Chemoprevention Trials in Cancer Research

Ethical Considerations

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The idea of preventing cancer with a pill sounds attractive to most people. But several ethical issues need to be addressed before a chemoprevention trial is started. Undue fear of cancer—not only among the participants—may be triggered if the information to the public is not formulated with great care. Since prolonged treatment is typically required, the participants' quality of life may become impaired; they may even perceive themselves as already sick. The ethical implications of placebo treatment for many years need careful consideration. The investigators must also have a plan for how to take care of the participants after the study. The benefits of the intervention are small and not noticeable for the individual, who will never know whether he/she would otherwise have developed cancer. But participants who get cancer despite their efforts to comply with the study protocol will likely feel double disappointment. It is of paramount importance that people are given a realistic, honest, and understandable account of both benefits and risks/disadvantages before they decide to participate.

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Chemoprevention is a special type of cancer prevention, where substances/drugs are administered to apparently healthy people, either to strengthen the protection against potentially carcinogenic mutations, or to stop or retard antecedents or early latent stages of the disease. Although the objective of preventing cancer is uncontroversial, imposing drug treatment on healthy people is not, and every proposal on chemoprevention requires a thorough ethical analysis. The purpose of this paper is to point to some of the issues that ought to be considered before a trial of chemoprevention is started, or a full-scale programme is implemented.

The term chemoprevention covers a number of interventions, from iron fortification of foods, via addition of trace elements to fertilizers, salt, or tap water, to individual prescriptions of, for example, dietary supplements (including antioxidative vitamins, calcium, or other minerals), acetylsalicylic acid, NSAIDs, antibiotics, or hormones. Thus, chemoprevention can be administered to communities as well as to individually consenting subjects. The present paper will focus on the latter situation, and particularly on ethical issues related to *trials* of such chemoprevention.

Cost-benefit considerations

Fig. 1 illustrates some of the considerations that should precede the decision to launch a chemoprevention trial. Certain aspects of both the disease and the intervention have to be weighed against each other. Clearly, if we are even to consider chemoprevention, the risk of the disease to be prevented should be tangible. The risk magnitude that is required depends to some extent on other factors; for instance, a risk required for considering preventive measures may be smaller if the disease is very serious, either in terms of the outlook for the individuals stricken, or in terms of cost to society. Moreover, the more efficient, safe, convenient, and cheap the intervention, the less absolute risk for the disease is required. It should be noted that there is a link between the risk and cost of the prevention programme; the rarer the outcome, the more subjects have to be treated for each prevented case. There are no easy solutions to the equation, especially since the units include both monetary and human values, such as degree of suffering and quality of life. The question often boils down to how much society is prepared to pay for each prevented case, both in terms of money and intervention-induced morbidity. Therefore, the planning of chemoprevention trials ideally should include cost-benefit estimations, based on qualified assumptions about the prevented fraction (1, 2). If the estimated costs are of such a magnitude that

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implementation of the chemoprevention regimen in routine health care appears unrealistic, it may be advisable to abstain from launching the study, particularly in view of the ethical concerns that are discussed below. If, on the other hand, the study also yields important insights on carcinogenic mechanisms in humans—insights that could not be gained in other ways—the cost/risk-benefit ratio might shift towards realization of the study.

Possible impact on society

The idea of preventing cancer with a pill is very attractive for the layman, and large-scale chemoprevention trials are bound to attract a great deal of public attention. In order to facilitate the recruitment of thousands of participants, investigators often take advantage of the press to boost public interest in cancer prevention. But this may also stir up undue fear of cancer in the population, and may result in widespread self-prescribed use of the substances in question before any efficacy has been proven.

Targeting high-risk populations

The absolute risks of specific cancers—even at common sites—are often too small to justify a preventive effort, both from the individual's perspective (provided that he/she can perceive the risk correctly) and judged from the point of view of study efficiency. To make such an endeavour efficient and worthwhile, population strata at increased risk are typically targeted. Such strata may be defined in terms of geographic areas with a high incidence (where people are often unaware of their increased risk), or through screening for people with high-risk behaviour patterns. In some instances, e.g. in the case of smokers, the individuals may be aware of the risks that they are taking, although their perception of the absolute magnitude of the excess may be biased upwards or downwards. In other instances, for example among people with certain medical conditions associated with an increased risk, the excess may be less well known. Another way of defining a high-risk population is to screen individuals for biological markers of the risk, e.g. to test for *Helicobacter pylori* seropositivity. In these instances, information about the excess risk may come as a perfect surprise to the subjects.

