A Brief History of the CCOP Program

In the early 1980s, two forces for the advancement of cancer care were in place: physicians trained at academic cancer centers were increasingly entering community practice to care for the majority of cancer patients in the country; but patients still had to travel to cancer centers to participate in cutting edge cancer clinical trials.

The identification of this problem was the impetus for the creation of the Community Clinical Oncology Program. The challenge was to design and implement a program to assure that cancer patients treated in their communities had access to clinical-trial quality medical care. By introducing up-to-date cancer management into the community in the form of research clinical trials, community physicians would also be more ready and able to apply the proven treatment regimens to all their patients. Diffusion of state-of-the art cancer treatment to the practices where people were being treated would be enhanced.

The Call to Physicians and Hospitals

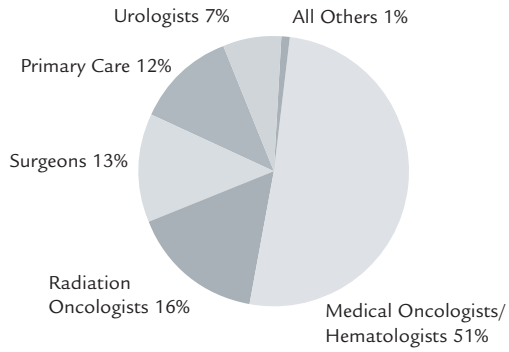
On July 16, 1982, the first call to physicians and hospitals to become part of NCI's new Community Clinical Oncology Program was released. In government parlance, this Request for Application or RFA had the goal of selecting organizations of hospitals and medical practices that would take part in treatment trials and build a network for cancer prevention and control clinical trials. Nearly 200 applications from groups seeking to become CCOPs were peer-reviewed. In September 1983, 62 CCOPs across the United States received funding, creating a nationwide network for community physicians to enter patients on NCI clinical trials. The sources of these approved clinical trials were 31 existing NCI Cooperative Groups and Cancer Centers, collectively called Research Bases.

All of the funded CCOP sites had some experience participating in clinical research via an earlier NCI program known as the Cooperative Group Outreach Program (CGOP). CGOP was created in 1978 as an avenue for community hospitals to participate in cooperative group cancer treatment trials. This program gave community physicians their first opportunity to show that they were capable of the rigor of clinical trials research. Once the CGOPS became CCOPs, the accrual to clinical trials from these centers markedly increased. (The CGOP program has since been discontinued).

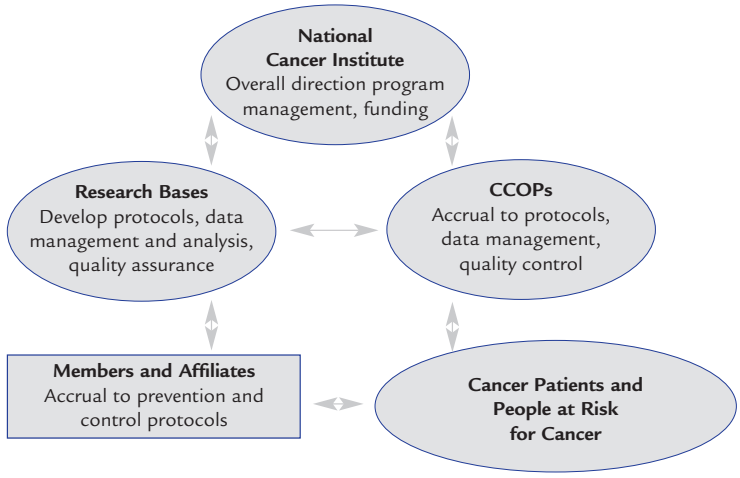
In 1986, the success of the CCOPs in accruing patients to treatment trials was clear, and a second RFA was released to continue the program. In this RFA, the scope of the program was expanded to explicitly incorporate cancer prevention and control. The Research Bases would get funding for the design and conduct of cancer prevention and control clinical trials and would also go through a peer-reviewed application process. The CCOPs were now required to accrue to cancer treatment, prevention, and cancer control trials.

This new requirement represented a significant departure from the status quo of most research institutions and created new

Medical Specialities in CCOPS



CCOP Organizational Relationships



Dr. Harry Hynes and Wichita CCOP staff circa 1988 (Pat Kastens by window; Marge Good, standing next to Dr. Hynes and Jodi Carlson at desk)

20-Year Research Bases

Research Bases develop and implement the cancer prevention and control clinical trials of the CCOP program. The following Research Bases have been a continuous part of the CCOP program since 1983 *(listed alphabetically by name with operations center location)*:

- Cancer and Leukemia Group B (CALGB), Chicago, Illinois
- Children's Oncology Group (COG), Arcadia, California (via legacy groups Children's Cancer Group and Pediatric Oncology Group)
- Eastern Cooperative Oncology Group (ECOG), Boston, Massachusetts
- National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, Pennsylvania
- North Central Cancer Treatment Group (NCCTG), Rochester, Minnesota
- Southwest Oncology Group (SWOG), San Antonio, Texas
- University of Rochester Cancer Center (URCC), Rochester, New York

challenges for both the CCOPs and the CCOP Research Bases. Few of the practicing oncologists had any experience with cancer prevention and control research. Few of the Research Bases were organized to design and implement large-scale prevention trials or cancer control trials. Many questioned the appropri-ateness of oncologists, who work with sick patients, participating in clinical prevention research that required healthy populations. However, the belief was that the successful multi-institutional network that was the CCOPs could be equally effective in conducting cancer prevention and control trials. The CCOPs thus became the focus of the full range of cancer care in a community.

