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Strategy for Chemoprevention of Human Breast Cancer

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My comments on chemoprevention derive from the milieu of the laboratory, clinic, and community levels rather than from the typical medical oncology approach which is quite different than the epidemiologic or public health approach.

Considering strategies for chemoprevention of human breast cancer, the facts are that we have had extensive experience so far with conduct of certain types of chemoprevention trials. (i) A low-risk skin cancer study accrued 3,000 subjects who are being followed. (ii) A high-risk skin cancer prevention study is ongoing in which we have obtained 300 of the 700 subjects projected. (iii) A cervical dysplasia study is underway, as well as (iv) two colon cancer prevention studies as well as some other phase II studies.

Nevertheless, prevention of human breast cancer presents a special challenge in and of itself. For all the different tumor types one needs to consider the chemoprevention strategy for that particular tumor, although there are perhaps certain generic principles that apply.

Considering breast cancer prevention in a generic way there can be two general types of approaches: proscriptive and prescriptive.

There has been epidemiologic evidence of various sorts for a relationship between total calories, fat, protein, and alcohol. There is evidence of several different types for dietary factors involved in breast cancer genesis. Epidemiologic studies include ecologic and analytic types.

In terms of laboratory studies, there is a background of both cellular and biochemical observations that would support the general notion that an individual biological factor would be involved. Animal studies are actual intervention studies, either true chemopreventive-type studies, adjuvant, or quasiadjuvant types of trials. The data for total calories is strong from an ecologic epidemiologic point of view, but not terribly strong from the analytical point of view. Mechanistic and animal studies certainly support a role of total calories in breast cancer.

In terms of fat, a similar pattern emerges although perhaps not as strong as in the animal studies. For total protein there is also some relationship but there has really been an absence of mechanistic studies that address that issue. For alcohol, the ecologic studies would not support a role, but there are few analytical studies that do. There have not been really extensive laboratory studies either way.

Chemoprevention, however, is prevention of cancer brought about by the use of defined chemicals or micronutrients. Although that seems like an obvious statement, we tend to forget that we are dealing with a defined chemical that has many and diverse effects on dietary and other hormonal factors which need to be taken into consideration in the evaluation of a very specific chemical or micronutrient.

An advantage of the specific agent is that it is easily administered, although possibly a long-term effect could

be achieved by changing lifestyle or diet, which are of course very hard to alter.

Definitive monitoring of a sort can occur. We often delude ourselves into thinking we do definitive monitoring when we measure these chemicals in the serum, the urine, or sometimes the feces when what we really should be interested in is the tissue levels and the effects of that agent on one particular tissue. When we look at the pharmacology of most of the chemopreventive agents, and to a certain extent even tamoxifen, there has been a real scarcity of studies which address tissue uptake and effect. The term definitive monitoring should really be used with italics. Pill-taking is a very complicated, complex issue. In our trials we do extensive compliance monitoring which is very difficult and time consuming. Compliance with pill-taking is certainly not as complex as that of dietary intervention but it is by no means straightforward. Disadvantages are lifelong pill-taking and possibly long-term side effects.

The candidate chemopreventive agents for breast cancers are summarized in Table 1. This classification of how effectively these various compounds might serve

as chemopreventive agents hardly represents the extensive literature which needs to be reviewed. In terms of micronutrients, we can see that there is very little ecologic data specifically related to breast cancer. For beta carotene, a few analytic studies have been reported, with negative mechanistic data and equivocal animal data. We do not have any evidence one way or another whether beta carotene is clinically active in the advanced or adjuvant setting, which might present some hope that it would work in an earlier stage. The same is true for vitamin A, that is real vitamin A, not the synthetic derivatives which raise many different questions.

For vitamin E the data is also weak. There is not a great amount of information, although certainly there have been a couple of case-controlled studies that showed a relationship between low vitamin E levels and risk for breast cancer. There are some mechanistic studies in culture for breast cancer and other cell types as well.