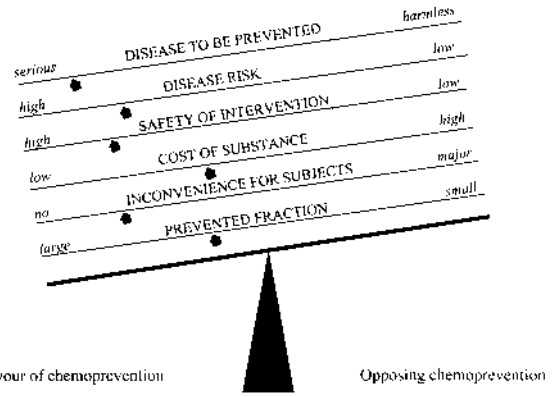

Fig. 1. 'Balance of considerations': Examples of aspects that may favour or oppose the implementation of a chemoprevention programme. Each aspect does not necessarily have the same weight in the final decision.

Recruiting healthy people—ethical implications

There are some features that clearly distinguish chemoprevention trials from regular clinical trials of therapeutics; the most evident difference is the absence of disease among the subjects in the former type of studies. As opposed to clinical trials of therapeutics, where the participants are *patients*, who may be dependent on the investigators for their care, or who may generally feel obliged to participate because they are indebted to health care, it is often easier for people considered for prevention trials to decline participation. On the other hand, since the numbers of participants required for a meaningful interpretation of prevention trials are usually much larger than those required for regular clinical trials, it may be tempting for the investigators to put pressure on the individual, for instance by exaggerating the benefits associated with participation. Whereas the benefits for the population may be easy to understand, the benefits for the participating individual may be much more uncertain and abstract; it is a matter of reducing an already small *probability* of contracting the disease. The word 'prevention' should perhaps be used with some reservations in this context, since it may, for some, imply that the risk is eliminated.

Thus, a medical problem of unknown—possibly no—significance for the individual is imposed on him/her. And the solution—drug treatment—may 'medicalize' the individual and hence render him/her a patient. As the carcinogenic threats to the cell are likely to prevail throughout life, most chemoprevention schemes implicitly presuppose prolonged, perhaps life-long, treatment. Therefore, the investigator assumes a responsibility, which is often greater than that laid on investigators conducting conventional therapeutic clinical trials on patients. A negative result, i.e. that the chemoprevention was shown to be ineffective, relieves the investigators from this responsibility, but telling the participants that they may have taken the drug for several years, and perhaps suffered minor side effects in vain is bound to be problematic. If, on the other hand, the treatment is shown to be truly effective, it may not be appropriate to recommend discontinuation of the chemopreventive agent after termination of the trial. Once having started the treatment, many subjects will likely feel the urge to continue. If the availability of the drug is limited, or the costs are high, the subjects may be forced to make difficult choices. This may evoke anxiety or resentment and might require individual counselling after termination of the study. Investigators should have a well-planned strategy for tackling these problems, in advance of launching the trial. These problems also emphasize the impor-

tance of making realistic sample size calculations; if the study result is a clear but statistically non-significant trend, counselling may be difficult.

Ethical aspects on placebo treatment in chemoprevention trials

As in conventional clinical trials of therapeutics on patients who are allocated to either an experimental drug or a reference treatment, it is ethically unacceptable to offer treatment—in either of the treatment arms—that is believed to be less effective than the one that would have been given if the subject had not participated in the study. In view of the concerns about future cancer risks that are imposed on the participants in cancer chemoprevention trials, nothing short of the best alternative treatment should serve as reference, even if it is not routinely available to the public. However, at present there are no regimens for primary chemoprevention that has unequivocally been shown to be superior to placebo. In practice, placebo is currently the only relevant reference. Even if the experimental substance is demonstrated to be clearly protective in observational epidemiological studies, the necessary equipoise (3), i.e. state of genuine uncertainty on the part of the investigator regarding the comparative therapeutic merits of each treatment arm, can still be considered to be at hand; recent experience has taught the medical community that observational data may need to be reconsidered when putative protective substances are tested in formal randomized trials (4–6).

