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Ongoing Use of Data and Specimens from NCI Sponsored Cancer Prevention Clinical Trials in the Community Clinical Oncology Program

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Abstract

Large cancer prevention trials provide opportunities to collect a wide array of data and biospecimens at study entry and longitudinally, for a healthy, aging population without cancer. This provides an opportunity to use pre-diagnostic data and specimens to evaluate hypotheses about the initial development of cancer. This paper reports on strides made by, and future possibilities for, the use of accessible biorepositories developed from precisely annotated samples obtained through large-scale National Cancer Institute (NCI)-sponsored cancer prevention clinical trials conducted by the NCI Cooperative Groups. These large cancer prevention studies, which have enrolled over 80,000 volunteers, continue to contribute to our understanding of cancer development more than 10 years after they were closed.

Introduction

The National Cancer Institute (NCI) Cooperative Groups have been an important program for the evaluation of effective cancer treatment regimens through the conduct of their clinical trials. Their scientific scope was expanded in 1989 to cover cancer prevention and control through the Community Clinical Oncology Program (CCOP). From the beginning, this program was envisioned as a network that would lead the way for innovative cancer prevention and control strategies.[1]

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Through their cooperative agreements as CCOP Research Bases, the Groups and selected Cancer Centers were funded to design, develop and conduct studies that would evaluate agents and approaches to: 1) reduce the risk of developing cancer; 2) mitigate cancer treatment-related side effects; and 3) improve quality of life. During the 1990s, several cancer prevention trials were initiated, including the Prostate Cancer Prevention Trial (PCPT),[2] the Selenium and Vitamin E Cancer Prevention Trial (SELECT),[3] the Breast Cancer Prevention Trial (BCPT),[4] and the Study of Tamoxifen and Raloxifene (STAR).[5] The previously funded CCOP Research Bases and the newly funded NCI Community Oncology Research Program (NCORP) Research Bases are listed in Table 1. In 2014, NCI restructured the community programs (CCOP, Minority Based Community Clinical Oncology Program, and the NCI Community Cancer Centers Program (NCCCP) into the NCI Community Oncology Research Program.[6]

From 1999 through 2014, over 300 studies of cancer prevention and control were conducted, 20% of which were prevention, 70% control, and 10% “other.” While the scientific scope of the cancer prevention and control program is quite broad, each CCOP Research Base was expected to focus on the aspects most relevant to its own overall cancer research agenda. The bulk of the prevention trials were smaller feasibility studies, but the large phase III trials were provided additional resources that allowed more comprehensive collection of data and specimens. In designing these studies, investigators also noted possibilities for the use of the specimens and data beyond the initial goals of the studies; the consent forms of the studies anticipated these possibilities and research needs. This article reviews the large prevention trials and the ongoing opportunities for using the data and specimens for addressing validation of hypotheses.

Cancer Prevention Trials

The large-scale prevention trials established whether an agent could reduce a person's risk for developing cancer. They were developed to have specimens and extended demographic information not typically collected in cancer treatment trials. Healthy participants without cancer were recruited, which provided the capacity to 1) evaluate markers for early detection of cancers, 2) develop risk models using demographic and biologic factors, and 3) assess risk for unexpected outcomes.

To answer important translational as well as clinical questions, biorepositories of blood and tissue were established along with an expanded baseline data set (including demographic data, diet, medication, specific co-morbidities, and other qualities). These samples and relevant clinical outcome data are now available to other researchers through a process established by each Group that conducted such a trial. While the primary objectives of these trials were the evaluation of a reduction in a specific type of cancer incidence or prevalence, additional clinically relevant outcomes were collected pertaining to other cancer endpoints, adverse effects, and quality of life (QOL). In studies with participants who were at increased risk of developing cancer, but who did not already have cancer, the data and specimens are linked to a variety of cancer outcomes. This provided unique opportunities to characterize cancer risk, and potentially validate markers for early detection and prognosis.

The target population in the phase III trials defined a number of important study design features, including recruitment strategies, expected event rate, duration of the study and generalizability of results. By targeting a population with an increased risk of cancer incidence, a smaller sample size was needed, and the study could theoretically be completed more quickly. A modified Gail model was utilized in the Breast Cancer Prevention Trial (BCPT) and Study of Tamoxifen and Raloxifene (STAR) prevention trials to identify women at increased risk for breast cancer and to quantify that risk.[7] Over 250,000 women underwent the risk assessment process to allow the entry of 33,135 women into the two trials. The result, however, was a population that was, on average, at more than twice the minimum eligible risk: both studies were thus able to reduce the required sample size. But recruiting a specific subpopulation can be challenging and results may not be generalizable to the larger population at risk. Prevention trials tend to target middle-aged or older participants who are at increased risk for most cancers, and they may be taking concomitant medication for other conditions. Possible interactions between medications and the prevention agent are thus interactions that should be considered, as well as competing risks from co-morbid conditions.

Unlike patients who have been diagnosed with cancer and who may be willing to trade some aspects of QOL for the possibility of a treatment benefit, the participant without active cancer may have different perceptions for this tradeoff decision. For this reason, prevention trials tend to evaluate changes in longitudinal assessment of QOL that may be attributed to the prevention agent.

