

Selenium and The Prevention of Cancer

Part I: Evidence for the Carcinostatic Activity of Se Compounds

Julian E. Spallholz*

There is a fairly long historical record showing that selenium can be used to treat cancers directly as well as prevent cancers with dietary selenium supplements. In 1915 Walker and Klein¹ used selenite and injected it directly into a lingual tumor, which effectively treated the patients condition. This is the first known report of selenium being used to successfully treat a pre-existing cancer. A 1992 U.S. Patent by Kralick et al² showed that selenodiglutathione could be injected into a tumor for therapeutic treatment. Most recently, several patents have been assigned whereby selenium has been covalently attached to antibodies, peptides and proteins and their seleno-conjugates have been demonstrated to inhibit cancer cell growth and viral replication in vitro. This latest technology offers the promise of specific targeting of cancers and viruses in vivo with covalent selenium conjugates³. Reports of other successful treatments of pre-existing cancers with selenium in animals and humans are almost non-existent.

What predominates the selenium literature over the last 20 years is an overwhelming compilation of mostly animal and human research showing that dietary selenium can and does prevent and/or reduce the incidence of naturally occurring and both chemically and virally induced cancer. The unfolding of the revelation that dietary selenium could reduce the formation of cancer began in 1943 with a report by Nelson⁴ et al that dietary selenium could induce liver cancer in rats. Others tried to repeat the observations that selenium could cause cancer but most were unsuccessful in repeating the Nelson study. The Nelson study and a later

Russian paper published in 1961 also indicating the formation of hepatic cancer in rats⁵ cast a cloud over the reported essentiality of dietary selenium in 1957⁶ that prevented dietary liver necrosis in rats.

The unexpected observation of the anticarcinogenic effects of supranutritional levels of dietary selenium had preceded the 1957 discovery of the nutritional essentiality of selenium. Little notice was taken of the 1949 work of Clayton and Baumann⁷ until two decades later, when experimental studies by Shamberger⁸ and others confirmed the inhibitory effects of selenium on chemical carcinogenesis in animal models.

At about this same period of time a number of epidemiological reports were being published showing an inverse relationship between selenium and cancer in humans. These early reports came from Shamberger and Frost⁹, Shapiro¹⁰, and Schrauzer¹¹.

About 1980 publications began to appear that selenium experimentally actually prevented cancer in animals. Griffin and Lane¹² summarized the very early chemoprevention studies, most of which employed the inorganic forms of selenium, selenite and selenium dioxide. A second review by Milner et al¹³ demonstrated that not only inorganic forms of selenium could prevent transplantable Erlich acites cancer cells in mice but organic forms of selenium also prevented cancer cell growth. The forms of selenium that prevented cancer cell growth in mice were selenite, selenate

*Food & Nutrition, Texas Tech University, 19th & University, P.O. Box 1162
 Lubbock, TX 79409-1162, USA. email: jspallholz@hs.TTu.edu

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Table 1 • Tumor Incidence in Mice Injected with Selected Selenium Compounds

Treatment	Experiment ¹		
	I	II	III
	Tumor Frequency		
Control-KRP	10/10	5/5	5/5
<i>Inorganic Forms</i>		<i>Dose, µg/g weight</i>	
	2	1	0.25
Selenium dioxide	0/10	0/5	1/4
Sodium selenite	0/10	0/5	0/3
Sodium selenate	0/10	0/5	2/5
<i>Organic Forms</i>			
Selenomethionine	0/10	5/5	5/5
Selenocystine	0/10	0/5	2/5

¹Tumor cells (5×10^5) were inoculated on day 0. Selenium or KRP were administered on days 0, 1, 3, 5, 11, 15 and 18

From Molner et al, early in 1980, shows the differences in efficacy and dosage of five different selenium compounds in affecting the tumor incidence of Erlich ascites cancer cells. From this data effectiveness of selenium compounds based upon dosage in tumor prevention would be ranked as selenite > selenium dioxide > selenate > selenocystine > selenomethionine

