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The role of chemoprevention in cancer control

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Abstract

Chemoprevention can be defined as the use of chemical compounds or medicines to prevent the occurrence of precancerous lesions (markers) or to slow down or revert the progression of clinically established disease. The use of randomized trial design is considered the gold standard for evaluating the preventive value of chemicals against cancer, since they control for confounding and avoid information bias. The principal school in relation to cancer control through chemoprevention is based on studies of cancer and diet. Initially, ecological studies set the cornerstone, but later case-control studies supported the hypothesis of an inverse association between foods and cancer risk (principally epithelial), suggesting that determined micronutrients participate as protection in this process. Other studies include specific chemical analyses, which have potential problems that could lead to erroneous conclusions, such as sample and measurement errors. During this decade randomized intervention trials have been carried out to test this hypothesis, but conclusions have been so diverse and the designs used have been so different in terms of levels of exposure, that consistent conclusions are not possible. We can conclude that using studies with randomized, double-blind, controlled designs is interesting, but problems remain to be solved, including: agent selection, the design to be chosen, and especially the balance between benefits sought and secondary effects, including cost-effectiveness, since some chemicals cannot compete with other preventive or therapeutic measures.

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El papel de la quimioprevención en el control del cáncer.
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Resumen

La quimioprevención puede definirse como el uso de medicamentos o compuestos químicos, que se utilizan para prevenir la ocurrencia de lesiones precancerosas (marcadores), o bien para retardar o revertir la progresión de padecimientos clínicamente establecidos. La utilización de diseños de ensayos aleatorizados, se considera el estándar de oro para evaluar el valor preventivo de los químicos ante el cáncer, al controlar la confusión y evitar sesgos de información. La corriente principal relativa al control del cáncer mediante la acción quimiopreventiva se origina en los estudios sobre dieta y cáncer. Al inicio, los estudios ecológicos fincaron la primera piedra, pero posteriormente, los estudios de casos y controles sustentaron la hipótesis, de una asociación inversa entre alimentos y el riesgo de contraer cáncer, principalmente de origen epitelial, sugiriendo que determinados micronutrientes participan como protectores en este proceso. Otros estudios lo constituyen los análisis químicos específicos que se encuentran dentro del organismo, sin embargo, tiene inconvenientes que podrían terminar en conclusiones erróneas, tales como errores de muestreo y errores de medición. En esta década se han llevado a cabo ensayos aleatorizados de intervención para probar esta hipótesis, no obstante, las conclusiones han sido tan diversas y los diseños han planteado tan diferente los niveles de esposición que las conclusiones no permiten tener resultados consistentes. Podemos concluir que es excitante recurrir a estudios con diseños aleatorizados, doble ciego y controlados; sin embargo, los problemas a resolver involucran aspectos tan relevantes como la selección del agente, el diseño mismo a plantear, y sobre todo, el balance entre los beneficios que se buscan y los efectos secundarios,

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así como el factor costo efectividad, ya que algunos químicos no pueden competir contra otras medidas preventivas o terapéuticas.

Palabras clave: neoplasmas/prevención & control, quimioterapia; revisión; ensayos clínicos

Chemoprevention may be defined as the use of chemical compounds or drugs to prevent the occurrence of pre cancerous lesions or markers (e.g. intraepithelial neoplasm) or to delay or reverse progression to a clinically manifest disease.[1]

The randomised trial design is considered the gold standard for evaluating the preventive potential of chemicals on cancer. This design, which is adapted from clinical trials, is based on the assumption that the random distribution of subjects in the study population into exposure to the agent under study or into control group ensures the baseline comparability of the two groups, thus avoiding the effect of confounders.

Further, information bias is avoided when both the observer and the involved subjects are blind towards the exposure-control status. This condition is achieved in chemoprevention trials through the administration to half of the subjects of a placebo that is physically indistinguishable from the agent under study.

In comparison with clinical trials, however, chemopreventive trials raise some specific issues. These are summarised in Table I.