Ongoing technical assistance and direction from NCI itself was needed to fully embrace this refined focus and NCI's Community Oncology and Rehabilitation Branch assumed the central coordinating role for cancer prevention and control. The Branch promoted protocol development, established protocol submission procedures, and reviewed and approved study concepts and protocols for study implementation.

In 1988, after the second CCOP RFA had already been awarded, a prospective evaluation that had been put into place with the first RFA was publicly presented. The evaluation reviewed a critical part of the CCOP program: the enhancement and diffusion of state-of-the-art treatment regimens. In a report to the NCI's Board of Scientific Advisors in October 1988, the results of the evaluation demonstrated that community physicians could accrue patients to cancer treatment trials at a rate equivalent to the university members of the Cooperative Groups. About one-third of all cancer patients participating in NCI treatment trials were being enrolled via the CCOPs. The data generated by the CCOPs met or exceeded all the quality control standards of the Cooperative Groups. Most importantly, the participation in clinical trials through the CCOP mechanism accelerated the adoption of new treatment regimens in the community. One year later, the Board determined that the CCOP program needed not just to be continued, but made a permanent and ongoing part of the NCI program. The Board voted to permit the annual release of the CCOP RFA.

In 1989, the Board also approved the development of a complementary program, the Minority-Based CCOPs (MB-CCOPs). The 1988 evaluation had shown that while community physicians were able to accrue patients within their communities, the participating hospitals did not have access to large minority populations. The Minority-Based CCOPs would also include universities in large, urban settings, which deliver community health care to significant minority populations. The first MB-CCOPs, 12 in all, were funded in June 1990.

In 1990, the second evaluation of the CCOP program, begun in 1986, was also complete. This was an evaluation of the level of implementation of cancer prevention and control research within the CCOP network, i.e., it sought to determine whether the CCOP mechanism was an effective and efficient way to conduct cancer control research in the community setting. There had been concern that the scientific treatment focus of the Research Bases would not be compatible with cancer control research efforts. The evaluation revealed, however, that Research Bases were successful with the integration of prevention and control trials with ongoing research, especially when they created special emphasis within their own systems to address these issues.

Also in 1990, sufficient evidence existed to undertake a large trial to determine if the cancer treatment drug tamoxifen could reduce a woman's chance of developing breast cancer, and it was decided that the CCOP mechanism was the most appropriate for conducting this large-scale trial. The National Surgical Adjuvant Breast and Bowel Project (NSABP), a longtime CCOP Research Base, successfully competed for the peer-reviewed supplement to design and conduct the randomized, placebo-controlled trial for women at increased risk of developing breast cancer, but who did not have the disease.

The Breast Cancer Prevention Trial, as it was named, was considered a natural and crucial progression of the previous research conducted by NSABP and others. The trial, which showed in 1998 that tamoxifen could reduce breast cancer risk by half, and its implementation via the CCOP system, was a success that paved the way for other large-scale trials to take place. Tamoxifen became the first cancer prevention drug approved by the U.S. Food and Drug Administration. Today, the CCOPs provide about one-third of all the accrual to NCI's large-scale prevention clinical trials.

Breast Cancer Prevention Trial press conference, April 6, 1998

Summation

Twenty years after its founding, the CCOP Program has accomplished the early goals of including the community physicians in the research process and expanding the research focus of the Cancer Cooperative Groups and Cancer Centers to include cancer prevention and control.

More than 4,000 community physicians now participate in NCI clinical trials through the CCOP network. In addition, 50 CCOPs and 11 Minority Based CCOPs are funded across 34 states, the District of Columbia, and Puerto Rico, providing access to cancer clinical trials in 403 community-based hospitals.

The program established an integrated clinical trials research network that extends beyond medical oncologists, and serves as a first-class mechanism for implementing landmark cancer prevention clinical trials. Since 1989, over 74,500 people at risk have been enrolled on cancer prevention clinical trials through this collaborative medium, making the CCOP network the premiere vehicle to conduct definitive phase III cancer prevention trials.

Through the dedication of the CCOP Research Base investigators, several novel and innovative cancer prevention clinical trials have been conducted. In 2003, over 90 cancer prevention and control protocols were open and actively accruing across 14 CCOP Research Bases. Just as they do with treatment research, each CCOP Research Base has tailored its cancer prevention and control research activities to its population and its scientific areas of interest.

Diane Von Ostenberg, BS, RN, Founding CCOP Administrator, Grand Rapids, Michigan CCOP

Since 1983, over 98,200 cancer patients have been entered onto cancer treatment clinical trials through the CCOP program. Consistently, CCOP sites account for one third of the accrual onto NCI sponsored treatment clinical trials, thereby ensuring that the results of these trials are applicable to patients in the community. Accrual takes less time, pressing questions are answered more quickly, and appropriate changes in clinical practice can be implemented faster.

Since 1986, the CCOPs have been a focal point of NCI research on supportive care, quality of life, and symptom management, which were orphan concepts in the 1980s. CCOP research over the past 17 years has been critical for pain management and the effective treatment of nausea and vomiting.