Major Prostate and Breast Cancer Prevention Trials

Summary information about the four large-scale prostate and breast cancer prevention trials is detailed in Table 2 and includes the sponsoring organization, intervention, study size, time of accrual, and results.

For prostate cancer, PCPT was undertaken to determine whether finasteride (an inhibitor of steroid 5-α-reductase, the enzyme that converts testosterone to the more potent androgen DHT), could reduce the prevalence of prostate cancer among initially healthy men aged 55 and older during a 7-year period. PCPT was a double-blind, placebo-controlled, phase III trial that began enrolling in 1993 and by 1997 had randomized 18,882 participants from 210 clinical sites in the U.S. and Canada. At study entry, men had a normal digital rectal exam (DRE) and a PSA ≤ 3.0 ng/dl. Prostate biopsies were recommended during the trial for men with either an elevated PSA (> 4.0 ng/ml adjusted) or DRE suspicious for cancer. All men were recommended to have an end-of-study biopsy at their 7-year anniversary regardless of their PSA level or DRE result. Tissue from all positive and negative biopsies along with prostatectomies was submitted, as was annual serum and a one-time white blood cell collection for DNA. Details of the design and implementation of PCPT are published.[8, 9] PCPT was stopped 15 months earlier than planned when it achieved its primary endpoint. A 25% relative risk reduction in prostate cancer was observed with finasteride. But Gleason grade 7 to 10 tumors (the higher the grade, the higher the risk of aggressive disease) also were more common in the finasteride group (280 versus 237).[2,10]

SELECT was a randomized, placebo-controlled, phase III trial of selenium and/or vitamin E supplementation for prostate cancer prevention. A discussion of the trial design and rationale are published.[11] In brief, both the selenium and vitamin E prevention evidence came from secondary analyses of prior phase III trials. Two other studies are worth noting here. The NPC study, which was conducted in an area of the U.S. where daily selenium intake is low, was a NCI-supported randomized trial of 1,312 patients with prior skin cancer randomized to 200 ug of elemental selenium (in the form of high-selenium yeast) or placebo. NPC yielded statistically significant reductions in the risks of prostate cancer (63%), lung cancer (46%) and colorectal cancer (58%).[12] Another study, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC), conducted in Finland and the U.S., was designed to determine whether α-tocopherol and /or β-carotene would reduce the risk of lung cancer among 29,133 male smokers, and also looked at other cancer incidence. The incidence of new prostate cancer cases and prostate-specific mortality significantly decreased by 32% and 41%, respectively with alpha tocopherol.[13]

In SELECT, a panel of experts was convened to decide on the form and daily dose of each supplement to be used. Selenomethionine (200 ug) and all rac-α-tocopherol acetate (400 IU = 400 mg) were chosen.[11] The major eligibility requirements included age of > 50 years for African American men and > 55 years for all other men, no prior prostate-cancer diagnosis, PSA < 4 ng/ml, and a DRE not suspicious for cancer. Participants were recommended during annual clinic visits to undergo a PSA test and DRE according to the standard of care at their study sites and the participants' wishes. A total of 35,533 men were accrued at 427 participating sites in the U.S., Canada and Puerto Rico from 2001 to 2004, achieving minority representation of 21% (15% African Americans). Also, 93% of men had at least one post-randomization PSA measure with 79% having three or more post-baseline PSA screens.

With a median follow-up of 5.5 years and based on a planned futility interim analysis, there were no statistically significant differences between the four arms in terms of prostate cancer incidence, incidence of any other pre-specified cancer endpoint, including lung or colorectal cancer, or survival.[3] In a subsequent analysis conducted at the time when the originally scheduled primary analysis was planned and included 521 additional prostate cancer cases, a statistically significant increase in the risk of prostate cancer was found in the vitamin E arm compared to placebo (hazard ratio 1.17, p=0.008), but this increase was not observed in the combined vitamin E and selenium arm. The interaction of selenium with vitamin E was statistically significant (p=0.02).[14] Active follow-up has ended for both PCPT and SELECT.

For breast cancer, the BCPT and STAR trials screened more than a quarter of a million candidates, and randomized more than 33,000 healthy women at increased risk for the future development of breast cancer. Both studies focused on the use of selective estrogen receptor modulators (SERMs) as a method to reduce the development of primary invasive breast cancer. Women who entered the studies were asked to submit a blood specimen prior to the start of protocol therapy. The samples are stored at −70° C as multiple aliquots of buffy coats and serum. The women were also consented to allow submission of tumor blocks of all breast cancers and other primary cancers, including endometrial cancers.

In June 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) began the P-1 trial, also known as BCPT, a Phase III randomized double-blind study to evaluate the effectiveness of 5 years of tamoxifen vs. placebo in the prevention of breast cancer in healthy women at increased risk for the disease.

