x	x	x
Pull specimens from CARET freezers for downsizing and shipping to laboratories	x	x	x	x	x	x	x	x	x	x
Create specimen pull lists	x	x	x	x	x	x	x	x	x	x
Integrate collaborative study results into CARET database			x		x		x		x	
Assist with publications	x	x	x	x	x	x	x	x	x	x
Upgrade systems as needed			x		x		x		x	
Maintain IRB compliance										

	Year 1		Year 2		Year 3		Year 4		Year 5	
	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half
Write and submit annual IRB renewal including modifications to the CARET protocol to reflect new studies using CARET samples and/or data	x		x		x		x		x	
Promote use of CARET samples	x	x	x	x	x	x	x	x	x	x
Perform strategic planning on maximizing the use of CARET biospecimens		x		x		x		x		
Incorporate treatment information into the specimen search pages as a search parameter, and into the search output page as a returned variable						x				
Pilot for obtaining consent and signed medical releases of information										
Develop procedures and tracking system	x									
Attempt IRB waiver of signed release of medical records for deceased participants	x									
Conduct CSS search	x									
Conduct CDS search	x									
Develop new consent and signed medical release form and obtain IRB approval	x									
Contact living participants to obtained new informed consent and signed medical release		x	x	x	x	x	x	x	x	
Monitor progress		x	x	x	x	x	x	x	x	
Pilot Tissue Collection										
Develop procedures and tracking system	x									
Send signed medical release or waiver to medical provider		x	x	x	x	x	x	x	x	
Add treatment data to database										x
Add returned tissue to specimen repository		x	x	x	x	x	x	x	x	x
Monitor progress		x	x	x	x	x	x	x	x	

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5. Human Subjects

5.A. Protection of Human Subjects

5.A.1 Human Subjects Involvement, Characteristics, and Design

We assessed cancer and death information in a cost-efficient and non-intrusive manner by making use of US cancer registries and national death records. We matched CARET information to these external registries up to 2012 to bring the CARET endpoint database up to date. CARET participants provided consent for us to determine their vital status and we matched our participant identifiers to publicly-funded databases in a manner consistent with the relevant state and federal laws that govern their access. No participants were contacted to perform the matching. We will be mailing consents and requests for medical records to 128 assumed living participants as part of Aim 2 and Aim 3 (2018-2023) (See Appendices 8-14)

5.A.2 Sources of materials

We will use the FRED HUTCHINSON CANCER CENTER Lost to Follow-Up Tracking Service (LFUTS) as part of the Collaborative Data Services (CDS) resource to locate a subset of CARET participants from the Seattle Study Center not known to be deceased (64) and with no known lung cancer diagnosis and another 64 with known lung cancer, in order to evaluate our ability to obtain new consent meeting more up-to-date standards for informed consent particularly relevant to data sharing. (See Appendices 8-14)

We will use the Cancer Surveillance System (the local SEER Cancer Registry) housed at FRED HUTCHINSON CANCER CENTER to identify hospitals where CARET participants received treatment. We will request a Waiver of Consent and approach medical facilities to obtain tissue and lung cancer treatment information (See Appendix 12)

All specimens, records, and data will be used for research purposes only.

5.A.3 Potential risks.

There is the potential risk of loss of confidentiality to the participant. Extensive measures are taken to maintain the confidentiality of participant records. This includes a password-protected database, locked storage of participant charts and biospecimens, de-identified specimen labeling using unique alpha-numeric codes, and confidentiality pledges for all investigators and staff with access to participant information. Any CARET biospecimens and/or data used for collaborative studies or pooled analyses are de-identified. The external databases (LFUTS/CDS, CSS, SSDI, NDI, cancer registries) to which we have and will match participant information have well-established procedures to protect confidentiality of individuals' protected health information.

5.B. Adequacy of Protection Against Risks

5.B.1 Recruitment and informed consent

CARET participants were recruited from 1983-1994 via letters sent to age-selected subscribers from participating local insurance groups, including Blue Cross and Blue Shield of Washington, Oregon, and California, Group Health Cooperative of Puget Sound, Kaiser Permanente of Oregon and Anaheim, California, Health Net, and Good Health Plan of Oregon; retired military organization; smoking cessation groups; AARP; and direct mail lists. Asbestos-exposed participants were identified and recruited through workers' compensation claims, union rolls, records of lawyers, and medical sub-specialty clinics.

5.B.1.1 Informed consent

Informed consent was obtained by the study staff at the time of the first study center visit. The consent form detailed the objectives of the trial, the nature of a double-blind placebo trial, the potential side effects of the intervention agents, the duration of the trial, and what was requested of the participants for follow-up. All signed consent forms are kept with the participant's study center records, and a copy was given to the participant.

In 2000, CARET centralized all participant and endpoint collection activities from the local study centers to the Coordinating Center in Seattle. To meet 45CRF 46.117 (c) guidelines for passive consent of this change in participant contact, a letter was sent from the local study center investigator to all living participants informing them of the change of contact status, study results to date, and the reasons for continued follow-up. The CARET study centers performed final local telephone contacts during the year 4/1/1999-3/31/2000. At the call they reminded the participants that their next routine call would be performed by the Coordinating Center in Seattle, Washington.

Although the CARET foundational consents do not explicitly address procedures for future use of specimens or data, there is general language which informs participants that CARET would retain records indefinitely for follow up or analysis. During the Centralization phase of CARET, all activities previously conducted by the

Study Centers were assumed by the CARET Coordinating Center. This included the follow up of participants to ascertain endpoints (cancers and death), via periodic searches of state cancer registries, SEER, or death indices. This is described in *Appendix 6.*

Our current plan to use the FRED HUTCHINSON CANCER CENTER LTFUTS to obtain updated contact information and to search the local SEER registry maintained by CSS is in accordance with these previously approved methods to update our database with new cancers and/or deaths.

In addition, participants signed subsequent consents, such as the *Medical Records Release Form* (Appendix 5) which states in *Section 6—Storing your Health Information: "Your health information is part of a database or repository. This permission will end when the data repository is destroyed. Unless you take back your permission, this form does not have an ending date."* Participants were aware that we would keep their data indefinitely and that we would periodically scan registries and death indices.

We will be approaching 128 participants not known to be deceased to attempt to obtain new consent meeting more up-to-date standards for informed consent particularly relevant to data sharing.

DNA consent

Approximately 80% of CARET participants have signed consent forms authorizing DNA analyses of stored whole blood.

IRB oversight

It is understood that cooperative research projects are responsible for safeguarding the rights and welfare of human subjects and complying with 45CFR46 regulations. The 45CFR46.114 states “with the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplications of effort.” In our desire to streamline the CARET IRB activities, while honoring and respecting our participants’ rights, we have entered into IRB cooperative agreements between the CARET study centers institutional IRBs and the FRED HUTCHINSON CANCER CENTER IRB. In compliance with federal regulations, all involved institutions hold FWAs, which are administered as an Inter-Institutional Agreement. The review of all modifications, updates, and annual reporting are conducted by the FRED HUTCHINSON CANCER CENTER IRB with copies of all applications sent to all participating institutions. At any time, a participating institution may request its own review of any changes to the protocol. Except in the unlikely event that an analysis may have clinical relevance to a participant, in the past the IRB has granted a waiver of the need to obtain explicit consent.

The cooperative agreement with *Kaiser Permanente Center for Health Research* was amended in August 2017 to acknowledge that Kaiser Permanente is no longer engaged in the Study per federal regulations and confirm that FRED HUTCHINSON CANCER CENTER will not approve any ancillary study that includes sharing of data/specimens from Kaiser CARET participants with a for-profit commercial entity.

5.B.1.2 Protection against risk

As of 2017, 8,437 participants were reported still alive. Data forms currently being accessed (e.g., for data extraction) are stored on-site in a locked office. Study center participant charts (except for Portland Study Center’s), X-rays, and mark-sense forms are stored off-site, in a secure location. To help ensure confidentiality, limited CARET staff has access to the off-site secure location. Data are transported to and from the off-site location in a locked briefcase. The Portland Study Center participant charts are archived at the Kaiser Permanente Center for Health Research in locked file cabinets and accessible only to authorized personnel.

Access to the CARET database is restricted to authorized CARET staff. Biological specimens are kept in either: 1) a locked freezer room at the FRED HUTCHINSON CANCER CENTER; or 2) under restricted access in the laboratories. We are taking extensive measures to maintain the confidentiality of participant records, including password-protection for the database, locked storage of participant charts and all biological samples, labeling of samples that are blinded so they cannot identify a participant without access to the central database, and confidentiality pledges for all new investigators and staff with access to participant information. Proposals for use of specimens or data from CARET’s repository can proceed only after they have been approved by the IRBs at both the proposing investigator’s institution and FRED HUTCHINSON CANCER CENTER. Once all approvals have been received, the CARET Coordinating Center confirms that all key staff have completed human subjects training and obtains from the collaborative study principal investigator a signed letter of confidentiality and a certificate of privilege to use CARET data and specimens. At this point, data and/or specimens will be released to the investigator to conduct the study.

Key personnel training in the use of human subjects in research

All investigators and key staff working on CARET have received NIH-required training in the conduct of studies involving human subjects. The Institutional Review offices of the FRED HUTCHINSON CANCER CENTER conduct training seminars and mandate participation from faculty members and key staff. In addition, all CARET staff are required to sign letters of confidentiality.

Health Insurance Portability and Accountability Act (HIPAA) compliance

In fall 2000, FRED HUTCHINSON CANCER CENTER formed a Steering Committee to review HIPAA regulations, evaluate their impact on the FRED HUTCHINSON CANCER CENTER, and serve as an informational resource overseeing the integration, coordination and implementation of HIPAA at the FRED HUTCHINSON CANCER CENTER. All CARET employees are required to take the FRED HUTCHINSON CANCER CENTER HIPAA compliance test.

5.C Potential Benefits of the Proposed Research to the Subjects and Others

Although participants will not benefit directly from this study, the data they provided may eventually be of help in developing clinically important insights and treatment protocols that may be of value to physicians treating others in the future. In addition, society as a whole will benefit from any insights gained.

5.D Importance of Knowledge to Be Gained

Studies using CARET's specimens and data may identify causes or markers of cancer incidence or disease mortality, potentially permitting detection of disease at an earlier, more treatable stage or identifying potentially efficacious treatment options that could improve public health.

5.E Inclusion of Women and Minorities

All CARET participants were recruited by 1994. There was no attempt to select for either gender or to enrich for a greater proportion of women in the heavy smoker study population. In the asbestos-exposed population, only men were recruited because there were very few women who would meet the asbestos exposure criteria. Members of any race have been included if they were eligible based on the criteria listed elsewhere; there was no attempt to enrich for or exclude any racial population.

5.F Inclusion of Children

CARET recruited participants over the age of 45. Children were not enrolled into CARET because their risk of lung cancer is very low.

5.G Inclusion of Elderly, Prisoners, Developmentally Disabled, or Decisionally Impaired Individuals

All CARET participants recruited were between the ages of 45-67, so over the course of the study, the number of elderly in the population naturally increased. The study design did not seek to enroll prisoners, developmentally disabled, or decisionally impaired individuals. However, given the length of the study, there is the possibility that some enrollees existed within these demographic groups without our knowledge.

6 CARET Ancillary Studies.

Listed below are CARET ancillary studies, including the date study was initiated, internal ID#, and any corresponding IR File numbers.

6.1 BC Clear-Determining the Plasma Disappearance and Pharmakokinetics of Beta-Carotene and Long Term Oral Supplementation

Date: 1/26/1996
ID#: 77
PI Name: Carrie Redlich
Organization: Yale University
Submitted: Submitted under IR File 4208 & 4239a
Specific Aims: To determine the serum concentrations of beta-carotene, retinol, retinyl palmitate, and alpha-tocopherol over time after CARET participants discontinued oral supplementation with beta-carotene.
Materials: Specimens and Data

6.2 Publication of Anonymous Research Date-Baseline Serum Concentrations of Beta-Carotene in Participants in CARET

Date: 6/17/1996
ID#: 78
PI Name: Mark Thornquist
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4284 & 4239a
Specific Aims: To publish data on the distribution of serum beta-carotene at baseline in participants in CARET, the Carotene and Retinol Efficacy Trial.
Materials: Data

6.3 Smoker Spiros-The Effect of the CARET Vitamins on Ventilatory Function in the CARET Smoker Cohort

Date: 12/8/1998
ID#: 80
PI Name: John Balmes
Organization: San Francisco General Hospital
Submitted: Submitted under IR File 4242 & 4239a
Specific Aims: To determine if the administration of the CARET vitamins had a protective effect on the age-related loss of lung function in current and former smokers.
Materials: Data

6.4 P-53 Prevalence of Anti-P53 antibodies and P53 Mutations in CARET Participants with Lung or Prostate Cancer

Date: 10/14/1996
ID#: 79
PI Name: Glen Trivers
Organization: National Cancer Institute
Submitted: Submitted under IR File 4363 & 4239a
Specific Aims: To determine the incidence of measurable concentrations of antibodies against the mutant P53 protein in CARET participants with and without lung cancer.
Materials: Specimens and Data

6.5 PSA Correlation between the increase in PSA and the Diagnosis of Prostate Cancer and Histologic Grade

Date: 11/13/1996
ID#: 87
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4364 & 4239a
Specific Aims: To retrospectively determine the slope of the increase in serum PSA (protein bound and free) in CARET participants diagnosed with prostate cancer, and to compare this increase with measurements from a set of healthy CARET participants and matched fcontrols.

Materials: Specimens and Data

6.6 Immunization-Vitamin Enhancement in Pneumococcal Vaccine Response

Date: 12/18/1996
ID#: 82
PI Name: James Williams
Organization: University of California, Irivne
Submitted: Submitted under IR File 4381 & 4239a
Specific Aims: To examine the effects of the combination of beta-carotene and retinyl palmitate on antibody responses to immunization for Streptococcus Pneumoniae and influenza infections among CARET participants.
Materials: Specimens and Data

6.7 Fatty Acids/Prostate-Association between plasma phospholipid Fatty Acid Levels and Prostate, breast, and Colon Cancer

Date: 11/18/1997
ID#: 84
PI Name: Irena King
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4391 & 4239a
Specific Aims: To determine the relationship between serum phospholipid fatty acid levels, biomarkers of recent fat intake (4-6 weeks), and prostate cancer using existing serum samples from selected male CARET participants. The second objective is to also determine the degree of correlation between assessment of dietary fat intake from the food frequency questionnaire on file and the biomarker fatty acids.
Materials: Specimens and Data

6.8 Determining the Plasma Disappearance and Pharmakokinetics of Beta-Carotene after Long-Term Oral Supplementation

Date: 1/13/1997
ID#: 76
PI Name: Carrie Redlich
Organization: Yale University
Submitted: Submitted under IR File 4393 & 4239a
Specific Aims: To determine the effects of long-term supplementation of Beta-carotene and retinyl palmitate on lipoptroteins (HDL, LDL, VLDL) and other carotenoids and retinoids by analysis of existing serum samples on 52 New Haven CARET participants stored at the CARET Coordinating Center. These results will be compared to existing chart data on CARET Seattle participants.
Materials: Specimens and Data

6.9 Consent Waiver for Deceased participants. DNA Protocol and Consent Mailing-Association between Genetic Factors and Risk of Lung Cancer and other Diseases

Date: 12/22/1997
ID#: 114
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4392 & 4239a
Specific Aims: To test stored serum from deceased participants for markers.
Materials: Specimens and Data

6.10 Folate/Homocysteine-Association Between Serum Homocysteine and Folate Levels and Cardiovascular Disease

Date: 12/4/1996
ID#: 83
PI Name: Gil Omenn
Organization: University of Michigan
Submitted: Submitted under IR File 4399 & 4239a
Specific Aims: To investigate associations and relative risks for the folic acid-homocysteine-cardiovascular

disease endpoints cascade in CARET participants, testing whether low folic acid generation and ingestion correlate with serum folate levels; serum folate with serum total homocysteine levels; and the relationship between homocysteine levels and cardiovascular disease and coronary heart disease.

Materials: Specimens and Data

6.11 Associations Between Genetic Factors and Risk of Lung Cancer and Other Diseases

Date: 2/10/1997
ID#: 115
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4406 & 4239a
Specific Aims: To determine possible associations between genetic factors and risk of lung cancer and other diseases. Existing participant samples from CARET serum bank will be sent to collaborating laboratories for analysis.
Materials: Specimens and Data

6.12 Diet and Genetic Risk for Lung and Prostate Cancers

Date: 10/06/1997
ID#: 98
PI Name: Ruth Patterson
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4541 & 4239a
Specific Aims: This proposal is for an investigation into the associations between the incidence of lung cancer and prostate cancer and diet, and modification of other potential risk factors by diet.
Materials: Data

6.13 Homocysteine Studies Collaboration: Release of CARET Data for Meta-Analysis

Date: 2/6/1998
ID#: 100
PI Name: Robert Clarke
Organization: University of Oxford
Submitted: Submitted under IR File 4618 & 4239a
Specific Aims: To release data on CARET participants in the study entitled “Association Between Serum Homocysteine and Folate Levels and Cardiovascular Disease” (IR File #4399) to the investigators of the Homosysteine Studies Collaboration based at the University of Oxford, England, to use in a meta-analysis.
Materials: Data

6.14 Pilot Study to Determine the Utility of the Washington Cancer Registry for CARET Endpoint Ascertainment

Date: 6/17/1996
ID#: 111
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4629 & 4239a
Specific Aims: To search the Washington State Cancer Registry (CSS & Eastern Washington) for cancer data on 6,750 CARET Seattle Study Center participants. We are evaluating how effective CARET is at capturing cancer incidence compared to the registry system.
Materials: Data

6.15 Association Between Genetic Risk Factors and Smoking Behavior”

Date: 6/16/1998
ID#: 103
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4667 & 4239a
Specific Aims: The goal of this study is to examine genetic influences on smoking behavior, with an emphasis on successful quitting.

Materials: Specimens and Data

6.16 Pilot of Poly2000 GeneChip for Scanning Polymorphisms in CARET Participants

Date: 6/16/1998
ID#: 106
PI Name: Lue Ping Zhao
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4668 & 4239a
Specific Aims: The goal of this study was to examine the usefulness of the Poly2000 GeneChip technology in scanning CARET samples for single nucleotide polymorphisms.
Materials: Specimens and Data

6.17 Association Between Flavonols and Risk of Lung Cancer Measurement of Plasma and\or Serum Quercetin Concentrations in CARET Participants

Date: 6/22/1998
ID#: 104
PI Name: Johanna Lampe
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4669 & 4239a
Specific Aims: To examine the association of baseline plasma and\or serum quercetin concentrations in lung cancer participants and controls. The hypothesis is that baseline plasma and\or serum quercetin concentrations will be lower in CARET participants who developed lung cancer compared to controls.
Materials: Specimens and Data

6.18 Association Between Chlamydia Pneumoniae Infection and Risk of Lung Cancer

Date: 6/16/1998
ID#: 105
PI Name: Alyson Littman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4670 & 4239a
Specific Aims: To determine whether chronic infection with Chlamydia Pneumoniae may increase risk of lung cancer.
Materials: Specimens and Data

6.19 Association Between Growth Factors and Risk of Lung Cancer and Other Diseases

Date: 8/6/1998
ID#: 107
PI Name: James Williams
Organization: University of California, Irvine
Submitted: Submitted under IR File 4671 & 4239a
Specific Aims: To determine in the CARET population if the following growth factors are associated with the incidence of lung cancer and cardiovascular disease.
Materials: Specimens and Data

6.20 CARET Ancillary Study: Association Between Serum Concentrations of Selenium and the Incidence of Lung and Prostate Cancer

Date: 12/16/1998
ID#: 88
PI Name: Gary Goodman
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4768 & 4239a
Specific Aims: To investigate the association between the serum concentrations of selenium and the incidence of lung and prostate cancer.
Materials: Specimens and Data

6.21 Hepatoxicity-Hepatic Effects of Low Dose Vitamin A Supplementation

Date: 4/9/1999
ID#: 85
PI Name: Carl Brodkin

Organization: Harborview Medical Center
Submitted: Submitted under IR File 4860 & 4239a
Specific Aims: To assess the technical feasibility of quantitatively determining procollagen levels from frozen banked serum on 10 participants from the CARET intervention group and compare them to 10 participants from the CARET placebo group. The specific aims of this data was to provide an estimate of mean values, variance, and distribution to utilize in sample size calculations for a larger, comprehensive study.
Materials: Specimens and Data

6.22 Release of Tabular Data to External Party

Date: 09/28/1999
ID#: 92
PI Name: Michael Freedman
Organization: National Cancer Institute
Submitted: Submitted under IR File 4942 & 4239a
Specific Aims: Dr. Michal Freedman of NCI has analyzed data from the Alpha-tocopherol-Beta-carotene (ATBC) trial and has found a disparity in the occurrence of amyotrophic lateral sclerosis (ALS) between those receiving beta-carotene and those receiving placebo. To help her interpret this finding, she has requested information on the incidence of ALS by intervention group IN CARET.
Materials: Data

6.23 Association between Folate and B12 Levels and Lung and Prostate Cancers

Date: 2/3/2000
ID#: 90
PI Name: Irena King
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5028 & 4239a
Specific Aims: To investigate the relationship between serum folate and B12 levels and lung and prostate cancer incidence in CARET participants. To determine the effect of intervention on the serum folate and B12 levels in CARET participants with and without the diagnoses of lung and prostate cancers.
Materials: Specimens and Data

6.24 The Relationship between Plasma IGF-1, IGF-2, and IGFBP-3 and Lung Cancer Risk

Date: 4/17/2000
ID#: 89
PI Name: Margaret Spitz
Organization: University of Texas, MD Anderson Cancer Center
Submitted: Submitted under IR File 5040 & 4239a
Specific Aims: To examine the relationship between serum IGF-1, IGF-2, and IGFBP-3 and lung cancer risk by conducting a nested lung cancer case-control study within the CARET trial cohort.
Materials: Specimens and Data