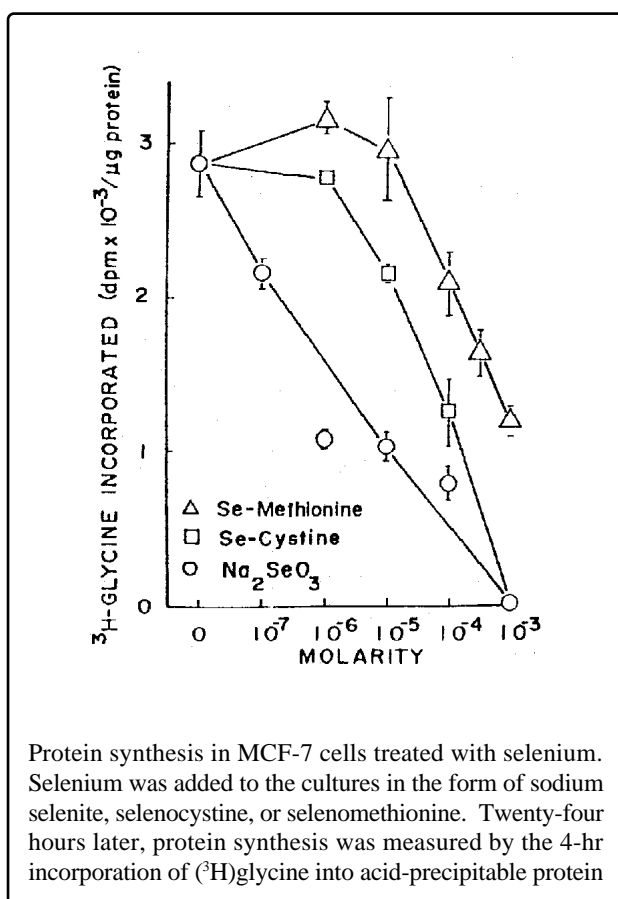


Figure 1 • From Lewko and McConnell in 1987 shows the same order of effectiveness of selenium compounds, selenite > selenocystine > selenomethionine affecting protein synthesis in a dose dependent manner on human breast cancer cells, MCF-7 cells, in culture

and selenium dioxide as well as the selenoamino acid selenomethionine, and selenocystine. Table 1. These experiments of Milner et al were not dramatically different from the 1915 selenite experiment reported by Walker and Kline. In his experiments, Milner repeatedly injected into mice selenium compounds either ip or sq and the growth of the transplanted acites cancer cells were generally prevented.

Over the next two decades to the present day, selenium compounds in a variety of cell culture and animal experiments have demonstrated the ability of most but not all selenium compounds to have carcinostatic activity which will arrest cancer cell growth and prevent or reduce induced carcinogenesis^{14,15}. In animals, dietary supplemental levels of selenium, <1-1.5 ppm selenium, *have not* been reported to have any carcinostatic activity. In humans, supplemental levels of 200-µg selenium/day have been reported to exhibit carcinostatic activity. This amount of selenium supplementation in humans is approximately 2-3 times the normal dietary level of selenium ingested each day from a western type of diet. Unlike in animal experimentation, dose regimen levels of dietary selenium supplementation to prevent cancer have not been conducted in humans.