Tamoxifen, an oral Selective Estrogen Receptor Modulator (SERM) had been used extensively in the treatment of advanced and primary estrogen receptor-positive breast cancer.[15,16,17,18,19,20,21,22,23,24] In the adjuvant setting, it not only reduced tumor recurrence and improved survival, it significantly reduced the risk of contralateral breast cancer.[25-29]

The drug had also been extensively evaluated in the laboratory, including evidence to indicate that it interfered with both the initiation and promotion of tumors in experimental systems.[30-34] By September 1997, 13,388 women 35 years of age or older with a 5-year predicted risk for breast cancer of at least 1.66% or a history of lobular carcinoma in situ (LCIS) had been randomized into the study. Breast cancer risk assessment was calculated using a modification of the algorithm developed by Gail, et al.[35,36]

With a mean time on study of 47.7 months, the initial results demonstrated that tamoxifen reduced the risk of invasive breast cancer by 49% ($p<.0001$, with a cumulative incidence through 69 months of 43.4 vs. 22.0 per 1,000 women in the placebo and tamoxifen groups).[37] Tamoxifen also reduced the risk of non-invasive breast cancer by 50% ($p<.002$). The risk of endometrial cancer was significantly increased in the tamoxifen-treated group (rr 2.53 C.I. 1.35-4.97 5.4 per 1,000 placebo vs. 13.0 per 1,000 tamoxifen). In the treatment of patients with breast cancer, tamoxifen use was associated with an increase in thromboembolic events. In the P-1 study, the rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group, but these events occurred more frequently in the post-menopausal group (50 years or older).

The Study of Tamoxifen and Raloxifene (STAR), also known as NSABP P-2, began in July 1999 and ultimately enrolled more than 19,000 women. The study is a Phase III prospective double-blind randomized trial that compared the relative effects and safety of tamoxifen and another oral SERM, raloxifene (Evista, Eli Lilly, Indianapolis, IN), on the risk of developing breast cancer and other disease outcomes. Raloxifene was approved for the treatment and prevention of osteoporosis in post-menopausal women. In fracture prevention studies, comparing raloxifene to placebo, breast cancer incidence was a secondary endpoint, but raloxifene dramatically reduced the risk of ER+ breast cancer by up to 72% with no excess of endometrial cancer.[38-45] Few of the women in these fracture prevention studies were at increased risk for breast cancer, and a head-to-head to comparison of tamoxifen and raloxifene in a group of women at increased risk was a logical next step.

The eligibility criteria for the STAR trial were almost identical to the BCPT (P-1) trial, including the Gail Score of at least 1.66%, but the study was restricted to post-menopausal women because raloxifene had not been fully evaluated in pre-menopausal women for either effectiveness or safety. By November 2004, 19,747 women were randomized to receive either tamoxifen or raloxifene. With a mean follow-up time of 3.9 years, there was no difference between the effect of tamoxifen and the effect of raloxifene on the incidence of

invasive breast cancer.[46] There were 163 cases in the tamoxifen group and 168 cases in those assigned to raloxifene. In the tamoxifen group the rate per 1,000 was 4.30; in the raloxifene group the rate per 1,000 was 4.41 (rr 1.02; 95% CI, 0.82-1.28). The cumulative incidence through 72 months was 25.1 for tamoxifen and 24.8 per 1,000 for the raloxifene group (p=0.83). Thromboembolic events were less frequent in the raloxifene group (rr, 0.70; 95% CI 0.54-0.91). There were 36 cases of uterine cancer in the tamoxifen group and 23 cases in the raloxifene group (rr, 0.62; 95% CI 0.35-1.08). No difference was found for other invasive cancer sites, or ischemic heart disease. The number of osteoporotic fractures were similar in the two groups. An updated analysis with an 81-month median follow-up (5 years of therapy plus follow-up off therapy) demonstrated that raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer with far less toxicity.[47]

After a prevention trial has reached its primary objective and has reported the results of the prevention agent, there are a number of follow-up hypotheses that can be addressed using the trial and other extended epidemiologic data merged with data generated from the interrogation of the biologic repository.

A. Opportunities Using the Randomized Trial Structure

Because prevention trials, unlike epidemiologic cohort studies, randomly assign exposure of one or more prevention agents to study participants, they provide a framework which allows for a number of valuable secondary hypotheses to be addressed, beyond the primary objective of each trial, with minimal bias expected in the assessment of factors related to treatment effect. Unlike treatment trials, prevention trials have the ability to look at risk in non-cancer patients. In total, more specimens and data are collected on these participants than would normally be collected on cancer patients. Table 3 details the biologic specimens and schedule of collection in the four large cancer prevention trials. These types of hypotheses can be grouped into five general categories: 1) evaluation of the prevention agent on prospectively identified outcomes other than the primary outcome of the trial; 2) ancillary studies for other endpoints; 3) assessment of subsets of participants that may be more or less likely to benefit from the preventive agent; 4) exploration of potential mechanistic pathways that might provide insight into why a prevention candidate agent did or did not work (e.g., did the agent hit the expected biologic target within each individual?); and 5) assessment of the economic impact of a particular prevention strategy.

(1) Other outcomes/safety

Some examples of “other endpoints” that have been evaluated in prevention trials include the findings that neither vitamin E nor selenium had an effect on incident bladder cancer;[48] other cancers or cardiovascular endpoints in SELECT;[16] and the preventive effect of finasteride on incident benign prostatic hyperplasia in PCPT.[49] In BCPT, the impact of tamoxifen use on benign disease was evaluated.[50] Additionally, the collection of long-term endpoints including cardiovascular, other cancers, and other medical events, can be used to assess the long-term safety of these prevention strategies. In the BCPT and STAR trials, the incidence of endometrial cancer, hysterectomy for benign disease, and thromboembolic events, all known side-effects of tamoxifen, have been evaluated for up to 10 years post-entry. In prevention trials where there is a relatively low tolerance for side effects by healthy

cancer-free participants, longitudinal QOL comparisons between prevention groups is important to evaluate.[51-54] Often, this can be done in a subset of local sites or a fraction of randomly selected patients to minimize the data collection burden for the participant, local site and coordinating center.

