

Controlled Trials and Chemoprevention of Cancer

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Epidemiological and laboratory studies provide preliminary evidence that a compound may prevent certain types of clinical cancer. The final proof for practical application demands two controlled trials with similar, decisive results. Controlled chemoprevention trials on clinical cancer are large, time-consuming and expensive, whereas studies on cancer surrogates are smaller but less reliable. Rational trial design often lacks sufficient information about the sensitive period and the time from that point to clinically detectable cancer. The correct dose of chemopreventive agent and an expected preventive fraction of cancer are also often based on informed guesswork. Long trials call for special arrangements to guarantee the staying will of the participants and key research personnel. Although large chemoprevention trials are currently being carried out without any certainty of successful outcome, the situation is not so different from the early days of chemoprevention trials for cardiovascular diseases. Cancer trials will be conducted based on the 'learning-by-doing' approach, and in the more distant future based on research designed to provide information for trial needs.

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BACKGROUND INFORMATION

The most important steps toward generally accepted chemoprevention of any disease are firm knowledge of the risk factors, positive controlled clinical trials either by first changing the risk factors and subsequently observing reduced disease incidence, and, finally, trials reducing the incidence by a chemical agent, or trials testing the preventive potential of an agent without subsequent risk factor intervention.

Often the first controlled trials are limited to high-risk population groups and surrogate endpoints are selected instead of the clinical disease. It is not uncommon to design the trial so that duration of follow-up at least partly depends on the observed phenomena during the study. Positive results from such preliminary trials enhance credibility of the hypothesis, but negative results do not necessarily rule out the main hypothesis that a chemopreventive compound really is capable of reducing incidence of clinical cancer.

Occurrence of many cancers shows wide international variation and is clearly influenced by lifestyles and environmental factors, consequently, their incidence might be reduced by intervention. For instance, several common types of cancer occur less frequently among those who eat lots of fruits and vegetables. Fruits and vegetables are rich in various antioxidants, which in laboratory experiments have several effects related to impaired cancer growth. These observations have inspired several controlled

chemoprevention trials using antioxidants to determine whether these agents do indeed prevent clinical cancer.

Perhaps the most attractive targets for chemoprevention trials are the least toxic agents against common cancers in which the results of clinical treatment have remained modest. Such agents are, for example, antioxidant vitamins and other chemical compounds in fruits and vegetables, such malignancies are lung, stomach, pancreas and ovarian cancers.

TECHNICAL ASPECTS IN TRIAL DESIGN

The main determinants of the size and duration of a chemoprevention trial aimed to reduce the number of incident cancer cases are: the number of specific cancer cases and, in particular, the difference between the intervention groups at the end of a randomized, double-blind, placebo-controlled trial. The number of cases depends mainly on the incidence of the cancer among the trial participants, on duration of the intervention and how fast the birth of the first cancer cells declines after the intervention begins and how long it takes from the first cancer cell cluster until it has grown to a clinically detectable tumor. Both the latent period and the necessary growth period are in most instances simply unknown. Furthermore, these matters are crucial not only for the trial design, but once the study is over and the sought difference in cancer endpoints between the intervention arms is finally observed, this question remains: does the chemical compound

truly reduce incidence of the first cancer cells and clinical cancer or does it merely retard tumor growth? The longer the trial lasts, the better are the chances that intervention covers the latent and tumor growth period. Long-lasting trials have large participant drop-out rates and hence less power in the final analysis. Most cancers occur in old age when other diseases reduce the patients' will to perhaps prevent one more disease. This decreases participation and increases drop-out rates in trials.

In practice, a reasonable balance between sample size and duration of the trial is sought, and at best, the estimated lower limit of the confidence interval of the intervention effect corresponds to the smallest effect that ever could be applied in cancer prevention in any population group. Statistical methods for such sample estimation are available. Factorial designs make it possible to test more than one substance in a single chemoprevention trial, this has become very common practice in large, costly trials.

Conventionally, the first preventive trials are carried out in risk groups in order to gain more endpoints with a smaller sample size. With the exception of smokers, for primary cancers and successfully treated, surviving cancer patients who form secondary cancers, risk groups cannot readily be found in a population for large-scale cancer studies. Surrogate endpoints are more common than clinical cancers but their relationship to clinical cancer is seldom well-defined, thus the positive effect of chemoprevention on, e.g., polyps does not mean that we can conclude that related clinical cancer can be prevented.