Because of its ongoing success, the CCOP program has been used as the prototype for other disease-specific clinical trials networks. In the late 1980's, the National Institute of Allergy and Infectious Diseases (NIAID) designed its AIDS clinical trials network after the CCOP approach. In 1999, the National Institute of Drug Abuse (NIDA) used the CCOP network to design and develop its network for community-based treatment centers to participate in clinical trials.

Charles Spurr, original founder of the Southeast Cancer Control Consortium, 1987

So, what is a CCOP?

Technically, a CCOP is a group of community hospitals and physicians funded by a peer-reviewed cooperative agreement to participate in NCI-sponsored cancer treatment, prevention and control clinical trials. But a CCOP is actually much more: it is an effective collaboration of dedicated and committed people who give of their time, energy, and compassion to provide all aspects of care for cancer patients and their families, and for people at risk for developing cancer. CCOPs are people who firmly believe that advances in cancer care are the direct result of participation in clinical trials.

20-Year Community Clinical Oncology Programs

CCOPs that have been continuously funded since 1983:

- Carle Cancer Center CCOP, Urbana, Illinois
- Columbus CCOP, Columbus, Ohio
- Dayton Clinical Oncology Program, Kettering, Ohio
- Duluth CCOP (previously Duluth Clinic CCOP), Duluth, Minnesota
- Evanston Northwestern Healthcare (previously Evanston Hospital), Evanston, Illinois
- Florida Pediatric CCOP, Tampa, Florida
- Geisinger Clinical Oncology Program, Danville, Pennsylvania
- Grand Rapids Clinical Oncology Program, Grand Rapids, Michigan
- Illinois Oncology Research Association CCOP (previously Methodist Medical Center CCOP), Peoria, Illinois
- Iowa Oncology Research Association CCOP, Des Moines, Iowa
- Kalamazoo CCOP, Kalamazoo, Michigan
- Kansas City Clinical Oncology Program, Kansas City, Missouri
- Marshfield CCOP, Marshfield, Wisconsin
- MeritCare Hospital CCOP (previously Fargo Clinic CCOP), Fargo, North Dakota
- Metro-Minnesota CCOP, St. Louis Park, Minnesota
- Northern New Jersey CCOP (previously Bergan-Passaic CCOP), Hackensack, New Jersey
- North Shore University Hospital CCOP, Manhassett, New York
- Northwest CCOP (previously Southwest Washington CCOP), Tacoma, Washington
- Ochsner CCOP, New Orleans, Louisiana
- Sioux Community Cancer Consortium CCOP (previously Sioux Falls Community Clinical Oncology Program), Sioux Falls, South Dakota
- St. Louis-Cape Girardeau CCOP (previously St. Louis CCOP), St. Louis, Missouri
- Southern Nevada Cancer Research Foundation CCOP, Las Vegas, Nevada
- Toledo CCOP, Toledo, Ohio
- Upstate Carolina CCOP (previously Spartanburg CCOP), Spartanburg, South Carolina
- Virginia Mason Research Center CCOP, Seattle, Washington
- Western Regional CCOP (previously Greater Phoenix CCOP), Phoenix, Arizona
- Wichita CCOP, Wichita, Kansas

Success of the Minority-Based CCOPs

In 1990, NCI determined that in order to develop and implement effective treatment and cancer prevention and control strategies that applied to all populations, there was a need for racial and ethnic minorities to have broader access to clinical research protocols. The Minority-Based CCOP program became an important part of efforts to improve access to clinical trials and state-of-the-art care to minorities. MB-CCOPs can be any institution, organization or physician group that has more than 40% of their new cancer patients from minority populations – which opened the door for university hospitals and other minority-serving institutions not normally included in the CCOP program.

Minority-Based CCOPs are designed to:

- Bring the advantages of state-of-the-art cancer treatment and prevention and control research to minority individuals in their own communities by having practicing physicians and their patients participate in NCI-approved clinical trials.
- Provide a basis for involving a wider segment of the community in cancer prevention and control research and investigate the impact of cancer therapy and control advances in community medical practices.
- Increase the involvement of primary health care providers and other specialists with the MB CCOP investigators in cancer treatment, prevention, and control research, providing an opportunity for education and exchange of information
- Facilitate wider community participation among racial/ethnic minorities, women and other underserved populations in NCI-approved cancer clinical trials
- Provide an operational base for extending cancer control and reducing cancer incidence, morbidity and mortality in minority populations by accelerating the transfer of newly developed cancer prevention, early detection, treatment, patient management, rehabilitation, and continuing care technology to widespread community applications.

Dionne Thorne, MPH, of Howard University Cancer Center MB-CCOP

An assessment of the program was completed in 1992, and MB-CCOPs clearly demonstrated their ability to participate in clinical trials. More than 70% of MB-CCOP patients in clinical trials were from minority poulations, and the 10 MB-CCOP programs contributed more than 10% of all the minority accrual to NCI sponsored treatment trials in these two years.

The MB-CCOPs demonstrate significant achievement in developing solutions to overcome participant and physician barriers to clinical trials, low literacy, limited education, and socioeconomic issues often endemic in minority and underserved communities. Many of the sites are celebrating more than 10 continuous years as CCOPs.

