VITAMIN E INVOLVEMENT IN OXIDATIVE STRESS (OS) ASSOCIATED WITH CARCINOGENESIS

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Abstract: Vitamin E is known as a substance with powerful antioxidant proprieties *in vivo*, along her vitaminic function, her intake reducing the oxidative stress produced by free radicals generators (ORS, etc): ionizing radiations, toxic compounds from air, water, food, etc. It’s well known her effect in numerous human affections, more or less; studies are done over the role & effects in other diseases: diabetes mellitus, cancer, etc. **Aim:** These researches are following to determine vitamin E effect in carcinogenesis associated OS and so with cancer, vitamin being used as food additive in diet for cancer patients (particularly head and neck cancers used in our study). Following OS reduction, obtaining so, an general status amelioration to subjects, associated with disease, in parallel with specific treatment recommended by medic (chemo- or radiotherapy). We supplementing with vitamin E the food, in calculated doses based on literature studies, with measurements of biochemical parameters in biological fluids from patients as integral blood, serum, plasma and urine – general: glucose, calcium, cholesterol, HDL-cholesterol, triglycerides, creatinine – OS specific: MDA, GSH, SOD, CAT, vitamin E, etc. We use an healthy subjects witness lot which receive an placebo and an witness lot with vitamin E, an subjects lot with cancer receiving an placebo and one with our vitamin E doses, biochemical analysis results up obtained being interpreted, resulting conclusions conducting us to the steps to follow, correlated with results. Expected effect is that one of carcinogenesis (cancer) associated OS reduction, with benefic effects on patient general status.

INTRODUCTION

Vitamin E is known to be an substance with powerful antioxidant properties *in vivo*, her intake reducing the oxidative stress originated from free radicals generators (ORS - oxygen reactive species, etc.), ionized radiations, toxic compounds from air, water, food, etc. (Fig. 2, 3). Is certified already, more or less, her effect in different human diseases, studies being conducted over vitamin E implications and roles in other diseases like cancer, diabetes mellitus, cellular aging, atherosclerosis, heart conditions, chronic hepatitis, viral hepatitis, neurons-degradation, etc. (10, 16, 17, 18, 19, 20, 21).

Vitamin E act as an antioxidant *in vivo* through an mechanism which implies an break point in the chain of radical reactions based on ORS, through her phenol head as also her fytyl chain, vitamin E being recognized as the most important lipophile antioxidant from organism, especially through donor capacity of 6-OH group, but not only (18, 41). Her deficiency in cellular membranes conducting to an high fragility of those for ORS, as to other free radicals (majority of them being highly liposoluble). From here we extract the necessity of an antioxidant protector mechanism on the level of different cellular membranes, which include vitamin E, and other compounds (Q10 coenzyme, retinol, omega-3 PUFA etc.). Vitamin E presents herself as two major forms tocopherols and tocotrienols, each ones with 4 variations: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, respectively α-tocotrienol, β-tocotrienol, γ-tocotrienol, δ-tocotrienol, last 4 with 3 double bonds in fitil chain (17, 18, 30, 37, 41)(fig.1).