6.25 Association Between S100 Proteins and Lung Cancer – A Pilot Study

Date: 5/2/2000
ID#: 108
PI Name: Samir Hanash
Organization: University of Michigan
Submitted: Submitted under IR File 5082 & 4239a
Specific Aims: The short-term goals of the pilot study are to test for S100 proteins (MRP8 and MRP14) in stored CARET serum. The long-term goals of this research are to investigate whether these biomarkers are correlated with disease and may help explain the effect of the intervention in the CARET study.
Materials: Specimens and Data

6.26 Detection of Aberrant Hypermethylation of Cancer-Related Genes in Serum as a Screening Tool for Early Detection of Lung Cancer

Date: 12/21/2000

ID#: 109
PI Name: David Sidransky
Organization: Johns Hopkins University
Submitted: Submitted under IR File 5154 & 4239a
Specific Aims: Pilot study to validate ability to use CARET samples to confirm the possibility of performing a study looking at aberrant promoter hypermethylation of cancer related genes (p16, MGMT, DAP-kinase, GSTP1, and APC) in serum\plasma samples as tool for the early detection of lung cancer in high-risk populations and\or monitoring patients with lung cancer during treatment utilizing CARET specimens.
Materials: Specimens and Data

6.27 Serum Concentrations of Mesothelin in the Early Diagnosis of Mesothelioma

Date: 2/1/2001
ID#: 110
PI Name: Ingegerd Hellstrom
Organization: Pacific North West Research Institute
Submitted: Submitted under IR File 5171 & 4239a
Specific Aims: The aim of this pilot study was to determine if mesothelin is elevated in patients with malignant mesothelioma. An initial phase II trial has been added to measure the concentration of MPF/Mesothelin in the serum of 10 patients with a diagnosis of malignant mesothelioma and 10 matched healthy controls.
Materials: Specimens and Data

6.28 The Association Between Physical Activity and Cancer Incidence and Mortality and Identifying the Correlates of Physical Activity

Date: 9/7/2001
ID#: 91
PI Name: Catherine Alfano
Organization: University of Memphis
Submitted: Submitted under IR File 5259 & 4239a
Specific Aims: This study aims to investigate physical activity in relation to all-site cancer and lung cancer incidence and mortality in the CARET study. A second purpose is to investigate how total time spent in physical activity and intensity of that time are related to cancer outcomes in this sample. Third, the study seeks to identify when in the lifespan physical activity in most important in terms of cancer outcomes.
Materials: Data

6.29 Validation of Protein Markers for Lung Cancer Using CARET Sera and Proteomics Techniques

Date: 9/25/2002
ID#: 93
PI Name: Samir Hanash
Organization: University of Michigan
Submitted: Submitted under IR File 5474 & 4239a
Specific Aims: The objectives of this study are to (1) validate the finding from pilot studies with CARET sera of autoantibodies annexins I and II and PGP9.5 as potential biomarkers for lung cancers before the clinical diagnosis, evaluating sensitivity and specificity by time before diagnosis, treatment arm, gender, histologic type, and smoking status; (2) identify additional antigens and antibodies in sera from CARET participants, evaluating sensitivity and specificity by time before diagnosis, treatment arm, gender, histologic type, and smoking status, and, (3) compare the findings for individual biomarker candidates in participants who were current smokers versus former smokers. This ancillary study was approved by the IRB on September 30, 2002. Add David Odelson, Invitrogen Corporation, as investigator to study. Provide Invitrogen Corporation the following de-identified data on participants from this study excluding participants from the Portland Study Center: a) date at the time of specimen collection; b) gender; c) race of donor; and d)disease stage, when available.
Materials: Specimens and Data

6.30 Endogenous Sex Hormones, Genetics, and Prostate Cancer

Date: 1/1/1998
ID#: 96
PI Name: Chu Chen
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5534 & 4239a
Specific Aims: To examine the association of prostate cancer risk with (1) serum concentrations of testosterone, sex-hormone binding globulin (SHBG), androstenedione, dehydroepiandrosterone sulfate (DHEAS), 3a-androstanediol glucuronide (3a-diol G), and estradiol; and (2) polymorphisms of the 5a reductase type II (SRD5A2) gene and of the androgen receptor gene. This protocol has been modified to include analysis of A49t polymorphism of the SRD5A2 gene. This study is funded through grant number RO1CA788 O1A1.
Materials: Specimens and data

Endogenous Hormones and Prostate Cancer Collaborative Group

Date: 2/2/2016
ID#: 228
PI Name: Naomi Allen
Organization: University of Oxford
Submitted: Submitted under IR File 4239a
Specific Aims: 1) Provide more precise estimates of the relative risks for each hormone, 2) identify which hormone is most closely associated with risk by allowing hormone analyses to be mutually adjusted, 3)examine the relationships between subject characteristics and hormone concentrations in a cross-sectional manner, and 4) examine the relative risks in subgroups by stage and grade of cancer and other factors.
Materials: Data

Data from study ID#96 will be released to the Dr. Andrew Roddam of the Cancer Research UK Epidemiology Unit/Radcliffe Infirmary in Oxford UK. Pooled deidentified data will be used in a pooled analysis (see attached protocol and data request form). IR File #4534 to be modified as well to show this data analysis. Specimens and Data

6.31 Analyzing CARET Specimens to Model Serum Markers for Cost Effective Ovarian Cancer Screening

Date: 1/19/1998
ID#: 152
PI Name: Garnet Anderson
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4588 & 4239a
Specific Aims: The primary objective of this research is to obtain preliminary data (pilot data) to determine whether markers that perform well in discriminating cancers from healthy controls (in Ovarian SPORE Project 4) will also be useful for early detection (i.e. detect elevation in pre-diagnostic specimens). This pilot project is ancillary to Ovarian SPORE Project 2 (PI: Garnet Anderson) currently funded at FRED HUTCHINSON CANCER CENTER. The specific aims of this pilot project are 1) to determine the concentrations of CA-125, soluble mesothelins and other markers in serum samples obtained prior to diagnosis of ovarian cancer, 2) to obtain preliminary information on the behavior of these individual biomarkers over the time interval preceding diagnosis in ovarian cancer cases and in a similar interval in women who remain free of the disease, 3) to use intact protein analysis system (IPAS), a mass spectrometry discovery platform, to identify markers in these pre-clinical samples that detect cancer cases early and complement CA-125, thereby helping us to predict which proteins have the capacity to elevate early in the clinical period, and 4) to estimate the

correlation between the candidate biomarkers in case and controls. In addition, MMP-7 has been shown to have some discriminatory power at the time of clinical diagnosis, and has been added to this protocol.

Materials: Specimens and Data

6.32 Diet and Genetic Risks for Lung Cancer

Date: 3/29/2000
ID#: 102
PI Name: Marian Neuhouser
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5053 & 4239a
Specific Aims: To better understand the association of fruit and vegetable intake with the reduced risk of lung cancer and to examine whether the associations between fruit and vegetable intake with lung cancer risk differs among participants grouped by their genetic risk. This study is funded through grant number CA89734-02.
Materials: Data

6.33 SNPs in Lung Cancer Risk and Therapeutic Response

Date: 02/24/2003
ID#: 94
PI Name: Effie Petersdorf
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5524 & 4239a
Specific Aims: To utilize CARET specimens to refine experimental techniques for DNA extraction that will be used in a larger study. This study was approved by the IRB on November 30, 2002.
Materials: Specimens and Data

6.34 Diet and Genetic Risks for Prostate Cancer

Date: 3/28/2003
ID#: 99
PI Name: Marian Neuhouser
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5609 & 4239a
Specific Aims: This proposal will investigate associations of dietary influences on oxidative balance (fat, fruit and vegetable intakes) and polymorphisms in oxidative stress regulatory enzymes with the risk of prostate cancer. The hypothesis is that dietary factors that increase oxidative stress (e.g., dietary fat) are associated with increased risk of prostate cancer; dietary factors that decrease oxidative stress (e.g., fruits and vegetables) are associated with decreased risk of prostate cancer; and the magnitude of these risks will vary by cancer susceptibility genetic profile. This study utilizing CARET specimens is funded through grant number RO1 CA 097678901A1.
Materials: Specimens and Data

6.35 SNPs and Cancer Risk and Response

Date: 03/08/2005
ID#: 153
PI Name: Effie Petersdorf
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5608 & 4239a
Specific Aims: This proposal will develop PCR arrays for a panel of 20 cytokine gene SNPs and apply the method to test a large clinical population of cancer patients and cancer-free individuals using samples from CARET. Investigators will collaborate with CARET and will genotype cytokine gene polymorphisms in genomic DNA that has been extracted from the archived blood spots, and will correlate the risk of cancer to each SNP using the cancer-free individuals as controls. We will investigate whether among cancer patients, the presence of certain SNPs correlates with survival. The specific aims of the study are to: 1) Develop and apply PCR arrays for genotyping SNPs in human genomic DNA; 1a) Design PCR arrays to detect SNPs encoded by cytokine genes; b) Define the extent and nature of CGPs in a

clinical population of patients with lung cancer and in cancer-free individuals; 2) Define the frequency of CGPs in patients with lung cancer and in healthy individuals; 3) Determine the effect of CGPs on lung cancer survival. This study was approved by the IRB on November 3, 2004.

Materials: Specimens and Data

6.36 Pilot Study Genetic Association Study of Diabetes Candidate Genes and Pancreatic Cancer in the CARET Cohort

Date: 3/25/2005
ID#: 121
PI Name: Megan Fesinmeyer
Organization: University of Washington
Submitted: Submitted under IR File 6000 & 4239a
Specific Aims: This proposal will investigate associations of single nucleotide polymorphisms (SNPs) and haplotypes in six diabetes candidate genes with risk for pancreatic cancer. DNA extraction from all samples will be completed in Year 1, using banked blood samples for all participants. Genotyping will be performed at the Functional Genomics Laboratory at the University of Washington with strict quality control procedures. Samples will be genotyped for half of the SNPs in Year 1, and the remaining SNPs will be genotyped in Year 2. Also in Year 2, haplotypes will be constructed using recently developed software, and both univariate and multivariate statistical approaches will be used to assess the genetic associations. The results of these analyses will not be disclosed to participants, because the genetic tests to be performed are not clinically relevant. This study was approved by the IRB on March 25, 2005.
Materials: Specimens and Data

6.37 Molecular Epidemiology of Lung Cancer

Date: 09/11/2006
ID#: 132
PI Name: Chu Chen
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 6258 & 4239a
Specific Aims: In a nested case-control study, this proposal is to determine whether polymorphisms of enzymes involved in the repair of smoking-induced DNA damage, namely those from the base excision (BER) and nucleotide excision repair (NER) pathways, are associated with risk of lung cancer. Genotyping of the functional single nucleotide polymorphisms (SNPs) as well as haplotype-tagging SNPs of 26 DNA repair genes, a total of 236 polymorphisms, that have been resequenced by the Seattle Variation Discovery Resource for the Environmental Genome Project. The lung cancer cases (N = 900) and controls (n = 1800) for this study will come from the CARET specimen repository. Genotyping of cases and controls will utilize DNA obtained from leukocytes extracted from frozen whole blood samples. Detailed quantitative information on smoking and dietary history (using a food frequency questionnaire), obtained prior to the diagnosis of lung cancer, is available through CARET records. Cases and controls will be compared with respect to the prevalence of putative "high risk" genotypes, alone and in combination with other putative "high risk" genotypes within each pathway and in the two pathways combined. Results will be interpreted with multiple comparisons taken into account. The proposed study has sufficient statistical power to identify interactions between some of the high-risk genotypes, and to investigate whether the risk associated with a particular genotype varies by other risk factors, such as intake of antioxidant-rich fruits (e.g. Rosaceae fruits) and vegetables (e.g. Cruciferae vegetables), and food-derived nutrients, such as alpha-carotene, beta-carotene, lycopene, and tocopherols.

The methodologies that will be used for the polymorphisms analyses will involve primarily Illumina 384-SNP platform. For the 62 SNPs tht are not compatible with the Illumina platform, we will assay them by assayed by TaqMan, SNaPshot and/or RFLP. For qualitry control purposes, we separate our pre-PCR and post-PCR work in separate rooms, we use

aerosol-barrier filter tips and disposable plastic ware or dedicated glassware for making reagents and assembling reactions. Samples with known genotypes and a negative control will be included in each batch of PCR samples.
IRB approval was given in May 2009 for additional collection of information on tumor characteristics, first course of treatment, and clinical outcomes for all lung cancer cases by conducting record linkages with the Washington, Oregon, and California state cancer registries and to obtain additional information on clinical outcomes, including vital status as acquired from the Social Security Death Index (SSDI) and treatment, from CARET. All searches of registries and SSDI will be conducted by CARET staff only, as is referenced in Section 10.2.2 Passive Follow Up, which demonstrates IRB approval for NDI and registry searches by CARET.
IRB approval was given in March 2010 for this group to do a pilot study using 30 de-identified DNA samples from CARET. The goal being to develop assays to determine global telomere length, and chromosome-specific telomere length, to provide pilot data for this group's RO1 grant application.

Materials: Specimens and Data

6.38 Integrated Biomarker Profiles for Lung Cancer and COPD

Date: 2/20/2007
ID#: 133
PI Name: David Au
Organization: University of Washington
Submitted: Submitted under IR File 4239a
Specific Aims: 1) Determine whether integrating circulating biomarkers discriminate between high-risk individuals who will not develop lung cancer. 2) Determine whether integrating biomarkers of the host response to cigarette smoke discriminate between CARET participants with and without COPD and whether the integrated biomarker predicts reapid rate of airflow decline.. CARET will supply specimen samples for this study.
Materials: Specimens and Data

6.39 Evaluation of soluble MICA as a biomarker for lung cancer

Date: 2/21/2008
ID#: 150
PI Name: Jason Chien
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a
Specific Aims: Determine whether soluble MICA can be detected in CARET serum samples.
Materials: Specimens and Data

6.40 Baseline Lung Cancer Model for Early Detection

Date: 2/22/2008
ID#: 65
PI Name: Bill Hazelton
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a
Specific Aims: To develop a baseline model for lung cancer to serve as a platform for evaluation of potential biomarkers for early detection and diagnosis. The model will be based on detailed histories of smoking and asbestos exposures, with or without Computerized Tomography (CT) screening.
Materials: Data

6.41 Soluble Mesothelin Related Peptide (SMRP) and Osteopontin (OPN) as Early Detection Markers for Malignant Mesothelioma (MM)

Date: 11/20/2008
ID#: 56
PI Name: Harvey Pass
Organization: New York University Medical Center
Submitted: Submitted under IR File 4239a

Specific Aims: The investigator's hypothesis is that SMRP and OPN are specific and sensitive biomarkers for malignant mesothelioma (MM), and a rise in the level of either or both markers in a high risk asbestos exposed cohort of patients will occur prior to the development of clinically apparent mesothelioma. The specific aims are 1) Determine the sensitivity and specificity of SMRP and Osteopontin, alone and in combination, for the early detection of malignant mesothelioma by evaluating these markers in individuals diagnosed with MM and in matched individuals (age, sex, asbestos exposure, year of randomization, and tobacco consumption) who do not develop MM; 2) Determine whether SMRP and OPN levels measured from patients who subsequently developed MM on the CARET trial rise over time prior to the development of clinically apparent MM; 3) Validate the association of OPN with markers of asbestos exposure including duration of asbestos exposure and ILO score; and 4) If the results of specific aims 1-3 demonstrate that SMRP and/or osteopontin are sensitive and specific markers for MM in individuals at high risk for the disease, further explore the specificity of these markers by determining their distributions in other control groups: (a) non-asbestos exposed controls, (b) lung cancer cases, and (c) cases with other common malignancies (prostate and colorectal), all matched as in specific aim 1.

Materials: Specimens and Data

6.42 Genome-Wide Association Study of Fibrosing Insterstitial Lung Diseases

Date: 3/23/2011

ID#: 15

PI Name: David Schwartz

Organization: University of Colorado, Denver

Submitted: Submitted under IR File 4239a

Specific Aims: The purpose of this proposal is to discover genes and gene variants that are central to the development of fibrosing interstitial lung diseases (fILD). Since both gene variants and the environment increase the risk of disease development, we seek to comprehensively identify gene variants associated with fILD by considering environmental exposures while studying the genetics of this group of complex diseases. The fILD study populations (familial interstitial pneumonia (FIP), sporadic idiopathic interstitial pneumonia (IIP), and asbestosis) will enable us to discover genes that are associated with fILD while spanning a spectrum of genes that confer susceptibility to fILD and are increasingly likely to be influenced by environmental exposures. Evidence for a genetic basis of fLD is substantial. fILD has been associated with pleiotropic genetic disorders, and at least 3% of cases of IIP have a first degree relative with a similar illness. Rare mutations in genes that maintain telomere length (TERT and TERC) have been reported to be associated with the development of FIP (defined as ≥ 2 cases of IIP in one family) and idiopathic pulmonary fibrosis (IPF), the most common form of IIP. Two families with FIP have been shown to have disease-associated mutations in surfactant protein C. We have performed a linkage study in 82 families with FIP, and have identified linked regions on chromosomes 10, 11, and 12. Furthermore, we have found common variants in *MUC5AC* (chr11 positional candidate) that are associated with both FIP and IPF. Approximately 40% of families with FIP have discordant types of IIP among family members, suggesting that IIP may be caused by common gene variants that are altered phenotypically by environmental exposures. In fact, FIP and IPF can be influenced by environmental exposures, occurring more frequently in males (occupational exposures) and cigarette smokers. IPF is also associated with exposure to metal or wood dust. Occupational exposure to asbestos can cause fILD that is indistinguishable from the histology of IPF (usual interstitial pneumonia, UIP). We have found that among patients with FIP, the chr11 LOD score is strongly influenced by cigarette smoking. Thus, we hypothesize that fILDs are caused by multiple genes, acting independently or in combination with environmental exposures and that the same gene variants can lead to different forms of fILD. We plan to identify the genetic causes of fILDs by determining the genetic variants associated with familial and sporadic IIP and asbestosis. This approach will identify genes that are common to lung fibrosis, and genes that are more unique to asbestos exposure and/or cigarette smoke.

2011 VA Merit Award addendum to study additional SNP MUC5B: The proposal focuses on genetic and epigenetic variants of MUC5B, cigarette smoke, and several types of fibrosing interstitial lung disease (fiLD) to determine why only some individuals with the MUC5B promoter polymorphism develop pulmonary fibrosis.

Materials: Specimens and Data

6.43 Evaluation of Pro-Gastrin Releasing Peptide (Pro-GRP) in Small Cell Lung Cancer

Date: 6/25/2009
ID#: 157
PI Name: Barry Dowell
Organization: Abbott
Submitted: Submitted under IR File 4239a
Specific Aims: Determine whether pro-GRP is elevated prior to the clinical detection of small cell lung cancer using a case-control study design, and compare serum versus plasma results in a small subset of samples.
Materials: Specimens and Data (MTA completed)

6.44 Validating a lung carcinogenesis model as a predictor of lung cancer mortality against the CARET data

Date: 7/15/2009
ID#: 156
PI Name: Olga Gorlova
Organization: University of Texas, MD Anderson Cancer Center
Submitted: Submitted under IR File 4239a
Specific Aims: Use the CARET data on smoking histories and lung cancer death outcomes to validate a model of lung carcinogenesis as a tool for predicting lung cancer mortality.
Materials: Data

6.45 Detecting early stage lung cancer with antibodies

Date: 8/12/2009
ID#: 149
PI Name: Bernard Bihain
Organization: Genclis, France
Submitted: Submitted under IR File 4239a
Specific Aims: To validate in pilot study the feasibility of detecting changes in antibodies directed against bioinformatically predicted aberrant peptides in samples from patients of CARET study diagnosed with lung cancer versus controls without cancer after five year follow-up. To next determine the timing of test positivity prior to lung cancer diagnosis in order to obtain a biochemical test enabling physician to monitor the course of lung cancer appearance; to verify the prognostic value of a combination of antibodies analyzed through support vector machine using 2 groups of patients diagnosed with early stage lung cancer the first group will include patients with good clinical outcome the second patients with poor clinical outcome occurring in spite of early stage diagnosis and surgical treatment; to expand this method of cancer detection to the 4 most common forms of cancer by conducting in parrallel breast, lung, colon and prostate cancer. The goal being to establish or rule out the presence of cancer, then define location and predict severity.
Materials: Specimens and Data (MTA completed)

6.46 NSAID and aspirin use in relation to risk of lung cancer: Evidence from the International Lung Cancer Consortium

Date: 9/10/2009
ID#: 148
PI Name: Valerie McCormack
Organization: International Agency on Research for Cancer (IARC)
Submitted: Submitted under IR File 4239a
Specific Aims: To investigate whether use of non-steroidal anti-imflammatory drugs (NSAIDs) and in particular aspirin is related to subsequent risk of lung cancer.
Materials: Data

6.47 Colorectal Cancer Genome-Wide Association Studies Consortium

Date: 12/3/2009
ID#: 64
PI Name: Ulrike Peters
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a
Specific Aims: 1) To identify genetic regions that are unequivocally associated with risk of CRC by:
a. Conducting a combined meta-analysis of all five CRC GWAS (total 5,914 cases and 6,763 controls) and
b. Genotyping 7,600 SNPs, selected based on the meta-analysis, in a large-scale replication study from eleven well-characterized study populations (9,192 CRC cases and 12,148 controls)

2) To aid the identification of the underlying causal variants within novel CRC susceptibility genetic regions by:
a. Sequencing 96 CRC cases and
b. Subsequent genotyping newly identified variants in the entire replication study.