10-Year MB-CCOPs

MB-CCOPs that have been continuously funded for 10 years:

- Gulf Coast MB-CCOP, Mobile, Alabama
- San Juan MB-CCOP, San Juan, Puerto Rico
- South Texas Pediatric MB-CCOP, San Antonio, Texas
- University of Hawaii MB-CCOP, Honolulu, Hawaii
- Virginia Commonwealth University MB-CCOP, Richmond, Virginia

Why CCOP Physicians Participate in Prevention

CCOPs initially arose as mechanisms that would enable community oncologists to participate in cooperative group's cancer treatment studies. Often such protocols would include the investigation of a new drug. Some studies would redefine the standard of care for a particular disease.

Although these programs have been quite successful, community oncologists have come to recognize that the greatest reduction in the cancer burden will only arise from disease prevention. All of the advances in prolongation of survival and reduction of relapse pale in comparison to cancer prevention. CCOP investigators have learned this from their patients, their patient's families, and from their communities. CCOPs now view themselves as the best medium for chemoprevention studies at the local level.

Indeed, CCOPs are the ideal platform for such prevention studies because of the alignment of the principal investigator's recognition of the promise of chemoprevention and his/her local community's desire to participate in the research process to reduce the cancer burden we all share. The successes of such cancer awareness events as the "Race for the Cure" and the "Walk for Life" are clues to how important local communities feel about doing their part to help. CCOPs then take this local interest and desire to participate to a higher level by enrolling at-risk individuals into studies designed to reduce cancer incidence.

The Cooperative Groups have a responsibility to harness their considerable expertise to design a national prevention program for all malignancies that are candidates for prevention strategies. When armed with good national large-scale prevention programs, the CCOPs can fulfill their initial promise of truly reducing the cancer burden.

James L. Wade III, M.D.
Principal Investigator
Central Illinois CCOP
Decatur, Illinois

Accomplishments in Cancer Prevention

In 1990, the Community Clinical Oncology Program turned a strong focus to prevention trials. Rather than pursuing traditional grants to conduct newly planned large-scale trials, the National Cancer Institute turned to the established CCOP clinical trials network.

Prevention trials require many more participants than treatment trials, because not all participants will develop cancer. The CCOPs, with their nationwide, broad reach, were considered an ideal focus for recruiting the thousands of people necessary for these trials. Working through established Research Bases, the network for prevention clinical trials was enhanced by the addition of university and outreach members of cooperative groups.

As was often the case, there was some skepticism that CCOPs could succeed in this new endeavor, but time has proven that they are up to the task.

Breast Cancer Prevention Trial

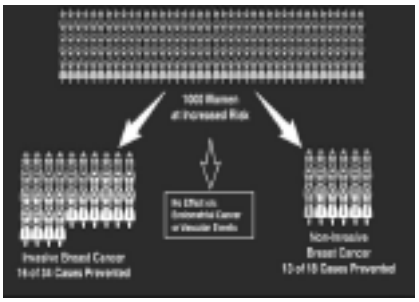
The first large-scale prevention trial to use the CCOP network was the Breast Cancer Prevention Trial (BCPT), in which tamoxifen was tested to prevent breast cancer in women at increased risk for the disease. The National Surgical Adjuvant Breast and Bowel Project (NSABP), led by Bernard Fisher, M.D., had more than 20 years of clinical trial experience with tamoxifen and successfully competed to conduct the study.

Tamoxifen is a selective estrogen receptor modifier -- it works like estrogen in some tissues, such as the uterus and bone, and against estrogen in others, like the breast. Previous NSABP research had shown that women with early stage breast cancer who took tamoxifen not only had fewer recurrences of their original breast cancer, but were also less likely to develop new breast cancers in the opposite breast. Tamoxifen was preventing new disease in these women at extremely increased risk for breast cancer.

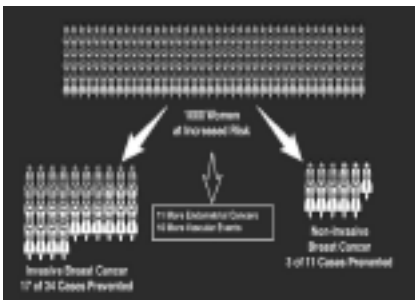
From this observation grew the Breast Cancer Prevention Trial, where 16,000 women age 35 and older, determined to be at increased risk of breast cancer, would be randomly assigned to take either tamoxifen or a placebo for 5 years. Throughout the trial, women would be evaluated not only for the development of breast cancer, but also for their likelihood of developing tamoxifen's rare, but serious side effects (blood clots and uterine cancer).

On April 29, 1992, the trial commenced at more than 270 centers across the United States and Canada, including nearly every CCOP. Recruitment was expected to take up to five years, but in September 1996 the BCPT study size was reduced from 16,000 to 13,000 because participants had a much greater underlying risk of breast cancer than anticipated. By September 1997, 13,388 women had joined the trial–4,092 from CCOPs (about 31%).

BREAST CANCER PREVENTION TRIAL
BENEFITS & RISKS TO PARTICIPANTS AGE 35-49



BENEFITS & RISKS TO PARTICIPANTS AGE 50+



These graphics depict the risk of developing breast cancer in 1,000 women in two age ranges.

As part of the study design, the BCPT data were regularly reviewed by an independent Endpoint Review, Safety Monitoring and Advisory Committee. At the committee's meeting on March 24, 1998, the recommendation was made that the participants and their physicians be told what pills each participant had been taking because there was clear evidence that tamoxifen reduced breast cancer risk.