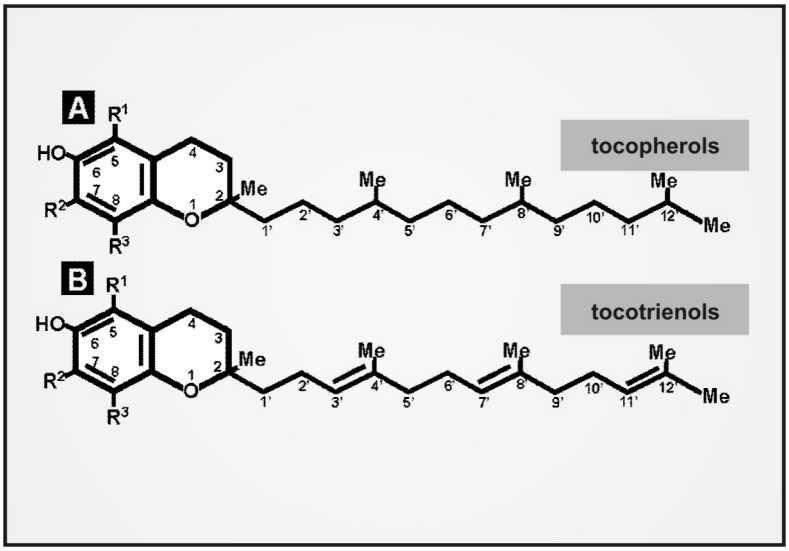


Fig. 1. Vitamin E: variations and nomenclature
A, R1 = R2 = R3 = Me, known as α-tocopherol, is designated as α-tocopherol or 5,7,8-trimethyltocol; R1 = R3 = Me; R2 = H, known as β-tocopherol, is designated as β-tocopherol or 5,8-dimethyltocol; R1 = H; R2 = R3 = Me, known as γ-tocopherol, is designated as γ-tocopherol or 7,8-dimethyltocol; R1 = R2 = H; R3 = Me, known as δ-tocopherol, is designated as δ-tocopherol or 8-methyltocol.
B, R1 = R2 = R3 = H, 2-metil-2-(4,8,12-trimetiltrideca-3,7,11-trienil) chroman-6-ol, is designated as tocotrienol; R1 = R2 = R3 = Me, formal known as ζ1 or ζ2-tocopherol, is designated as 5,7,8 trimethyltocotrienol or α-tocotrienol. Name as tococromanol-3 is used to; R1 = R3 = Me; R2 = H, formal known as ε-tocopherol, is designated as 5,8-dimethyltocotrienol or β-tocotrienol; R1 = H; R2 = R3 = Me, formal known as γ-tocopherol, is designated as 7,8-dimetiltocotrienol or γ-tocotrienol. Name as plastocromanol-3 is used to; R1 = R2 = H; R3 = Me is designated as 8-metiltocotrienol or δ-tocotrienol (30, 37).

We could represent the protector mechanisms of the cell against ORS in normal physiological conditions, which in oxidative stress conditions are overwhelmed by the huge amount of ORS and the generation speed of those (18)(Fig. 2):

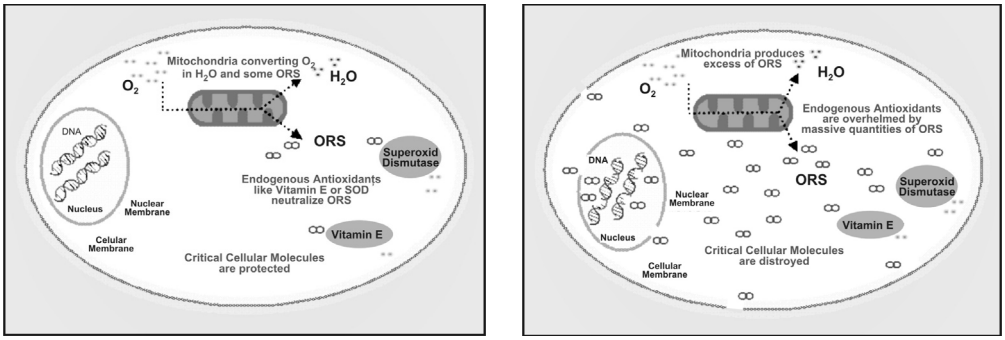


Fig.2. Cellular physiological OSR sources and neutralization pathways in normal conditions and pathological (18, modified)

Specialty literature study permitted us to extract some values quasi accepted in a lot of countries around globe, concerning the maximal intake of vitamin E (as α-tocopherol) for an adult respectively ~ 10 mg/day adult (8 mg/day woman, 12 mg/day man, maxim 15 mg/day, see *Table 1*) (1):