3) To investigate whether associations with genetic variants are modified by established risk factors for CRC, including age, sex, obesity, physical activity, non-steroidal anti-inflammatory drugs (NSAIDs), postmenopausal hormone use, folate, calcium, red meat, alcohol, and smoking (gene-environment interactions).
Materials: Specimens and Data

6.48 Nucleotide Excision Repair Gene Variation and Lung Cancer Prognosis

Date: 1/19/2010
ID#: 57
PI Name: Lori Sakoda
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a as a subproject of 6258
Specific Aims: The proposed study seeks to clarify the relationship between genetic variation in the nucleotide excision repair (NER) pathway and the prognosis of individuals diagnosed with incident non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). It is hypothesized that the overall survival of lung cancer patients is related to their intrinsic capacity to perform NER, the primary DNA repair mechanism involved in the recognition and removal of bulky DNA adducts. Since platinum-based chemotherapy, which principally exerts cytotoxicity by platinum-DNA adduct formation, is commonly administered as first-line treatment for SCLC and advanced stage NSCLC, intrinsic NER capacity is further hypothesized to affect the overall survival of these patients, specifically by modulating their initial response to chemotherapy. The primary and secondary study aims, respectively, are:
1). To determine whether tag and putative functional single nucleotide polymorphisms (SNPs) of the NER pathway genes XPA, XPC, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLE, and LIG1 influence overall survival after SCLC and/or NSCLC diagnosis, and
2). To determine whether these SNPs influence overall survival in SCLC and/or stage IIIB/IV NSCLC patients initially treated with platinum-based chemotherapy
Materials: Specimens and Data

6.49 Serum Test for Preclinical detection of Ovarian Cancer

Date: 1/19/2010
ID#: 20
PI Name: Anna Lokshin
Organization: University of Pittsburgh
Submitted: Submitted under IR File 4239a
Specific Aims: Currently, serum markers for ovarian cancer, e.g. CA-125 and HE4, have been used primarily for disease monitoring following diagnosis to assist in determining treatment response and identifying disease recurrence. While CA 125 and HE4 levels faithfully track changes in tumor burden, the limited efficacy of treatment for persistent or recurrent disease has limited their utility. CA125, HE4 and other biomarkers may offer greater promise for the

early detection of ovarian cancer. We have identified 4-biomarker panel in serum with SN=86% for stages I-IIB ovarian cancer (SN=75% for stage IA) at SP=98%, as well as several alternative panels with similar performance. However, this algorithm used to identify these panels was based on measurements made in sera collected at or around the time of diagnosis, and was less robust when applied to samples collected 6-24 months prior to diagnosis. Our preliminary data identified 27 candidate biomarkers with levels significantly different in women whose blood samples were collected 6-12 months prior to diagnosis with ovarian cancer. We *hypothesize* that to develop an effective screening algorithm for identification of preclinical (pre-diagnostic) ovarian cancer, algorithm training should be performed on samples collected prior to diagnosis. Our primary *objectives* are to develop and validate reliable and highly sensitive multimarker assays for early (preclinical) detection and diagnosis of ovarian cancer.

Materials: Specimens and Data

6.50 Genome-Wide Association Study for Pancreatic Cancer (PanScan 3)

Date: 6/1/2010
ID#: 18
PI Name: Rachael Stolzenberg-Solomon
Organization: National Cancer Institute
Submitted: Submitted under IR File 4239a
Specific Aims: 1) To conduct a GWAS study of pancreatic cancer by genotyping approximately 1,600 recently identified incident pancreatic cancer cases and *controls with previous GWAS data drawn from cohort studies of the NCI cohort consortium*.

a. Using a joint analysis of these and PanScan 1 and 2 data, we will identify novel regions of the genome associated with pancreatic cancer susceptibility. As needed, we will participate with the Pancreatic Cancer Case-Control Consortium (PanC4) for replication of findings

2) The genotype results and executive summaries of individual SNP analyses will be made available to bonafide researchers through a restricted-access website within several months of completion and following assessment of quality control.

Materials: Specimens and Data

6.51 Effect of CARET Intervention on Pro-Gastrin Releasing Peptide in Small Cell Lung Cancer

Date: 7/1/2010
ID#: 146
PI Name: Barry Dowell
Organization: Abbott
Submitted: Submitted under IR File 4239a
Specific Aims: Pro- gastrin releasing peptide (Pro-GRP) has been proposed as an early detection marker in small cell lung cancer (SCLC). In conjunction with investigators at Abbott, CARET has conducted a pilot study measuring plasma ProGRP in 10 patients and matched controls with SCLC. The study found some patients with SCLC had elevated plasma concentrations of ProGRP prior to diagnosis but also that CARET participants randomized to the active intervention (cancer free controls) had high levels of ProGRP. This raises the hypothesis that the CARET intervention (beta carotene and retinol) increases the plasma concentration of ProGRP. This proposal expands that small trial and will study 55 cancer-free participants on the placebo group and 55 participants on the active intervention to determine if beta carotene and retinol supplementation increases plasma concentrations of ProGRP.

Materials: Specimens and Data (MTA completed)

6.52 MicroRNA and Lung Cancer

Date: 11/2/2010
ID#: 41
PI Name: Chu Chen
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a

Specific Aims: In a case-control study of lung cancer nested in the Carotene and Retinol Efficacy Trial (CARET) population, with 793 cases and 1586 controls, all of whom are smokers, we propose to address the following primary aims:
1) To examine whether polymorphisms in known miRNA genes are associated with lung cancer risk;
2) To examine whether tag and putatively functional SNPs in miRNA biogenesis genes are associated with lung cancer risk;
3) To examine whether SNPs in miRNA target sites of (a) known genes in identified lung cancer susceptibility loci and (b) selected genes involved in DNA repair and other processes relevant to carcinogenesis are associated with lung cancer risk; and
4) To examine whether the genetic polymorphisms under investigation are also associated with survival after lung cancer diagnosis.
Secondarily, we will examine whether any observed associations vary by age, extent of smoking history, and tumor histology. Also, since the minor allele frequencies for a large number of SNPs residing in miRNA genes is currently undocumented in the public SNP database (dbSNP) curated by the National Center for Biotechnology Information, we will be able to contribute this information for SNPs genotyped to the scientific community.
Materials: Specimens and Data

6.53 Blood-Based Biomarkers for Lung Cancer: Early Detection and Evaluation of CT-based Lesions

Date: 12/9/2010
ID#: 27
PI Name: Samir Hanash
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 5880 & 4239a
Specific Aims: The DOD has awarded funding to discover serum markers for the early diagnosis of lung cancer. The proposal is to critically evaluate through blinded validation studies candidate markers from genomic (mutation analysis, DNA methylation and microRNAs), proteomic (circulating proteins and autoantibodies) and metabolomic (altered glycans, metabolites and volatile organic compounds) studies that show promise for yielding blood-based tests for lung cancer. Two specific blood biomarker application goals to be addressed:
1) Development of a marker panel for evaluation of lesions identified by chest CT scans.
2) Development of a marker panel to determine need for CT scan among subjects at risk for lung cancer to detect lung cancer before it is so advanced that treatment is ineffective.
Materials: Specimens and Data

6.54 Replication genotyping for selected SNPs in relation to serum beta-carotene, retinol, and alpha-tocopherol and lung cancer risk

Date: 3/23/2011
ID#: 53
PI Name: Albanes Demetrius
Organization: National Cancer Institute
Submitted: Submitted under IR File 4239a
Specific Aims: 1) to replicate an association between candidate SNPs and follow-up serum concentrations of beta-carotene, retinol,and alpha-tocopheral by CARET intervention arm, and 2) To replicate an association between candidate SNPs and lung cancer risk by CARET intervention arm.
Materials: Specimens and Data

6.55 Biomarkers for Early Detection of Mesothelioma

Date: 8/10/2011
ID#: 22
PI Name: Michele Carbone
Organization: University of Hawaii Cancer Center
Submitted: Submitted under IR File 4239a

Specific Aims: In a case-control study of lung cancer nested in the Carotene and Retinol Efficacy Trial (CARET) population, with 793 cases and 1586 controls, all of whom are smokers, we propose to address the following primary aims:
1) Evaluate HMGB1 as a diagnostic marker to distinguish MM from lung cancer.
2) Evaluate HMGB1 as a biomarker of mineral fiber exposure and a possible marker of MM
3) Determine whether different fiber types, such as crocidolite, chrysotile and tremolite asbestos, and erionite, elicit similar increases of HMGB1 in the serum
4) Determine whether treatment with aspirin modulates HMGB1 in the sera of an asbestos-exposed cohort in a prospective, double blind, double crossover study.

Materials: Specimens and Data

6.56 Telomeres and Lung Cancer Survival

Date: 8/10/2011
ID#: 11
PI Name: Jen Doherty
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 7538 & 4239a

Specific Aims: 1) To examine whether global telomere length, measured in blood samples collected prior to lung cancer diagnosis, is associated with an increased risk of lung cancer;
2) To examine whether telomere length of specific chromosome arms, measured in blood samples collected prior to lung cancer diagnosis, is associated with an increased risk of lung cancer;
3) To examine whether approximately 5,400 tag and putative functional SNPs in telomere maintenance-related genes (*TERT, TERC, DKC1, NOLA1, NOLA2, NOLA3, TERF1, TERF2, TINF2, TERF2IP, ACD, POT1, TEP1, DCLRE1B, PINX1, TNKS, BICD1* and *PIKC3C)* identified using data from the 1,000 Genomes Project, are associated with lung cancer risk; and
4) To examine whether blood telomere length (both global and chromosome arm-specific), and variation in telomere maintenance genes, are associated with survival among individuals who develop lung cancer.
Because participation in the TRICL project requires CARET data to be uploaded to dbGaP, these changes to IR File#7538 include a new Data Use Agreement for any investigators who wish to access CARET data in dbGAP.

Materials: Specimens and Data

6.57 Circulating 25-hydroxy vitamin D and risk of breast & colorectal cancer

Date: 9/21/2011
ID#: 12
PI Name: Stephanie Smith-Warner
Organization: Harvard University
Submitted: Submitted under IR File 4239a

Specific Aims: To examine the association between prospectively collected circulating 25-hydroxyvitamin D [25(OH)D] levels and risk of breast and colorectal cancer in a consortium of 15 cohort studies. We would like to include participants from CARET in both the breast cancer and colorectal cancer analyses. We decided to examine these cancer sites because they are among the top three most common cancers in men and women in the United States; their incidence rates vary multifold worldwide, supporting the possibility for environmental or dietary influences in their etiology; and epidemiologic and experimental data suggest that vitamin D is associated with reduced risk of these cancer sites [3]. We propose to pool the primary data from 15 prospective cohort studies (10 studies for breast cancer, 14 studies for colorectal cancer) to investigate the association between circulating 25(OH)D levels and risk of these cancer sites overall, by tumor subtype, and by population subgroups defined by personal characteristics, lifestyle factors, vitamin D receptor (VDR) polymorphisms, and other biomarkers. Together, these cohorts will have 25(OH)D levels measurements in over 5,000 colorectal cancer cases and over 6,800 breast cancer cases. These analyses should contribute substantially to characterizing the dose-response relationships of these

associations and will inform recommendations regarding sun exposure, vitamin D intake requirements, and design issues for any future randomized trials.
Addendum, February 27, 2013: The Harvard Pooling group has requested a limited dataset of blood draw dates on CARET participants. Given that this data is considered protected health information, we are submitting a HIPAA Waiver to allow for the release of this dataset.
A sub-study of the Pooling Project of Prospective Studies of diet and Cancer (Pooling Project), from section 10.70 of this protocol. The main focus of the Pooling Project is to evaluate associations between specific dietary factors and risk of incident of advanced prostate cancer, rectal cancer, estrogen receptor negative (ER-) breast cancer, and gliomas. CARET data will be provided to the consortium for these pooled analyses. No CARET participant identifiers will be given per HIPAA compliance.

Materials: Specimens and Data.

6.58 Vita D intake and lung cancer: a case-cohort study in the Carotene and Retinol Efficacy Trial

Date: 11/16/2011
ID#: 144
PI Name: David Cheng
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 7602 & 4239a
Specific Aims: This study is to test whether high vs. low total vitamin intakes are associated with reduced lung cancer incidence and mortality in the Carotene and Retinol Efficacy Trial (CARET). The objectives of this activity are 1) extract the supplement brand names or individual supplements on the CARET baseline questionnaire; 2) identify the dose of vitamin D in the supplements.
Materials: Data and review charts

6.59 Fibulin-3 and early detection & diagnosis of mesothelioma

Date: 2/15/2012
ID#: 26
PI Name: Harvey Pass
Organization: New York University Medical Center
Submitted: Submitted under IR File 4239a
Specific Aims: FIBULIN-3 is a specific and sensitive biomarker for malignant mesothelioma (MM) and a rise in the level of the marker in a high risk asbestos exposed cohort of patients will occur prior to the development of clinically apparent mesothelioma.
1) Determine the sensitivity and specificity of FIBULIN-3 for the early detection of MM by evaluating these markers in individuals diagnosed with MM and in matched individuals (age, sex, asbestos exposure, year of randomization, and tobacco comsumption) who do not develop MM;
2) Determine whether FIBULIN-3 levels measured from patients who subsequently developed MM on the CARET trial rise over time prior to the development of clinically apparent MM; and
3) Satisfy the reviewers of the NEJM so that the FIBULIN-3 study can be published
Materials: Specimens and Data

6.60 Detection of Epithelial Ovarian Cancer in the CARET Study using ^{1}H-NMR Metabonomics

Date: 3/14/2012
ID#: 23
PI Name: Kunle Odunsi
Organization: Roswell Park Cancer Institute
Submitted: Submitted under IR 4239a
Specific Aims: To validate 1H-NMR based on metabonomics for early detection utilizing samples from the Carotene and Retinol Efficacy Trial (CARET) study. The primary goal is to evaluate, as a function of time before clinical diagnosis, the capacity of metabonomics to detect preclinical disease. Specimens obtained within 3 years of the closet time point to diagnosis from ovarian cancer cases will be tested utilizing NMR metabonomics. For each case, two age-

matched controls will be included.

Materials: Specimens and Data

6.61 Identifying the role of BRM and BRM polymorphisms with the CARET Trial outcomes

Date: 7/24/2012

ID#: 17

PI Name: David Reisman

Organization: University of Florida

Submitted: Submitted under IR File 4239a

Specific Aims: 1) Determine if there is a greater frequency of BRM and/or BRG1 loss in tumors from the retinoid-treated patients compared with the placebo group. Perform immunohistochemical (IHC) staining to evaluate the BRM and BRG1 status of available tumor slides derived from lung cancers in this trial.

2) Determine if BRM polymorphisms are statistically enriched in retinoid-treated patients compared with placebo-control patients. Calculate odds ratios to determine if there is a statistically significant increase in the frequency of BRM polymorphisms in the cases. Explore whether there exists differences in the association between BRM polymorphisms and cancer risk in the retinoid-treated participants, as compared to the placebo-treated, both through subset analyses (by treatment arm), and in a treatment arm-polymorphism interaction analysis.

3) Determine whether there is a statistically significant association between HIS staining and BRM polymorphisms in this set of patients from the CARET trial; perform logistic regression.

Materials: Specimens and Data

6.62 Auto-antibodies to p53 for early ovarian cancer detection

Date: 12/18/2012

ID#: 19

PI Name: Nicole Urban

Organization: Fred Hutchinson Cancer Center

Submitted: Submitted under IR 4563 & 4239a

Specific Aims: To test the hypothesis that addition of the p53 autoantibody assay to CA125, HE4 and mesothelin will enhance the ability to detect ovarian cancer in its early, curable stage.

Materials: Specimens and Data

6.63 mRNA Biomarkers for Early Ovarian Cancer Detection

Date: 6/18/2013

ID#: 10

PI Name: Muneesh Tewari

Organization: Fred Hutchinson Cancer Center

Submitted: Submitted under IR 6757 & 4239a

Specific Aims: Assess performance of miR-135b as a single biomarker in pre-clinical samples from the Carotene and Retinol Efficacy Trial (CARET) repository. Secondary analyses will include sensitivity using the PEB longitudinal algorithm, sensitivity at other levels of specificity, contribution to a decision rule including CA125, HE4, and Mesothelin and evaluation of miR-135b in a risk algorithm.

Materials: Specimens and Data

6.64 Development and Validation of Lung Cancer Risk Prediction Models

Date: 7/18/2013

ID#: 167

PI Name: Martin Tammemagi

Organization: Brock University

Submitted: Submitted under IR File 4239a

Specific Aims: 1) In CARET data, externally validate existing lung cancer risk prediction models in their ability to predict incident lung cancers[2-10], and lung cancer mortality. Almost all of the currently published models have been designed to identify becoming a lung cancer case. But some recent discussion regarding selection criteria for screening has suggested identification of those who will die from lung cancer may also be relevant.

2) To validate the Tammemagi 2012 Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial model[9] into which asbestos and secondhand smoke have been synthetically added as predictors. And if found to be deficient use CARET data to improve the parameter estimates for asbestos and secondhand smoke in the Tammemagi 2012 model.
3) To develop and validate lung cancer risk prediction models for never-smokers.
4) To develop a sense of the prevalence and adjusted risk magnitudes associated with asbestos exposure, secondhand smoke exposure, and additional exposures, so that they can be employed and evaluated in risk prediction models.

Materials: Data

6.65 Epidemiologic Methods I

Date: 9/13/2013
ID#: 122
PI Name: Janet Rosenbaum
Organization: State University of New York (SUNY) Medical Center
Submitted: Submitted under IR 4239a
Specific Aims: Use the CARET dataset from the JNCI paper on CARET results, published in November of 1996. Dr. Rosenbaum will assign students in her course, "Epidemiologic Methods I" to analyze the CARET data in an attempt replicate the findings described in the CARET 1996 papers published in the NEJM and JNCI.
Materials: Data

6.66 OncoArray Genotyping of Studies of Five Cancer Types

Date: 11/12/2013
ID#: 138
PI Name: Chris Amos
Organization: Baylor College of Medicine (previously Dartmouth)
Submitted: Submitted under IR File 4239a
Specific Aims: To integrate ongoing genetic studies to identify cancer susceptibility factors for common cancers, to evaluate biological mechanisms by which these factors influence cancer development and to evaluate the effects of these factors in well characterized epidemiological studies.
1) Perform genotyping of 210,00 previously unstudied cancer cases along with 200,000 controls using a set of 400,000 markers. By querying a large number of individuals we will be able to to characterize more fully risk loci for each cancer site, define the effects of genetic factors in multiple ethnic groups and evaluate gene-environment effects.
2) Perform meta-analysis jointly evaluating risk to identify shared and cancer-specific risks for common cancer development
3) Perform detailed fine mapping of established loci from each cancer site to identify candidate functional and causative variants.
4) Perform integrative analyses that allow us to partition competing risk for common cancers, allowing for effects from genetic and environmental factors that are commonly measured across sites.
Amendment, May 31, 2014--Dataset Upload to dbGaP: The data generated by the OncoArray genotyping of CARET specimens is required to be uploaded to dbGaP. Dr. Christopher Amos (Dartmouth) leads the project and will upload the data to dbGaP as part of the larger GameOn project. Due to the wording of the CARET consents, restrictions are in place regarding any requests to access CARET data housed in dbGaP. Researchers requesting CARET data from dbGaP must complete a DUA to be signed by the CARET Repository gatekeeper, Dr. Gary Goodman.

Amendment, December 5, 2018—dbGaP data sharing: In an opinion letter dated July 23, 2014, the FRED HUTCHINSON CANCER CENTER IRO outlined restrictions relating to sharing by dbGaP of CARET genotype and phenotype data associated with the OncoArray and Axiom array analyses led by Dr. Christopher Amos. The letter made no distinction in restrictions between release of individual-level data and summary results. The NIH is

updating its data management procedures under the NIH Genomic Data Sharing (GDS) Policy,and has requested an updated Institutional Certification for the CARET data with specification of access permissions for genomic summary results (GSR).

For the purposes of the NIH GDS Policy, genomic summary results are defined to include those provided by a study's investigator, if any, as well as summary statistics that may be computed by the relevant NIH-designated data repository across all non-sensitive studies with data included in that repository. Genomic summary results include systematically computed statistics such as, but not limited to: 1) frequency information (e.g., genotype counts and frequencies, or allele counts and frequencies), and 2) association information (e.g., effect size estimates and standard errors, and p-values). These values may be defined and calculated using scientifically relevant subsets of research participants included within study populations (e.g., disease, trait-based, or control populations).

With this modification we are requesting the opinion letter be updated to allow for unrestricted access (data made publicly available to everyone) to CARET GSR data in dbGaP and to confine the restrictions found previously to the access of individual-level data.

Amendment, 02/20/2019—added Genomic Data Sharing Supplement submitted with modification #3 and updated letter of opinion from FRED HUTCHINSON CANCER CENTER IRB.

Amendment, 4/28/2021—FRED HUTCHINSON CANCER CENTER IRB provided an updated Opinion Letter on 4/5/2021 (administrative changes only) to remove references to Dartmouth as the institution is no longer affiliated with this project; the genomic studies are continuing at Baylor College of Medicine under Dr. Amos.