On April 6, 1998 initial results were released: BCPT had shown that tamoxifen reduced breast cancer incidence by 45% compared to women on placebo. In the study,

healthy women assigned to take tamoxifen developed 85 cases of invasive breast cancer compared to 154 cases in women assigned to the placebo. Due to the strong finding and the intense interest, NSABP researchers announced the trial results to investigators, participants, and the public immediately, without waiting for a journal to publish the data. There was a flurry of media coverage and an unprecedented attendance at a press conference to present trial data.

The data were subsequently further analyzed and published in the Journal of the National Cancer Institute in September 1998; the final analysis showed a 49% reduction in invasive estrogen-receptor positive breast cancer from tamoxifen. Additionally, tamoxifen increased the women's chances of developing uterine cancer, pulmonary embolisms (blood clot in the lung), and deep vein thrombosis (blood clot in major vein). Women under age 50, however, did not seem to suffer added risk of these adverse effects.

On October 29, 1998, the U.S. Food and Drug Administration approved tamoxifen for the reduction of breast cancer risk based on landmark BCPT data–the first cancer prevention indication for any drug.

Followup studies with the BCPT cohort continue to bring more critical information to light, such as the role of BRCA1/2 genes in breast cancer risk.

Reference: Fisher, B, Costantino JP, Wickerham DL, Redmond CK, et al. **Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study**. *J Natl Cancer Inst* 1998; 90:1371-88

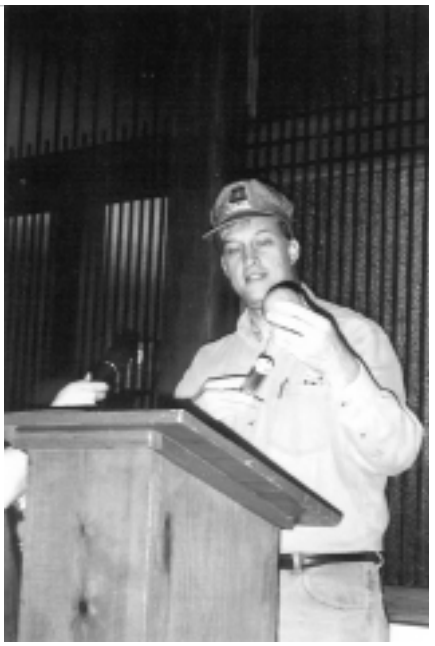
Prostate Cancer Prevention Trial

Shortly after the Breast Cancer Prevention Trial began, NCI joined with the adult cooperative groups, coordinated by Charles Coltman, M.D., of the Southwest Oncology Group, to design and implement a large-scale trial for the prevention of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) was designed to determine if the drug finasteride would prevent prostate cancer in healthy men.

Research had shown that hormones played a key role in prostate cancer development. Men born with a rare deficiency in 5-alpha-reductase, an enzyme that converts testosterone to the more potent dihydroxy-testosterone, never develop prostate cancer. Finasteride inhibits 5-alpha reductase, shrinking the prostate. The drug was approved by the FDA in 1992 to treat benign prostate enlargement, and later, at a lower dose to treat male pattern baldness.

The Southwest Oncology Group designed a study where 18,000 men age 55 and older would take either finasteride or a placebo daily for seven years. Men would get yearly PSA tests and digital rectal exams to look for prostate cancer, and at the end of 7 years, participants would be asked to have a biopsy to truly determine if they had developed cancer.

In October 1993, the trial was kicked off at 221 sites, including 86 CCOPs (including MB-CCOPs). Despite concern that men would not be interested in such a long trial where the drug might have sexual side effects, the study accrued rapidly. More than 12,000 men joined within one year, and 18,882



Scott and White CCOP, Temple, Texas Michael Hermans, M.D., PI for PCPT, demonstrates a core biopsy on an apple during a luncheon held at a train depot.

were randomized by May 1997, two years ahead of schedule. In total, 7,360 of these men were from CCOPs, or nearly 40% of all PCPT participants.

As part of the study design, the PCPT data were regularly reviewed by an independent Data and Safety Monitoring Committee (DSMC). On March 3, 2003, the DSMC notified the chair of SWOG that the primary goal of the trial had been met: finasteride reduced the risk of prostate cancer by 25 percent and it was extremely unlikely that continuing the trial would change that finding. The DSMC recommended that the trial be stopped early and that the men and their physicians be told what pills the participants had been taking.

To make the study findings available to the medical community, a report on the study findings was submitted to the *New England Journal of Medicine* on March 24 for expedited review. The report was published in the online version of the journal on June

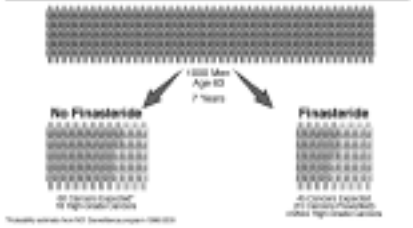
24, 2003, and in the print journal on July 17, 2003.

Finasteride is the first drug found to reduce the risk of prostate cancer in a prospective clinical trial with prostate cancer as the primary endpoint. The drug worked for men at low risk for prostate cancer, as well as those at high risk. Age, PSA level at enrollment, family history of prostate cancer, and race or ethnicity did not affect the drug's ability to prevent the disease.