Table 1

RDA for man's	alpha-tocopherol (vitamin E)
19-30 years	15 mg (34,9 µmoli) / day
31-50 years	15 mg (34,9 µmoli) / day
51-70 years	15 mg (34,9 µmoli) / day
>70 years	15 mg (34,9 µmoli) / day
RDA for women's	alpha-tocopherol (vitamin E)
19-30 years	15 mg (34,9 µmoli) / day
31-50 years	15 mg (34,9 µmoli) / day
51-70 years	15 mg (34,9 µmoli) / day
>70 years	15 mg (34,9 µmoli) / day

RDA = Recommended Dietary Allowance, from "Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and carotenoids (full report), (2000), National Academy Press, Washington D.C.", modified

Vitamin E in cancer

From a long time ago was supposed that a lot of cancer types are as result of DNA deterioration cause by free radicals, ipothesis demonstrated later experimentaly on different types of cancer (Fig. 3) (18, 22, 38, 39).

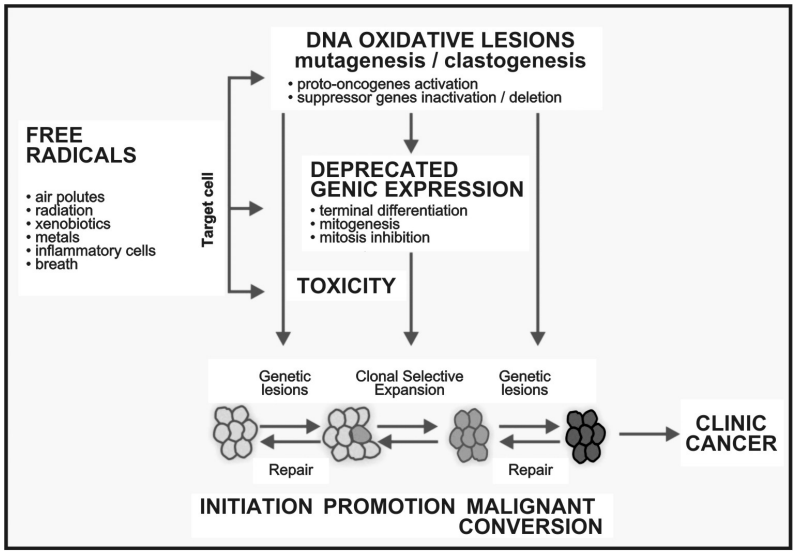


Fig. 3. FR (Free radicals) and oxidative lesions on DNA in carcinogenesis (22, modified)

Her actions being associated to the powerful antioxidant function, but also apoptotic and anti-proliferative functions, anti-inflammatory, immunity etc. On post-translational level, α-tocopherol inhibits protein-kinase C, 5-lipooxigenase and phospholipase. Some genes (ex. "scavenger" receptors, α-tropomyosin, matrix 19-metaloproteinase and collagenase etc.) are specific modulated by α-tocopherol on transcriptional level. Also α-tocopherol inhibits cellular proliferation, platelet aggregation and monocytes adesivity, effects which are characterized as unrelated with antioxidant properties of vitamin E, more as an result of α-tocopherol interaction

(and of the other forms of vitamin E) with enzymes, structural proteins, lipids and transcription factors (inhibit of protein kinase C, phosphatase 2A activation and diacyl-glycerol kinase pathways) also inhibits production of nitric oxide (NO) by leukocytes (41, 44). Non-reddox mode of action is responsible mitotic rate modulation and defective DNA, involved in carcinogenesis (44). In what's concerning vitamin E derivatives as α-tocopherol-succinate (α-TS, VES), and acetic ether of α-tocopherol (TAE), digestive non-hydrolysable, could act not as antioxidants but as restaurateurs of cellular signaling pathways for apoptosis start (27).