(2) Ancillary studies

Large population-based prevention trials offer the ability to look at disease endpoints. For example, the Women's Health Initiative (WHI) enrolled healthy post-menopausal women into a set of clinical trials and an observational study to evaluate multiple endpoints including cardiovascular disease, breast cancer, bone disease, and others. Individual protocols are developed and carefully integrated into prevention trials. From the perspective of the funding agencies, ancillary studies are an efficient mechanism to answer important questions in the same population as the randomized trial, using pre-existing clinical study sites with reduced recruitment efforts and use of existing study data.

SELECT had a primary objective of assessing the impact of selenium and vitamin E on prostate cancer incidence. At the time of design, interest in other disease endpoints and anti-oxidants was very high. Four ancillary studies were incorporated in SELECT. One ancillary study with several endpoints was added to STAR. While this approach can provide an efficient way to explore additional hypotheses, issues of coordination exist. Table 4 enumerates the ancillary studies in two of the large cancer prevention trials. Common characteristics of these ancillary studies to SELECT were that they had study objectives independent of prostate cancer prevention, with hypotheses that involved either selenium, vitamin E or the combination.[55] They used the SELECT participant data, recruited from the participants within SELECT, added additional specimen collections specific to their participants (not listed here), provided additional data management, and were co-managed by SELECT together with their independent ancillary study teams.[56] The ancillary eye study concluded that long-term daily supplementation with selenium and/or vitamin E is unlikely to have a large beneficial effect on age-related cataract.[57] The ancillary study showed no effect of supplementation with selenium and/or vitamin E on lung function. However, for current smokers who were randomized to selenium, there was an attenuated decline in FEV 25-75.[58] The ancillary study for STAR was similarly nested into the primary study.

(3) Subsets and varying preventive effect

Within the design of the primary trial it may be possible to identify specific mechanistic studies to evaluate subsets. Once the primary endpoints are complete, the data and specimens become a resource for epidemiological studies with careful delineation of exposure to the intervention, and evaluation for associations and interactions, and generation of hypotheses. It is also of general public interest to try and refine the target population that potentially should, and should not receive a cancer prevention agent after the trial is completed and reported. This second group of hypotheses can be evaluated in the randomized trial setting by estimating the statistical interaction of the preventive agent effect with factors defining a subpopulation of interest. This factor can be something as simple as a phenotype such as race, age, body size (BMI, waist-hip ratio), family history of disease, or level of physical activity. The effect modifying factor may be related to concomitant

medications, or lifestyle factors such as obesity, smoking, or alcohol use, or other co-morbid conditions such as diabetes.[59,60,61] More importantly, the candidate factor may be biologically-based, such as pre-study serum c-peptide and its impact on the effect of finasteride on prostate cancer incidence in PCPT;[62] a genetic marker such as selenium-metabolizing genes and the impact of selenium on prostate cancer incidence in SELECT; or some combination of genetic, blood-based and demographic factors requiring careful and sometimes complex statistical modeling. The relative risk of finasteride versus placebo in terms of prostate cancer incidence was relatively consistent across all pre-specified groups of interest including race, family history, age group, and baseline PSA level.[2] In SELECT, there was a pre-specified evaluation of the effects of selenium and vitamin E by smoking status (current vs. former vs. never) based on the ATBC smoking population that provided the tocopherol rationale for SELECT. There was no evidence of an interaction between smoking and either study supplement.[3]

Because the breast cancer prevention trials involved a higher-risk cohort, subset studies have evaluated breast cancer specific subsets for efficacy, such as deleterious BRCA gene mutations,[63] effects of the SERMS on mammographic density,[64] estrogen receptor expression,[65] possible association between thrombotic events Factor V Leiden and Prothrombin levels,[66,67] in addition to evaluating risk factors such as obesity and physical activity. Frequently, evaluations of subsets for varying effects of the prevention intervention are underpowered. There are also concerns about the impact of multiple testing on the rate of false positive and false negative conclusions about effects on subsets. Further validation would likely be required before an impact would be accepted with regard to the pattern of use of the preventive agent.