There was a cautionary note: Although almost all of the men in the study who developed prostate cancer had early stage prostate cancer, those that were taking finasteride were more likely to have cancers that appeared to be high Gleason grade. High-grade cancers, when found in the general population, may spread quickly even if the tumors are small. The reason men on finasteride appeared to have more high-grade tumors is currently unknown, but the researchers are studying several possibilities. The drug may affect the architecture of the prostate gland, a well-known affect of androgen therapy, leading to a false estimate of tumor grade. Another possible explanation being examined is whether finasteride truly causes more aggressive tumors to develop.

Two types of follow up studies are already under way. All participants in the trial were encouraged to take part in a long-term follow-up study in which PCPT researchers continue to contact them to collect additional information about the effects of finasteride use, prostate cancer, and survival. Using the blood and tissue samples collected during the trial, a comprehensive program of translational research studies will look at the molecular biology of

Estimated Benefits & Risks from Finasteride on Development of Prostate Cancer



This graphic depicts the risk of developing prostate cancer in 1,000 men.

prostate cancer to try to determine who is at risk for developing this disease and who might benefit most from finasteride.

Reference: Thompson IM, Goodman PH, Tangen CM, Lucia MS, et al. **The Influence of Finasteride on the Development of Prostate Cancer**. *N Engl J Med* 2003:349:213-22

Colorectal Adenoma Prevention Study

Numerous epidemiologic studies have shown that people who regularly take aspirin and aspirin-like drugs to treat conditions such as arthritis have lower rates of colorectal adenomas (polyps), colorectal cancer, and colorectal cancer deaths. These drugs, known as non-steroidal anti-inflammatory drugs or NSAIDs, reduce levels of prostaglandins and decrease inflammation. Colorectal and other cancers are known to cause increased levels of prostaglandins.

Based on these promising epidemiologic data, as well as animal models and laboratory data, the Cancer and Leukemia Group B began the Colorectal Adenoma Prevention Study (CAPS) in 1993. The CAPS included men and women ages 30 to 80 diagnosed with an early stage colorectal cancer that was curatively treated with surgery alone. These men and women were at increased risk of developing new colorectal adenomas or cancer.

Participants were assigned to take either 325 mg of aspirin or a placebo daily, and were stratified based on gender and stage of initial cancer. By January 2000, 635 men and women were enrolled on the trial .

At a regularly scheduled data and safety monitoring board meeting in late 2002, the recommendation was made to terminate the study early and release the statistically significant results of the interim analysis: daily aspirin use reduced the development of adenomas by 35% in patients with previous colorectal cancers. Aspirin treatment reduced the number of adenomas and the time to development of adenomas without causing significant adverse effects.

The results were presented at the American Society of Clinical Oncology meeting in May 2002, and published in the *New England Journal of Medicine* on March 6, 2003.

Reference: Sandler RS, Halabi S, Baron JA, Budinger S, et al. **A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer**. *N Engl J Med* 2003;348:883-90.

13-cis Retinoic Acid for Upper Aerodigestive Cancers

Several of the leaders in clinical chemoprevention come from the University of Texas M.D. Anderson Cancer Center in Houston, Texas. Waun Ki Hong, M.D. pioneered the use of retinoids for prevention of both lung cancer and head and neck cancers in several critical clinical trials. Retinoids are one of the most intensively studied cancer

prevention agents; various laboratory and animal studies have shown that retinoids can destroy cancer cells and reverse premalignant tissues to normal. M.D. Anderson's first landmark trial of 13-cis retinoic acid in men and women with head and neck tumors was published in the *New England Journal of Medicine* in 1990 and showed a significant reduction in new cancers in patients treated with short-term, high-doses of 13-cis retinoic acid. This trial was the proof of principle that an agent could disrupt the progression of cells to cancer. However, another key principle of making prevention intervention viable is that the treatments have tolerable side effects and be applicable to a wide population. High-dose 13-cis retinoic acid did not fulfill this second principle.

Based on the data, as well as the very high incidence of second primary cancers in patients already diagnosed with head and neck cancer, a larger trial of long-term, low doses of the drug in men and women with early stage disease was begun using the CCOP network. The change to low dose 13-cis retinoic acid was made in the hope of translating the efficacy of the drug seen in the first trial into a tolerable treatment for larger populations. Beginning in 1991, 1,190 participants were randomized to receive either 13-cis retinoic acid or a placebo daily for 3 years, in addition to usual medical follow up appropriate for cancer survivors. Participants were then followed for an additional 4 years. The last patient was enrolled on the trial in September 2002.

Results presented at the American Society of Clinical Oncology meeting in May 2003 showed no significant difference in overall survival, recurrence-free survival or, likelihood of developing new head and neck cancers (second primary tumors) between the groups. However, while participants were actively taking 13-cis retinoic acid, there seemed to be decreased likelihood of disease recurrence, although this disappeared once the drug was stopped.

Analysis of tumors found during the study will look at molecular characteristics to better distinguish new cancers from recurrent cancers, and to determine if and how the drug might be suppressing recurrence for some patients.

Also based on the same promising data published in 1990, M.D. Anderson began a CCOP trial of the retinoid 13-cis retinoic acid to prevent new lung cancers in 1,166 men and women who had surgery to remove an early stage, nonsmall cell lung cancer. These men and women were at extremely increased risk of having their lung cancers recur, and for developing new lung cancers. Beginning in February 1993, patients were randomized to take either low dose 13-cis retinoic acid or placebo daily for three years. The last person joined the study in June 1997.