Materials: Specimens and Data

6.67 Infection with MCPyV, KIV, WUV, and HPV as potential risk factors for lung carcinogenesis

Date: 12/20/2013
ID#: 126
PI Name: David Colombara
Organization: University of Washington
Submitted: Submitted under IR File 4239a
Specific Aims: 1) To test whether individuals with evidence of prior MCPyV, KIV, and WUV infection are at increased risk for developing lung cancer, when compared to those without prior infection, as measured by antibody seropositivity; Sub-aim: To identify factors associated with serpositivity to MCPyV, KIV, and WUV.
2) To test whether individuals with evidence of HPV 6, 11, 16, 18, 31, 33, 52, and 58 infection are at increased risk for developing lung cancer, when compared to those without prior infection, as measured by antibody serpositivity.
Materials: Specimens and Data

6.68 Replicating Several Discovered SNPs that Interact with Smoking in Lung Cancer

Date: 5/9/2014
ID#: 137
PI Name: Lue-Ping Zhao
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR File 4239a
Specific Aims: 1) To develop an analytic strategy for eGEWIS analysis, when GWAS data are available for GEWIS analysis
2) To evaluate eGWIS design strategy and compare it with alternative designs
3) To apply eGEWIS strategy to one cancer etiology study and another one to pharmacogenetic study
Materials: Data

6.69 Leanness as a risk factor for lung cancer

Date: 1/8/2015
ID#: 175
PI Name: Isabelle Stucker
Organization: Inserm
Submitted: Submitted under IR File 4239a and ILCCO IR#10-0057-E
Specific Aims: The aim of the study is to examine the association between BMI and lung cancer risk based on cohort studies conducted among ILCCO participating centers. More specifically, the goals of the project are to:
1) Investigate in detail the association between BMI at different times of adulthood and the risk of lung cancer
2) Study the correlation between intensity/duration of smoking and BMI
3) Examine the role of weight changes during adulthood in the risk of lung cancer
4) Explore the statistical interaction between smoking status and BMI in the risk of lung cancer assessment.
Materials: Data

6.70 Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project)

Date: 10/03/2007
ID#: 131
PI Name: Stephanie Smith-Warner
Organization: Harvard
Submitted: Submitted under IR 4239a
Specific Aims: The Pooling Project is an international consortium of cohort studies. The main focus of the project is to evaluate associations between specific dietary factors and risk of incident of advanced prostate cancer, rectal cancer, estrogen receptor negative (ER-) breast cancer, and gliomas. CARET data will be provided to the consortium for these pooled analyses. No CARET participant identifiers will be given per HIPAA compliance.
Materials: Data

6.71 Investigation of REG1A, ALCAM, ICAM1, and TIMP1 as Biomarker Panel for Early Detection of Pancreatic Cancer

Date: 4/6/2009
ID#: 117
PI Name: Samir Hanash
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR 6007 & 4239a
Specific Aims: The objective of the proposal is to do a pilot study to test the potential utility of a panel of 4 proteins, REG1A, ALCAM, ICAM1, and TIMP1, as potential markers for early detection of pancreatic cancer.
In February 2011, the pilot study was amended to test the utility of an additional set of proteins as potential markers for pancreatic cancer titled: “Investigation of a set of proteins as biomarkers for early detection of pancreatic cancer”. The 10 new proteins are as follows: LRG1, HE4, Endostatin, TNFRSF1A, IGFBP4, Lysozoyme, A1BG, AREG, CHI3L1, DKK1, and MMP14.
Materials: Specimens and Data

6.72 International Lung Cancer Consortium (ILCCO) Family History Pooled Analysis

Date: 4/6/2009
ID#: 118
PI Name: Chu Chen
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR 6007 & 4239a
Specific Aims: To obtain from CARET information of family history of lung cancer and other cancers on the CARET lung cancer cases and controls who are included in the ancillary study entitled “Molecular Epidemiology of Lung Cancer” (PI: Chu Chen), and to contribute the data for pooled analyses by ILCCO Family History Working Group to address the following aims:

1) To estimate the contribution of family history to risk of developing lung cancer in various population groups, by age of the proband and in never smokers.
2) To estimate cumulative risk of cancer (lung and others) in family members of lung cancer, by age, race/ethnicity, and smoking status.
3) To participate in the phase II study of a whole genome association study to identify markers associated with lung cancer. The phase I study will involve the collaboration between GELC and ILCCO and will identify markers associated with lung cancer through whole genome association study of 400 strongly familial cases (with at least three affected family members) and 400 unrelated controls using an Illumina 650k single nucleotide polymorphisms. The Phase II study will genotype selected markers in 1200 lung cancer cases with a first degree family history of cancer and unrelated controls.

Materials: Data

6.73 International Lung Cancer Consortium (ILCCO) Whole Genome Association Study

Date: 4/6/2009
ID#: 119
PI Name: Chu Chen
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR 6007 & 4239a
Specific Aims: to contribute CARET DNA samples extracted from the whole blood aliquots from cases (n=793) and controls (n=1586) include in the ancillary study "Molecular Epidemiology of Lung Cancer" (PI: Chu Chen) and information on these participants for the whole genome association study of ILCCO to address the following aim:
1) To participate in the Phase II study to validate selected genetic polymorphic markers that will be identified by the initial 3-4 Phase I ILCCO whole genome association studies to be associated with the risk of developing lung cancer in various population groups.
2) To participate in the subsequent Phase I whole genome scan studies to identified candidate SNPs and genes that are associated with lung cancer risk.
September 2011 Addendum: a proposed ILCCO replication study titled "An investigation into asbestos exposure-gene interaction on lung cancer risk existing", will use existing GWAS data from this project combined with an additional dataset from CARET.

Materials: Specimens and Data

6.74 FRED HUTCHINSON CANCER CENTER PHS Virtual Biospecimen Repository

Date: 6/1/2010
ID#: 177
PI Name: Chris Li
Organization: Fred Hutchinson Cancer Center
Submitted: Submitted under IR 7241 & 4239a
Specific Aims: Collaboration. The PHS Strategic Plan identified the development of a PHS Virtual Biospecimen Repository (PHS-VBR) as a divisional priority that could ultimately be of broader benefit to the Center and the Consortium. The PHS Biospecimen Repository Committee was created to come up with a viable plan for facilitating the use of the rich PHS biospecimen collections. This work would be done in collaboration with the investigators who accrued the specimens with the goal being maximization of specimen value. The Comprehensive Center for the Advancement of Scientific Strategies (COMPASS), a program within the PHS Division, was charged with developing the PHS-VBR. CARET will be contributing to the PHS-VBR. CARET staff will store de-identified tables based on the PHS-VBR Common Data Elements on its server, granting access rights to COMPASS to only these de-identified tables. The PHS-VBR will consolidate the data from CARET and other contributing PHS study repositories into a website query system. Besides the query system, the PHS-VBR will include from each contributing repository study investigator and relevant staff contact information; study design; study status/current funding status; protocol abstracts; consents used to obtain samples; number of samples, sample type, location, and storage conditions; numbers and types of endpoints collected; types and methods of data collection; and numbers of participants enrolled. No CARET participant identifying data will

be available. Investigators who are interested in CARET specimen and CARET specimen associated data will need to contact CARET directly and go through the formal CARET review process (see Section 4).

Materials: Data

6.75 Transdisciplinary Research in Cancer of the Lung (TRICL), Risk modeling for lung cancer

Date: 2/18/2015
ID#: 160
PI Name: Chris Amos
Organization: Baylor College of Medicine (previously Dartmouth University)
Submitted: Submitted under IR File 8293
Specific Aims: 1) Generalizability of genetic association across populations: To compare allele frequencies and magnitude of disease risk for the pan-ethnic risk variants (N~50) selected in Area 1 of TRICL, as the result of the fine-mapping effort for characterization across the four ethnic/racial groups (Northern/Southern European, Asian, and African) and across regions (North America, Europe, Asia, and Australia
2) Epidemiologic architecture of genetic effects on lung cancer risk: To investigate heterogeneity of effects for the same ~50 lung cancer-associated variants by specific subject and disease characteristics.
3) Epidemiologic architecture of genetic effects on smoking behavior: To test the relationship between the same ~50 lung cancer-associated variants and detailed smoking behavior phenotype.
4) Lung cancer risk modeling and population attributable risk: To validate and calibrate existing lung cancer risk models using a nested case-control sample from population-based cohort studies; to assess and develop metrics to evaluate discriminatory power improvement for nested models that incorporate top genetic hits; to construct and validate multigenic risk models, that incorporate the effect of smoking and other environmental risk factors, as well as medical co-morbidities (COPD), using population-based cohort studies.
Amendment, 02/20/2019—added Genomic Data Sharing Supplement submitted with modification #3 and updated letter of opinion from FRED HUTCHINSON CANCER CENTER IRB.

Materials: Data

6.76 Pooled analysis of 25-hydroxy vit D & colorectal cancer survival (Harvard Pooling project)

Date: 2/18/2015
ID#: 36
PI Name: Veronica Fedirko
Organization: Emory University
Submitted: Submitted under IR File 8293
Specific Aims: 1) Investigate association between pre-diagnostic 25(OH)D levels and CRC-specific and overall mortality among CRC cases in the VDPP project. This will be accomplished by conducting traditional and competing risks survival analyses, with adaptations to accommodate the pooled study design;
2) Examine whether these associations are a) stronger for colon or rectal cancer, b) vary by sex, anatomical sub-site in the colon, tumor characteristics (*i.e*. stage and grade), time interval between blood collection and cancer diagnosis or common genetic variation in the *VDR* gene (*BsmI* and *FokI*; exploratory analyses in a sub-set of cohorts); and c) are modified by lifestyle/dietary factors (*i.e.,* body mass index, physical activity, dietary calcium intake, supplement use, and smoking habits).

Materials: Data

6.77 Serologic inflammatory markers and esophageal adenocarcinoma risk

Date: 6/17/2015
ID#: 171
PI Name: Michael Cook
Organization: National Cancer Institute

Submitted: Submitted under IR File 8293
Specific Aims: 1) To evaluate the association of pre-diagnostic circulating inflammation markers with incident esophageal adenocarcinoma, and
2) To evaluate body mass index and waist circumference as potential effect modifiers for the relationships of inflammation markers with incident esophageal adenocarcinoma
Materials: Data

6.78 Polymorphisms in bone turnover genes in lung cancer

Date: 8/12/2015
ID#: 186
PI Name: Angela Cox
Organization: University of Sheffield (ILCCO)
Submitted: Submitted under IR File 8293
Specific Aims: 1) Identify genetic variants in bone turnover genes associated with risk of developing bone metastases in lung cancer, and
2) Identify genetic variants in bone turnover genes associated with survival in lung cancer
Materials: Data

6.79 Biomarkers to improve lung cancer risk prediction and reduce false positive lung cancer screens

Date: 1/27/2016
ID#: 227
PI Name: Jennifer Doherty
Organization: Dartmouth
Submitted: Submitted under IR File 8293
Specific Aims: 1) Identify specific markers from genome-wide profiles of DNA methylation in leukocytes that are associated with subsequent lung cancer risk, and determine if those associations are mediated by differences in immune cell subtypes as well as epigenetic variation contributing to variable immune function; and
2) Examine whether removing the confounding effects of inter-individual differences in proportions of blood cell subtypes allows for a refined assessment of associations between global and chromosome arm-specific telomere length and subsequent lung cancer risk.
Materials: Specimens and data

6.80 Validating and update cancer risk models

Date: 2/2/2016
ID#: 164
PI Name: M. Dawn Teare
Organization: University of Sheffield (ILCCO)
Submitted: Submitted under IR File 8293
Specific Aims: 1) Identify and review all existing lung cancer risk models (LCRMS),
2) evaluate the performance of LCRMs when applied to populations similar and distinct to those developed for; and
3) formulate a robust and flexible means to assess lung cancer risk.
Materials: Data

6.81 Diabetes and Cancer Initiative: Investigating the diabetes-cancer relationship within the NCI Cohort Consortium

Date: 9/14/2016
ID#: 180
PI Name: Marc Gunter
Organization: IARC
Submitted: Submitted under IR File 8293
Specific Aims: 1) Quantifying the association of T2D with cancer risk at all major anatomic sites
2) Investigate the association of diabetes diagnosis with cancer survival; and
3) Explore the impact of diabetes treatments on cancer development and survival
Materials: Data

6.82 Alcohol use and risk of cancers with inconsistent prior evidence, with an emphasis in non-smokers

Date: 6/7/2017
ID#: 185
PI Name: Pietro Ferrari
Organization: IARC
Submitted: Submitted under IR File 8293
Specific Aims: 1) Conduct a pooled analysis of the role of alcohol use and risk of cancer for sites for which there is limited evidence,
2) Evaluate associations between alcohol use and cancers of prostate, pancreas, kidney, and UADT in non-smokers, and
3) Evaluate associations of lifetime alcohol use with risk of advanced/localized prostate, pancreatic, kidney, and thyroid cancer, and NHL.
Materials: Data

6.83 Biomarkers for early detection of pancreatic cancer

Date: 2/21/2018
ID#: 234
PI Name: Ru Chen
Organization: Baylor College of Medicine
Submitted: Submitted under IR File 8293
Specific Aims: Evaluation of proteomics biomarkers in detecting pancreatic cancer at asymptomatic or pre-cancer stages.
Addendum, February 12, 2020: The PI has moved from the UW to Baylor College; the samples CARET provided to the PI, currently housed at UW, will be transferred to Baylor College after gaining IRB approval and updating the MTA on file with the PI.
Addendum, November 12, 2020: The investigator obtained approval from CARET leadership to evaluate 10 additional proteomics biomarkers.
Materials: Specimens and data

6.84 Antibodies to HE4 and mesothelin predictive for future ovarian cancer

Date: May 10, 2018
ID#: 6
PI Name: Ingegerd Hellstrom
Organization: University of Washington
Submitted: Submitted under IR File 8293
Specific Aims: To investigate whether antibodies to two biomarkers, mesothelin and HE4, are related to the development of ovarian carcinoma (OvC) by being more frequently detected in sera from symptom-free women who later developed OvC cancer than in sera from women who did not.
Materials: Specimens and data

6.85 Evaluating associations between lung cancer risk variants and second primary lung cancer

Date: May 10 2018
ID#: 247
PI Name: Summer Han
Organization: Stanford
Submitted: Submitted under IR File 8293
Specific Aims: To identify the genetic, environmental, clinical, and demographic risk factors for SPLC and to develop a risk prediction model for SPLC.
Amendment, 02/20/2019--The PI will receive extracted DNA from CARET on ~487 lung cancer cases, to perform genome-wide genotyping. Data generated from these analyses will be uploaded to dbGaP by the PI, NCI, Dartmouth (PI Olga Gorlova), or Baylor College of Medicine (PI Chris Amos), covered by the Opinion Letter from the FRED HUTCHINSON CANCER CENTER IRB regarding guidelines for depositing to dbGaP.
Amendment, 4/28/2021—the Fred Hutch IRO issued an updated Opinion Letter on 4/5/2021 to remove Dartmouth College since the institution is no longer affiliated with this

project.
Materials: Specimens and Data

6.86 Metabolomics, bacterial translocation and risk of liver cancer: a proposed study within the LCPP and other US based cohorts

Date: May 10, 2018
ID#: 323
PI Name: Kathryn McGlynn
Organization: NCI
Submitted: Submitted under IR File 8293
Specific Aims: To examine the relationships between the metabolome, biomarkers of bacterial translocation pathways, and liver cancer risk
Materials: Specimens and Data

6.87 Antibodies to the HE4 protein and development of lung adenocarcinoma

Date: September 5, 2019
ID#: 350
PI Name: Erik Karl and Ingegerd Hellstrom
Organization: University of Washington
Submitted: Submitted under IR File 8673
Specific Aims: To test whether healthy subjects who have antibodies to the HE4 antigen have increased risk to develop lung adenocarcinoma. Addendum 3/03/2020—the Hellstrom analytic lab at the University of Washington is covering the cost of this pilot study via funding they have received from an industry sponsor, Fujirebio. CARET will be compensated by the Hellstrom Lab for efforts to identify, retrieve and ship specimen to the Hellstrom Lab and to prepare demographic and clinical data files for analytic purposes.
Materials: Specimens and data

6.88 Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL)/CIDR Genotyping Project

Date: April 28, 2021
ID#: 349
PI Name: Chris Amos
Organization: Baylor College of Medicine, INTEGRAL
Submitted: Submitted under IR File 8673
Specific Aims: 1. From within the ILLCO consortium, assemble and genotype on bead arrays of an additional 23,103 lung cancer cases and 23,103 unrelated controls not previously studied by genomic wide association studies, including studies originating from South America, Asia, Europe and North America. These generated data will be shared on dgGaP. These samples will be genotyped in collaboration with CIDR;
2. Undertake a joint analysis of close to 54,000 cases and 76,000 controls by combining this new data with existing lung cancer GWAS of 29,683 cases and 55,586 controls. From these analyses we will a) identify novel genetic variants, and consider how these susceptibility loci differ across multiple geographical and ethnic groups, b) validate top SNPs technically, particularly focusing on samples for which tumor sequencing has been completed;
3. Refine lung cancer risk prediction algorithms by incorporating the new genetic findings. Drawing upon our statistical core in our INTEGRAL project, we will explore novel statistical approaches in order to select the most informative SNPs for incorporation into our PRS.

Regarding data being uploaded to dbGaP, the Fred Hutch IRO issued an updated Opinion Letter on 4/5/2021 in reference to this study.
Materials: Specimens and data

6.89 Overall and Subtype-Specific Breast Cancer Risk Predictions for Stratified Prevention (BCRP)

Date: March 9, 2022
ID#: 351
PI Name: Nilanjan Chatterjee

Organization: Johns Hopkins
Submitted: Submitted under IR File 8673
Specific Aims: 1. Develop a comprehensive and multi-ethnic model for estimating absolute risk of breast cancer by incorporating information on family-history, polygenic risk-score (PRS), anthropometric, life-style and reproductive factors, hormonal biomarkers and mammographic density;
2. Extend multi-ethic model for breast cancer risk prediction to account for tumor heterogeneity;
3. Evaluate the validity of the risk assessment tool in integrated health care systems, mammography registries, and an ongoing risk-based mammographic screening trial in the US.
Amendment, 05/16/2024: This section was prematurely submitted to the IRB with incomplete updates in our November 2023 submission, now corrected. This study has moved institutions and has a new PI.

Materials: Data

6.90 Environmental Factors, GxE Interactions, and Bladder Cancer Risk

Date: March 9, 2022
ID#: 342
PI Name: Roger Milne
Organization: Cancer Council Victoria
Submitted: Submitted under IR File 8673
Specific Aims: 1. Assess associations for smoking habits, aspirin/NSAID use, body size, reproductive and hormonal risk factors, alcohol, coffee, tea and other beverage consumption, personal history of diabetes, and dietary factors;
2.Assess the above associations, plus physical activity, by sex, smoking status, and disease subtype;
3.Assess GxE interactions for the above factrs using GWAS data;
4. Develop a risk prediction model integrating information on lifestyle and genetic risk factors.

Materials: Data

6.91 Improving Precision Prevention of Colorectal Cancer by Accounting for Familial Risk

Date: March 9, 2022
ID#: 414
PI Name: Jeanine Genkinger
Organization: Columbia University
Submitted: Submitted under IR File 8673
Specific Aims: 1. To examine whether associations between intake of alcohol, processed meat, red meat, dietary fiber, whole grains, and dairy products and colorectal cancer risk are modified by underlying familial risk profile;
2. To examine whether associations between BMI, waist circumference, A Body Shape Index (ABSI), physical activity and colorectal cancer risk are modified by underlying familial risk profile.

Materials: Data

6.92 The Lung Early Proteins project: A LEAP toward implementing biomarkers in lung cancer screening (LEAP)

Date: November 15, 2022—see addendum below
ID#: 364
PI Name: Hilary Robbins
Organization: International Agency for Research on Cancer (IARC)

Submitted: Submitted under IR File 8673
Specific Aims: Determine whether repeated measurements of protein markers over time can better predict development of lung cancer than a single measurement.
Addendum, December 30, 2023: update to this section to include the correct study information and remove incorrect information submitted in the November 15, 2022 submission.

Materials: Specimens and Data

6.93 The Lung Cancer Cohort Consortium (LC3)/ Evaluating risk prediction models for use in lung cancer screening across diverse populations around the world.

Date: July 19, 2023
ID#: 0E, 445
PI Name: Hilary Robbins
Organization: International Agency for Research on Cancer (IARC)
Submitted: Submitted under IR File 8673
Specific Aims: This project will establish an external data repository to which CARET will supply cohort data. CARET efforts will be supported with funds from Dr. Robbins LEAP project, (section 6.92 above). The mission of the LC3 is to facilitate and carry out collaborative research on lung cancer risk and aetiology. The LC3 is committed to facilitating the use of LC3 data by the wider research community for research within its scientific mandate, including:
1) Research on the aetiology of lung cancer incidence and survival;
2) Research on lung cancer risk assessment, early detection, and screening; and
3) Research on tobacco exposure and tobacco-related health outcomes.
Amendment, 04/16/2024: updating entry to include the foundational study associated with the establishment of the LC3 repository. This study, ID#445, has the objective to determine whether established lung cancer risk models can be validly applied in diverse populations worldwide, and to develop new tools for emerging settings in lung CT screening.

Materials: Data

7 CARET Public Website

The CARET public website provides a mechanism for the scientific community to query the CARET database to learn the availability of CARET specimens and the associated de-identified demographics, risk factors, endpoints, and survival. The web-accessible repository allows investigators to determine if a proposed hypothesis can be adequately addressed using CARET specimen. The website provides instructions on how to apply for the CARET specimen. Screen shots of the website and search components are demonstrated in Appendix 7.

7.1 Confidentiality safeguards

All participant identifying information will be de-identified. No participant identifying information are available to the community. Only basic demographics, age or year of event (e.g. blood draw, cancer diagnosis, death), type of cancer, and cause of death is available on the website.

7.2 Encryption of data over the public internet

Data will be shared most commonly through the transmission of an electronic file containing the approved study data. Data will be sent via secure FTP (sFTP) to specific individuals approved to receive such data. Data files will not be sent as e-mail or e-mail attachments. The sFTP servers used will be hosted and managed by FRED HUTCHINSON CANCER CENTER or the collaborating institution, and will require a unique user id and password to send and receive the data. CARET will monitor the evolving technology and adapt its method of data transmission as needed to remain abreast with current IT security best practice.

7.3 Information for Participants

The public website includes the following statement for participants: “The CARET Repository has been a valuable resource for the continuation of cancer research. To enhance our database, in 2015 we obtained cancer and mortality data from national death indices and the state cancer registries of Washington, California, and Connecticut. We remain committed to maintaining our participants’ confidentiality, and all new data received are secured in the CARET central database. Any data shared with investigators for research will have all identifiers removed to maintain confidentiality. Should you wish to learn more about this, please click to contact CARET staff.”