(4) Mechanism

Some results of prevention trials are unexpected, and further exploration of potential mechanisms of action of the agent may provide insight into the observed findings. Because SELECT results suggested a negative effect of vitamin E supplementation on prostate cancer risk, of great public health interest was the assessment of an individual's baseline plasma alpha- and gamma-tocopherol level (or baseline toenail selenium) and whether the response to vitamin E or selenium supplementation varied by tocopherol (or selenium) level.[68,69] With millions of men taking daily dietary supplements, knowing whether there is a risk for healthy men to take too much vitamin E or selenium has implications far beyond the SELECT trial population. The SELECT trial had pre-specified hypotheses related to the potential effect modification of baseline levels of plasma alpha and gamma tocopherol on the relationship between vitamin E supplementation and prostate cancer, and effect modification of both plasma and toenail selenium on the relationship between selenium supplementation and prostate cancer. These could also be characterized as “safety” hypotheses related to dose of agents. Findings indicated that higher alpha-tocopherol concentrations may interact with selenomethionine supplements to increase high grade prostate cancer risk,[68] and selenium supplementation did not benefit men with low selenium status but increased the risk of high-grade prostate cancer among men with high selenium status.[69]

In PCPT, there was an observed slightly higher incidence of high-grade prostate cancer (potentially a more lethal form of disease) in men randomized to the finasteride arm compared to the placebo arm. Again, potential mechanisms of action were critical to explore. Having collected and banked longitudinal serum measures on all subjects during the conduct of this trial made it possible to explore whether changes in serum androgen levels in the finasteride arm were correlated with subsequent prostate cancer outcomes (high grade vs. low grade vs. no cancer). No obvious connection was found.[70]

Similarly, CYP2D6 enzyme activity was thought to potentially impact tamoxifen effectiveness in the adjuvant treatment of invasive breast cancer. A nested case control study of BCPT and STAR participants evaluated the impact of alterations in CYP2D6 metabolism and found no association on either tamoxifen or raloxifene efficacy in the chemoprevention of breast cancer.[71] In conjunction with the Pharmacogenomics Research Group at the Mayo Clinic, and the RIKEN Center for Integrative Medical Science in Ykohama, Japan, a genome-wide association study (GWAS) using DNA samples from BCPT and STAR was performed. The results of the study provided not merely candidate biomarkers for SERM breast cancer prevention, but also novel insight into the mechanisms of SERM action. [72] A follow-up deep sequencing study has been conducted.

(5) Cost of implementing the prevention strategy

Prevention trials that are interpreted to be positive for the outcome of interest eventually are evaluated in terms of the acceptability of implementing the strategy. While none of the prevention trials captured economic data for a formal cost effectiveness analyses, some analyses were done to consider the tradeoffs between benefits for reducing the development of cancer with the development of side effects and unexpected outcomes. Evaluating the number of subjects needed to treat (i.e., number needed to treat, or NNT) with a prevention agent for a specific duration of time in order to prevent one case of cancer provides a framework for evaluating the impact of the prevention strategy if applied to the larger population. In PCPT, patients were stratified at study entry by their predicted baseline risk of prostate cancer based on a statistical model using age, race, family history and PSA level. The preventive effect of finasteride was seen in all risk groups, and those with a higher baseline risk of prostate cancer therefore had, as one would expect, a lower NNT.[73] Similar evaluations have been conducted using the data from the BCPT and STAR trials.[74] The risks and benefits of treatment with tamoxifen or raloxifene depend on age, race, breast cancer risk, menopausal status and history of hysterectomy. A benefit/risk index has been developed to assist in the clinical evaluation to initiate chemoprevention and to compare the benefits and the risks of specific SERMs.[74]

B. Opportunities for Epidemiologic Research

The samples and the relevant clinical outcome data are available to other researchers through a process established by the Group that conducted the trial. Both the PCPT and SELECT were developed and conducted through the Southwest Oncology Group (SWOG) taking the lead role. The BCPT and STAR trials were developed and conducted through the National Surgical Adjuvant Breast and Bowel Project (NSABP). Each organization has

presented these studies with their biorepositories as resources for use by other investigators at a variety of professional meetings.[75,76]

After the trial is completed, resources are needed to continue to store, access and distribute the data and specimens to the research community. Some trials, such as the WHI, the Carotene and Retinol Efficacy Trial (CARET), the ATBC, PCPT and SELECT have transitioned into cohorts which are included in the Cancer Epidemiology Descriptive Cohort Database (CEDCD). This is a public database with descriptive information on cohorts studying cancer as a primary outcome. The database, which seeks to increase transparency by providing information on existing cohort infrastructures to foster collaboration and maximize utilization, can be accessed via the following URL: http://cedcd.nci.nih.gov/.

Utilization and Conservation of the Biologic Repository

In order to both utilize and conserve the valuable biologic samples in the repository, epidemiologic sub-studies can be designed which allow for a sampling of the “cases” of interest and also those who are not cases, but still providing strong statistical properties for testing biologic hypotheses of interest. A nested case-control study was chosen for addressing the biologic hypotheses in the PCPT, and the same sampling design has been used as the backbone for other translational proposals to allow for cross-project collaborations using multiple biologic measures. A case-cohort study was imbedded within SELECT. The case-cohort design was chosen as an efficient sampling method where all incident prostate cancer cases and a subset of the overall trials were chosen. Because ancillary study endpoints were a highly integrated priority, having a common cohort that can be used across ancillaries was a valuable feature.