Vitamin D is an interesting dilemma because it does cause differentiation of some specific breast cancer cell lines, but there is not a great deal of available information. A problem that deserves attention is the question of

Table 1
Candidate Chemopreventive Agents for Breast Cancer

Compound	Evidence				
	Epidemiologic		Laboratory		
	Ecologic	Analytic	Mechanistic	Animal	clinical
Micronutrients					
β -Carotene	ND	+b	—	±	ND
Vitamin A	ND	—	+	±	ND
Vitamin E	ND	+b	+	ND	ND
Vitamin D			+	ND	ND
Hormonal					
Tamoxifen	NR	++/--	++	++	+++ ^a
Danazol	NR	NR	+	ND	+
LHRH _A	NR	NR	+	ND	+
DHEA	NR	+	+	+	ND
Other					
4HPR	NR	NR	+	+++	—

^aContralateral, adjuvant, advanced.

+b, case control, biochemical.

calcium. Calcium has been advocated as a chemopreventive agent for colon cancer for a variety of reasons. If we think about calcium as being necessary for all epithelial maturation, and low calcium being associated with excessive epithelial proliferation, then a generic strategy might be possible. Certainly calcium is a very safe agent. There is some interesting new data on omega-3 fatty acids. Tamoxifen certainly has an enormous amount of indirect epidemiologic and mechanistic and animal data to support its use as a chemopreventive agent. The clinical data for activity is also strong in advanced cancer.

There is weaker data for danazol, LHRH analogs in dehydroepiandrosterone (DHEA), mostly of a mechanistic nature. There are several epidemiologic studies of a biochemical type suggesting that DHEA might be important in suppressing breast cancer. In terms of the retinoids, there is an important point about the current data. There have now been several clinical trials in advanced cancer showing no activity for 4HPR, but that should not be a reason to abandon its possible use as a chemopreventive agent. One thing to consider about 4HPR is that it proved a strong chemopreventive agent in animal trials while many other retinoids were found to be negative. This may be related to the particular pharmacology of 4HPR, its concentration in the breast, or it might truly be different than the other retinoids. We do not know the answer at this point.

Why a clinical trial? First, the epidemiologic data identifies possible associations but rarely defines etiology. The strength of the associations is very suggestive but not exceedingly so, such as for smoking and lung cancer, that we could interpret the data as causative on face value.

Second, laboratory experiments suggest biological relevance. However, very importantly, and not sufficiently emphasized, is the fact that carcinogens of all types, and inhibitors of carcinogenesis, are type, dose, time, tissue, organ, and species specific. That is, even though we can learn a great deal in a general way about the process of carcinogenesis from animal studies, translating the information directly to humans or any other species, for that matter, is a very uncertain issue. Results from laboratory experiments can be interpreted only as a general guideline in any approach to human carcinogenesis.

A clinical trial will confirm a generated hypothesis by measuring a definitive endpoint in response to a defined intervention.

Carcinogenesis and tumor development in a generic way has been delineated from many thousands of different experiments that have been done in animal models. If you take the Y-axis as the number of tumors and the x-rays

as time, it appears that at least in breast cancer and perhaps other cancers, the initiation event begins with your genes *per se*. We know increasingly that genetic makeup puts one at risk for different types of cancers and that the presence of different types of proto-oncogenes or similar gene structures will put one at increased risk. Therefore, in a fashion, cells are initiated from a genetic point of view before one can even see chemicals. That is an important consideration in identifying people at increased risk. It may well be that the most efficient way will be a genetic identification, and that may be attainable within a very few years.

After an initiator event, followed by any type of promoter; in breast cancer the relevant one might be fat or a fat-related molecule, a variable latency period occurs followed by the rapid development of tumors. The duration of this latency period is unknown, of course, for humans. Studies from an anthropological approach suggest that the major early promotional events for breast cancer occur in childhood before the age of 12. If true, that means risk has been determined from a very early age. Certainly we would not advocate starting patients at the age of 12 on an intervention agent unless we knew the risk was astronomical.

In terms of anti-initiators, gene therapy is probably not too far away to be considered. Vitamin E might be useful. Demonstration of effect in a reasonable time frame would be difficult. Antipromoters are primarily under consideration. Opinions differ as to whether tamoxifen is considered an antipromoter or a chemosuppressant. Certainly there is compelling data to indicate that tamoxifen will need to be administered in long-term studies.