Table I
COMPARISON OF SOME RELEVANT FEATURES IN CLINICAL AND INTERVENTION TRIALS

	Clinical trials	*Intervention trials*
Recruited population	Affected by the disease	Disease-free
End point	Frequent, single	Rare, multiple
Follow-up	Short	Long
Expected decline of risk	Sharp	Slow
Acceptable side-effects	Substantial	Low
Sample size	Small	Large
Compliance	High	Low
Costs	Low	High
Potential reduction of cancer incidence or mortality	Low	High

From:[2]

The scientific background

The major impetus for cancer control through chemopreventive action stems from studies on diet and cancer. The earliest of these studies were ecological, based on geographical differences of cancer risk between populations and on the correlation of these differences with the amount of consumption of food items at a population level. Ecological studies have shown high correlation between colon cancer and meat consumption, breast cancer and fat intake, stomach cancer and a diet rich in cereals.[3,4] More convincing evidence has been provided by case-control and cohort studies. Several reviews have considered a huge number of studies which evidenced an inverse association of several food items with cancer risk, and especially of a high consumption of different [1] varieties of fresh fruits and vegetables with a low risk of epithelial cancers of various sites.[5-7] These findings have generated the inference that the protective effect could be due to some specific micro nutrient shared by the protective foods. Among these, carotenoids (and mostly beta-carotene) ascorbic acid, selenium and tocopherols (mostly gamma-tocopherol) have been considered most promising in terms of preventive potential. In fact, for each of these a convincing mechanism of action at a molecular level has been suggested, based on experimental studies.[8]

A further step in gaining evidence on the role of micronutrients in cancer protection is represented by the analysis of specific chemicals in the body, particularly in the blood, during prospective cohort studies. In fact, these studies have shown a relatively consistent protective role of high blood levels of carotenoids and specifically beta-carotene, and vit.C for several cancers among which lung, stomach and other aereodigestive sites.[9-12]

It has been noted however that the strength of the association between dietary factors and cancer risk appears to be inverse in relation with the specificity of the hypothesis tested, being higher in ecological studies compared with case-control and cohorts, and among these higher in studies in which food items are analysed compared with those in which specific micro nutrients and their blood levels are considered.[13] This apparent contradictory finding can basically be explained according to two hypotheses:

- Misclassification of exposure to micronutrients may increase with increasingly direct measurement methods. In other words, the sporadic measure of the level of beta-carotene in plasma could be a worse representation of the long-lasting average internal dose of the chemical in comparison with its estimate through the intake of foods in the individual or their consumption at a population level, because of the variability of levels over time (sampling error) and of the limits of laboratory measurement (measurement error).
- The measured micro nutrients may only represent a proxy of other undetermined factors contained in protective foods. In this last case, the hypotheses based on a possible chemoprevention potential of these micronutriens would simply have missed the true point.

In order to fully understand the role of specific micronutrients in protection against cancer, many chemoprevention trials have been or are being conducted, based on treatment with micronutrients, single or in combination. A synthesis of the main ones is presented in Table II.[2]

More than 50 chemoprevention trials based on micro nutrients, mostly antioxidants as beta-carotene, alpha-tocopherol and ascorbic acid, were identified as published or ongoing in the quoted review of 1994. Since then, some of the major ones have reached the stage of publication. These were based on treatment with beta-carotene, alone or in combination with other micro nutrients.

Synthesis of results from the main published chemoprevention trials

The four main studies which published early results are: the Linxian study on oesophageal and stomach cancer;[14] the Alpha-tocopherol, Beta-carotene Cancer Prevention Study on lung cancer (ATBC trial,[15,16]); the Beta-carotene and Retinol Efficacy Trial on lung cancer (CARET,[17,18]); and the Physicians Health Study (PHS,[19]). A synthesis of their design is presented in Table III.

The four studies differ in terms of the characters of the population : while the ATBC and the CARET trial involve heavy smokers and subjects at very high risk for lung cancer (asbestos exposed who are or recently were heavy smokers), the Linxian study and the PHS refer to subjects who had a low exposure to cigarettes or are non-smokers; further, the Linxian trial has been developed in an area with dietary conditions typical of third world, with average low plasmatic levels of micro nutrients at baseline, while this is not so for the other study populations.