While it has been demonstrated that many but not all inorganic and organic selenium compounds have carcinostatic activity it is also evidentially clear that selenium compounds differ greatly in their effectiveness as carcinostatic agents. The work of Milner et al¹³ cited earlier, showed that the most carcinostatic forms of selenium were the inorganic salts; selenite and selenium dioxide. Selenate, selenocystine and selenomethionine on a dose related selenium basis were less effective as carcinostatic

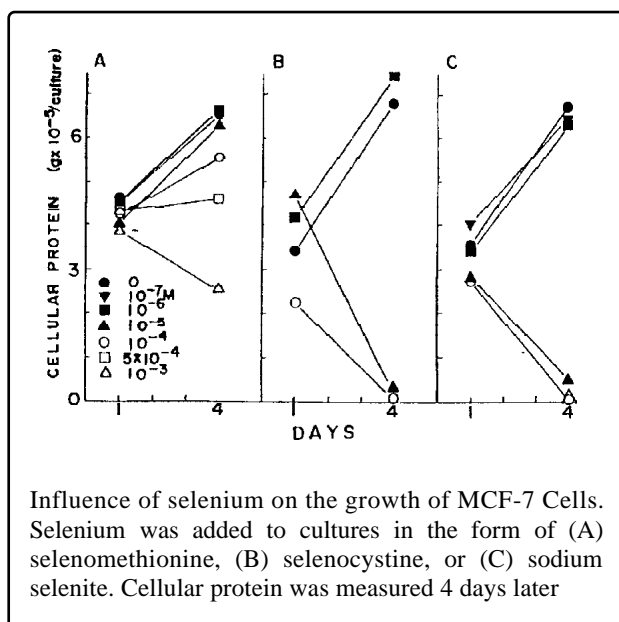


Figure 2 • Also from Lewko and McConnell, 1987, shows the effect of time and dose of the same three selenium compounds tested on protein synthesis and the effect of selenium dose on the cellular decline of the major cellular thiol, glutathione

agents in preventing tumor growth. Table 1. A similar effect has likewise been shown to be true when cancer or normal cells are incubated in a dose dependent manner with different selenium compounds in vitro. Figures 1 and 2. It is hard to find any experimental reports where selenite or selenium dioxide is reported to be less carcinostatic or toxic to cells in vitro or whole animals than selenate, selenocystine or selenomethionine when selenium concentrations are adjusted and expressed on a comparable

selenium basis. Even more potent against cancer cells than selenite is selenodiglutathione. Vernie et al¹⁷ and Milner et al¹⁸ have both extensively experimented with selenodiglutathione testing its ability to inhibit cancer cell growth. In vitro and in vivo selenodiglutathione more readily arrests cancer cell growth than selenite or any other selenium compound. Table 2. Also more effective than selenite in controlling cancer cell growth is the reaction product of selenite with monothiols other than glutathione including, cysteine, thioglycolate, mercaptoethanol, thiophenol, cysteamine as well as others¹⁹. Such experiments demonstrate that it is the selenium moiety and not the thiol side chain that is important in the anticarcinogenic activity of the selenotrisulfide (RSSeSR) compounds so formed. As noted by Kralick et al in their 1992 patent, selenodiglutathione was very effective in curtailing the growth of all eight different cancer cell lines at approximately the same selenium concentration, 10⁻⁶ to 10⁻⁵ M, to which the authors referred to this selenium concentration as the cellular "crisis zone". Such results imply an underlying common effect of selenium compounds interacting with thiols, such as glutathione, (see Figure 3) in preventing cell growth on a variety of very different cancer cell lines.

From the earliest animal carcinostatic experiments involving mostly inorganic selenium; selenite, selenium dioxide and selenate, the more recent experimentation in animals and the limited human experimentation on the carcinostatic activity of selenium compounds has focused mostly on the organic selenium compounds. The organic focus for experimentation evolved because the inorganic forms of selenium had been found to be very toxic in comparison to the organic forms of selenium, like L-selenomethionine. L-selenomethionine became the primary focus of carcinostatic research for it is the predominant dietary form of selenium in foods associated with protein and it is the

Table 2 • Effect of Various Forms of Se on the Growth of Neoplastic and Nonneoplastic Mammary Cells^a