8 Appendix 1- CARET Project Application

1. **Project Title:** _____
2. **Date:** _____
3. **Principal Investigator:** _____
   Current Position: _____
   Academic Department: _____
   Telephone: _____ Fax: _____
   Street Address: _____
   City, State, Zip: _____
   E-mail Address: _____
4. **Other Involved Investigators and Contact Information:** _____
   _____
   _____
5. **Funding plan/source(s):** _____
   _____
   _____
6. **Project Description:**
   Attach a brief description (7 page maximum, 11 font; not including budget and cited literature) that addresses specific aims, background and significance, preliminary results (if available), and experimental methods and design. The design and methods section should describe the study population (e.g., inclusion/exclusion criteria, case-control matching criteria), data and specimens being requested, laboratory methods, and statistical analyses and power calculations, as appropriate. When requesting specimens please specify the types of sample needed for analyses (serum, plasma, whole blood, processed dna); volume of specimen needed for proposed assays; the maximum allowable number of freeze-thaw cycles undergone by the sample; and timing of the blood draw with respect to CARET intervention (baseline/pre-intervention vs post-baseline) and diagnosis of cancer (specify years prior to diagnosis, etc.).
7. **Type of project proposed (check all that apply):**
   - ☐ Mechanism of CARET's Intervention Effect
   - ☐ Early Detection of Disease
   - ☐ Risk Factors for Disease
   - ☐ Prognostic Factors
   - ☐ Pooled-data Analysis
   - ☐ Other (specify): _____

8. If access to CARET data will be requested from an existing data repository, please specify the repository/gatekeeper:

- ☐ Harvard Pooling Project (S. Smith-Warner)
- ☐ IARC (P. Brennan)
- ☐ ILCCO (R. Hung)
- ☐ TRICL (C. Amos)
- ☐ LC3 (H. Robbins)
- ☐ dbGaP
- ☐ Other (specify): _____
- ☐ N/A (data are requested directly from CARET data repository only)

9. Estimated study sample size required: Cases_____ Controls_____

9a. Case Type: _____

9b. Brief description of study inclusion/exclusion criteria:

Cases: _____

_____

Controls: _____

_____

10. Required data (attach list separately if preferred)

10a. Outcome data: _____

_____

10b. Covariates: _____

_____

11. Intervention arm / population to be studied (check all that apply):

- ☐ Placebo participants
- ☐ Active intervention participants
- ☐ Current smokers
- ☐ Ex-smokers
- ☐ Asbestos workers
- ☐ Other (specify): _____

If CARET specimens are to be requested for this project please complete items 12-16 on the next page. If only data are requested, skip to item 17.

Sample Blinding Policy:

All laboratory analyses will be conducted in blinded fashion with respect to case-control status. CARET will maintain the blind until all laboratory assay data have been delivered to CARET and all samples exhausted or returned. Any exception to the blinding policy will require approval of the CARET Scientific Committee.

12. Analytes: _____

_____

_____

13. Sample type requested (check all that apply), and amount of specimen requested for proposed assay(s):

	Amount	**Can samples be previously thawed*?**		
		No	Yes	If "yes," maximum # of thaws*
Serum	µL	☐	☐	
Plasma	µL	☐	☐	
DNA (from peripheral blood)	µg	☐	☐	
Tissue		N/A (FFPE blocks and slides)		

*Blood samples aliquots for approved studies are created at a FRED HUTCHINSON CANCER CENTER laboratory, undergoing a single freeze-thaw cycle. Samples that have been accessed for previous studies will have undergone one or more prior freeze-thaws. Please specify the total number of freeze-thaw cycles that are acceptable.

14. Timing of blood draw (CARET samples are all pre-diagnosis; no post-diagnosis samples available)

Check all that apply:	baseline / pre-intervention	post-baseline	prior to, but close to time of diagnosis	serial samples
Serum	☐	☐	☐	☐
Plasma	☐	☐	☐	☐
DNA (from peripheral blood)	☐	☐	☐	☐

15. Comments: _____

_____

16. Laboratory name and location: _____

17. Budget for costs incurred by CARET:

There are CARET costs associated with sample selection, pulling of samples, data analyses, IRB approval, downsizing of samples, restocking of samples, etc. that will need to be incurred by the applicant. These costs will need to be negotiated with the CARET Project Manager. If submitting a grant proposal, please discuss costs with the CARET Project Manager to include in your grant.

18. Publication Policy:

All presentations and manuscripts utilizing CARET data will include at least one (1) author from CARET. Conduct with respect to research publications and co-authorship will be agreed to and circulated to CARET investigators for review two (2) weeks prior to submission of abstracts or manuscripts. All publications will acknowledge the author's academic affiliation and the support of the CARET grand awards, U01-CA36373, UM1-CA-167462 and U01-CA167462.

19. Use of human subjects requires approval of the appropriate Institutional Review Board (IRB). Has an application for IRB approval been submitted for review?

☐ **Yes** ☐ **No** ☐ **Pending**

IRB approval date: ____/____/_____

IRB File# _____

_____

Applicant Signature Date

Please submit applications to:

e-mail: CARET@fredhutch.org

or fax: 206-667-5964

Questions about the application process may be sent to CARET@fredhutch.org, or to the CARET Project Coordinator at 206-667-4990

9 Appendix 2- Certificate of Privilege to Use CARET Specimens and/or Data

The Scientific Review Committee of the Carotene and Retinol Efficacy Trial (CARET) and the Institutional Review Boards (IRBs) of the Fred Hutchinson Cancer Center (FRED HUTCHINSON CANCER CENTER) and your institution have approved the use of CARET specimens and/or data for the protocol entitled **<Study title>**. This certificate documents your rights and responsibilities with regard to these specimens.

You will receive from the CARET the following:

<description of numbers, volumes, and types of specimens and/or datasets>

The numbers of specimens and/or data are those specified in the protocol named above. If any specimens are unusable (due to, for example, compromised vials or insufficient sample in vials), CARET will replace them, subject to availability of replacement specimens.

You are approved to perform the following analyses:

<list of analyses; if some analyses are to be performed on only a subset of samples (e.g., analyses done only on cases) then the subset must be specified.>

This is a complete list of approved analyses based on the protocol. You may not perform any analyses not on this list. Performing unapproved analyses is a violation of OHRP (Office for Human Research Protections) regulations and may lead to sanctions from your institution including prevention of your publishing your results; it will also result in a revocation of your privilege to use CARET specimens and/or data for this or any future protocol.

If you wish to perform additional analyses not currently approved, you must first receive written approval from the CARET Scientific Review Committee, your institutional IRB, and the FRED HUTCHINSON CANCER CENTER IRB. Once approval is granted, you will receive a new certificate listing the additional analyses you are approved to perform. You may not begin an analysis until you receive a certificate listing that analysis as approved.

Sample Return:

When you have completed your approved analyses, you must return to CARET any residual specimen within 12 weeks of analysis completion, including specimens that were considered unusable and usable specimen products (e.g., extracted DNA). Any datasets created from specimen analyses must be returned to CARET for archiving.

Dataset Return:

When you have completed your approved analyses, all datasets must be returned to CARET for archiving, and the original CARET dataset sent must be destroyed.

Blinding Policy:

All laboratory analyses will be conducted in blinded fashion with respect to case-control status. CARET will maintain the blind until all laboratory assay data have been delivered to CARET and all samples exhausted or returned. Any exception to the blinding policy will require approval of the CARET Scientific Committee.

10 Appendix3- Confidentiality Pledge

CONFIDENTIALITY PLEDGE
For the Use of CARET Samples

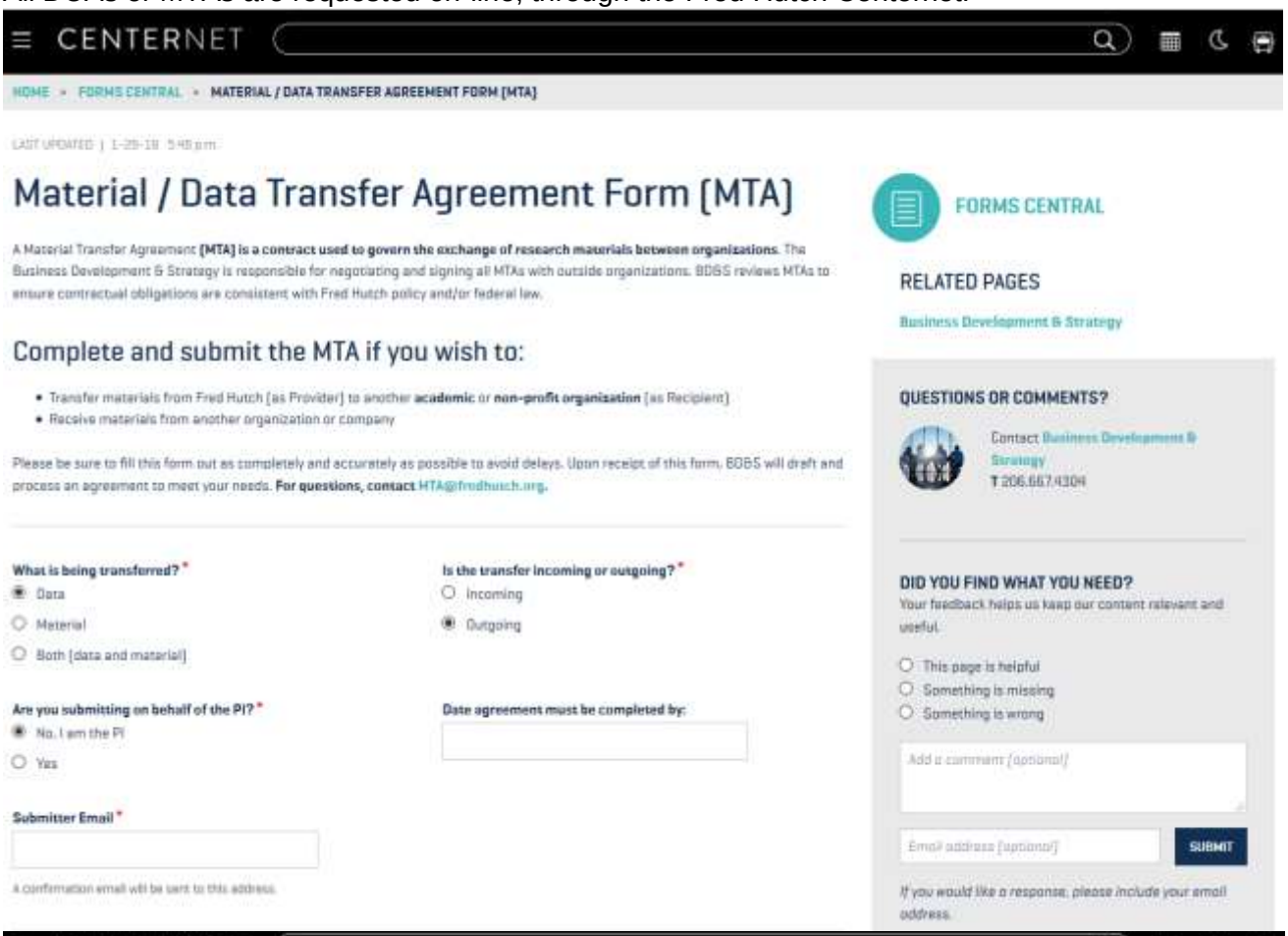
In consideration of my access to the CARET Specimen Bank and information described below and maintained at or belonging to Fred Hutchinson Cancer Center (FRED HUTCHINSON CANCER CENTER), I agree as follows:

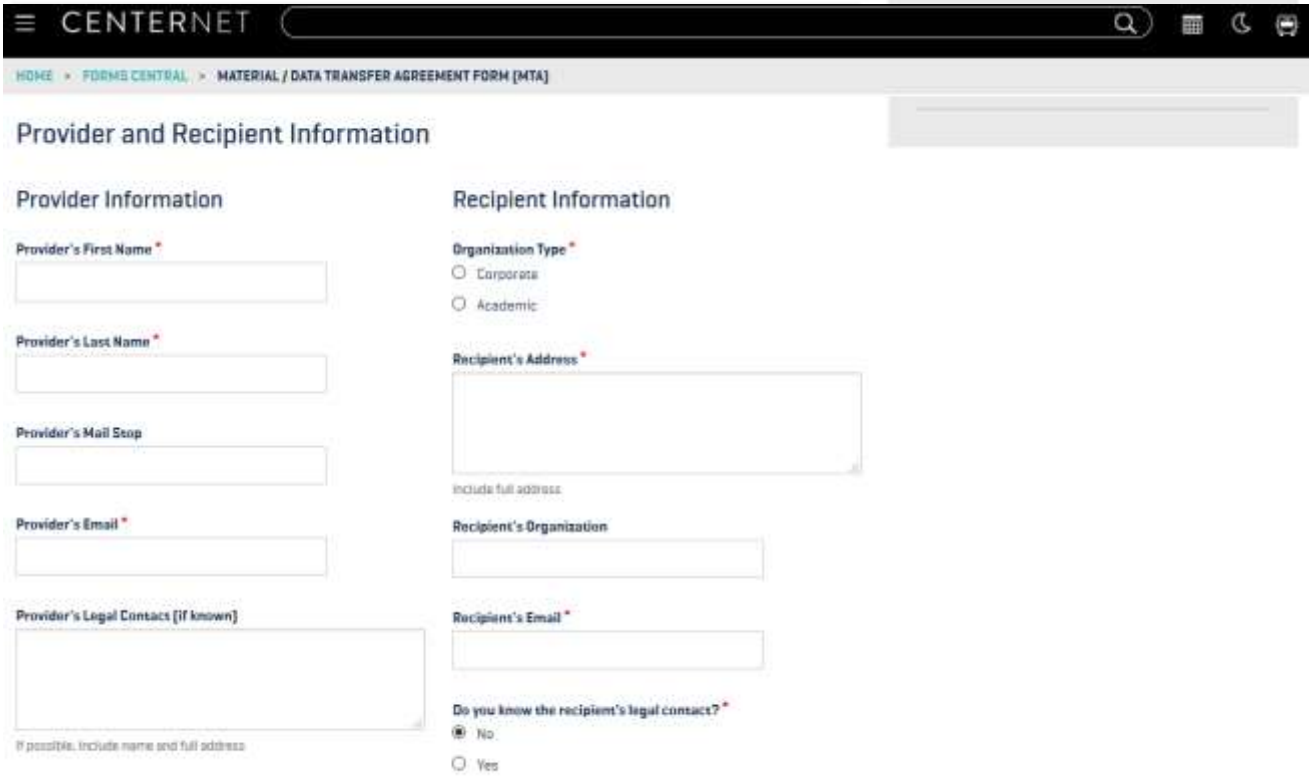
1. "Confidential information" means the following records, data, biological specimens, and information to be provided by the CARET Coordinating Center for the study <TITLE>.
2. I agree not to make use of, disseminate, disclose, or in any way circulate any confidential information except as expressly permitted by this Confidentiality Pledge. Confidential information may be published or otherwise disclosed in connection with the study entitled <TITLE>, <PI NAME / Institution>, IRB number <nnn> / FRED HUTCHINSON CANCER CENTER IRB number 8673; provided, however, that no disclosure may be made which permits identification of any individual participant or the participant's contacts unless permitted by applicable law and approved by an Institutional Review Board of FRED HUTCHINSON CANCER CENTER. Confidential information may also be disclosed to other persons working on the study who have signed a confidentiality pledge.
3. I agree not to provide access to confidential information to any unauthorized person.
4. I agree to indemnify, defend and hold FRED HUTCHINSON CANCER CENTER harmless from any causes of action, claims, damages or liabilities arising or alleged to arise from my failure to comply with any of the provisions of this Confidentiality Pledge.
5. I agree to maintain appropriate procedures to ensure that confidential information remains confidential to the extent required by this confidentiality pledge.
6. I agree to destroy all individual identifiers contained in any confidential information which would serve to identify a CARET participant or participant contact as soon as the purposes of the research for which I have been given access to the confidential information have been accomplished and to notify the CARET Coordinating Center to this effect in writing.
7. I agree to return all unused samples, portions of samples, or derivatives (including DNA) to the CARET Coordinating Center.
8. I agree to comply with all applicable laws and regulations regarding the confidentiality of individually identifiable health care information, including, without limitation, the Washington version of the Uniform Health Care Information Act, RCW Chapter 70.03.
9. I understand and acknowledge that this agreement may not be amended and that use of confidential information in a manner not permitted by this Confidentiality Pledge is not permitted without the prior written consent of the chair of the approving Institutional Review Board and CARET Principal Investigator Marian Neuhouser PhD.

Dated: _____
Name of Individual (Print): _____ Phone Number: _____
Title: _____
Signature: _____

11 Appendix 4- Data Transfer and Use Agreement

All DUAs or MTAs are requested on-line, through the Fred Hutch Centernet.





Data/Material and Project Information

Description of data being transferred: *

Describe the research project: *

Please provide a brief but complete description of the research project, and how the data/material will be used.

SUBMIT

12 Appendix 5 - Authorization to Use, Create, and Share Health Information for Research

FRED HUTCHINSON CANCER RESEARCH CENTER

Advancing Knowledge, Saving Lives

CARET
COORDINATING CENTER
1100 Fairview Ave. N, #MP-859 P.O. Box 19024
Seattle, Washington 98109-1024
PHONE: 1-800-339-0109 FAX: 1-866-702-5291

CHEMOPREVENTION OF LUNG CANCER WITH RETINOIDS/BETA-CAROTENE
MEDICAL RECORDS CONSENT FORM

Principal Investigator:

Gary Goodman, M.D., M.S.
Medical Oncologist
Tumor Institute, Swedish Hospital
Fred Hutchinson Cancer Research Center
Seattle, Washington
1-800-339-0109

AUTHORIZATION TO USE, CREATE AND SHARE HEALTH INFORMATION FOR RESEARCH

IR number: 4239a Protocol number: n/a

Title of Research Study: The Carotene and Retinol Efficacy Trial

By law, we must protect the privacy of health information about you. We may use, create, or share your health information for research only if you let us. This form describes what we would do. Please read it carefully. If you agree with it, please sign your name at the bottom and return it in the enclosed envelope. Please keep the second copy for your records.

If you sign this form, information would be shared with Fred Hutchinson Cancer Research Center, its staff, and others who work with them. In this form, all these people together are called "Researchers." Their names will appear on any Research Consent form that you sign.

The Researchers will use the health information only for the purposes named in this form.

1. What "health information" includes:

   - All information about you from research studies carried out by the Researchers. These are studies you agreed to join by signing a Research Consent Form. They may also be studies you will agree to join later, by signing a Research Consent Form.
   - All health information in your medical records.

2. What the Researchers may do with health information:

   The Researchers may use and create your health information for the Study. They may also share your health information with certain people and groups. These may include:

   - The sponsor of the Study, "National Cancer Institute". The sponsor reviews the Study. By law, Researchers share some information with the sponsor.

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- Government agencies, review boards, and others who watch over the safety, effectiveness and conduct of the research.
- Others, if the law requires.

3. Removing your name from health information:

The Researchers may remove your name (and other information that could identify you) from your health information. No one would know the information was yours.

If your name is removed, the information may be used, created, and shared by the Researchers and Sponsor as the law allows. (This includes other research purposes.) This form would no longer limit the way the Researchers use, create, and share the information.

4. How the Researchers and the National Cancer Institute protect health information:

The Researchers and the National Cancer Institute will follow the limits in this form. If they publish the research, they will not identify you unless you allow it in writing. These limitations continue even if you take back this permission.

5. After the Researchers learn health information:

The limits in this form come from a federal law called the Health Insurance Portability and Accountability Act. This law applies to your doctors and other health care providers, not to the Researchers.

Once the Researchers get your health information, this law may no longer apply. But other privacy protections will still apply.

6. Storing your health information:

Your health information is part of a database or data repository. This permission will end when the database or data repository is destroyed. Unless you take back your permission, this form does not have an ending date.

7. Please note:

You do not have to sign this permission ("authorization") form. If you do not, you may not be allowed to continue in the Study.

You may change your mind and take back your permission anytime. To take back your permission, write to "The Carotene and Retinol Efficacy Trial". If you do this, you may no longer be allowed to continue in the Study. If we have health information by then, it may stay in the Study record.

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Signature

I, _____, agree to let my doctors and other health care providers use, create, and share health information that identifies me with the Researchers.

My doctors and other health care providers could include:

_____

_____

_____ _____

Signature of participant or participant's Legal Representative

Date

_____ _____

Printed name of participant or participant's Legal Representative

Representative's relationship to participant

13 Appendix 6 – Documentation of Previous Endpoint Ascertainment Procedures

Endpoints were ascertained by active and passive follow-up. The exact methods of passive follow-up varied between study centers.

Active follow-up

Information on general health and the diagnosis of cancer was obtained at each routine visit and phone contact.

Participants who did not return to the study center for scheduled visits were contacted by phone or post card.

If the participant could not be contacted, another contact source such as a relative, neighbor, friend, or local physician was contacted.

Passive follow-up

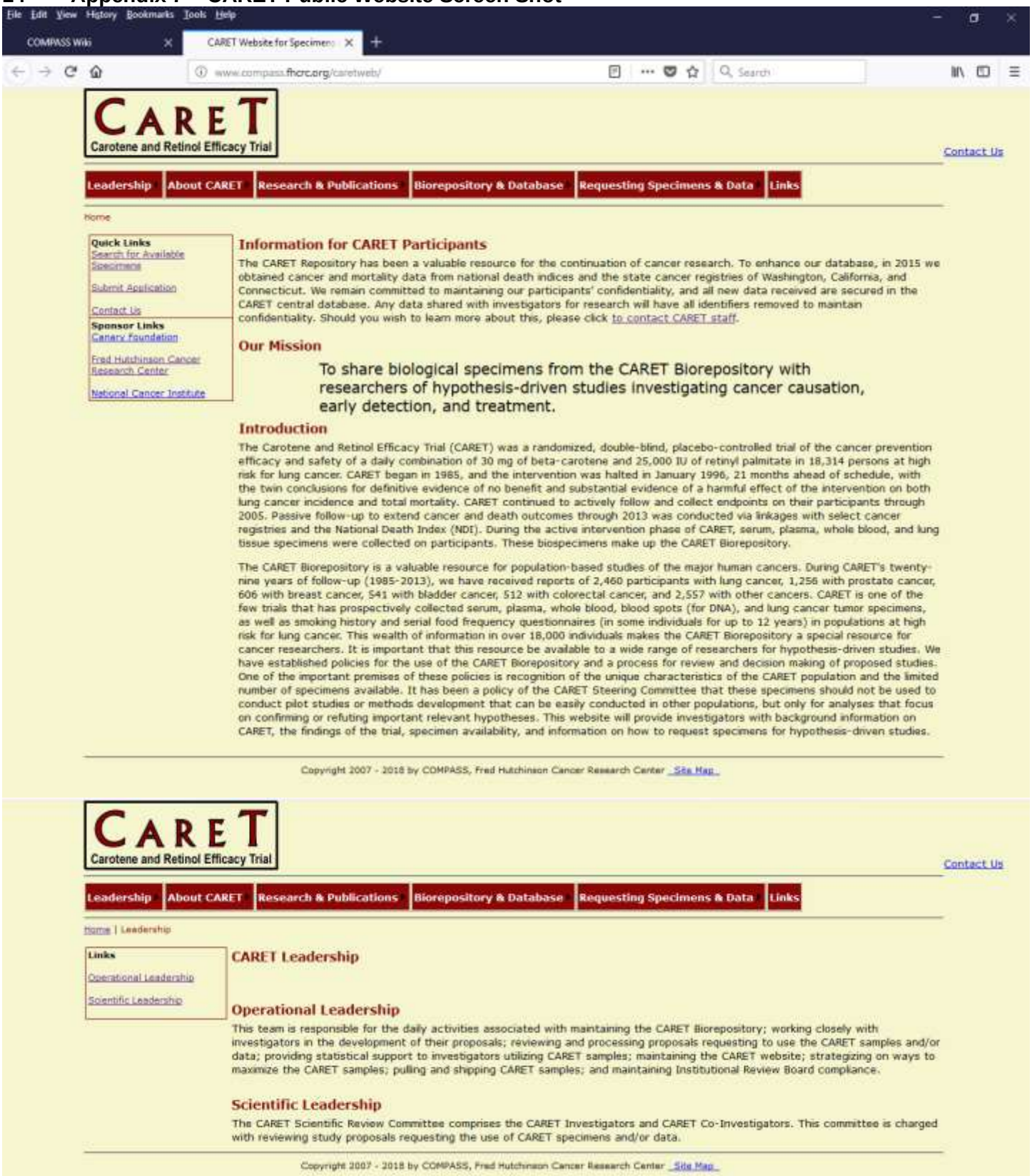
In areas covered by a SEER registry (Seattle, Irvine and San Francisco, and the state of Connecticut) or other centralized registry (Portland and the state of Maryland), periodic scans of registry databases were made to learn of new cancer endpoints and this confirmation was forwarded to the Endpoints Review Committee for review.