Data and Biologic Samples

The expanded demographic and baseline information was dependent upon the target population and the anticipated co-morbidities that may have interacted with the anticipated side effect profiles. Thus, smoking and family history was captured on all studies, and dietary information and supplement use was captured on SELECT. Sometimes there is a common theme among biologic and clinical hypotheses that allows the combining of aims in a thematic project, and also allows for project interactions. One example is “The Biology of the Prostate Cancer Prevention Trial (PCPT P01),” which was funded in May 2005 shortly after the primary study results were published. The theme unifying the five projects within the P01 was the genetic, metabolic and environmental factors associated with the risks of prostate cancer overall and high-grade prostate cancer specifically; and the effects of these factors on the efficacy of finasteride as a cancer prevention agent. This program also included studies to better understand the mechanisms underlying these risk factor associations. The five projects were related to androgen metabolism, diet and diet-related factors, insulin-like growth factor axis and insulin resistance, genotypic and phenotypic studies of inflammation, and oxidative damage and DNA repair in the PCPT.[77]

A selection of some results from the PCPT program project included finding no association between CAG repeat length and prostate cancer,[78] no association of serum vitamin D and prostate cancer,[79] and no association of serum lycopene and prostate cancer.[80] For serum

cholesterol, men with low concentrations had a lower risk of high-grade prostate cancer risk; however, there were no associations with total, Gleason 2-6 and Gleason 7 prostate cancer.[81] A treatment interaction was noted with serum C-peptide. Among men in the placebo arm of PCPT, those with higher vs. lower serum C-peptide had a nearly two-fold increase risk of high-grade prostate cancer. In contrast, for men on the finasteride arm, C-peptide was not associated with overall or high grade disease.[62]

Each trial had patient information collected at baseline about pre-existing conditions (hypertension, diabetes, history of thromboembolic events) that was specific to the population of participants in the trial and the agents that were used. These factors along with blood samples collected serially over the course of the trial can be used to develop risk calculators,[82] models for disease progression, and epidemiology studies. Examples of ongoing studies include: GWAS for risk of pancreatic cancer[83] or esophageal cancer, baseline selenium levels and risk of different types of cancer, and association of baseline risk of inflammatory markers and cancer.

Leveraging External Data for Clinical Trial and Epidemiologic Hypotheses

While on cancer treatment trials, patients often are followed for survival; in the prevention trials, the follow-up ends within a predefined timeframe. Complete and accurate ascertainment of death and other disease outcomes are critical during the trial, but often are also of interest after the trial has completed. In order to evaluate the long-term outcomes, an approach to passive follow-up has been used. The Social Security Death Index (SSDI) was used to search for deaths in both PCPT and SELECT that had not been reported during the trial or after closure of the study sites. The SSDI returns a date of death, but unfortunately not a cause of death. When last performed in May 2012, 27% of men in the PCPT and 8% of those in SELECT had died, but cause was known only for those who died during the active conduct of each trial. In order to supplement the SSDI information, the National Death Index Plus (NDI) is being used to obtain information on cause of death. Upon review of the NDI Plus data, all previously undocumented cancers identified as either the primary or contributory cause of death will be documented.

Another useful approach to understanding long-term outcomes is to link the clinical trial database to the NCI Surveillance, Epidemiology, and End Results (SEER) Program-Medicare Database at http://appliedresearch.cancer.gov/seermedicare/. The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about elderly persons with cancer, and can be used for epidemiological and health services research.

This approach allows investigators to identify and/or validate the diagnosis of cancers in trials. Furthermore, they can learn about other conditions and outcomes like neurologic diseases or cardiovascular events, late-term effects of the prevention agent, and medications received. This approach is feasible when the bulk of the population is over 65 years of age. This database can enhance an investigator's ability to evaluate blood and tissue markers that are prognostic of prostate cancer survival. The trial provides information about risk factors, cancer incidence, and biologic materials. Other databases, such as SSDI, NDI, and SEER-

Medicare, allow for correlation of biologic factors with overall survival and cause-specific survival endpoints.

The WHI has used Medicare data to obtain or validate cardiovascular endpoints that were self-reported by women in their trial.[84,85] The CARET trial used SEER data to identify prostate cancer cases in order to enhance their molecular and nutritional epidemiology studies.[86-88]

Other Prevention Questions and Study Designs

In addition to the four large cancer prevention trials, several smaller phase III cancer prevention studies evaluating agents to reduce the development of second primary cancers have been completed. Some of these studies had prospective translational endpoints built into the design and thus, were able to establish biospecimen repositories as well.

In these “secondary prevention” trials, the patients have a higher risk for multiple cancers either because of their exposure to tobacco, or due to an underlying hereditary risk. Examples of smaller secondary prevention trials are listed in Table 5.[89-94] Two of these are in early stage non-small cell lung cancer patients who are at risk for other aerodigestive malignancies. However, these patients often have recurrence of their primary disease prior to the development of their second cancer, which would obviate the benefit from chemoprevention.

Not all prevention questions can be asked in the setting of a randomized controlled trial. In 2002, when BRCA mutation testing was not widespread, the Gynecologic Oncology Group (GOG) initiated a prospective observational cohort of women at high risk for ovarian cancer who chose either to be followed with an intensive screening regimen, or to undergo prophylactic bilateral salpingo-oophorectomy (GOG-0199).[95] Over 2,500 women at increased risk for ovarian cancer were entered with over 900 women on the prophylactic surgery arm, and all were tested for their BRCA mutation status. In particular, this study has high-risk women with known negative BRCA mutations. A biorepository of serial samples collected in the screening arm, and pathologic tissue collected in the surgical arm exists with a variety of risk data and patient reported outcomes. These samples have been included in several international projects, such as the Consortium of Investigators of Modifiers of BRCA 1/2 (CIMBA), designed to evaluate rare variants and modifiers of BRCA mutations.[96-99] Other projects include: 1) central pathology review of those high-risk women who undergo risk reducing salpingectomy and the incidence of clinically-occult ovarian cancers; and 2) evaluating ovarian volume and circulating hormones as predictive markers for the development of ovarian cancer.