On those premises studies were effectuated all over the world, either population studies, either experimental (on lab animals and humans). In what concern those population studies, 2 ample studies are highlighted themselves as much cited in literature, which them used enriched food with vitamin E as dietary supplement (mixed).

In what concerns population studies 2 ample studies are highlighting themselves in literature which have used food supplements with vitamin E content (mixed). One of them take place in China on a population with high alimentary deficiencies, in which were used supplements β-carotene, α-tocopherol and selenium and was associated with an reduced incidence and mortality caused by gastric cancer and general rate of mortality due cancer disease with 13% till 21%. In the second study, which take place in France, using an food supplementation with vitamin C, vitamin E, selenium and zinc, was observed that cancers rate was reduced with 31% on male subjects but not on women's (1)(*Table 2*).

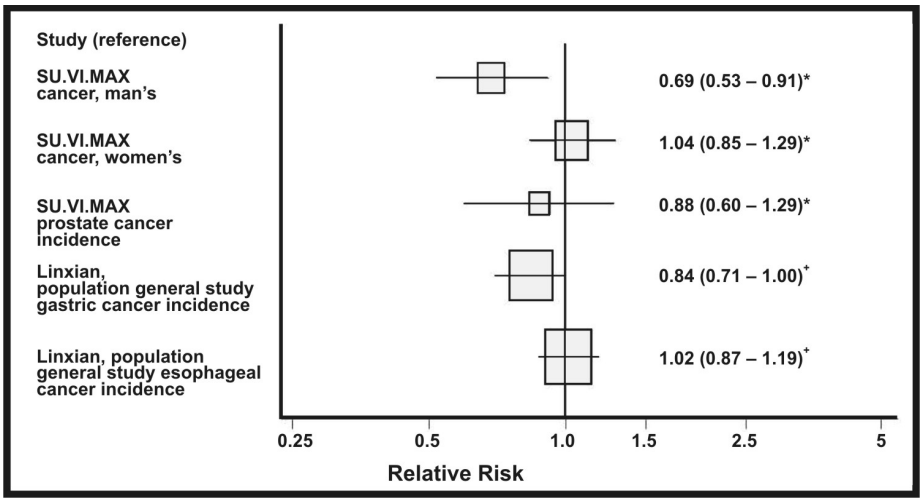
Table 2. **Randomly controlled characteristics of multivitamin supplements efficacy, used in primary cancer prevention (24)**

Study (Reference)	Linxian, general population study (7, 8, 31)	SU.VI.MAX (24)	SU.VI.MAX: Prostate cancer (32)
Locatie	Linxian District, China, were esophageal cancer incidence was high	France	France
Design	RCT; fractional factorial design: placebo, AB, AC, AD, BC, BD, CD, ABCD, were: A = retinyl palmitate, 10 000 IU + zinc oxide, 45 mg; B = riboflavin, 5.2 mg + niacin, 40 mg; C = ascorbic acid, 180 mg + molybdenum (yeast complex), 30 μg; si D = β-carotene, 15 mg _ selenium (yeast), 50 μg α-tocopherol, 60 mg	RCT; dual lot design: vitamin C, 120 mg + vitamin E, 30 mg + β-carotene, 6 mg + selenium 100 μg + zinc, 20 mg vs. placebo	RCT; dual lot design: vitamin C, 120 mg + vitamin E, 30 mg + β-carotene, 6 mg + selenium 100 μg + zinc, 20 mg vs. placebo
Exclusion criteria	Age <40 or >69 years; Anterior usage of vitamins supplements, esophageal or stomach cancer history, debilitation disease; don't live in 1 from 4 communes from Linxian	Men's age <45 or >60 years; women's age <35 or >60 years the disease must permit displacement or treated with 5 years survival; usage of any supplement used in study, comportment or extreme conviction related diet	Age of <45 or >60 years; women's; cancer presence; without "severe health problems"; usage of any supplements like any from the study; study