We periodically searched national death indexes such as the National Death Index and the Social Security Death Index to confirm vital status of randomized participants.

In December, 1997, CARET requested permission from the IRB to use the FRED HUTCHINSON CANCER CENTER Tracking Resource Center to obtain an updated vital status on CARET Seattle Study Center participants who had been difficult to locate and for those who had a contact status of 'do not contact.' Fourteen of the participants who were located had not received the CARET results letter described. Of these fourteen, 3 of them had had their last contact within five years of the CARET results. CARET sent the results letter to these 3 participants.

The CARET Coordinating Center used the FRED HUTCHINSON CANCER CENTER Tracking Resource Center to obtain an updated "vital status" on those participants who were "difficult to locate" (last date known to be alive greater than 21 months) and for those who have a contact status of "do not contact". For those participants who have not limited our contact, we would use all sources available and make further attempts to reach the participant directly. The following script would be used if the participant asks how we located them "*We used public sources and databases to obtain a recent address or phone number.*" For those participants who have limited our contact, we would use the Public Records to update "vital status" only and no further attempts to reach the participant would be made.

14 Appendix 7 – CARET Public Website Screen Shot



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Operational Leadership

Scientific Leadership

Operational Leadership

Chu Chen, M.S., Ph.D., D.A.B.C.C., is a biochemist, molecular biologist and clinical chemist by training and a board-certified Diplomat of the American Board of Clinical Chemistry. Her involvement with CARET began in 1993, when she founded the Public Health Sciences Core Laboratory at the Fred Hutchinson Cancer Research Center, in which capacity she oversaw the analyses of carotenoids and micronutrients for the CARET study. For over two decades since that time, she has received a number of National Institutes of Health awards to support her research, which has focused on the molecular epidemiology of tobacco-related cancers (head and neck, lung) and hormone-related cancers (breast, endometrium, prostate, testes) and on the development of prognostic gene signatures for patients diagnosed with oral squamous cell carcinoma. Several of these studies were based on CARET samples and data. Dr. Chen received her Ph.D. in biochemistry from the University of Washington. (List of publications via PubMed)

Gary Goodman, M.D., M.S., was the Principal Investigator of the Carotene and Retinol Efficacy Trial (CARET) and was primarily responsible for the overall design of the CARET trial with his experience as a clinical investigator in lung cancer clinical trials. He was responsible for the development of methodology to assess participants for side effects and the laboratory serum vitamin assay. As the Principal Investigator of CARET, Dr. Goodman was responsible for the overall direction of the trial. Dr. Goodman holds a joint membership with the Fred Hutchinson Cancer Research Center and the Swedish Cancer Institute. Dr. Goodman received his M.D. and M.S. in Pharmacology from the University of Illinois. (List of publications via PubMed)

Mark Thornquist, Ph.D., is the lead statistician on the Carotene and Retinol Efficacy Trial (CARET) and has been the Director of the CARET Coordinating Center. Dr. Thornquist was responsible for the analytic methods used to design, monitor, and analyze CARET data. Dr. Thornquist is the Director of the Comprehensive Center for the Advancement of Scientific Strategies (COMPASS), a program within the Cancer Prevention Program in the Public Health Sciences Division of the Fred Hutchinson Cancer Research Center that provides full-spectrum operational support for research. Dr. Thornquist received his Ph.D. in Statistics from the University of Wisconsin. (List of publications via PubMed)

Matt Barnett is the CARET Analytic Section Manager of COMPASS. He has served COMPASS in this role for over two decades, and has been a statistician on CARET even longer. Mr. Barnett consults with scientific investigators on study design issues and provides statistical analyses for publications and reports. He works with scientists and staff on study coordination procedures, providing statistical guidance in the design and development of data collection forms, data management procedures, quality control reports, and quality assurance procedures. Mr. Barnett received a Master of Science degree in Biostatistics from the University of Washington.

Becky Harbine is the Project Coordinator for CARET, working closely with investigators in the coordination of their research projects. Ms. Harbine has been with CARET since 1996, working her way up from a Data Technician to Project Coordinator, and now oversees most activities associated with the CARET Biorepository. This includes processing all proposals requesting the use of CARET samples and/or data, Institutional Review Board compliance, communications between investigators, developing policies, assisting in study implementation, development of research materials, and maintaining the integrity of the CARET specimens. Ms. Harbine has extensive historical knowledge of the CARET Study and Biorepository, benefiting better specimen management. Ms. Harbine received a Bachelor of Arts degree from Western Washington University.

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Scientific Leadership

Chu Chen, M.S., Ph.D., D.A.B.C.C., is the Principal Investigator of the Carotene and Retinol Efficacy Trial (CARET); her expertise is in molecular epidemiology, genomics, transcriptomics, and clinical chemistry). She is the chair of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data. (webpage)

Gary Goodman, M.D., M.S., served as the Principal Investigator of CARET until 2018 and continues to serve as a co-investigator; his expertise is in medical oncology. He is a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data. (webpage)

Mark Thornquist, Ph.D., served as the Co-Principal Investigator of CARET until 2018 and continues to serve as a co-investigator; his expertise is in biostatistics. He is a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data. (webpage)

Marian Neuhouser, Ph.D., is a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data; her expertise is in nutritional epidemiology. (webpage)

Charles Kooperberg, Ph.D., is a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data; his expertise is in biostatistics and statistical genetics. (webpage)

Noel Weiss, M.D., Dr.P.H., is a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data; his expertise is in epidemiology. (webpage)

Gilbert Omenn, M.D., Ph.D., served as the Principal Investigator of CARET until 1997 and continues to serves as a member of the CARET Scientific Review Committee, which reviews proposals requesting the use of CARET specimens and data; his expertise is in genetics and proteomics.

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About CARET

CARET was a randomized, double-blind, placebo-controlled trial of the cancer prevention efficacy and safety of a daily combination of 30 mg of ?-carotene and 25,000 IU of retinyl palmitate in 18,314 persons at high risk for lung cancer. We studied two high-risk populations: 4,060 men with extensive occupational exposure to asbestos, and 7,965 men and 6,289 women with at least 20 pack-years of cigarette smoking history. CARET began in 1985 with two pilot studies (Vanguard cohort) and expanded to six sites beginning in 1988 (Efficacy cohort). The design projected active intervention until 1997, encompassing 110,000 person-years of follow-up for the 18,314 randomized participants. The CARET intervention was halted in January 1996, 21 months ahead of schedule, with the twin conclusions for definitive evidence of no benefit and substantial evidence of a harmful effect of the intervention on both lung cancer incidence and total mortality. During the intervention phase of CARET, serum, plasma, whole blood, and lung tissue specimens were collected on participants. These biospecimens make up the CARET Biorepository. The overall results of CARET were presented at a special NCI press conference January 18, 1996, followed by a publication (NEJM 334:1150-5, 1996). Further details about lung cancer were published (JNCI 88:1550-9, 1996) soon after. Lung cancer incidence and cardiovascular disease mortality findings during the first six years of post-intervention follow-up were published in 2004 (JNCI 96:1743-50, 2004).

On June 30, 2005, CARET stopped active follow-up of participants. Passive follow-up to extend cancer and death outcomes through 2013 was conducted via linkages with select cancer registries and the National Death Index (NDI). CARET continues to support the extensive biological repository and ancillary studies that utilize the CARET samples and data.

For further details, see the CARET Protocol (PDF).

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Rationale for Study

Lung cancer is a highly lethal disease with an 80-90% mortality rate. In 2005, it was estimated that approximately 170,000 Americans would be diagnosed with lung cancer and 155,000 would die. In the United States, lung cancer is the most common cause of cancer death in men and women, exceeding the combined total for breast, prostate, and colon cancers. Lung cancer is also one of the few diseases with a well-defined etiology: inhalation of tobacco smoke. While tobacco use has become less common over the past 25 years, approximately 25% of the American public still currently use tobacco. Moreover, former smokers continue to be at elevated risk; and the majority of Americans who now develop lung cancer are former smokers. Thus, even if cigarette smoking could be eliminated as an environmental carcinogen, lung cancer would remain a problem for the foreseeable future.

Over the past 20 years there has been intense interest in cancer chemoprevention, the use of agents to prevent, arrest, or reverse the development of cancers. On the basis of epidemiological observations and *in vivo* animal studies, dietary micronutrients (including beta-carotene and vitamin A) were some of the first agents to attract wide interest as potential lung cancer prevention agents. The Beta-Carotene and Retinol Efficacy Trial (CARET) was one of several trials started in the early 1980s to assess the chemopreventive efficacy and safety of beta-carotene and vitamin A.

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Eligibility Criteria

Eligibility criteria for the two CARET exposure populations were as follows:

Asbestos-exposed participants (N = 4,060)

Men who, on entry to the study,

- were aged 45-69*
- were current smokers or quit within 15 years prior to enrollment*
- had their first exposure to asbestos on the job at least 15 years prior to enrollment
- had a chest X-ray positive for changes compatible with asbestos exposure according to International Labour Organization (ILO) criteria; or had been employed in a protocol-defined high-risk trade for at least 5 years, at least 10 years prior to enrollment

Heavy smoker participants (N = 14,254)

Men and women who, on entry to the study,

- were aged 50-69
- had a cigarette smoking history of 20 or more pack-years
- were current smokers or had quit within the previous 6 years

* For the asbestos pilot study there was no smoking eligibility requirement and the age criterion was 45-74 years. Among the asbestos-exposed participants enrolled during the pilot phase (N = 816), 16% were never smokers and 36% were former smokers who had quit more than 15 years prior to enrollment; 10% were between 70 and 74 years of age.

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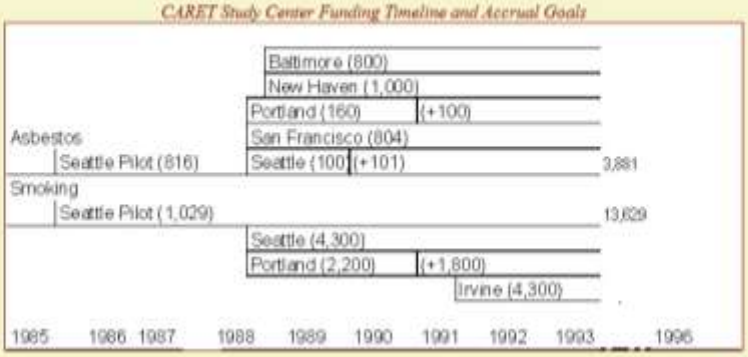
Recruitment

Six study centers performed participant recruitment under the direction of the Coordinating Center, located in Seattle, Washington. Study centers were located in Baltimore, Maryland; Irvine, California; Groton, Connecticut (referred to as the New Haven Study Center); Portland, Oregon; San Francisco, California; and Seattle, Washington. Recruitment began in 1985 in Seattle with two pilot studies (one for asbestos-exposed participants and the other for heavy smokers). Pilot recruitment ended in 1988, at which time the full-scale efficacy trial was initiated. Accrual was completed in September 1994. The Baltimore, New Haven, and San Francisco Study Centers recruited primarily asbestos-exposed participants. In August 1992, the CARET Steering Committee approved the recruitment at these three study centers of smoker-eligible spouses and other members of the asbestos-exposed participants' households who met the heavy smoker eligibility criteria for CARET. Seattle and Portland recruited a small number of asbestos-exposed participants, but their primary goals were for heavy smokers. Irvine recruited only heavy smokers. Participants randomized after July 1988 into CARET are referred to as the Efficacy cohort. The participants in the pilot studies were incorporated into CARET as the Vanguard cohort. The figure below shows the timing of adding study centers and their accrual goals (total accrual goal 17,510).

CARET Study Center Funding Timeline and Accrual Goals



The initial contact with a potential participant was usually a mailing that included an introductory letter, an interest survey, and a study fact sheet. The interest survey included questions about the individual's age, sex, smoking status and smoking history, asbestos exposure, and potential interest in joining the study. The study center reviewed the returned interest surveys and screened out ineligibles. Study centers telephoned individuals who were not clearly ineligible. The purpose of the phone call was to review or clarify information on the interest survey, ask questions about the study exclusion criteria, and schedule an appointment for the First Visit for those who seemed to be eligible.

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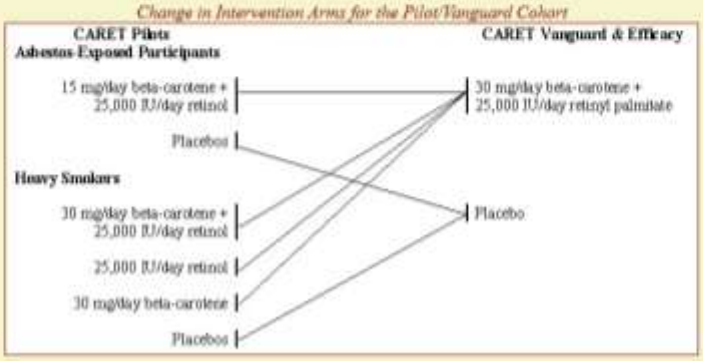
Intervention

Prior to randomization, interested and eligible participants were followed during a 3-month run-in period receiving placebo medication to determine their adherence to taking the study vitamins (as well as to establish their baseline levels of symptoms, signs, and liver function tests). Participants who took at least 50% of their placebo capsules were randomized to either active study vitamins or placebo.

The asbestos pilot study randomized participants to daily doses of either 1) 15 mg beta-carotene and 25,000 IU retinol or 2) placebos. The heavy smoker Pilot study consisted of four intervention arms: 1) 30 mg beta-carotene and 25,000 IU retinol; 2) 30 mg beta-carotene; 3) 25,000 IU retinol; and 4) placebos daily. In the full-scale trial, participants in both exposure populations were assigned to either 1) 30 mg beta-carotene and 25,000 IU retinyl palmitate or 2) placebos daily. Beginning in July 1988, pilot study participants were transitioned to the new protocol. As part of the full-scale trial, pilot study participants were referred to as the Vanguard cohort. The following figure shows the change in intervention arms for pilot study participants on the transition to the full-scale study.

Change in Intervention Arms for the Pilot/Vanguard Cohort



As depicted in the figure, Vanguard participants who were on active arms during the pilot studies had their daily study vitamin dosage changed to 30 mg beta-carotene and 25,000 IU retinyl palmitate; those on placebos continued on placebos. Thus, heavy smoker Pilot participants have a 3:1 allocation to the CARET intervention arms. The form of vitamin A that participants received was changed from retinol to retinyl palmitate to allow the vitamin A and the beta-carotene to be administered in a single capsule.

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Follow-up

Throughout the intervention phase of the trial participants were followed with routine clinic visits and phone contacts. While the intervention was being administered, participants enrolled during the pilot phase were contacted more frequently than those enrolled during the full-scale trial. These Pilot/Vanguard participants were monitored more closely for indications of toxicity related to the study vitamins, because their longer time on study meant that any toxicity related to cumulative dose would have been most likely observed in them prior to those enrolled later in the larger (Efficacy) cohort.

The intervention was stopped in January 1996, and participants were invited to return to their study centers for a "transition" visit and final blood draw. For the remainder of active post-intervention follow-up (through 2005), participants were contacted annually by phone (1997-2000) or by mailed questionnaire (2000-2005). State cancer registry and National Death Index (NDI) linkages were conducted in 2015 to extend follow-up for endpoints. Death outcome information from the NDI linkage was complete through 2013; state cancer registry data were through 2012 for WA and CA, and through 2013 for CT. A summary of contact schedules and methods follows below.

Intervention phase, Pilot studies (1985 - 1988):

Visits	Three times a year, four months after randomization and every four months thereafter
Phone contacts	Three times a year, two months after randomization and every four months thereafter

Intervention phase, Pilot/Vanguard (1989 - 1995):

Visits	Semiannually, on and six months after the anniversary dates of randomization to the pilot study
Phone contacts	Semiannually, three and nine months after the anniversary dates of randomization to the pilot study

Intervention phase, Efficacy (1989 - 1995):

Visits	Six months and 12 months after randomization, and annually thereafter on the anniversary dates of randomization
Phone contacts	Three and nine months after randomization during the first year; and semiannually thereafter, four and eight months after the anniversary dates of randomization

Post-intervention, Transition phase (1996 - 1997):

Visits	Once on the anniversary dates of randomization
Phone contacts	Semiannually, four and eight months after the anniversary dates of randomization

Post-intervention, Phone Follow-up phase (1997 - 2000):

Phone contacts	Annually on the anniversary dates of randomization

Post-intervention, Mail Follow-up phase (2000 - 2005):

Mailed questionnaire	On the anniversary dates of randomization

Post-intervention, Passive Follow-up phase (2005 - 2013):

Registry linkages	One-time linkage to the NDI and three state cancer registries: California Cancer Registry, Connecticut Tumor Registry, and Washington State Cancer Registry. Because of state regulatory restrictions, we were not able to access the cancer registries of Oregon or Maryland.

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Select the area of interest for details about CARET data collection.

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Collection

The CARET Biorepository includes biologic material from the 18,314 CARET participants. Participants enrolled in the two pilot studies which preceded CARET (all of whom remain part of CARET) had blood collected at the first visit, the 4th-month visit, and each annual visit. Participants enrolled after the pilot had blood collected at the first visit and at every other annual visit. Blood draws ended in 1997, one year after the CARET intervention had been stopped. Serum samples were collected at all draws. Plasma collection occurred throughout the duration of the pilot studies (1985 â€" 1988), and continued at Vanguard/Efficacy visits through February 1990. Collection of whole blood and dried blood spots was attempted at a single time point for each participant during visits conducted from 1994-1997. The Specimen Collection Timeline (PDF) shows the type, quantity, and timing of blood specimen collection.

Tumor and normal tissue, in the form of pathology slides and paraffin blocks, was collected from 1995 to 1997 and from 1999 to 2003. However, collection was both prospective and retrospective; attempts to obtain tissue were made for all confirmed lung cancer cases reported by June 2003.

Storage

Blood aliquots were stored at -20°C at the study centers immediately after the draw. Within two weeks of collection, samples were shipped on dry ice to the Coordinating Center, where they entered long-term storage at -70°C.

Availability

Additional information about the CARET biorepository and specimen bank can be found by either viewing one of the report snapshots or through use of the search utility:

CARET Blood Specimen Summary (PDF)
CARET Tissue Specimen Summary (PDF)
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Endpoints

Collection and Adjudication

The endpoints review process has undergone several procedural modifications over the 20-year history of CARET. During the intervention phase and continuing through the first year of post-intervention follow-up (1985 - 1997), the procedure was as follows. We obtained medical records and pathology reports for all participants who reported a cancer diagnosis. We also requested slides or tissue blocks for lung, mesothelioma, and unknown primaries for central pathology review. Pathology reports were reviewed for all other cancers. Endpoint materials were reviewed independently by three reviewers from CARET's Endpoints Review Committee (ERC). If there was disagreement among the reviewers as to the primary site, histology, or date of diagnosis, the case was reviewed and closed during a meeting of the ERC. Prior to 1995, tissue specimens were returned after central pathology review.

From March 1997 through September 1998, a streamlined endpoint review and closure process was followed. Three changes were implemented for this period: 1) a single reviewer adjudicated all cases independently, unless questions arose; 2) for all cancers other than lung cancer, only pathology reports were required to confirm the endpoint; and 3) only the death certificate was required to confirm cause of death. The process was further streamlined in October 1998, allowing for review by endpoint specialists from the CARET Coordinating Center staff and a single reviewer from the ERC.

The final change during the active follow-up phase came in October 2003 when, as a cost-saving measure, we eliminated the collection and review of pathology reports and began relying solely on self-reports of cancer. Our decision to make this change was based on an evaluation of the accuracy of participant self-report of cancer, especially lung cancer, our primary endpoint. We examined the adjudication outcome of participant reported cancers and found that 91% of cases reported as lung cancer were closed as such. Most of the discrepancies in reporting were due to reporting recurrences or reporting metastases as new primaries. The confirmation rates were high for other commonly reported cancers as well, including prostate (96%), breast (94%), bladder (97%), and colorectal (88%). These findings assured us that self-report of cancer was an acceptable procedure. Based on this evaluation, we made several modifications to the data collection questionnaire to address the reasons for self-reported diagnoses with the review of medical records. In the majority of cases, this was concerned with differentiating a new primary cancer from recurrent, metastatic, and benign diseases. Thus, actual rates of agreement during the self-reporting period (October 2003 - June 2005) are likely higher than we observed in our evaluation.