	Selenium addition (µg/ml)	Cells (nonneoplastic, (x 10 ⁵))	CMT-13 (x 10 ⁵)	CMT-11 (x 10 ⁵)
Control	0	4.40	9.54	15.21
Selenomethionine	0.75	4.46	8.94	13.26
Selenocystine	0.75	4.56	6.59	14.25
Sodium selenite	0.75	4.28	4.55	8.78
Selenodiglutathione	0.75	4.46	0.50	3.60
PSEM		0.21	0.77	0.76

^aInitially plated at 1.0, 1.2, and 1.0 x 10⁵. Nonneoplastic cells were a primary culture obtained from a lactating dog. CMT-13 represents a selenium-responsive cell line and CMT-11 represents a selenium-nonresponsive cell line. Selenium was added 24 hr after plating in fresh medium. Cell counts were determined 48 hr after the addition of selenium.

From Milner and Fico, 1984, shows again the effect of the different selenium compounds on two different cell lines of Canine Mammary Tumor (CMT) cells. This table is particularly instructive in clearly showing the greater effectiveness of selenodiglutathione in affecting cell growth over that of selenite as reported by other authors (see also Vernie). The remaining order holds, selenite > selenocystine > selenomethionine in affecting CMT cell growth. Interestingly, non-cancer cells were not reported to be affected by any selenium treatment.

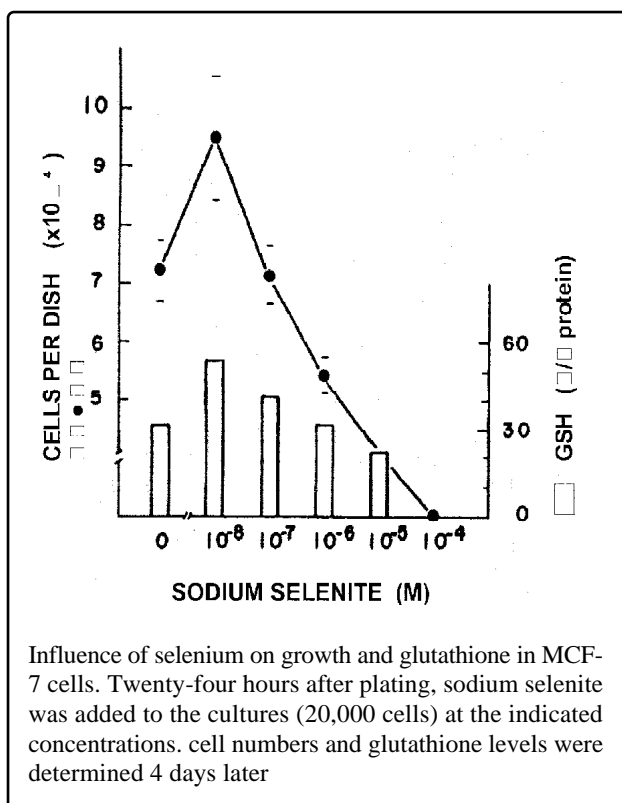


Figure 3 • From Lewko and McConnell, 1987, showing again how incubation of selenite with mammary cancer cells affects levels of cellular glutathione. As noted in Summary number 3, many authors have shown a strong interaction of thiols with selenite, less so with other selenium compounds in vitro. These five figures representative of some of the early selenium literature partially holds the key to understanding selenium's anticancer activity

major form of selenium in selenium-yeast supplements^{20,21,22}. Others researchers, particularly Dr. El-Bayoumy has tested many synthetic organo-selenium compounds in the search for new non-toxic selenium compounds that would be effective as carcinostatic agents²³. Some of these synthetic organic selenium compounds, such as 1,4-phenylene-bis(methylene)selenocyanate (p-XSC) have been found to have carcinostatic activity in animals. Most recently the work of Ip et al, to be discussed in detail in Part 2, has identified L-Se-methylselenocysteine (SeMC), a naturally occurring selenoamino acid found in very low concentrations in plants²⁴ to be a potent carcinostatic dietary selenium supplement in an animal mammary cancer model²⁵. This same amino acid, SeMC can be enriched in garlic and broccoli by placing inorganic selenium compounds in soil or by spraying the plant leaves²⁶. Very recently, Finley et al have reported that SeMC, the predominant form of selenium in enriched broccoli, was very effective in reducing colon cancer in rats^{27,28}. Thus L-selenomethionine and L-Se-methylselenocysteine have emerged from the most recent research on the anti-cancer properties of selenium as the dietary supplements of choice based upon experimental

efficacy in animals with the latter, SeMC, clearly the most potent carcinostatic selenium compound.