Conclusion

Like other large disease prevention clinical trials, the target populations in the large NCI cancer prevention trials are people without cancer. This provides an opportunity to use pre-diagnostic data and specimens to evaluate hypotheses about the initial development of cancer. The baseline information collected in these studies includes elements not typically collected in cancer treatment trials including smoking, family history, dietary consumption,

other medications or supplements. The clinical outcomes include health-related QOL, a variety of cancer endpoints, and sometimes other disease endpoints in addition to the primary endpoints. As such, these studies continue to contribute to our understanding of cancer development more than 10 years after they were closed. The study data and specimens are available to investigators for use through the processes identified at the study specific websites listed in Table 2.

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Table 1

All CCOP Research Bases Funded from 1989 through 2014

CCOP Legacy Research Bases (1989-2014)	Current NCORP Research Bases As of August 1, 2014 http://ncorp.cancer.gov
Cancer and Leukemia Group B (CALGB) North Central Cancer Treatment Group (NCCTG) American College of Surgeons Oncology Group (ACOSOG)	➡ Alliance for Clinical Trials in Oncology http://www.allianceforclinicaltrialsinoncology.org
Children's Cancer Group Pediatric Oncology Group	➡ Children's Oncology Group http://www.childrensoncologygroup.org/
Eastern Cooperative Oncology Group (ECOG)	➡ ECOG-ACRIN http://ecog-acrin.org/
National Surgical Adjuvant Breast and Bowel Project (NSABP) Radiation Therapy Oncology Group Gynecologic Oncology Group	➡ NRG Oncology http://www.nrgoncology.org/
Southwest Oncology Group (SWOG)	➡ SWOG http://swog.org
University of Rochester Cancer Center (URCC)	➡ Wilmot Cancer Institute http://www.urmc.rochester.edu/cancer-institute.aspx
Wake Forest University Cancer Center SunCoast CCOP Research Base at the University of South Florida University of Texas MD Anderson Cancer Center	➡ Wake Forest University Cancer Center http://www.wakehealth.edu/cancer/researchbase/

Table 2

Summary of Results of Large-Scale Prevention Trials

Study Name NCT Identifier	Sponsoring Organization	Intervention	Study Size	Time of Accrual	Results
Prostate Cancer Prevention Trial (PCPT)	Southwest Oncology Group (SWOG) http://swog.org	Finasteride vs. Placebo with serial PSA screening and end-of-study biopsy	18,882 men age 55+ randomized from	January 1994 to May 1997	Men taking finasteride had 25% fewer prostate cancers, but seemed to have a slightly higher incidence of aggressive tumors. Further pathological analysis and data have shown that reduced prostate size contributes to finding more high-grade tumors.
Selenium and Vitamin E Cancer Prevention Trial (SELECT) NCT00006392	Southwest Oncology Group (SWOG) http://swog.org	Selenium vs. Vitamin E vs. both vs. placebos in men	35,543 men age 55+ (50+ for African Americans)	August 2001 to June 2004	Neither selenium nor Vitamin E separately or together prevented the development of prostate cancer. On follow-up, men who took vitamin E alone had a 17 percent relative increase in numbers of prostate cancers compared to men on placebo.
Breast Cancer Prevention Trial (BCPT)	National Surgical Adjuvant Breast and Bowel Project (NSABP), now part of NRG Oncology http://nsabp.pitt.edu	Tamoxifen vs. Placebo in women at increased risk of breast cancer	13,388 women ages 35+ accrued	April 1992 to May 1997	Women taking tamoxifen had 49% fewer diagnoses of invasive and noninvasive breast cancers, as well as increased risk of blood clots and uterine cancers. Tamoxifen approved by U.S. Food and Drug Administration (FDA) in 1998 for reduction of breast cancer risk in women at increased risk.
Study of Tamoxifen and Raloxifine (STAR) (breast) NCT00003906	National Surgical Adjuvant Breast and Bowel Project (NSABP), now part of NRG Oncology http://nsabp.pitt.edu	Tamoxifen vs. Raloxifene in postmenopausal women at increased risk of breast cancer	19,747 women age 35+ accrued from July 1999 to November 2004		Raloxifene found equivalent to tamoxifen for reducing invasive breast cancer risk with reduced risk of blood clots and uterine cancers; follow-up showed raloxifene reduced risk of noninvasive breast cancer. Raloxifene approved by FDA in 2007 for reduction of breast cancer risk in postmenopausal women at increased risk.

