Which Studies Are Most Helpful in Making Cancer Care Decisions?

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Introduction

Clinical trials are research studies in which people help doctors find ways to improve health and cancer care. Each study tries to answer scientific questions and to find better ways to prevent, diagnose, or treat cancer.

If you or someone you know has cancer, you might want to learn what the best research has to say about its prevention, diagnosis, or treatment. But what constitutes the "best" research? If it's well designed, any clinical trial can produce reliable findings. But reliable findings aren't always definitive.

Research findings that are most likely to set the standard of cancer care usually come from phase III clinical trials that have been randomized and controlled, and that have enrolled enough participants to yield statistically significant results.

This article explains what these terms mean, and why a phase III randomized, controlled clinical trial with a specific number of participants is considered the gold standard in cancer research. With this knowledge, you'll be better able to tell which cancer studies are the most definitive, and therefore the most helpful, in guiding your medical decisions.

Clinical Trials Are Experimental & Prospective

The first thing to realize is that there are different kinds of cancer studies. A clinical trial is a particular kind of cancer study, one that is both experimental and prospective.

What's an experimental study?

Experimental studies can be understood in contrast to observational studies.

In an experimental study, investigators ask participants to take something (such as a drug) or do something (such as attend a support group). Investigators then record what happens to the participants as a result. The "something" that participants take or do is called an intervention.

In an observational study, by contrast, there is no intervention. Investigators simply observe and record naturally occurring events: for example, the number of lung cancer cases that occur within a group of people who live or work in cities along the East Coast.

Observational studies are important, and can provide useful information about many issues such as risk factors for cancer. For example, the link between smoking and lung cancer was established through observational studies.

However, observational studies cannot be used to draw conclusions about how best to prevent or treat cancer. Prevention and treatment strategies need to be tested in experimental studies.

What's a prospective study?

Prospective studies can be understood in contrast to retrospective studies.

In a prospective study, investigators follow participants forward in time for weeks, months, or years and record what happens to them.

In a retrospective study, by contrast, investigators look back at what happened to a group of people in the past. For example, they may take information from participants' medical records or ask participants to recall what they ate or did during a defined period of time.

Retrospective studies, while helpful in cancer research, are of limited use in determining new medical care because information about what happened to participants in the past is often incomplete.

Prospective studies don't rely on the reconstruction of past events, so they are generally considered to produce more reliable results than retrospective studies.

What's a Phase III Clinical Trial?

Most clinical research that involves the testing of a new intervention progresses in an orderly series of steps, called phases. Clinical trials are usually classified into one of three phases:

- **Phase I trials:** These are the first studies to look at how a new intervention works in people -- the manner and frequency of its application and, if it's a drug, what dose is safe. A phase I trial usually enrolls only a small number of participants, sometimes as few as a dozen.

- **Phase II trials:** A phase II trial continues to test the safety of the intervention, and begins to evaluate how well it works. Phase II studies usually focus on a particular type of cancer.

- **Phase III trials:** These studies test a new intervention in comparison to the current standard of care. Phase III trials often enroll large numbers of people and may be conducted at many doctors' offices, clinics, and cancer centers nationwide.

Because they build on reliable findings from earlier clinical trials, phase III trials are usually considered to be the ultimate test of a new intervention.

Controlled Studies Allow Comparisons

In trying to judge how definitive a clinical trial's results are, note whether it was a controlled or uncontrolled trial.

In a controlled clinical trial, one group of participants serves as a control group. These participants do not receive the intervention being studied.

Having a control group in a clinical trial enables investigators to answer the question "Compared to what?" Do participants receiving the intervention (the investigational group) fare better, worse, or the same as those who get standard therapy or a placebo?

In an uncontrolled study, which has no comparison group, investigators cannot be sure whether the outcomes they observe are caused by the intervention, by chance, or by unknown factors.

In a cancer treatment trial, participants in the control group usually receive the current standard treatment for their disease. Only when no standard treatment exists for that particular kind of cancer would participants in the control group receive a placebo, or dummy treatment.

In a cancer prevention trial, participants in the control group may receive an intervention known to help in the prevention of cancer. Those in the experimental group receive the new intervention. In those cases where no proven intervention exists, participants in the control group would receive a placebo.

Randomization: Chance, Not Choice

Randomization is an important way of minimizing bias in a clinical trial.