TECHNICAL ASPECTS IN TRIAL FOLLOW-UP

The most important issues under surveillance during the intervention are: chemopreventive agent compliance, participation compliance and possible adverse effects. It is also pertinent that strong risk factors remain in good balance between the intervention groups, such as smoking in lung cancer studies, thus these factors must be monitored periodically.

There is a lack of good, objective methods to monitor the agent compliance. The few available marker substances have been developed for trials with short-acting drugs, prevention trials often use long-acting interventions in which the occasional missed dose is of less importance. One or two doses taken just before a follow-up visit may conceal the really relevant longer non-compliance when a short-term marker is used. It would not be too difficult to develop a good long-detectable marker substance for the purposes of large-scale trials.

The drop-out rate is usually around 5% per year in trials of subjects of cancer age. Thus 50% of the participants at baseline remain active after 10 years, but after 20 years there are very few. Uneven drop-out rates by the intervention groups create considerable interpretation problems at

the end. In long trials the research personnel also become tired, and smooth transitions are possible only if the early departure of key persons is anticipated in the planning phase of the trial. Regular contact between investigators and all field workers is a prerequisite for success, particularly in long-term trials, and must be budgeted for in advance.

Endpoint assessments are done centrally in controlled trials, strict criteria are applied and in cancer trials the reliability of diagnoses is measured by the paired recordings of two pathologists and clinical gradings by two clinicians.

Large trials produce vast amounts of data to be retrieved in real time. Smooth-riding data monitoring during the follow-up of large trials calls for sufficient computing capacity and simulations of anticipated procedures in advance. Functional storage of forms and biological samples is no mean task when the number of items runs into the millions.

TECHNICAL ASPECTS IN TRIAL CLOSURE

The final analysis of the trial results is carried out in accordance with the intention-to-treat principle. Once the subject enters the study, he or she remains under follow-up until endpoint, death or closure of the study irrespective of interrupted participation in the chemoprevention. The reasoning traits for including all recruited trial participants in the final analyses are intricate but abiding by this rule is mandatory. Follow-up of the drop-outs toward the end of the trial is always more complicated than follow-up of the still-active participants.

Subjects lost to follow-up have to be counted and presented by the intervention group in the study report. In large, long-term trials there are always people who travel round the globe, get sick and die for a variety of reasons in various countries. To gather relevant health information about them is time-consuming and costly.

The prevented fraction of cancer incidence and its confidence intervals are preferably reported in percent rather than as reduced relative risk, which is more in line with its use in the practice of prevention. Findings from the analyses of effect modification are seldom more than a hint of future research, since anything can emerge in eager research and ample testing among various trial subgroups. In advance expected and in the study protocol expressed effect modifications are the exceptions, perhaps also clear linear trends within an effect modifier.

Ethical aspects of chemoprevention cancer trials are pondered in an enclosed article by Nyrén (1).

LESSONS OF THE ATBC STUDY

The Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study was a randomized, double-blind, 2 × 2 factorial design, primary prevention trial testing the

hypothesis that α -tocopherol (50 mg/day) and α -carotene (20 mg/day) supplements reduce the incidence of lung cancer and possibly other cancers (2–4). This was carried out in Finland. A total of 29133 male smokers aged from 50 to 69 years entered in the study (mean duration 6.1 years) accumulating 169751 follow-up years.

The supplementation compliance was excellent. Furthermore, 9061 participants (31%) left the study for various reasons, including death. A total of 3570 deaths occurred during the trial. A total of 21% of all participants stopped smoking during the study.

Cases of lung cancer were identified through the Finnish Cancer Registry. To enhance the verification of cases of lung cancer, a chest x-ray was obtained during a study visit every 29 months and at the end of the trial. Information on morbidity unrelated to cancer was obtained from the Finnish National Hospital Discharge Registry. Deaths and causes of death were identified from the National Causes of Death Registry.

The study failed to demonstrate a protective effect of antioxidant supplements on lung cancer, and raised the possibility that β -carotene might be harmful.

Contrary to the initial hypothesis, an excess cumulative incidence of lung cancer was observed in the β -carotene group after 2 years, and this increased progressively thereafter, resulting in a 16% difference in incidence (482 cases vs. 412 cases) by the end of the study ($p < 0.01$). Lung cancer was only 1% lower in the vitamin E-supplemented group. There was no interaction between the two supplements in their effect on lung cancer.