While a placebo treatment arm—given that there are no alternatives available—is ethically acceptable in short-term therapeutic clinical trials, the use of placebo in chemoprevention trials, which typically last for several years, is more complicated. Clearly, having to take ineffective placebo pills day after day for such a long time without the slightest chance of any benefit is not a particularly attractive prospect for the participants-to-be. Needless to say, it is ethically unacceptable to have people take placebo for many years unless they are fully informed about the possibility and have understood the consequences. Putting emphasis on this possibility, though, may dampen people's willingness to participate in the study. It would be tempting to skip the control condition and to use incidence or mortality statistics from the source population as reference. But since those who accept the offer to participate may have lifestyles that entail a cancer risk which is different compared with that in the entire population, the controls have to be recruited from the very same population strata as the participants in the active treatment arm. A randomized open study, where the subjects in the control arm are not required to take placebo pills, may be one way of avoiding the ethically questionable long-term placebo treatment. The concern about future cancer risks raised in connection with recruitment and randomization may, however, prompt the subjects in the control arm to change risk behaviours to a greater extent than is done in the active treatment arm, and perhaps to self-medicate with the substance under study (if available). This could lead to failure to capture a true advantage for the active treatment. Moreover, an open study is sensitive to ascertainment bias during follow-up. Thus a placebo arm is desirable, but if possible, a pure placebo arm should be kept as small as possible, for instance by combining trials of different chemoprevention agents, using the same control group—perhaps with a factorial design (7).

Quality of the research—an ethical concern

As in all medical research, studies that have insufficient power to answer the research question or a design that opens for invalid conclusions are both at risk of being unethical; not only have the participants then taken the trouble to comply with the study protocol in vain (which is particularly serious if the study has required participation over many years), but researchers in the field may be put on the wrong track, and scientific progress may become delayed. Since cancer chemoprevention trials are usually major undertakings, the study may never be repeated, and it may take decades before incorrect conclusions can be refuted. It is, therefore, essential to make realistic estimates of the required sample size and in doing so take into account that people volunteering as participants in prevention studies are likely to lead a healthier life and thus to have lower incidence rates of cancer. Likewise, the investigators must allow for a realistic latency period before any effects of the intervention can be expected. Chemoprevention studies are long-term commitments, but investigators may feel pressed by parties involved, e.g. funding agencies or drug manufacturers, into making over-optimistic assumptions as to the time required for any effects on cancer incidence to become discernible. For agents that presumably act early in the carcinogenic process, and where the latency period thus is expected to be very long, it may be necessary to use intermediate endpoints for cancer outcome (8). Such endpoints must reliably reflect the disease process (and not just causative exposures), and the predictive value for the individual needs to be known and be high. At present, there are few candidates that meet these requirements. Regardless of whether cancer incidence or intermediate endpoints are used as an outcome measure, no efforts should be spared to maximize compliance with the studied medication and to minimize self-prescribed concurrent use of the substance, which may otherwise threaten to cancel true effects of the intervention.

Respect for the individual's right to choose

In the final ethical evaluation of chemoprevention studies, two fundamental ethical principles are particularly relevant; the first one pertains to respect for the individual's autonomy, i.e. each person should not only have the right to decide, freely and without undue pressure, whether to

participate or not, but he/she should also be given correct and sufficient information to make this freedom of choice real and meaningful. It is the responsibility of the investigator to ensure that the information is sufficiently adapted to each potential participant's level of education and intellectual capabilities so that the important points can and will be understood. As opposed to therapeutic clinical trials, which usually have a limited number of participants, and where the informed consent in most cases is obtained through a direct interaction between the investigators and the patients considered for the study, large-scale chemoprevention studies may include many thousands of participants. Therefore, the investigators have to rely on written information or on representatives when soliciting the consent. This may make it more difficult to verify that each individual has fully understood all the consequences of his/her consent, but it does not relieve the investigator of the responsibility. If the study is done in population strata at increased cancer risk, it is of particular interest how the subjects are told about the extra risk. It is tempting for the investigator to dramatize the excess in order to increase the participation rate. Relative risk data often appear more spectacular than absolute risk. However, most laymen cannot interpret relative risk data, which should be avoided in this context. It is a formidable pedagogic challenge to convey a realistic appreciation of the prevailing absolute risk and the risk reduction that is expected with the intervention.