This may be less true for certain types of retinoids and certain carcinogens. It appears that one can truly irreversibly suppress the development of cancer. If we put in an antipromoter and it is there constantly, there is a delay in the latency phase, a plateau that parallels the control curve. Importantly, however, as soon as we remove that antipromoter, after a little lag, regeneration of the control number of tumors will occur. Thus when to start administering antipromoters is an essential issue. If you start treatment with an antipromoter at age 60 and you continue it for ten years without side effects, and it suppresses the breast cancer for another 10 years, that might be adequate to show an impressive chemopreventive or chemosuppressive effect. However, this approach might not be adequate in dealing with 40-year-old women.

The criteria we have evolved for proposing an intervention trial are not too much different than a phase III clinical trial with particular procedures related to breast

cancer prevention that we have come to recognize over the last five or six years while dealing with other types of chemoprevention.

The choice of agent and dose for a particular intervention is probably the most practically difficult issue that has to be dealt with. It is hard to express how much wailing and gnashing of teeth has gone into the choice of chemopreventive agents for particular trials. Risk-reduction estimates are enormously difficult. For feasibility, one has to think about general and recruitment issues, compliance and follow-up, long-term consequences, particularly those which are unexpected outcomes, and their measurement, as well as the risk-benefit both for individuals and, importantly, for society.

In examining the agent of choice and the dose in epidemiologic studies, major type II errors can occur. That is, there may be a strong association in studies but the wrong agent is selected. The epidemiologic association may be reflecting something else. For example, vitamin A is selected and the real active agent might be beta carotene, a possibility because of the methodology of epidemiologic studies. Tamoxifen does not have the problem of efficacy versus side effects which is an enormously difficult issue. Basically, if there is a high enough risk population, one is willing to accept some side effects. In dealing with a very low-risk population, one is not willing to have very many side effects, or only those of a minor nature.

Pharmacology in terms of the dose is a difficult issue. Is it 10 mg or 1 mg of tamoxifen? From the experience of Jordan and others it appears that 10 mg is the indicated dose to show a biological effect and prove efficacious. However community public health and epidemiologically oriented people would recommend the lowest possible dose, 1 mg, to eliminate side effects completely. In considering a large trial we have to take both of these factors into account. In breast cancer it is complicated in that we do not have a convenient intermediate endpoint such as a dysplasia and the endpoint will probably have to be the development of cancer. How about risk-reduction estimates? Very simply stated, the data are soft. The number of subjects estimated thus far for all chemoprevention trials has always been underestimated. As NCI people report, it causes havoc with their budgets. It also causes havoc in terms of planning these trials. If we underestimate the number of patients required, put in 2,000 when we really need 4,000, no conclusive results can be expected. On the other hand, if we double the number of patients or subjects in a trial, the cost goes up astronomically. If the cost rises from \$1,000 to \$2,000 it would

not be a problem, but when the cost goes from \$50 to \$100 million, it is very troublesome indeed.

Breast cancer prevention has some particular problems. There is really no intermediate marker such as can be found for colon cancer or for oral cancer or cervical dysplasia. Pathologic changes in the breast are complex. Mammographic changes are complicated and there is no general agreement.

How about feasibility? Well, it would be impractical to suggest a skin cancer prevention study in Alaska. It would be also unwise to suggest a breast cancer prevention study in an area for a group of subjects who are not at high risk. Yet those types of things are being done. The difficulties of recruitment are underestimated by most investigators who believe they can provide a great many patients for a study. In the current Women's Health Trial, only 3% of those women estimated to be eligible at the beginning of the trial were actually randomized to the study. The number ranges from 3% to around 15% for all current ongoing trials of which there are about 30 in the United States. Before proposing a trial, it is helpful to stimulate recruitment all the way up to the point of the subject signing the consent form, or at least demonstrate from eligibility check lists those 2,000 subjects who are available. Otherwise you risk being unable to actually proceed with the trial.

The next problem is compliance, which has been with us for a very long time, particularly with regard to certain types of groups. Compliance is dealt with in several different ways. Early losses are a serious problem and one way of dealing with that issue is to have what is called a run-in period. That is, to have about a three-month test period during which you see whether people are really willing to go on the study.