State cancer registry and National Death Index (NDI) linkages were conducted in 2015 to extend follow up for endpoints. NDI linkage was complete through 2013; state cancer registry linkage was through 2012 for WA and CA, and through 2013 for CT. Cancer registries of the five states in which CARET enrollments occurred were targeted for the linkage, with approval obtained for three registries: California Cancer Registry, Connecticut Tumor Registry, and Washington State Cancer Registry. Regulatory guidelines in Maryland and Oregon at present prohibit access to cancer registry data for the aims of the current CARET grant. Of the 18,314 total CARET participants, 12,927 (71%) were enrolled by a study center located in CA, CT, or WA; and another 1,109 (6%) enrolled by other study centers had a history of residence in one of the three states. In total, records from 14,036 (77%) participants were included in the cancer registry linkages. Probabilistic software was used to match CARET records to cancer registry records based on data elements common to both repositories, including full social security number, name, sex, race, and date of birth (which are complete for 99% of CARET participants). Linkage results were classified as matches to previously reported CARET endpoints or new endpoints based on degree of matching between common data elements (e.g., date of diagnosis, cancer site, and histologic type) and manual review of pathology reports and other medical records collected during active follow up. The registry data were also used to adjudicate cases closed previously based on self-report only.

NDI linkage was performed to ascertain vital status and underlying cause of death on a total of 13,830 participants who were alive at the end of active follow-up or for whom report of death had not been confirmed by death certificate. Matches were determined on the basis of the NDI probabilistic score and classification group assignment, electronic evaluation of CARET data elements not incorporated in the NDI algorithms (e.g., date of last contact), and manual review of records. Discrepancies in cause of death and cancer diagnoses between NDI and cancer registry records were reviewed as part of the adjudication process.

Cancer Incidence and Mortality

- Number of participants with cancer endpoints by cancer type and intervention arm assignment (PDF)
- Number of deceased participants by cause of death and intervention arm assignment (PDF)

Cancer Staging

Medical records obtained for adjudication were reviewed subsequently to determine TNM staging on the four most common CARET cancer endpoints: lung, prostate, breast, and colorectal cancer. Extensive medical records, including pathology reports, surgical reports, hospital records, and scan and radiograph reports, as well as clinical notes by the medical personnel attending the patient, were obtained for most cancers. Information was sufficient to determine staging on 75% of cases across the four cancer types reviewed. Almost 50% of cases that could not be staged were cancers reported during the self-reporting period (October 2003 - June 2005), after the collection of medical records was discontinued. Staging summary data, updated in November 2015, are provided in the links below:

- Number of CARET Lung Cancer Primaries by Stage of Disease (PDF)
- Number of CARET Prostate Cancer Primaries by Stage of Disease (PDF)
- Number of CARET Breast Cancer Primaries by Stage of Disease (PDF)
- Number of CARET Colorectal Cancer Primaries by Stage of Disease (PDF)

 Site Map

Links

Specimens

Endpoints

Data Collection Forms

CARET Data Collection Forms and Contact Schedule

		Contact schedule[1] (✓ = collection was at all time points unless otherwise noted) CV = Clinic Visit PC = Phone Contact MQ=Mailed Questionnaire			
				Post-intervention phases	
	Data collection forms[2]	Baseline (1985-1994)	Intervention phase (1985-1995)	Transition (1996-1997)	Follow-up (1997-2005)
		CV (x1)	CV (x1/year) & PC (x2/year)	CV (x1) & PC (x2)	PC or MQ (1x/year)
Cancer and death endpoints	Confirmation of Cancer Endpoint Confirmation of Death Endpoint	N/A	✓	✓	✓
Blood specimens	Blood Collection and Processing	✓	✓ (CVs, every two years only)	✓ (CV only)	
Dietary intake	Food Frequency Questionnaire	✓	✓ (CVs, every two years only)	✓ (CV only)	
Smoking history	Questionnaire #1 (baseline, Q.1-Q.7) Health questionnaire #4 (follow-up, Q.27)	✓	✓	✓	✓
Supplemental vitamin use	Contact Summary (Q.59)	✓	✓ (CVs only)	✓	
Health history	Health Questionnaire #4	✓	✓ (CVs only)	✓	
Family history of cancer	Questionnaire #1 (Q.9-Q.11)	✓			
Respiratory history	Respiratory History Questionnaire	✓	✓ (CVs, every two years only)	✓ (CV only)	
Spirometry (asbestos workers only)	Spirometry	✓	✓ (CVs, every two years thereafter)	✓ (CV only)	
X-ray (asbestos workers only)	Study Center X-Ray Review	✓			
Work history	Questionnaire #1 (Q.13-Q.17)	✓			
Demographics	Questionnaire #1				
Demographics (age, race, sex, marital status[3], and education level)	Questionnaire #1 (Q.18-Q.21) Contact Information Update	✓			
Height, weight, blood pressure	Contact Summary (Q.59-Q.61)	✓	✓ (CVs only)	✓ (CV only)	

[1] Reflects contact schedule for most participants; participants enrolled during the pilot phase were contacted more frequently than those enrolled during the full-scale trials. Contact schedule specifics can be found here.
[2] Examples of commonly used data collection forms are provided. Forms were modified over the course of the study, but data items within the questionnaires were generally consistent, if not identical.
[3] Marital status was collected at all contacts

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Primary Publications

- Omenn G, Goodman G, Thornquist M, Balmes J, Cullen M, Glass A, Keogh J, Meyskens F, Valanis B, Williams J, Barnhart S, Hammar S.
  Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease.
  (New England Journal of Medicine 334:1150-5, 1996)
- Omenn G, Goodman G, Thornquist M, Balmes J, Cullen M, Glass A, Keogh J, Meyskens F, Valanis B, Williams J, Barnhart S, Cherniack M, Brodkin C, Hammar S.
  Risk factors for lung cancer and for intervention effects in CARET, the beta-Carotene and Retinol Efficacy Trial.
  (Journal of the National Cancer Institute 88:1550-9, 1996)
- Goodman G, Thornquist M, Balmes J, Cullen M, Meyskens F, Omenn G, Valanis B, Williams J.
  The beta-Carotene and Retinol Efficacy Trial: Incidence of Lung Cancer and Cardiovascular Disease Mortality During 6-Year Follow-up After Stopping Beta-Carotene and Retinol Supplements.
  (Journal of the National Cancer Institute 96:1743-50, 2004)

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Consortia Publications

Publications

Publications may be listed in more than one category.

Design

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Primary Results

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Prostate Cancer

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CARET
Carotene and Retinol Efficacy Trial

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Lung Cancer

Title: **Investigating regions of identity-by-descent associated with lung cancer risk and smoking behaviors**
Investigator: **Aldrich, Melinda**
Institution: **Vanderbilt-Ingram Cancer Center**
Objective: To identify regions of identity-by-descent associated with lung cancer risk; to identify regions associated with smoking behavior through identity-by descent mapping.

Title: **Polymorphisms in bone turnover genes in lung cancer**
Investigator: **Cox, Angela**
Institution: **University of Sheffield Department of Oncology**
Objective: To identify genetic variants in bone turnover genes associated with risk of developing bone metastases in lung cancer, and identify genetic variants in bone turnover genes associated with survival in lung cancer.

Title: **Telomeres and Lung Cancer Incidence and Survival**
Investigator: **Doherty, Jennifer**
Institution: **Fred Hutchison Cancer Research Center Public Health Sciences**
Objective: 1) To examine whether global telomere length, measured in blood samples collected prior to lung cancer diagnosis, is associated with an increased risk of lung cancer; 2) To examine whether telomere length of specific chromosome arms, measured in blood samples collected prior to lung cancer diagnosis, is associated with an increased risk of lung cancer; 3) To examine whether approximately 5,400 tag and putative functional SNPs in telomere maintenance-related genes (TERT, TERC, DKC1, NOLA1, NOLA2, NOLA3, TERF1, TERF2, TINF2, TERF2IP, ACD, POT1, TEP1, DCLRE1B, PINX1, TNKS, BICD1 and PIKC3C) identified using data from the 1,000 Genomes Project, are associated with lung cancer risk; and 4) To examine whether blood telomere length (both global and chromosome arm-specific), and variation in telomere maintenance genes, are associated with survival among individuals who develop lung cancer.

Title: **GWAS of small cell lung cancer**
Investigator: **Malhotra, Jyoti**
Institution: **Mount Sinai School of Medicine**
Objective: To test the hypothesis that genetic variations are associated with altered susceptibility to SCLC. We further hypothesize that environmental and lifestyle factors like smoking modulate the genetic associations with SCLC risk.

Title: **Leanness as a risk factor for lung cancer**
Investigator: **Stucker, Isabelle**
Institution: **French Institute of Health and Medical Research (INSERM)**
Objective: To examine the association between BMI and lung cancer risk based on cohort studies conducted among ILCCO participating centers.

Title: **Development and validation of lung cancer risk prediction models**
Investigator: **Tammemagi, Martin**
Institution: **Brock University Applied Health Sciences**
Objective: 1. In CARET data, to externally validate existing lung cancer risk prediction models in their ability to predict incident lung cancers2-10, and lung cancer mortality. Almost all of the currently published models have been designed to identify becoming a lung cancer case. But some recent discussion regarding selection criteria for screening has suggested identification of those who will die from lung cancer may also be relevant. 2. To validate the Tammemagi 2012 Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) model9 into which asbestos has been synthetically added as predictors. And if found to be deficient use CARET data to improve the parameter estimates for asbestos in the Tammemagi 2012 model. 3. To develop and validate lung cancer risk prediction models for never-smokers (if data permits).

Title: **Validation and updating lung cancer risk models**
Investigator: **Teare, M. Dawn**
Institution: **University of Sheffield School of Health and Related Research**
Objective: 1) To identify and review all existing lung cancer risk models (LCRMS). Pay attention to the features of the target population the model was developed for; 2) To evaluate the performance of LCRMs when applied to populations similar and distinct to those developed for. This will produce aggregate data to take to the next stage.(Using ILCCO participating studies); 3) To systematically review and apply the multivariate analyses to combine the evidence for each component predictor and evaluate the performance. Following a framework such as outlined by Gasparini which can handle non linear associations; 4) To formulate a robust and flexible means to assess lung cancer risk.

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Breast Cancer

Title: **OncoArray genotyping of studies of five cancer types**
Investigator: **Amos, Chris**
Institution: **Dartmouth Geisel School of Medicine**
Objective: To integrate ongoing genetic studies to identify cancer susceptibility factors for common cancers, to evaluate biological mechanisms by which these factors influence cancer development and to evaluate the effects of these factors in well characterized epidemiological studies.

Title: **Pooled Analysis of Circulating 25-hydroxy Vitamin D and Risk of Breast and Colorectal Cancer**
Investigator: **Smith-Warner, Stephanie**
Institution: **Harvard T.H. Chan School of Public Health**
Objective: Objective: To examine the association between prospectively collected circulating 25-hydroxyvitamin D [25(OH)D] levels and risk of breast and colorectal cancer in a consortium of 15 cohort studies. We would like to include participants from CARET in both the breast cancer and colorectal cancer analyses. We decided to examine these cancer sites because they are among the top three most common cancers in men and women in the United States; their incidence rates vary multifold worldwide, supporting the possibility for environmental or dietary influences in their etiology; and epidemiologic and experimental data suggest that vitamin D is associated with reduced risk of these cancer sites 3. We propose to pool the primary data from 15 prospective cohort studies (10 studies for breast cancer, 14 studies for colorectal cancer) to investigate the association between circulating 25(OH)D levels and risk of these cancer sites overall, by tumor subtype, and by population subgroups defined by personal characteristics, lifestyle factors, vitamin D receptor (VDR) polymorphisms, and other biomarkers. Together, these cohorts will have 25(OH)D levels measurements in over 5,000 colorectal cancer cases and over 6,800 breast cancer cases. These analyses should contribute substantially to characterizing the dose-response relationships of these associations and will inform recommendations regarding sun exposure, vitamin D intake requirements, and design issues for any future randomized trials.

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Colon Cancer

Title: **OncoArray genotyping of studies of five cancer types**
Investigator: **Amos, Chris**
Institution: **Dartmouth Geisel School of Medicine**
Objective: To integrate ongoing genetic studies to identify cancer susceptibility factors for common cancers, to evaluate biological mechanisms by which these factors influence cancer development and to evaluate the effects of these factors in well characterized epidemiological studies.

Title: **Pooled Analysis of 25-hydroxy Vitamin D and Colorectal Cancer Survival (Harvard Pooling project)**
Investigator: **Fedirko, Veronica**
Institution: **Emory University School of Public Health**
Objective: To investigate association between pre-diagnostic 25(OH)D levels and CRC-specific and overall mortality among CRC cases in the VDPP project.

Title: **Pooled Analysis of Circulating 25-hydroxy Vitamin D and Risk of Breast and Colorectal Cancer**

Investigator: **Smith-Warner, Stephanie**

Institution: **Harvard T.H. Chan School of Public Health**

Objective: Objective: To examine the association between prospectively collected circulating 25-hydroxyvitamin D [25(OH)D] levels and risk of breast and colorectal cancer in a consortium of 15 cohort studies. We would like to include participants from CARET in both the breast cancer and colorectal cancer analyses. We decided to examine these cancer sites because they are among the top three most common cancers in men and women in the United States; their incidence rates vary multifold worldwide, supporting the possibility for environmental or dietary influences in their etiology; and epidemiologic and experimental data suggest that vitamin D is associated with reduced risk of these cancer sites 3. We propose to pool the primary data from 15 prospective cohort studies (10 studies for breast cancer, 14 studies for colorectal cancer) to investigate the association between circulating 25(OH)D levels and risk of these cancer sites overall, by tumor subtype, and by population subgroups defined by personal characteristics, lifestyle factors, vitamin D receptor (VDR) polymorphisms, and other biomarkers. Together, these cohorts will have 25(OH)D levels measurements in over 5,000 colorectal cancer cases and over 6,800 breast cancer cases. These analyses should contribute substantially to characterizing the dose-response relationships of these associations and will inform recommendations regarding sun exposure, vitamin D intake requirements, and design issues for any future randomized trials.

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Esophageal Cancer

Title: **Serologic inflammatory markers and esophageal adenocarcinoma risk**

Investigator: **Cook, Michael**

Institution: **National Cancer Institute Division of Cancer Epidemiology and Genetics**

Objective: 1) To evaluate the association of pre-diagnostic circulating inflammation markers with incident esophageal adenocarcinoma, and 2) To evaluate body mass index and waist circumference as potential effect modifiers for the relationships of inflammation markers with incident esophageal adenocarcinoma.

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Ovarian Cancer

Title: **OncoArray genotyping of studies of five cancer types**

Investigator: **Amos, Chris**

Institution: **Dartmouth Geisel School of Medicine**

Objective: To integrate ongoing genetic studies to identify cancer susceptibility factors for common cancers, to evaluate biological mechanisms by which these factors influence cancer development and to evaluate the effects of these factors in well characterized epidemiological studies.

Title: **miRNA Biomarkers for Early Ovarian Cancer Detection**

Investigator: **Tewari, Maneesh**

Institution: **Fred Hutchinson Cancer Research Center Human Biology**

Objective: To assess performance of miR-135b as a single biomarker in pre-clinical samples from the Carotene and Retinol Efficacy Trial (CARET) repository. Secondary analyses will include sensitivity using the PEB longitudinal algorithm, sensitivity at other levels of specificity, contribution to a decision rule including CA125, HE4, and Mesothelin and evaluation of miR-135b in a risk algorithm.

Prostate Cancer

Title: **OncoArray genotyping of studies of five cancer types**
Investigator: **Amos, Chris**
Institution: **Dartmouth Geisel School of Medicine**
Objective: To integrate ongoing genetic studies to identify cancer susceptibility factors for common cancers, to evaluate biological mechanisms by which these factors influence cancer development and to evaluate the effects of these factors in well characterized epidemiological studies.

Title: **Body mass index and risk of prostate cancer in the Carotene and Retinol Efficacy Trial**
Investigator: **Bonn, Stephanie**
Institution: **Karolinska Institutet**
Objective: To examine the association between baseline body mass index and prostate cancer risk among men in the Carotene and Retinol Efficacy Trial (CARET).

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Dietary/Micronutrient Studies

Title: **Pooled Analysis of 25-hydroxy Vitamin D and Colorectal Cancer Survival (Harvard Pooling project)**
Investigator: **Fedirko, Veronica**
Institution: **Emory University School of Public Health**
Objective: To investigate association between pre-diagnostic 25(OH)D levels and CRC-specific and overall mortality among CRC cases in the VDPP project.

Title: **Pooled Analysis of Circulating 25-hydroxy Vitamin D and Risk of Breast and Colorectal Cancer**
Investigator: **Smith-Warner, Stephanie**
Institution: **Harvard T.H. Chan School of Public Health**
Objective: Objective: To examine the association between prospectively collected circulating 25-hydroxyvitamin D [25(OH)D] levels and risk of breast and colorectal cancer in a consortium of 15 cohort studies. We would like to include participants from CARET in both the breast cancer and colorectal cancer analyses. We decided to examine these cancer sites because they are among the top three most common cancers in men and women in the United States; their incidence rates vary multifold worldwide, supporting the possibility for environmental or dietary influences in their etiology; and epidemiologic and experimental data suggest that vitamin D is associated with reduced risk of these cancer sites 3. We propose to pool the primary data from 15 prospective cohort studies (10 studies for breast cancer, 14 studies for colorectal cancer) to investigate the association between circulating 25(OH)D levels and risk of these cancer sites overall, by tumor subtype, and by population subgroups defined by personal characteristics, lifestyle factors, vitamin D receptor (VDR) polymorphisms, and other biomarkers. Together, these cohorts will have 25(OH)D levels measurements in over 5,000 colorectal cancer cases and over 6,800 breast cancer cases. These analyses should contribute substantially to characterizing the dose-response relationships of these associations and will inform recommendations regarding sun exposure, vitamin D intake requirements, and design issues for any future randomized trials.

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Types of Study

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- Intervention Effect

Pilot & Unpublished Studies

Lung Cancer

Title: **Replication genotyping for selected SNPs in relation to serum beta-carotene, retinol, and alpha-tocopherol and lung cancer risk**
Investigator: **Albanes, Demetrius**
Institution: **National Cancer Institute Division of Cancer Epidemiology and Genetics**
Objective: To replicate an association between candidate SNPs and 1) follow-up serum concentrations of beta-carotene, retinol,and alpha-tocopheral by CARET intervention arm and 2) lung cancer risk by CARET intervention arm.

Title: **Detecting early stage lung cancer with antibodies**
Investigator: **Bihain, Bernard**
Institution: **Genclis**
Objective: Pilot study to validate the feasibility of detecting changes in antibodies directed against bioinformatically predicted aberrant peptides in samples from patients of CARET study diagnosed with lung cancer versus controls without cancer after five-year follow-up.

Title: **Evaluation of soluble MICA as a biomarker for lung cancer**
Investigator: **Chien, Jason**
Institution: **Fred Hutchinson Cancer Research Center Clinical Research**
Objective: To determine whether soluble MICA can be detected in CARET serum samples.

Title: **EGFR pathway & lung cancer risk: haplotype analysis ILCCO**
Investigator: **Chen, Chu**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To identify and determine whether certain haplotypes of the EGFR and of downstream signalling molecules are associated with the development of lung cancer.

Title: **Evaluation of Pro-Gastrin Releasing Peptide (ProGRP) in Small Cell Lung Cancer**
Investigator: **Dowell, Barry**
Institution: **Abbott Diagnostics**
Objective: To determine whether pro-GRP is elevated prior to the clinical detection of small cell lung cancer using a case-control study design, and compare serum versus plasma results in a small subset of samples.

Title: **Effect of CARET Intervention on Pro-Gastrin Releasing Peptide in Small Cell Lung Cancer**
Investigator: **Dowell, Barry**
Institution: **Abbott Diagnostics**
Objective: To determine if beta carotene and retinol supplementation increases plasma concentrations of pro-gastrin releasing peptide (ProGRP) in 55 cancer-free participants in the placebo group and 55 participants on the active intervention, as an initial step in exploring the hypothesis that the mechanism of the adverse effect of beta carotene and retinol on lung cancer incidence may be through an increased plasma concentration of Pro-GRP/GRP.

Title: **Associations Between Genetic Factors and Risk of Lung Cancer and Other Diseases**
Investigator: **Goodman, Gary**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To determine possible associations between genetic factors and risk of lung cancer and other diseases. Existing participant samples from CARET serum bank will be sent to collaborating laboratories for analysis.

Title: **Pilot Study of S100 Proteins as Cancer Biomarkers Using CARET Sera**
Investigator: **Hanash, Samir**
Institution: **University of Michigan**
Objective: Pilot study with the short-term goal to test for S100 proteins (MRP8 and MRP14) in stored CARET serum. The long-term goals of this research are to investigate whether these biomarkers are correlated with disease and may help explain the effect of the intervention in the CARET study.

Title: **Association between Folate and B12 Levels and Lung and Prostate Cancers**
Investigator: **King, Irena**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To investigate the relationship between serum folate and B12 levels and lung and prostate cancer incidence in CARET participants. To determine the effect of intervention on the serum folate and B12 levels in CARET participants with and without the diagnoses of lung and prostate cancers.

Title: **SNPs in Lung Cancer Risk and Therapeutic Response**
Investigator: **Petersdorf, Effie**
Institution: **Fred Hutchinson Cancer Research Center Clinical Research**
Objective: To develop PCR arrays for a panel of 20 cytokine gene SNPs and apply the method to test a large clinical population of lung cancer patients and cancer-free individuals. We will collaborate with CARET and will genotype cytokine gene polymorphisms in genomic DNA that has been extracted from the archived blood spots, and will correlate the risk of lung cancer to each SNP using the cancer-free individuals as controls. We will investigate whether among lung cancer patients, the presence of certain SNPs correlates with survival.

Title: **Role of BRM Loss in Tumor Development in the CARET Trial**
Investigator: **Reisman, David**
Institution: **University of Florida Health**
Objective: 1) To determine if there is a greater frequency of BRM and/or BRG1 loss in tumors from the retinoid-treated patients compared with the placebo group. Perform immunohistochemical (IHC) staining to evaluate the BRM and BRG1 status of available tumor slides derived from lung cancers in this trial. 2) To determine if BRM polymorphisms are statistically enriched in retinoid-treated patients compared with placebo-control patients. Calculate odds ratios to determine if there is a statistically significant increase in the frequency of BRM polymorphisms in the cases. Explore whether there exists differences in the association between BRM polymorphisms and cancer risk in the retinoid-treated participants, as compared to the placebo-treated, both through subset analyses (by treatment arm), and in a treatment arm-polymorphism interaction analysis. 3) To determine whether there is a statistically significant association between HIS staining and BRM polymorphisms in this set of patients from the CARET trial; perform logistic regression.