An obligation to minimize harm

The second important principle that is particularly relevant in the ethical evaluation of chemoprevention studies is non-maleficience, i.e. an obligation on the part of the investigator to minimize any harm that might ensue from the investigation. This not only pertains to physical harm due to toxicity or other medical side effects from the trial substance, but also to possible harm to the quality of life because of anxiety and perturbation that may be aroused by the study. Clearly, the safety of the studied substance is a paramount concern; the tolerance even for mild or rare side effects is very low if the substance is to be used on a large scale among healthy individuals. The benefits, which in the case of cancer are mostly reaped at an age when the life expectancy is short anyway, may be outweighed if a potentially lethal side effect occurs in some participants at a much younger age. In the overall assessment of a prevention programme, it may be appropriate to assign different weight to risks and benefits according to the age when they occur. The medical risks may sometimes extend beyond the participants; in the case of large-scale antibiotic treatment of *Helicobacter pylori* for the prevention of gastric cancer and lymphoma, the induction of antibiotic resistance in various micro-organisms may become a problem for the entire population.

Psychological and social harm has not attracted much attention but may represent the most important adverse effect of chemoprevention studies (9). Such harm is not only limited to the participants, who will be perpetually reminded of cancer risks that are best forgotten, and whose quality of life may be further impaired by fear of forgetting to take the pill and by repeated testing. The harm can also fall upon the public, where mass cancerophobia might be induced (9). Of particular concern is the well-being of people who are reached by the offer to participate, but who decline. Notwithstanding the strong rationale behind their decision, they may feel remorse and profound guilt if they later develop the cancer that was going to be prevented. Those who participate in the trial may also develop the cancer in question; while it is impossible to know who was really helped by the chemoprevention (i.e. who would have developed the cancer had they not taken the substance), and the benefits thus pass unnoticed, a participant who is given a cancer diagnosis may perceive it as a double catastrophe. He/she may feel betrayed and duped about having taken the pills for years, in vain, but may also feel remorse and guilt, although unfounded, about forgetting to take the drug every now and then. When the medication has to be taken for a very long period, it is almost unavoidable that healthy people will fail to comply completely with the study protocol. There is a need for studies of the effects of preventive interventions on the quality of life and mental health of the population subjected to them (9).

CONCLUSION

In the ethical evaluation of a cancer chemoprevention trial, a comparably small public health benefit (but often also a great scientific benefit) should be weighed against a number of possible adverse effects, many of which are psychosocial in character. Some of these undesirable effects may also fall upon people who are not participants in the study. Hence, although the intervention may seem innocuous, the ethical deliberations are far from simple. Since the benefits, as opposed to the adverse effects, are uncertain and not noticeable for the individual, the investigators must seek to resolve the ethical dilemma of a conflict between the interest of the collective and the interest of the single participating individuals. Clearly, the potential participants must be given a free choice, based on an honest account of both benefits and risks. The information given to the public and to potential participants is of crucial importance; it must not stir up undue fear of cancer, or exaggerate or dramatize the benefits, and the full consequences of a consent to participate must be explained in detail. Some of the potential psychological and social ill-effects mentioned above may, however, seem speculative and it may not be appropriate to discuss them in an information pamphlet. On the other hand, laymen may

not be able to foresee all psychological and social consequences of their participation. Therefore, a heavy responsibility rests on the investigators' shoulders not to cause psychological harm to the participants or the public. To provide guidance to investigators in their difficult decisions, research on how preventive interventions affect the mental well-being of the public is clearly warranted.

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