Results from the four studies are accordingly non consistent, and are summarised in Table IV as regards lung cancer incidence and mortality.

It should be noted that lung was not the target organ for the Linxian trial; the power of this study for this site is low, also due to the low baseline incidence and mortality rates, related with low smoking exposure in this population. However, in the same treatment group in which a non significant protective effect of beta-carotene, alpha-tocopherol and selenium is suggested for lung cancer, the rates of stomach cancer incidence and mortality were also lower with borderline significance.[14]

In conclusion, beta-carotene alone or in combination has been found to be slightly protective on lung cancer in one study (Linxian), to be ineffective in another (PHS) and to significantly increase lung cancer risk in two (ATBC and CARET, ad interim analysis). These last results originated the decision of stopping the CARET trial treatment before the scheduled end. In synthesis, the CARET and ATBC studies provide evidence of a positive association with lung cancer risk of synthetic beta-carotene, given at doses of 20-30 mg / day to subjects who have been recently, or are currently heavily exposed to cigarette smoking in combination or not with asbestos, if treatment is given in the late stages of carcinogenesis (i.e. at the age of 50-69). This effect is apparently immediate (very short follow-up).

A further analysis by sub-groups in both studies confirmed that the excess of risk is concentrated in heavy current smokers, and affects both exposed and non exposed to asbestos.[16,18]

Interestingly, the separate analysis of lung cancer risk in the placebo group of the two studies confirmed that subjects with “spontaneous” high plasmatic levels of beta-carotene are at lower risk compared to those with low levels, consistently with observational cohort studies.[16,18]

These findings are relevant in terms of public health and for the understanding of interactions at a cellular level between carcinogens such as those in cigarettes and antioxidants. In fact, the interaction of smoking with levels of antioxidants deriving from the diet is not well understood,[22] and even less is known about their interaction with synthetic antioxidants given as drugs. However, some hypotheses about a possible carcinogenic action related with interaction have been advanced.[23]

Table II

SUMMARY OF CHEMOPREVENTION TRIALS BASED ON MICRO NUTRIENTS PUBLISHED OR ONGOING DURING THE 1990s

	Cancer site	*N. of trials*			*Dose range*
		Published	*ongoing*	*Total*	
Vitamin A	Oral	2	1	3	50-60 mg/week
	Lung	1	3	4	25-50 000 IU/d
	Skin	-	3	3	25 000 IU/d
	Total	3	7	10	
Vitamin C	Colon	1	-	1	3 g/d
	Stomach	-	2	2	2 g/d
	Total	1	2	3	
Synthetic retinoids	Oral	2	1	3	0.25-2 mg/kg/d
	Cervix	-	1	1	topic
	Lung	-	1	1	
	Skin	2	3	5	5-70 mg/d
	Head and neck	1	2	3	50-100 mg/mc
	Breast	-	1	1	200 mg/d
	Total	5	9	14	
Beta-carotene	Colon	-	2	2	30 mg/d
	Oral	3	1	4	15-40 mg/d
	Cervix	-	1	1	18 mg/d
	Lung	1	5	6	20-50 mg/d
	Skin	1	1	2	50 mg/d
	Stomach	1	1	2	
	Total	6	11	17	
Combined vitamins	Colon	1	3	4	
	Oral	2	2	4	
	Oesoph	1	1	2	
	Cervix	-	1	1	
	Lung	-	3	3	
	Stomach	-	2	2	
	Total	4	12	16	
Other vitamins	Oral	-	1	1	
	Cervix	1	1	2	
	Lung	1	1	2	
	Total	2	3	5	

From:[2], modified

It has also been remarked that these two studies are characterised by high doses of beta-carotene (higher than in the Linxian and PHS trials). If this may have a meaning in terms of a possible dose-response effect is not known by now, as the groups involved in the studies are also strikingly different in terms of smoking.