			abandon in the first 4 days of randomly election
Participants character-ristics	Recruited from community; age 40–69 years; 55% women's; nutritional deprivation; small intake of fresh fruits and meat or other animal products; reduced level of circulator micro -nutrients, etc	Recruited from community; 62% women's; women's average age, 46,6 years (SD, 6.6) (interval of, 35–60 years), and men's, 51,3 years (SD, 4.7) (interval of, 45–60 years); women's have presented serum levels of β-carotene and vitamin C slightly up but slightly decreased for zinc and selenium comparative with men's level on basal line	Recruited from community; medium age: 51,3 years (SD, 4.6)
Samples number	29584	12741	5141 (men's)
Period/ Study duration Continuation /Loss on continuation or retreat	1986–1991/ Total, 5.25 years/NR	1994–2002/ Total, 8 years; median, 7.5 years/5.8% loss on continuation; 5.8% retreated	1994–1995/ median, 8.9 years/NR
Auto-select of identical supplements before and in the time of study	NR (but anterior users of any supplements were non-eligible**)**	NR (but anterior users of any supplements were non-eligible**)**	-

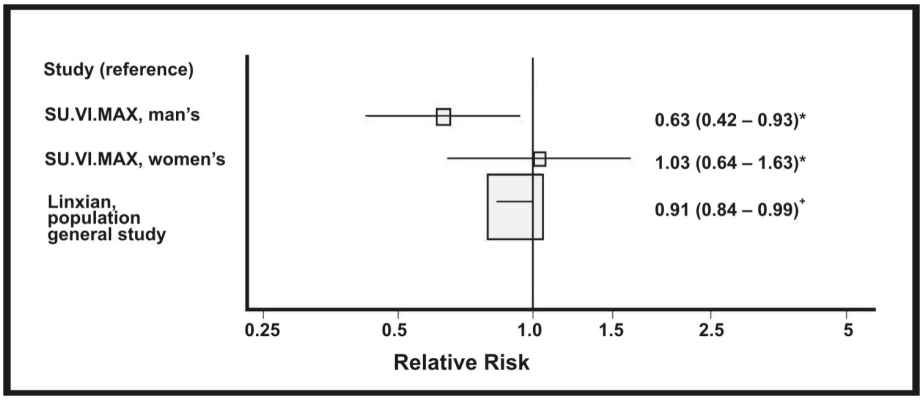
RCT = randomized, controlled trial; SU.VI.MAX _ SUpple´mentation en VItamines et Mine´raux AntioXydants;
NA = not applicable; NR = not reported

Relative risk of up mentioned cancers incidence in case of minerals and multivitamin supplements usage is suggestively observable in the down graph from fig. 4:



Lines represent 95% from cancer incidence, lines middle represents estimated relative risk, and boxes represent relative dimension of study echantilion.
SU.VI.MAX = SUpplémentation en VItamines et Mineraux AntioXydants.
*Vitamin E + Vitamin C + β-carotene +Selenium + Zinc, + Vitamin E + β-carotene + Selenium.
Fig. 4.

Respectively the relative risk of mortality from all possible causes (Fig. 5):



Lines represent 95% from cancer incidence, lines middle represents estimated relative risk, and boxes represent relative dimension of study echantilion.
SU.VI.MAX = SUpplémentation en VItamines et Mineraux AntioXydants.
*Vitamin E + Vitamin C + β-carotene +Selenium + Zinc, + Vitamin E + β-carotene + Selenium
Fig. 5.

Here could be cited the ATBC (Alpha-Tocopherol Beta-Carotene) Finnish study for pulmonary cancer prevention: the study was randomly type with 4 lots (AT, AT+BC, BC, without AT or BC), controlled by placebo lot, which starts from the hypothesis saying that administrating α-tocopherol (50mg/day) and β-carotene (20mg/day) could reduce the pulmonary cancers incidence, but also the other forms of cancer. In this study was monitored total and specific mortality for disease (cancer or other affections if present) also the incidence of specific symptom varieties for safety. Between years 1985 and 1993, 29133 eligibly males, smokers, with

ages between 50 and 69 years on study enrolment date were randomly distributed for receiving an placebo or an unique dose daily of vitamins (capsules) in conformity of what was upper enounced, for 5 till 8 years (median at 6.1 years) with accumulation of almost 161751 comebacks in the allocated time (Fig. 6) (2, 3).