Table 3

Biospecimens and Data Collected from Large-Scale Prevention Trials

	PCPT	SELECT	BCPT	STAR
BASELINE SAMPLES (PRE-THERAPY)				
Serum	X		X	X
Plasma		X		
White Blood Cells	X	X	X	X
Red Blood Cells		X		
Toenail Clippings		X		
SERIAL SAMPLE COLLECTIONS DURING TRIAL (DURING AND POST-THERAPY)				
Blood (as above)	Annual	Year 5 (all) 6 months, Year 1, 2, 4, 6, 8 (subset)		
TUMOR TISSUE COLLECTED				
Invasive Target Cancers	X	X	X	X
All Other Invasive Cancers			X	X
DATA COLLECTION				
Sociodemographic	X	X	X	X
Family Cancer History	Prostate	Prostate, lung, colon	Breast	Breast
Medical History, including height, weight, cardiovascular health, prior cancers.	X Plus detailed anthropomorphic data	X	X Plus hysterectomy and menopausal status	X Plus hysterectomy status
Medications	Limited	Extensive	Limited	Limited
Diet	At year 1	At baseline	At baseline and updated	
Supplement Use	X	X	Calcium supplements only	Calcium supplements only
Smoking	Baseline only	Baseline and updated	Baseline and updated	Baseline only
Quality of Life	X	On subset only	On subset only	On subset only
OTHER PROCEDURES				
Screening Procedures	Annual PSA and DRE	Prostate screening per local site guidelines	Annual Mammography Endometrial biopsy on subset	Annual Mammography

Table 4

Ancillary Studies in Large Prostate and Breast Cancer Prevention Trials

Study	Study Name	PI/Organization	Outcomes Evaluated	Funding Agency
SELECT	Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) NCT00040378	Frederick Schmitt, Ph.D., Richard Kryscio, Ph.D., University of Kentucky	To determine if supplements studied can help prevent memory loss and dementia.	National Institute on Aging
	SELECT Eye Endpoints Study (SEE) NCT00784225	William Christen, Sc.D. Harvard Medical School	Long-term daily supplementation with selenium and/or vitamin E is unlikely to have a large beneficial effect on age-related cataract. Christin, et al, JAMA Opthalmol, 2014.	National Eye Institute
	Respiratory Ancillary Study NCT00782678	Patricia A. Cassano, Ph.D. Weill Medical College of Cornell University	To understand whether supplements being studied have an impact upon loss of lung function from aging.	National Heart, Lung and Blood Institute
	Colon Polyps Sub Study NCT00706121	M. Peter Lance, M.D. Arizona Cancer Center	To see if the supplements affect the growth of colon polyps	National Cancer Institute
STAR	Co-STAR (Cognition in the Study of Tamoxifen and Raloxifene) NCT00687102	Sally Shumaker, Ph.D. Wake Forest School of Medicine	Compare the effects of tamoxifen and raloxifene on cognitive functions, such as thinking and memory	National Institute on Aging

Table 5

Selected Smaller Cancer Prevention Trials and Studies

Study Name NCT Identifier	Sponsoring Organization	Intervention	Study Size	Time of Accrual	Results
E5597 Lung cancer	Eastern Cooperative Oncology Group http://www.ecog.org/	Selenium vs. placebo to prevent second lung cancers in people with early stage non-small cell lung cancer	1,960 lung cancer patients	October 2000 to November 2009	Selenium supplementation was safe, but conferred no benefit over placebo in the prevention of second primary tumors in patients with resected non-small cell lung cancers.
RTOG-9115 Head and neck cancer	Radiation Therapy Oncology Group, now part of NRG Oncology http://www.rtog.org/	Low-dose isotretinoin to prevent second cancers in stage I and II head and neck cancer patients	1,190 head and neck cancer patients	November 1991 to June 1999	Isotretinoin did not reduce the number of second primary tumors in this population. Smoking increased the risk of second primary cancers and death.
MDA-ID-91025 Lung	University of Texas M.D. Anderson Cancer Center http://www.mdanderson.org/	Istretinoin to prevent second primary lung cancers in people with stage I non-small cell lung cancer	1,166 lung cancer patients	December 1992 to April 1997	No difference was seen between placebo and intervention in second primary cancers, recurrence, or mortality.
Colorectal Adenoma Prevention Study (CAPS) CALGB	Cancer and Leukemia Group B (CALGB), now part of the Alliance for Oncology http://www.allianceforclincicaltrialsinoncology.org	Aspirin vs. placebo in people with surgically-cured early stage colorectal cancer	635 colorectal cancer patients	May 1993 to January 2000	Daily aspirin use reduced the development of adenomas by 35%. Aspirin treatment also reduced the number of adenomas and increased the time before adenomas developed, without significant adverse events.
Selenium in Preventing Cancer in Patients with Neoplasia of the Prostate S9917 NCT00030901	Southwest Oncology Group http://swog.org	Selenium vs. placebo to prevent prostate cancer in men with high-grade Prostatic Intraepithelial Neoplasia	452 men with high-grade PIN	February 2000 to November 2006	Selenium supplementation had no effect on prostate cancer risk.
National Ovarian Cancer Prevention and Early Detection Study GOG-0199 NCT01139957	Gynecology Oncology Group, now part of NRG Oncology http://www.gog.org/	Prospective study of risk-reducing salpingooopherectomy and longitudinal CA-125 screening assay among women	1,916 women at increased risk of ovarian cancer, especially	June 2003 to November 2006	Initial results show 2.6% of women who underwent surgery had ovarian cancer, despite no

Study Name NCT Identifier	Sponsoring Organization	Intervention	Study Size	Time of Accrual	Results
		at increased genetic risk	BRCA1/2 carriers		clinical signs of disease.