We've made the fascinating observation, which we have not previously reported, that if candidate subjects even mention that they might have any difficulties with a trial (any general sort of comment) it is best not to include them because of the strong likelihood that they will not remain in the study. This observation was revealing to us in terms of how to go about recruiting patients. It is important to eliminate these subjects before they are randomized because of the enormous effect they have on dropout rates.

Late losses are very variable and nobody really has sufficient extended experience with these trials to predict the future. However, compliance does seem to "hit a wall" at about three years. That is, patients become restless about, "I don't have cancer, why do I have to keep having to take this. I'm getting some minimal side effects, etc., etc." The best solution to that problem is ongoing

"tender, loving care" which is a hard budgetary item to justify in a grant request.

Among the unexpected long-term consequences, one is improvement in the control group referred to earlier as a result of secular changes in the environment. For example, if the percentage of fat by calories in our diet went down from about 38% the normative in the United States, to 30%, that might play havoc with even a tamoxifen trial. Certainly such a secular trend would play havoc with any dietary trial. Trial influences on the individual are also important, for as soon as a trial is started subjects tend to change their behavior.

Of course there is the very important issue of adverse effects of agents. Though I would take some issue with Love, we all want to know as much as possible about side effects, and they are doing an elegant two-year study. The problem is: do we have to do a 10-year pilot study before we start or initiate a trial? What is really needed is a bellwether or vanguard group. Love's group will provide a group of 200 patients intensely studied that should be two years ahead of the 2000 subject group. This is one way of avoiding the problem of having to do a 10-year study for side effects before doing the actual study.

How about outcomes? If it is a tertiary outcome such as a precancer in which one can measure progression in a relatively a short time, one can certainly determine whether progression occurs. How do we study progression of leukoplakia, for example, or cervical dysplasia? We could study, perhaps, some patients going from mild to moderate or perhaps from moderate to severe dysplasia, but we really cannot allow the lesions to progress to cancer.

Even if we had good intermediate pathologic markers for breast cancer, what could we study? An agent may cause regression of a lesion. In leukoplakia, cervical dysplasia, and bronchial metaplasia this has been shown to occur rapidly. Would regressive pathologic changes in the breast occur rapidly? An interesting study that could be done, perhaps, is to take women with mammographic changes and see if their mammographic appearance improves with an agent. That is a nice, simple study that might provide very valuable information.

In secondary intervention, in the absence of cancer, one may need a long time to see an effect, but in some patients we would say "no" to intervention since you are going to cut the top part of the curve off and measure a difference between the control and treatment group within a very short period of time (less than 5 years). Others would not intervene or halt the study since their opinion may differ as to the slope of the curve and it will take 10, 15, or 20 years to show a difference.

Finally, regarding the risk/benefit in individual people with high-risk conditions, agents with even considerable side effects are warranted. In women with a low-risk status, agents with no or minimal side effects are probably the only acceptable intervention. That obviously presents a variety of difficulties. To examine the magnitude of the problem, in 1985, about 120,000 breast cancers developed and 40,000 deaths occurred. Dole and Peto estimate approximately 50% of breast cancers are preventable. If we study 60,000 cases at \$10,000 a case we are up to a cost of \$600 million a year. Nevertheless, I believe a substantial investment in chemoprevention is worth considering since even though we certainly have made advances in the treatment of breast cancer, prevention is always better than attempted post-hoc cure. Obtaining the agent for use will be at least ten times more difficult than expected. Many people in this field wanted to begin a chemoprevention trial with tamoxifen for high-risk breast cancer five to ten years ago. Initial risk reduction determinations are always wildly overoptimistic, particularly before one gets the grant. The number of subjects will actually be five to ten times more than was originally estimated. Only 10% or so of subjects estimated to be eligible for a study will ever be randomized to the trial. Performing clinical chemoprevention trials is indeed very hard work. Nevertheless, I think that the important question to ask is: Can breast cancer be prevented? The question can't be answered solely by epidemiologic methods or laboratory investigations; hopefully this effort will lead to some type of clinical prevention trial for breast cancer.