The lesson from the four studies

From the public health point of view, the above mentioned findings exclude beta-carotene from the list of possible preventive agents for lung cancer. In fact, even if its protective effect could be demonstrated in non-

Table III

SIZE, POPULATION INVOLVED, CHEMOPREVENTIVE AGENTS, DOSE AND DURATION OF TREATMENT IN FOUR CHEMOPREVENTIVE TRIALS DEALING WITH BETA-CAROTENE, OTHER ANTI-OXIDANTS AND TRACE ELEMENTS AS PREVENTIVE AGENTS

Study	*Population*	*Age*	*Agent*	*Dose*	*Duration*
Linxian	29 000 Chinese males and females, mostly low or non-smokers, deprived diet	40-69	factorial: 1. ret + zinc 2. ribof + niac 3. vitC + molyb 4. Bcar + vitE + selenium 5. placebo	 5 000 IU + 15 mg 3.2 mg + 40 mg 120 mg + 30 ug 15 mg + 30 mg + 50 ug	5 years
ATBC	29 000 Finnish male heavy smokers, sufficient diet	50-69	factorial: 1. vitE 2. Bcar 3. vitE + Bcar 4. placebo	 50 mg 20 mg	5-8 years
CARET	15 000 US smokers or recent ex-smokers, 4 000 asbestos exp. sm. or ex-sm; males and females, sufficient diet	50-69	factorial: 1. vitA + Bcar 2. placebo	 25 000 IU + 30 mg	stopped after 4 years
PHS	22 000 US male physicians, mostly non or low smokers, sufficient diet	40-84	factorial: 1. Bcar 2. asp 3. Bcar + asp 4. placebo	 50 mg/two days 325 mg/two days	

From:[20], modified
ret=retinol; ribof=riboflavin; niac=niacin; molyb= molybdenum; Bcar= beta-carotene; asp= aspirin

smokers (which is not by now), the interest of its application at a population level would be limited, given the low lung cancer risk in those not exposed to cigarettes.

These results, however, do not contradict observational epidemiology studies on diet and lung cancer. In fact, the usual inverse associations are found in the placebo group of both ATBC and CARET trials. Simply, it is apparent that treatment with synthetic beta-carotene for 4-13 years beginning in middle age cannot be compared with a life-long diet rich in fresh fruit and vegetables.

Further, it could well be that beta-carotene is not the chemical which explains the protective effect seen in observational studies on lung cancer, but simply the one which has been more frequently measured.[24]

Some other useful points come out from the experience gained through the published trials.

1. Trials based on synthetic analogues of "natural" chemicals are not necessarily innocuous. Treatment in chemoprevention trials should be considered with the same cautions of treatment with regular drugs in clinical trials. Therefore, phase 1 and 2 trials are mandatory before including groups from the general population into proper full-scale double-blind randomised trials.
2. Duration of treatment and follow-up issue. Although no quantitative information is available to suggest a clear strategy for choosing duration of treatment, several results suggest that a "sufficient" duration of treatment represents a crucial issue in trial design. Chemopreventive treatment is intended to simulate long-lasting (or life-lasting) natural exposures. Further, evidence from studies on synthetic derivatives of retinol used as chemopreventive agents towards pre cancerous

Table IV
RESULTS ON LUNG CANCER FROM LINXIAN, ATBC, CARET AND PHS

Study	Lung cancer incidence Rate x 10 000 py	RR	Lung cancer mortality Rate x 10 000 py	RR
Linxian[21]				
Bcar + Atoc + sel			1.5	0.55 ns
placebo			2.7	
ATBC				
Atoc	51.3	0.98 ns	33.6	1.02 ns
non-Atoc	52.4		32.8	
Bcar	56.3	1.18 sign	35.6	1.15 sign
non-Bcar	47.5		30.8	
CARET				
Bcar + retinol		1.28 sign		1.17 sign
placebo				
PHS				
Bcar	no significant		no significant	
placebo	association		association	

From:[20], modified

lesions of the mouth suggests that when treatment is interrupted the progression towards cancer enters a new active phase.[25] In fact, this finding is not surprising as, in most instances, exposure to risk factors is maintained.