Overall, 13-cis retinoic acid did not reduce the rate of disease recurrence or survival in the participants. However, subset analyses suggested that the drug is actually harmful to those who continue to smoke while taking the drug, but beneficial to those who have never smoked (a small minority of lung cancer patients).

Reference: Khuri F, Lee, JJ, Lippman SM, Kim ES, et al. **Isotretinoin effects on head and neck cancer recurrence and second primary tumors.** American Society of Clinical Oncology annual meeting, May 2003.

Reference: Lippman, SM, Lee JJ, Karp, DD, Vokes EE, et al. **Randomized Phase III Intergroup Trial of Isotretinoin to Prevent Second Primary Tumors in Stage I Non-Small-Cell Lung Cancer**. *J Natl Cancer Inst* 2001;93:605-18.

Ongoing Prevention Trials

Based upon the success of these initial studies, the CCOP network has proven the feasibility of implementing large-scale prevention trials in both individuals at increased risk for cancer and in those with early stage cancer at increased risk of second cancers.

Ongoing CCOP prevention trials include:

- Study of Tamoxifen and Raloxifene (STAR), the 19,000-woman trial to compare these drugs for the prevention of breast cancer. STAR is headed by NSABP;
- Selenium and Vitamin E Cancer Prevention Trial (SELECT), the 32,400-man prostate cancer prevention trial, coordinated by SWOG;
- a study of celecoxib, a selective NSAID, for the prevention of adenomas in early stage colorectal cancer patients at risk (NSABP); and
- selenium for the prevention of second tumors in people with early stage lung cancer, headed by the Eastern Cooperative Oncology Group.

In addition, novel agents are actively under development in other Division of Cancer Prevention programs for head and neck, lung, and other cancers, with the aim of leading to large-scale definitive CCOP trials.

Accomplishments in Cancer Control

Charles L. Loprinzi, M.D., chairman of the North Central Cancer Treatment Group, credits the Community Clinical Oncology Program's emphasis on cancer control and symptom management as a facilitating factor in his ability to introduce a ground-breaking series of articles focused on symptom control into the *Journal of Clinical Oncology*. This series, titled "The Art of Oncology: When the Tumor is Not the Target," was reprinted as a special supplement to the journal in April 2002.

Loprinzi said, "It is through the CCOP program that I have been able to facilitate the development, conduct, and eventual publication of a large number of symptom control studies in patients with cancer." His introduction in the special supplement follows:

The CCOP Role in Cancer Control

As successful cancer treatment regimens resulted from clinical trials over time, questions emerged regarding treatment-related morbidity, symptom management, quality of life, and survivorship. Practicing oncologists found themselves being asked to address patient care situations that did not involve treating the cancer itself. Importantly for health care quality generally, the CCOP program was instrumental in reclaiming these "orphaned" patient care issues and moving them forward into the realm of clinical study.

The Art of Oncology INTRODUCTION

Charles L. Loprinzi, Guest Editor
Division of Medical Oncology, Mayo Clinic,
200 First Street Southwest,Rochester, MN 55905
Reprinted with permission from American Society of Clinical Oncology

CANCER OVER the last century has consistently been amongst the most feared diagnoses. Oncologists, the physicians who classically have been most intimately involved with the care of patients with cancer, provide expertise with regard to surgery, radiation therapy, and cytotoxic chemotherapy. In addition to providing these anticancer therapies, oncologists are commonly called to care for patients with cancer in ways other than trying to directly kill/eliminate cancer cells.

How does an oncologist honestly, yet in a compassionate manner, tell patients and their families that things are not going well; that there is no good remaining anticancer therapy to give; that it is time to focus primarily on symptom control, not anticancer therapy; that resuscitation is not recommended in the event of a cardiopulmonary arrest; and about other end-of-life issues? How do oncologists deal with the emotional issues they themselves have when they deal with patients with end-of-life issues? These questions are addressed in this collection of manuscripts. In addition, this collection also addresses cancer survivorship issues and issues related to hospice care and symptom control.

The works in this collection were all published between January 2000 and December 2002 in a special section of the Journal of Clinical Oncology entitled, "The Art of Oncology: When the Tumor is Not the Target." This section of the journal was inspired by work done when the 1997-1998 President of the American Society of Clinical Oncology (ASCO), Dr. Robert Mayer, convened a task force to study how oncologists deal with end-of-life care for their patients. This task force concluded that there was room for improvement in the care of patients as they approached the end of their lives. An outcome recommendation from this task force was that this issue could nicely be highlighted in a special section of the *Journal of Clinical Oncology*.

Although the *Journal of Clinical Oncology* is primarily geared for oncology physicians, it was recognized, at the initiation of this section of the journal, that the issues addressed would be applicable for multiple other groups, including non-oncology physicians, nurses, other health care providers, and students.

In 1986, the CCOP scope of research was expanded to include patient management, continuing care, and rehabilitation. The CCOPs took on supportive care research, quality of life, and symptom management, which were orphan concepts in the 1980s. The past 17 years have demonstrated the success of this expansion: the landmark studies in pain management and the effective treatment of nausea and vomiting were achieved by CCOP research.