The participants who received α -tocopherol had 32% fewer cancers of the prostate than those who did not (99 vs. 147). The mortality from prostate cancer was 41% lower, respectively. The intervention effects on other cancers were minor (3–5).

The main result that a dose of α -carotene about 7-fold of the mean daily dietary intake actually increase lung cancer was soon confirmed by another chemoprevention trial from Seattle, USA, conducted at the same time (6). The evidence of reduced prostate cancer incidence after vitamin E supplementation has not been studied in other controlled trials.

Practical learning from the study can be summarized as follows:

- Always use two-sided tests as a basis for sample size calculations.
- Make sample size determination flexible. Men over 65 years of age did not have the same interest in participating in the trial as younger men. We had to increase the sample size about 50% during the recruitment phase.
- Data retrieval must have capacity and all data monitoring and editing devices have to be in place before the study is started. The volume of data in a large-scale trial can be surprising.

- Sensitive monitoring of compliance demand several methods.
- Regular feedback of progress information to every person involved in the research project and personal contacts help to gather information quickly on problems at all levels of the study.
- It is difficult to keep good research persons working on one trial for extended periods. Difficulties begin after 5 years.
- Endpoint assessment is time-consuming. We had about 10000 cancer specimens to be reviewed by a band of prominent but busy pathologists.
- Research into issues important to the trial design and to outcome interpretation is really sparse in the sphere of cancer chemoprevention.
- Unexpected study results are generally considered incredible and can harm practical plans for further trials if there are no other parallel on-going trials.

CHEMOPREVENTION AND PUBLIC HEALTH

Chemoprevention of cancer is a much more recent phenomenon than chemoprevention of coronary heart disease even though both diseases are fatal and have a large impact on public health. Both cancer and cardiovascular diseases are difficult to cure, and for a half century their occurrence has been known to vary according to lifestyle and environment. For these reasons one might expect that both disease groups would to the same extent generate the inspiration to seek prevention by chemical agents.

Chemoprevention today is an established method to prevent myocardial infarction and stroke. It has played an important role in reducing the incidence and mortality of cardiovascular diseases worldwide. Chemoprevention of cancer has thus far had very modest achievements (7). Since controlled clinical trials are the cornerstones in developing chemoprevention in practice, it is of interest to compare the first attempts in both disease groups and to ponder inherent differences of preconditions for trial designs for cancers and cardiovascular diseases. This may help to forecast the future of cancer chemoprevention.

The presumptions for trial design are much more favourable in cardiovascular diseases than in cancers. Possible endpoints are few, mainly myocardial infarct and stroke compared to numerous malignancies. For cancers, real risk groups are difficult to find in a population, for recruitment into a trial; for heart disease, smoking, arterial blood pressure and serum lipids are relatively easy to study in a population. Any specific cancer is less frequent than myocardial infarction or stroke in most populations. This means that controlled cancer prevention trials must be even larger and more expensive than trials for cardiovascular diseases.

In heart disease and stroke, chemoprevention immediately changes blood lipids or blood pressure; many good

surrogate measures of the clinical disease are available. This helps in the selection of the most efficient chemical agents and suitable doses in series of small studies prior to designing large primary prevention trials of myocardial infarct or stroke. Risk factors and surrogates of cancers are not readily available for measurable chemical manipulations.

Risk factors of cardiovascular diseases have been known for over 50 years and chemoprevention has been used widely for 10 years. The first three large chemoprevention trials included men with previous myocardial infarct. All three failed and controlled trials went out of fashion for many years. Chemoprevention via lowering blood lipids failed in 18 out of the first 20 controlled trials. The first trials to prevent myocardial infarcts via lowering blood pressure also failed. Despite this discouraging start, hard work and persistence have produced a well-tested, impressive chemoprevention arsenal to reduce cardiovascular diseases. But it took about 40 years.

It is too early to predict what the role of chemoprevention of cancer will be some three decades from today. There is no reason to believe that development will differ greatly from that in cardiovascular diseases. Meanwhile, a lot of research effort will be focused on discovering genes that increase cancer risk. Once these genes are identified in most cancers, large population groups will be screened in order to find the real risk groups. It will not take very long before these test are feasible on a large scale. The unfortu-

nate carriers of such genes will hope that medicine can offer them some form of prevention. Rational response presumes well-thought research policy, time and money. More research is needed before chemoprevention can be applied in public health, but there is no reason to doubt that the possibilities are there.

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