3. The phase at which treatment should initiate also represents a potential crucial point. Its terms can be illustrated, taking as an example the natural history of colon cancer.[26]

Colon cancer chemoprevention is mostly based on evidence deriving from animal studies, referring to calcium, fibers and micro nutrients. Typically, these studies are based on the induction of polyps with the use on chemical carcinogens, and the inhibition of this induction as a consequence of treatment. Being the life span of experimental animals (rats) on average two years, treatment with carcinogens and with micro nutrients in most studies last several months, and the exposure to the two types of drugs is at least partially overlapping. The efficacy of micro nutrients treatment in this case is based on the assumption that protective agents begin to act in early phases of carcinogenesis (induction). In terms of human life span, this would be equivalent to treatment beginning around age of 20-30 and lasting 20-30 years.

In conclusion, methodological issue, appropriate use of observational evidence, adherence of the study design to a sound hypothesis on the mechanism of action of the tested chemicals are still open fields of research in chemoprevention trials.

Other fields of interest of chemoprevention trials

Apart from trials based on micro nutrients, some other groups of chemicals are now being tested.

First results on calcium as a chemopreventive agent for colon cancer however were not positive for a protective effect. Results from ongoing studies will further clarify this point.[26]

Three large trials are now being conducted on breast cancer prevention based on Tamoxifen treatment because of its anti-oestrogenic effect.[2] The potential of Tamoxifen as chemopreventive agent is based both on animal and clinical studies.[27] In fact, a pooled analysis of clinical trials involving Tamoxifen as adjuvant therapy in women with breast cancer has shown that the treated group had a lower risk of developing a new contra lateral breast neoplasia.[27]

The three ongoing trials main features are summarised in Table V.

The development of these trials has stimulated international concern on their ethical appropriateness. In fact, Tamoxifen has been shown to increase endometrial cancer (and possibly liver cancer) risk in treated subjects.[28] For this reason the Italian trial is involving only hysterectomised women. This choice however will limit the inferences to the general population of possible positive results. The other two trials, involving high risk women because of age or of familiarity, mostly with the uterus, are based on the assumption that the expected advantages in terms of incidence / mortality for breast cancer, but also of CV mortality and prevention of osteoporosis, will overwhelm the potential adverse effects.[27] It should be noted however that the secondary expected positive effects, as the adverse ones, are based on the "contradictory" mechanism of Tamoxifen action, which behaves as an anti-estrogen (from which the possible protective effect on breast cancer) but also as an estrogen (from which the other protective and adverse effects). New generation anti-estrogens are being now developed, but their positive potential and side-effects are still under study.[27]

In conclusion, the ongoing trials on Tamoxifen should be capable of giving answers on the appropriateness of its use as chemopreventive agent. The concern about the ethicity of these trials strongly suggests

Table V
MAIN FEATURES OF THREE CHEMOPREVENTION TRIALS BASED ON TAMOXIFEN

Area	*Subjects*	*No.*	*Dose*	*Duration*	*End-points*
Italy	Voluntary women aged 35-70, hysterectomised	12 000	20 mg/day	5 years	Breast cancer incidence and mortality. Bone fractures, CV mortality, Trombo-embolic events
UK	Women aged 35-65, with positive familial history of Breast Cancer	15 000	20 mg/day	5 years	Breast cancer incidence and mortality. Other secondary outcomes
USA	Voluntary women aged 60 or more; women aged 35-60 at high risk	15 000	20 mg/day	5 years	As above

From:[2] modified

to wait for their results and since then avoid the application of the drug in healthy women for preventive reasons.

Conclusions

The use of double-blind, placebo controlled randomised trial design for evaluating preventive actions is indeed very stimulating. However, many problems are still open when dealing with chemopreventive agents, in terms of the choice of the agent to be tested, the design of the study, the balance between expected advantages and side-effects. A new generation of trials is now needed, taking into account the gained experience also in terms of unexpected and disappointing results.

Further, even more research is needed before deciding the application of chemoprevention at a population level, in terms of cost-effectiveness of the intervention. In fact, it is well possible that even chemicals showing some protection will not be able to compete with other preventive or therapeutic measures if evaluated from the point of view of cost-effectiveness.[29]

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