In a randomized trial, participants are assigned by chance, rather than choice, to either the investigational group or the control group. Random assignment is the most reliable way of ensuring that participants in the two groups are similar and therefore comparable.

If a trial is not randomized, investigators might unconsciously assign participants with a better prognosis to the investigational group, making the intervention seem more effective than it really is. Conversely, participants with a poorer prognosis might be more likely to choose the investigational group, making the intervention look less effective than it really is. (For a fuller discussion of this subject, see What is Randomization?)

To Blind or Not to Blind

A word about *blinded* studies.

When possible, medical researchers like to blind, or mask, their clinical trials. In a single-blinded trial, participants do not know whether they are in the intervention group or the control group until the trial ends. In a double-blinded trial, neither investigators nor participants know which group a participant is assigned to until the trial's conclusion.

Blinding is another way of reducing bias that may distort a study's results. For example, investigators may behave differently toward participants whom they know are receiving the experimental intervention.

However, blinding is not always feasible. In a trial comparing surgery with chemotherapy, for example, blinding would be impossible -- both doctors and participants would know which intervention was being applied.

Cancer prevention clinical trials are sometimes blinded, but cancer treatment trials rarely are.

Study Size Matters

Finally, the size of a clinical study is important when weighing how definitive the study's results are likely to be.

Investigators try to enroll as many participants as they need to get a statistically significant result -- that is, a result that is not due to chance. The total number of participants needed to get such a result varies depending on what questions the trial's researchers are hoping to answer.

In a very small study, the participants may not be representative of all people with the disease being studied. When a study involves a larger number of participants, there's a better chance those participants are a representative subset of the population with the disease. So in a broad sense, the most definitive studies tend to have a larger number of participants.

But again, what matters is not whether the number of participants is small or large, but whether they are the right number to get a statistically significant result.

Cancer prevention trials are usually much larger than treatment trials. Participants in prevention trials are healthy, although they may be at higher risk for a particular type of cancer than the general population. To be able to detect a significant difference between an intervention group and a control group in the number of cancer cases or cancer deaths, investigators need to enroll thousands of people and, usually, follow them for many years.

Example 1: A Cancer Treatment Trial

Cancer researchers theorized in the 1980s that "dose-dense" chemotherapy -- given at two-week instead of conventional three-week intervals -- would be a more effective way of killing cancer cells and extending patients' lives. But there was a problem: chemotherapy, which suppresses the immune system, usually made patients too prone to infections to tolerate treatment every two weeks.

In the 1990s, however, a drug called filgrastim became available. Filgrastim promotes the growth of white blood cells and helps patients receiving chemotherapy to withstand infections. With support from filgrastim, researchers thought patients might better tolerate dose-dense chemotherapy.

Researchers also wanted to know whether concurrent chemotherapy -- giving more than one drug at a time -- resulted in better outcomes than sequential chemotherapy -- giving one drug after another. They designed a large phase III, controlled and randomized clinical trial for

women with breast cancer to try to answer two questions: Is dose-dense chemotherapy superior to conventional chemotherapy? And is concurrent therapy superior to sequential therapy?

Like all clinical trials, this one was both prospective -- it followed patients forward in time -- and experimental -- it tested an intervention: schedules of chemotherapy that were more intense than the standard of care.

Between 1997 and 1999, the trial enrolled 2,005 women whose breast cancer had spread to their lymph nodes. After surgery to remove the tumor either by mastectomy (removal of the entire breast) or lumpectomy (removal of the tumor and some nearby breast tissue), participants were assigned at random to one of four treatment groups.

- Group I received the *conventional sequential therapy*: the drug doxorubicin every three weeks for four cycles, followed by paclitaxel (also called Taxol) every three weeks for four cycles, followed by cyclophosphamide every three weeks for four cycles. All together, this treatment lasted 36 weeks.
- Group II received the same regimen as Group I, but at two-week intervals, along with filgrastim to reduce infection risk. This *dose-dense sequential therapy* lasted 24 weeks.
- Group III, the control group, received the *conventional concurrent therapy* every three weeks for four cycles, followed by paclitaxel every three weeks for four cycles. This treatment lasted 24 weeks.
- Group IV received the same regimen as Group III, but at two-week intervals with the support of filgrastim. This *dose-dense, concurrent therapy* lasted 16 weeks.