Title: **Detection of Aberrant Hypermethylation of Cancer-Related Genes in Serum as a Screening Tool for Early Detection of Lung Cancer**
Investigator: **Sidransky, David**
Institution: **Johns Hopkins Medicine**
Objective: Pilot study to validate ability to use CARET samples to confirm the possibility of performing a study looking at aberrant promoter hypermethylation of cancer related genes (p16, MGMT, DAP-kinase, GSTP1, and APC) in serum/plasma samples as tool for the early detection of lung cancer in high-risk populations and/or monitoring patients with lung cancer during treatment utilizing CARET specimens.

Title: **Prevalence of Anti-P53 antibodies and P53 Mutations in CARET Participants with Lung or Prostate Cancer.**
Investigator: **Trivers, Glen**
Institution: **National Cancer Institute Human Carcinogenesis**
Objective: To determine the incidence of measurable concentrations of antibodies against the mutant P53 protein in CARET participants with and without lung cancer.

Title: **Association between Growth Factors and Risk of Lung Cancer and Other Diseases**
Investigator: **Williams, James**
Institution: **University of California Irvine Department of Medicine**
Objective: To determine in the CARET population if particular growth factors are associated with the incidence of lung cancer and cardiovascular disease.

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Ovarian Cancer

Title: **Serum Test for Preclinical Detection of Ovarian Cancer**
Investigator: **Lokshin, Anna**
Institution: **University of Pittsburgh Department of Medicine**
Objective: To test the hypothesis that to develop an effective screening algorithm for identification of preclinical (pre-diagnostic) ovarian cancer, algorithm training should be performed on samples collected prior to diagnosis. Our primary objectives are to develop and validate reliable and highly sensitive multimarker assays for early (preclinical) detection and diagnosis of ovarian cancer.

Title: **Detection of Epithelial Ovarian Cancer in CARET study using H-NMR metabonomics**
Investigator: **Odunsi, Kunle**
Institution: **Roswell Park Cancer Institute Gynecologic Oncology**
Objective: To validate 1H-NMR based on metabonomics for early detection utilizing samples from the Carotene and Retinol Efficacy Trial (CARET) study. The primary goal is to evaluate, as a function of time before clinical diagnosis, the capacity of metabonomics to detect preclinical disease. Specimens obtained within 3 years of the closet time point to diagnosis from ovarian cancer cases will be tested utilizing NMR metabonomics.

Title: **Auto-antibodies to p53 for Early Ovarian Cancer Detection**
Investigator: **Urban, Nicole**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To test the hypothesis that addition of the p53 autoantibody assay to CA125, HE4, and mesothelin will enhance the ability to detect ovarian cancer in its early, curable stage.

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Prostate Cancer

Title: **Association between Folate and B12 Levels and Lung and Prostate Cancers**
Investigator: **King, Irena**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To investigate the relationship between serum folate and B12 levels and lung and prostate cancer incidence in CARET participants. To determine the effect of intervention on the serum folate and B12 levels in CARET participants with and without the diagnoses of lung and prostate cancers.

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Multiple Cancers

Title: **SNPs in Cancer Risk and Response**
Investigator: **Petersdorf, Effie**
Institution: **Fred Hutchinson Cancer Research Center Clinical Research**
Objective: To determine the clinical significance of SNPs in immune respone genes in patients diagnosed with cancer. SNPs will be genotyped using PCR-based platforms. We will define the extent and nature of SNPs in a clinical population of patients with cancer cancer (all types excluding non-melanoma skin cancer) and in cancer-free individuals (controls). The frequency of SNPs in the cases and controls will be determined in order to assess the effect of SNPs on cancer survival and response to therapy.

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Asbestosis

Title: **Serum Concentrations of Mesothelin in the Early Diagnosis of Mesothelioma**
Investigator: **Hellstrom, Ingegerd**
Institution: **Pacific Northwest Research Institute**
Objective: Pilot study to determine if mesothelin is elevated in patients with malignant mesothelioma. An initial phase II trial has been added to measure the concentration of MPF/Mesothelin in the serum of 10 patients with a diagnosis of malignant mesothelioma and 10 matched healthy controls.

Title: **Genome-Wide Association Study of Fibrosing Interstitial Lung Diseases**
Investigator: **Schwartz, David**
Institution: **University of Colorado Denver School of Medicine**
Objective: To discover genes and gene variants that are central to the development of fibrosing interstitial lung diseases.

Title: **Is there an Association between Glutathione -S-transferase M1 Deletion and the Severity of Asbestos-Related Lung Disease**
Investigator: **Thornquist, Mark**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To determine if Glutathione S-transferases Mu1 gene deletion is a risk factor for asbestos related fibrosis in this subset of the CARET population.

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Cardiovascular Disease

Title: **Association Between Serum Homocysteine and Folate Levels and Cardiovascular Disease**
Investigator: **Omenn, Gilbert**
Institution: **University of Michigan School of Public Health**
Objective: To investigate associations and relative risks for the folic acid-homocysteine-cardiovascular disease endpoints cascade in CARET participants, testing whether low folic acid generation and ingestion correlate with serum folate levels; serum folate with serum total homocysteine levels; and the relationship between homocysteine levels and cardiovascular disease and coronary heart disease.

Title: **Association between Growth Factors and Risk of Lung Cancer and Other Diseases**
Investigator: **Williams, James**
Institution: **University of California Irvine Department of Medicine**
Objective: To determine in the CARET population if particular growth factors are associated with the incidence of lung cancer and cardiovascular disease.

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Mesothelioma

Title: **Biomarkers for Early Detection of Mesothelioma**
Investigator: **Carbone, Michele**
Institution: **University of Hawaii Cancer Center**
Objective: To evaluate HMGB1 as 1) a diagnostic marker which can distinguish MM from lung cancer, and 2) as a biomarker of mineral fiber exposure and a possible marker of MM, determine whether different fiber types elicit similar increases on HMGB1 in the serum, and whether treatment with aspirin modulates HMGB1 in the sera of an asbestos-exposed cohort from a prospective, double-blind, double cross-over study.

Title: **Serum Concentrations of Mesothelin in the Early Diagnosis of Mesothelioma**
Investigator: **Hellstrom, Ingegerd**
Institution: **Pacific Northwest Research Institute**
Objective: Pilot study to determine if mesothelin is elevated in patients with malignant mesothelioma. An initial phase II trial has been added to measure the concentration of MPF/Mesothelin in the serum of 10 patients with a diagnosis of malignant mesothelioma and 10 matched healthy controls.

Title: **Soluble Mesothelin Related Peptide (SMRP) and Osteopontin (OPN) as Early Detection Markers for Malignant Mesothelioma (MM)**
Investigator: **Pass, Harvey**
Institution: **New York University Medical Center**
Objective: To determine whether SMRP and OPN are specific and sensitive biomarkers for malignant mesothelioma (MM), and whether a rise in the level of either or both markers in a high risk asbestos exposed cohort of patients will occur prior to the development of clinically apparent mesothelioma.

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Dietary/Micronutrient Studies

Title: **Association between Folate and B12 Levels and Lung and Prostate Cancers**
Investigator: **King, Irena**
Institution: **Fred Hutchinson Cancer Research Center Public Health Sciences**
Objective: To investigate the relationship between serum folate and B12 levels and lung and prostate cancer incidence in CARET participants. To determine the effect of intervention on the serum folate and B12 levels in CARET participants with and without the diagnoses of lung and prostate cancers.

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Intervention Effect

Title: **Hepatoxicity-Hepatic Effects of Low Dose Vitamin A Supplementation**
Investigator: **Brodkin, Carl**
Institution: **Harborview Medical Center**
Objective: To assess the technical feasibility of quantitatively determining procollagen levels from frozen banked serum on 10 participants from the CARET intervention group and compare them to 10 participants from the CARET placebo group. The specific aims of this data was to provide an estimate of mean values, variance, and distribution to utilize in sample size calculations for a larger, comprehensive study.

Title: **Release of Tabular Data to External Party**
Investigator: **Freedman, Michal**
Institution: **National Cancer Institute Radiation Epidemiology**
Objective: Dr. Michal Freedman of NCI has analyzed data from the Alpha-tocopherol-Beta-carotene (ATBC) trial and has found a disparity in the occurrence of amyotrophic lateral sclerosis (ALS) between those receiving beta-carotene and those receiving placebo. To help her interpret this finding, she has requested information on the incidence of ALS by intervention group in CARET.

Title: **Determining the Plasma Disappearance and Pharmakokinetics of Beta-Carotene and Long Term Oral Supplementation**
Investigator: **Redlich, Carrie**
Institution: **Yale University School of Medicine**
Objective: To determine the serum concentrations of beta-carotene, retinol, retinyl palmitate, and alpha-tocopherol over time after CARET participants discontinued oral supplementation with beta-carotene. This study began at the time the CARET intervention ended.

Title: **Determining the Plasma Disappearance and Pharmakokinetics of Beta-Carotene after Long-Term Oral Supplementation**
Investigator: **Redlich, Carrie**
Institution: **Yale University School of Medicine**
Objective: To determine the effects of long-term supplementation of Beta-carotene and retinyl palmitate on lipoptroteins (HDL, LDL, VLDL) and other carotenoids and retinoids by analysis of existing serum samples on 52 New Haven CARET participants stored at the CARET Coordinating Center. These results will be compared to existing chart data on CARET Seattle participants.

Title: **Immunization-Vitamin Enhancement in Pneumococcal Vaccine Response**
Investigator: **Williams, James**
Institution: **University of California Department of Medicine**
Objective: To examine the effects of the combination of beta-carotene and retinyl palmitate on antibody responses to immunization for Streptococcus Pneumoniae and influenza infections among CARET participants.

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CARET Specimen Search

CARET Project Application (docx)

Submit Application

by e-mail:
CARET@fredhutch.org

by fax:
206-667-5964

Requesting Specimens & Data

Application Process

CARET has a formal process for submitting and reviewing proposals to use CARET data and specimen samples. Investigators are asked to submit maximum 7 page (11-pt font) scientific proposal addressing specific aims, background and significance, preliminary results (if available), and experimental methods and design. The design and methods section should describe the study population (e.g., inclusion/exclusion criteria, case-control matching criteria), data and specimens being requested, laboratory methods, and statistical analyses and power calculations, as appropriate.

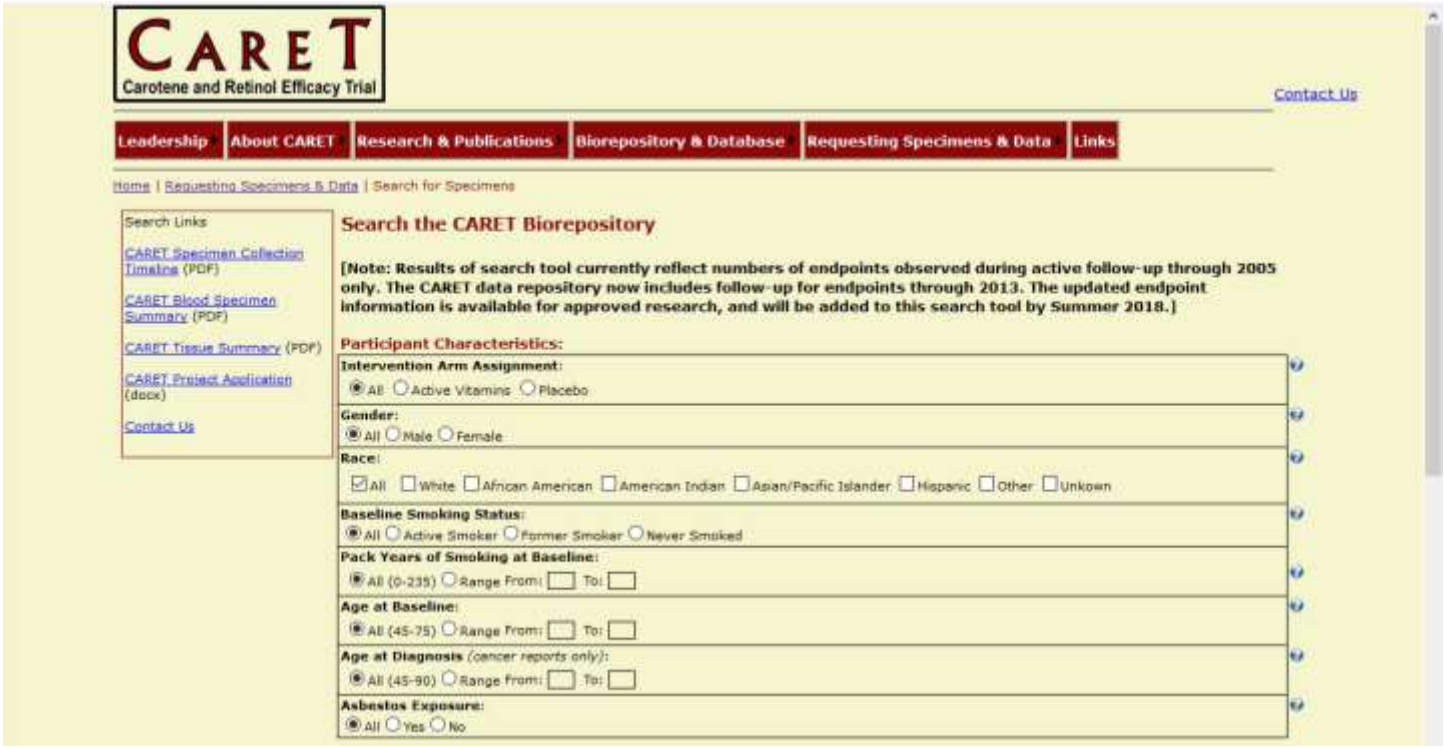
There are CARET expenses associated with sample selection, pulling of samples, data analyses, IRB approval, downsizing of samples, restocking of samples, etc. that will need to be incurred by the applicant. These expenses will need to be negotiated with the CARET Project Manager. If submitting a grant proposal, please discuss these expenses with the CARET Project Manager to include in your grant's budget and justification.

Please submit the CARET Project Application Face Page with your maximum 7 page scientific proposal, and a statement that CARET costs incurred for the study will be negotiated and borne by the investigator by e-mail to CARET@fredhutch.org or by fax to 206-667-5964. Questions about the application process may be sent to CARET@fredhutch.org.

Review Process

The CARET Principal Investigator selects a primary and two secondary reviewers from the CARET Scientific Review Committee. If the proposed area of study is not consistent with any of the CARET investigators' expertise, an independent outside reviewer may be suggested as the primary reviewer.

The primary reviewer is responsible for summarizing the proposal and presenting his or her critique to the CARET Scientific Review Committee. The two secondary reviewers are responsible for presenting their critiques. All members of the CARET Scientific Review Committee discuss the proposal and vote to approve or disapprove and prioritize the proposal relative to other currently approved proposals.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Search the CARET Biorepository
[Note: Results of search tool currently reflect numbers of endpoints observed during active follow-up through 2005 only. The CARET data repository now includes follow-up for endpoints through 2013. The updated endpoint information is available for approved research, and will be added to this search tool by Summer 2018.]
Participant Characteristics:
Intervention Arm Assignment:
All Active Vitamins Placebo
Gender:
All Male Female
Race:
All White African American American Indian Asian/Pacific Islander Hispanic Other Unkown
Baseline Smoking Status:
All Active Smoker Former Smoker Never Smoked
Pack Years of Smoking at Baseline:
All (0-235) Range From: To:
Age at Baseline:
All (45-75) Range From: To:
Age at Diagnosis (cancer reports only):
All (45-90) Range From: To:
Asbestos Exposure:
All Yes No

Endpoints Selection:

Select one or more cancer and/or death endpoints. Although reports in this search tool are restricted to endpoint cases, the CARET Biorepository also includes numerous specimens from disease free participants.

Cancer Endpoints:

☐ All Cancer Types (reports will be based on cancer with earliest date of diagnosis)

Lung Cancer:

☐ Lung, small cell ☐ Lung, all NSCLC ☐ Lung, unknown
☐ Lung, adenocarcinoma ☐ Lung, squamous cell

Other Cancers:

☐ Bladder	☐ Brain	☐ Breast (f)
☐ Colon	☐ Esophagus	☐ Gallbladder
☐ H & N, hypopharynx/ larynx	☐ H & N, nasopharynx/ nasal cavity	☐ H & N, oropharynx/ oral cavity
☐ H & N, salivary glands	☐ Kidney	☐ Leukemia
☐ Liver	☐ Lymphoma	☐ Melanoma
☐ Mesothelioma	☐ Multiple myeloma	☐ Ovary
☐ Pancreas	☐ Prostate	☐ Rectum
☐ Stomach	☐ Uterus, NOS/ corpus uteri	

☐ Other cancers, specify

Mortality Endpoints:

Cancer Mortality Endpoints:

☐ All Cancers

☐ Lung	☐ Bladder	☐ Brain
☐ Breast (f)	☐ Colon	☐ Esophagus
☐ Gallbladder	☐ H & N, hypopharynx/ larynx	☐ H & N, nasopharynx/ nasal cavity
☐ H & N, oropharynx/ oral cavity	☐ H & N, salivary glands	☐ Kidney
☐ Leukemia	☐ Liver	☐ Lymphoma
☐ Melanoma	☐ Mesothelioma	☐ Multiple myeloma
☐ Ovary	☐ Pancreas	☐ Prostate
☐ Rectum	☐ Stomach	☐ Uterus, NOS/ corpus uteri

☐ Other cancers, specify

CVD and other non-cancer causes

☐ All CVDs and non-cancer causes

☐ CVD, ASCHD	☐ CVD, cerebrovascular	☐ CVD, ASCVD
☐ CVD, other	☐ Alzheimer's disease	☐ Asbestosis
☐ Chronic liver disease and cirrhosis	☐ COPD and allied conditions	☐ Diabetes mellitus
☐ Pneumonia	☐ Postinflammatory pulmonary fibrosis	☐ Renal failure
☐ Septicemia	☐ Suicide	☐ Unknown cause

☐ Other causes, specify

Specimen Type Selection:

Select specimen type:

○ Serum (collected 1985-1997) ○ Plasma (collected 1985-1989) ○ DNA/Whole Blood

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- Fred Hutchinson Cancer Research Center
- National Cancer Institute

Related Studies

- Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)
- International Lung Cancer Consortium (ILCCO)
- Physicians' Health Study (PHS)

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If you have questions about the Carotene and Retinol Efficacy Trial, please contact us:

By phone: (206) 667-4990
By fax: (206) 667-5964
By mail: CARET
FHCRC/COMPASS
1100 Fairview Ave. N. M3-A306
P.O. Box 19024
Seattle, WA 98109-1024
By e-mail: send to CARET@fredhutch.org or use the form below

Your name:

Your email address:

Your Institution:

Your telephone:

Subject of email: Select the subject of the email from this list...

Message:

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16 Appendix 9 – Cover Letter for Consent (No Cancer) – Separate Document

17 Appendix 10 – Consent – Separate Document

18 Appendix 11 – Medical Release Form – Separate Document

19 Appendix 12 – Letter to Pathology and Tissue Request

CARET
an enduring legacy of the CARET
Lung Cancer Prevention Study
1100 Fairview Ave N, M3-A306
PO Box 19024
Seattle, WA 98109-1024
206-667-4990

Date: _____:
Institution: _____:
Name: _____:
DOB: _____:
SS#: _____:

CARET
Chu Chen, PhD, NRCC, DABCC
Principal Investigator
Mail Stop M3-A306
Tel: 206.667.4990
Fax: 206.667.5964
E-mail:cchen@fredhutch.org

Attention Medical Records:

The Fred Hutchinson Cancer Center is involved in a national cancer prevention trial (CARET) which studied the effect of vitamin A and beta-carotene and the incidence of lung cancer in high-risk populations. Although the active intervention has been stopped, the CARET Investigators have an infrastructure grant to support the biorepository.

_____ is/was a participant in this study. As part of our study, we collect pathology samples of those participants diagnosed with lung cancer. This group will represent a unique national resource to study the genetics of lung cancer. These specimens will be retained in our tissue bank permanently.

We understand that your department may have blocks/slides and the corresponding pathology report from this participant in connection with a diagnosis of lung cancer. We would like to obtain representative blocks of tumor and the corresponding diagnostic H&E slide. If no blocks are available, any slides would be appreciated. We will also accept images of the H&E slide if you are unable to release.

Enclosed is a copy of the _____ as well as our Request Form.

Please send the specimens to:

Fred Hutchinson Cancer Center
CARET Coordinating Center
ATTN: _____
1100 Fairview Ave N, M3-A306
Seattle, WA 98109

Thank you for your prompt attention to this request. If you have any questions or concerns, please feel free to call CARET at (206) 667-4990. Thank you.

Sincerely,

Chu Chen, PhD, NRCC, DABCC
CARET Principal Investigator

CARET
an enduring legacy of the CARET
Lung Cancer Prevention Study
1100 Fairview Ave N, M3-A306
PO Box 19024
Seattle, WA 98109-1024
206-667-4990

FRED HUTCH
CURES START HERE

To: _____
From: _____
Date: _____
Re: NAME: _____
Vital Status: _____
DOB: _____
SS#: _____

Please include copies of the selected reports:

- ❒ Lung Cancer Endpoint
  - ❒ Pathology Report
  - ❒ Pathology Tissue Specimens (Facility "check all that you are able to provide")
    - ❒ Block(s)
    - ❒ H&E Slide(s)
    - ❒ Unstained Slide(s)
    - ❒ Image(s) of H&E Slide(s)
    - ❒ None of the above
- ❒ Initial Treatment (check all that apply)
  - ❒ Chemotherapy
    - ❒ Names of agents:

      _____
      _____
      _____
  - ❒ Radiation
  - ❒ Surgery

If the patient referenced above is known to be deceased, please provide date of death _____ and cause of death _____

Please send the specimens to:

Fred Hutchinson Cancer Center
CARET Coordinating Center
ATTN: _____
1100 Fairview Ave N, M3-A306
Seattle, WA 98109

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20 Appendix 13 – Telephone Scripts – Separate Document