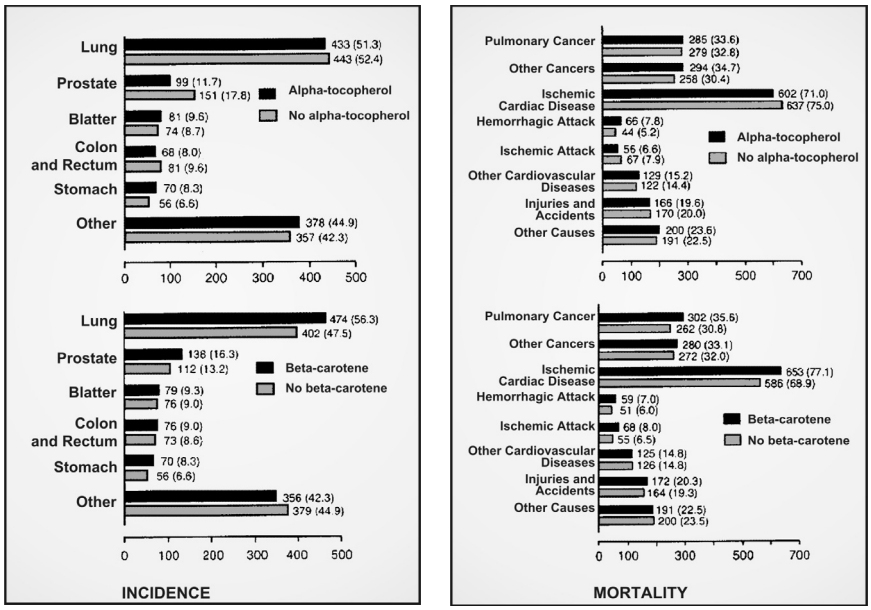


Fig. 6.

From other reviews of population studies we observed contradictory results, respectively that vitamin E doses used in those population studies didn’t have significant effects on cancer patients, with the exception of 3 studies which showed decreases of cancer relative risk statistically significant (17).

Vitamin E ability (as alpha-tocopherol, but not only) of free radical neutralization, have transformed her in an ideal candidate for cancer prevention studies, but any way some of these studies failed in proving this with clarity in cases of intestinal and breast cancer’s. (4).

In an study based on placebo lot system which analyze α-tocopherol supplementation on patients with intestinal cancer on smokers was obtained an decrease of incidence with 34% of prostate cancer, on administration of supplements with 50mg/day synthetic alpha-tocopherol (equivalent with 25mg/day RRR- α-tocopherol) (5). From this cause was organized on extended scale study of α-tocopherol effects prostate cancer apparition risk (6, 32). Experimental study of supplement intake with vitamin E content in prostate cancers, after other authors which followed this experiment, didn’t give any positive effects on evolution course of prostate cancer, in maximal doses recommended for diet, and over dosage being not recommended because of possible severe side effects (36).

Recent studies show the fact that vitamin E and progesterone protect the organism against ovarian metaplasia through oxidative stress inhibition ovulation inducted and through increased reparatory capacities (genomic integrity) on epithelial surface level. Ovary cancer with origin in surface epithelia is an insidiously deadly disease because characteristically remains

asymptomatic till full metastasis in entire abdominal cavity with an unfavorable prognostic, from here we hardly depict the necessity of prevention through all treatment methods, via food supplements inclusive enriched with antioxidants like vitamin E (41).