In June 2002, after three years of following how patients fared post-treatment, the researchers were able to report statistically significant findings: Patients in the two dose-dense chemotherapy groups lived longer, and experienced fewer recurrences of their cancer, than women in the conventional dose groups. This was true regardless of whether the dose-dense therapy was given sequentially or concurrently.

Specifically, 85 percent of the women who received dose-dense chemotherapy were alive and disease-free after three years, compared with 81 percent of those treated at the conventional three-week intervals. At three years, overall survival (i.e., whether disease-free or not) was 92 percent in patients who received the dose-dense regimen, compared with 90 percent in conventionally treated patients.

Concurrent therapy produced no better results than sequential therapy, but women receiving sequential therapy suffered slightly fewer side effects. These findings were eventually published in the April 15, 2003, issue of the Journal of Clinical Oncology (see the journal abstract of the study).

Cancer researchers generally prefer to have five-year follow-up data before they consider a study's results to be definitive enough to change the standard of care. If this study's findings are confirmed after two more years of follow-up, sequential dose-dense chemotherapy is likely to become the new standard of care for breast cancer patients whose disease has spread to the lymph nodes.

Example 2: A Cancer Prevention Trial

Findings from observational studies in the 1980s led researchers to wonder whether supplements of beta carotene and vitamin A (also called retinol) might reduce the incidence of cancer, particularly lung cancer. The body converts beta carotene, which is found in plants, to vitamin A, and vitamin A is known to play a part in preventing the uncontrolled growth of cells. The phase III Beta Carotene and Retinol Efficacy Trial (CARET) was designed to test whether supplements of these nutrients could prevent lung cancer in people at high risk for the disease.

CARET was a clinical trial because it was both experimental and prospective. It was experimental in that it was studying the effects of an intervention – in this case, vitamin supplements. And it was prospective in that researchers tracked the health of participants forward in time, after they enrolled in the trial.

The multicenter trial was both controlled and randomized. Between 1983 and 1994, 18,314 men and women who were smokers, former smokers, or workers exposed to asbestos were randomly assigned to one of two groups: the control group received dummy pills (placebos) each day; the intervention group received daily supplements of beta carotene and vitamin A.

The trial was also double-blinded, meaning neither participants nor their doctors knew who was taking the supplements and who was taking the dummy pills.

In January 1996, researchers reported that a preliminary analysis found 28 percent more lung cancer cases and 17 percent more lung cancer deaths in the intervention group than in the placebo group. In other words, there was "clear evidence of no benefit and substantial evidence of possible harm" with regard to the supplements.

Though researchers had planned to continue the experiment for another two years, the trial had progressed far enough and had enrolled enough participants for these early findings to be statistically significant. Researchers immediately told participants to stop taking both the supplements and the placebos, but kept following the participants' health for the next several years. The initial findings were subsequently published in the November 6, 1996, issue of the Journal of the National Cancer Institute. (See the journal abstract of the study.)

The CARET results confirmed the findings of an earlier phase III, randomized, controlled clinical trial, the Alpha-Tocopherol and Beta Carotene (ATBC) trial, published in 1994 (follow-up data were published in 2003; see the journal abstract). The ATBC trial, conducted in Finland, involved more than 29,000 male smokers. Participants taking beta carotene supplements experienced 16 percent more cases of lung cancer than those taking either a vitamin A supplement or a placebo.

On the strength of the ATBC and CARET findings, current medical consensus is that taking beta carotene supplements does not help to prevent lung cancer, and may in fact be harmful.

Summary: Questions to Ask About a Cancer Study

In summary, the following questions may help as you look through various cancer studies, looking for the most medically definitive findings:

Question	Look For
▪ Was the study a clinical trial? In other words, was the study *experimental* (there was an intervention that people were asked to take or do) and *prospective* (investigators followed study participants forward in time)?	A study that is both experimental and prospective
▪ What phase was the trial -- phase I, phase II or phase III?	A phase III study
▪ Did the clinical trial have a control group? That is, did one group of participants receive the experimental intervention while another did not?	A controlled study
▪ Were participants randomly assigned to either the investigational group or the control group?	A randomized study
▪ How many participants were enrolled in the study?	A study that is large enough for the results to be statistically significant; not due to chance