Despite the accomplishments, troublesome symptoms remain a problem for cancer patients. Two surveys of chemotherapy patients taken six years apart showed that more than half the latter group continued to experience the same five symptoms as the first. There remains a continuing and pressing need for research to better manage symptoms for cancer patients. The most common symptoms addressed in CCOP trials have been pain, anorexia, mucositis, and hot flashes.
Several Research Bases have made unprecedented contributions to this field:

- The North Central Cancer Treatment Group has had more than 75 cancer control protocols approved by NCI, the vast majority related to symptom control. They have conducted more cancer anorexia/cachexia trials than any other group in the world. Their work established megestrol acetate for anorexia and venlafaxine for hot flashes. NCCTG has extensively evaluated means of reducing or preventing mucositis from chemotherapy or radiation therapy.
- University of Rochester Comprehensive Cancer Center was the first research base to be approved for cancer control only. A major focus of their research efforts is on the reduction of treatment related morbidity to maximize the potential curative effect of cancer treatments and improve quality of life, concentrating in the areas of nausea, fatigue and hot flash control.
- The Radiation Therapy Oncology Group (RTOG) has completed several trials designed to prevent the acute complications of radiation therapy. One major finding was that prophylactic pilocarpine reduced the development of xerostomia (dry mouth) in head and neck patients: Pilocarpine has become utilized during radiation therapy to the head and neck.

Pain

Early in the development of cancer control research, ECOG conducted a landmark survey of oncologists and their patients. This report revealed cancer patients often had inadequate treatment for pain. This report and others lead to greater evaluation of patients' pain. Research has since focused on the efficacy of various routes of administration for pain medications, while other studies continue for identifying agents to treat postsurgical neuropathic pain.

Anorexia/Cachexia

CCOP studies have defined the role of megestrol acetate in the treatment of the severe weight loss and wasting associated with many cancers and known as anorexia and cachexia. Ongoing trials are evaluating the efficacy of other agents, such as infliximab (a monoclonal antibody to tumor necrosis factor), etanercept, and oxandrolone.

Mucositis

Mucositis, the inflammation of mucous membranes in the digestive tract, results from chemotherapy or radiation, and can cause pain and other symptoms from the mouth to the colon. This fundamental problem can lead to treatment delays or to a patient receiving reduced doses of effective drugs. CCOP studies have demonstrated that several treatments are not useful for this condition. Open trials are assessing the utility of L-glutamine for oral mucositis and octreotide to treat diarrhea resulting from radiation or chemotherapy affecting the colon.

Hot Flashes

A unique success of CCOP research has been the identification of a class of agents (serotonin and norepinephrine reuptake inhibitors) that provides nonhormonal relief for hot flashes. This finding has been particularly important for patients with a history of breast cancer, for whom estrogen replacement is contraindicated, but recent findings from the National

Institute of Health Women's Health Initiative (WHI) regarding the safety of hormone replacement therapy in healthy women suggest that these agents being studied in the CCOPs may be useful for other menopausal women suffering from hot flashes.

Smoking

Cigarette smoking causes 30% of all cancer deaths, and not smoking is the single most effective way for individuals to protect themselves from developing cancer – it is both prevention and control. The CCOP network has demonstrated its ability to recruit adults to three smoking cessation studies, which have assessed the effectiveness of nicotine replacement therapy (patch and nasal spray), bupropion, and behavioral interventions. These studies have shown modest effectiveness in the short term for nicotine replacement therapy. As new pharmacologic agents are developed for relieving nicotine addiction, the CCOP network can readily initiate studies to evaluate efficacy for these agents.

Complementary and Alternative Medicines

Cancer patients frequently use complementary and alternative medicines with or without the knowledge of their physicians. Most of these agents have little evidence to support their use. NCI has initiated evaluations of the efficacy of CAM agents, and CCOPs are a part of this focus. The safety of these agents in the setting of cancer and cancer treatment is critically important, as patients are already taking these agents for their symptoms.

Those agents with demonstrable efficacy and safety can find a legitimate role in cancer care, whereas those without proven benefit or those with safety concerns might fall into disuse. One study, for example, did not find that soy protein was effective for relief of hot flashes. Among agents currently under investigation are ginkgo biloba for cognitive function, St. John's Wort for depression, black cohosh for hot flashes, and ginger for chemotherapy-induced nausea.

Quality of Life

Improving quality of life is one of the primary goals of cancer care, and many CCOP trials are designed to include an assessment of general quality of life as part of evaluating an intervention. For example:

- The Children's Oncology Group (COG) completed a validation study for a comprehensive assessment of health/quality of life in survivors of childhood cancer. The data provide evidence for the validity and reliability of the MMQL-Adolescent Form as a comprehensive, multidimensional self-report instrument for measuring HRQL among survivors of childhood cancer.
- COG also completed a randomized comparison between antibiotics alone and antibiotics plus G-CSF in pediatric patients with chemotherapy induced febrile neutropenia. The results show that therapy containing G-CSF significantly reduces the time to recovery of febrile neutropenia and neutropenia.
- H. Lee Moffitt Cancer Center CCOP Research Base created a portfolio of studies in its first three years with the network that included quality of life studies in adults receiving radiation therapy and children experiencing cognitive loss from CNS therapy. Additional pediatric studies include interventions to overcome weight loss associated with chemotherapy.

CCOP Cancer Control Trials* Since 1987

- 241 Total Cancer Control Trials
- 136 (56%) Symptom Management Trials
- 79 Closed
- 57 Ongoing

* The CCOP Network is the primary mechanism for conducting phase III clinical trials in symptom management, palliative care, and other cancer control issues.