Cancer cells rapidly proliferate and are resistant to death by apoptosis (programmed cellular death). Studies on cancer cell cultures indicated the fact that succinate ester of vitamin E (α-tocopheryl succinate) could inhibit proliferation and can induce apoptosis, in some cancer cell lines (9, 10). So only vitamin E succinate could induce those effects and *not* vitamin E as itself free, the mechanism through this it's acting here is not yet elucidated, and remains to be discovered (12). In conclusion succinate form of vitamin E and not vitamin E itself is necessary for proliferation suppression and apoptosis induction (11). Exist also studies on lab animals on which injection of alpha- tocopheryl succinate conducted to encouraging results in tumoral growth inhibition (12, 13, 14). So speaking this ester could be useful in cancer therapy as preventive and ameliorative, but only injectable!, orally the ester being intestinally hydrolyzed in alpha-tocopherol + succinate, with the loss of action upper described. Are not known experimental data which to demonstrate that ester oral intake could conduct to a non hydrolyzed delivery to tissues.

CONCLUSIONS

Increased fruits and vegetables intake appears to be one of the simplest way to decrease the cancer apparition risk. Preventive effects in cancer case, for fruits and vegetables was observed in various epidemiologic studies, which any way didn't permitted to make an clear distinction of different and multiple ingredients effects.

Anti-oxidant defense was proposed as a chemoprevention mechanism, but inconclusive data were obtained. Population random studies results showed as an example that β-carotene from different supplements or individually taken, has a limited value or in some cases has proved to be nocive! Vitamin E (α-tocopherol) is a liposoluble antioxidant which can neutralize free radicals, in general vitamins being good markers in case of fruit an vegetable ingestion, those being present as itself or as specific metabolites in different biological fluids. Was observed so, that vitamin E doesn't have an significant effect on pulmonary cancer apparition risk, in cases of long term smokers (as observed from upper cited studies), but proved to have an decreasing effect on incidence and mortality caused by prostate cancer; any way was observed an increase of brain hemorrhages occurrence with 50% on male subjects whom received vitamin E. As an collateral example, dietary fibers was considerate as being connected with risk decrease in colorectal cancer, but in many recent reported observational studies, this fact was infirmed. The purpose of resolving these paradoxes, reside in the fact that first we must to understand more clearly physiological, biochemical and genetic aspects, which on are based those evident contradictory results. In this purpose, will be necessary to develop new experimental studies on lab animals and humans, to which design to be precisely constructed and well pointed, correlated with each type of cancer (knowing that exist a lots of types of cancer, with origins, genetic and biochemical mechanisms highly variate) developing in this way hypothesis and mechanisms which can be tested and reproduced in clinical trials on humans. Till then, our enthusiasm must be reserved for preventive and protector action of chemo-micronutrients and mineral supplements.

In what concerns Romania, should be desired the implementation of some population and experimental studies based on Romanian subjects, first ones in an eloquent time frame (5-10 years), the other ones based on high efficiency design, and existence of an material base for medical and biological research (genetics, biochemistry) on international standards. Also, will be

necessary to take count of the education and culture level of population, which now is pretty low in what concerns trial participation (experimental and population ones), taking care that participation on those types of studies suppose an serious approach from the subjects part (many of them from rural regions, with reduced mobility, reduced to inexistent general and medical knowledge, but not only, even those from the city not being far from those from country side) this fact supposing an intense popularization, comparative with subjects from Linxian, SU.VI.MAX., ATBC studies which have been beneficiary in case of 1st one of an population with an relatively low level of medical culture, but very disciplined (specific to the yellow race) and in case of the other ones with an elevated level of medical culture (French , Finnish people) also disciplined.

From the experimental point of view, is detached the idea of finding the right dose of vitamin E with highest efficiency on each form of cancer, that efficient multivitamin combination, and new ways of oral intake as food supplement (liposome’s, nano-capsules etc.) taking care of fact that we speak of esters of vitamin E as succinate, acetic ethers etc. especially in cancer case.

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