While animal experimentation continues to reveal the chemopreventative effects of selenium, real human data on the chemopreventative effect of selenium alone, outside of the epidemiological data cited,²⁹ remains sparse indeed. The sole exception is the report of Clark et al³⁰ showing that selenium supplementation of humans with 200-µg selenium/day as selenium yeast, containing mostly L-selenomethionine and small amounts of Se-methylselenocysteine, reduced the incidence of lung, prostate and colorectal cancer by nearly 50%. This is the first double blind, placebo controlled human selenium supplementation intervention trial that has evaluated selenium as a chemopreventative agent. A new human intervention trial now in its second year, the PRECISE trial, (Prevention of Cancer by Interaction with Selenium) recruited and included 33,000 Europeans from Sweden, Denmark and the United Kingdom where dietary selenium ingestion levels are reported to be less than in other parts of the world.

Much of the information on the anti-carcinogenic properties of selenium gained over the last twenty years or so can be summarized as follows and for which there is at least some agreement among researchers working in this field of research. The following summarization is the author's point of view of the present state of understanding of the anticarcinogenic effects of selenium compounds from his personal research experience along with having the insight of colleagues and the literature upon which to draw enlightenment.

Low Dietary Ingestion of Selenium May Contribute to an Increase Risk of Cancer (as well as other health related effects).

This statement is supported by the early human epidemiological evidence that cancer rates were higher in populations with low selenium dietary selenium intake²⁹. Additionally, total cancer related mortality rates were inversely related to levels of selenium in plants and to levels of selenium in human blood. These correlations are undoubtedly related to the level of dietary intake of selenium and to the amounts of the family of selenium containing enzymes, the glutathione peroxidases. More recent evidence supports the hypothesis that low dietary levels of selenium ingestion in animals and humans may enhance infectious viral diseases related to heart disease, liver cancer and AIDS¹⁵.

Supranutritional Levels of Dietary Selenium Ingestion Likely Prevents and Reduces the Incidence of Naturally Occurring, Viral and Chemically Induced Cancers.

It appears that both inorganic selenium compounds and several but not all organic selenium compounds are effective

as carcinostatic agents. This observation provided over the past twenty-five years has posed the question how a variety of different inorganic and organic selenium compounds could all be carcinostatic? It is clear to most researchers and I believe the general consensus is that the anti-carcinogenic effects of dietary selenium supplements are not due to the elevation of selenium enzymes or proteins. The glutathione peroxidases and other selenium proteins all become saturated at maximal levels of endogenous synthesis prior to the induction of the carcinostatic action of selenium supplementation¹⁴ (see Figure 4).

Selenium Compounds that Exert a Chemopreventative Dietary Effect in Reducing Various Cancers Likely do so using a Common Mechanism.

The literature suggests that all inorganic selenium compounds which express carcinostatic activity against cancer cells in vitro or cancer cells in vivo do so by interaction with thiol compounds (see Figure 3). This is a very common unifying thread that runs through the selenium literature^{14, 18, 32}. Organic selenium compounds of any and all kinds to be effective carcinostatic agents in vitro or in vivo must express a selenide anion (RSe⁻). Whether it is a selenotrisulfide (RSSeSR) from inorganic selenium compounds or a methylselenol (RSeH) from an organic selenium compound²⁴, the end result is the common

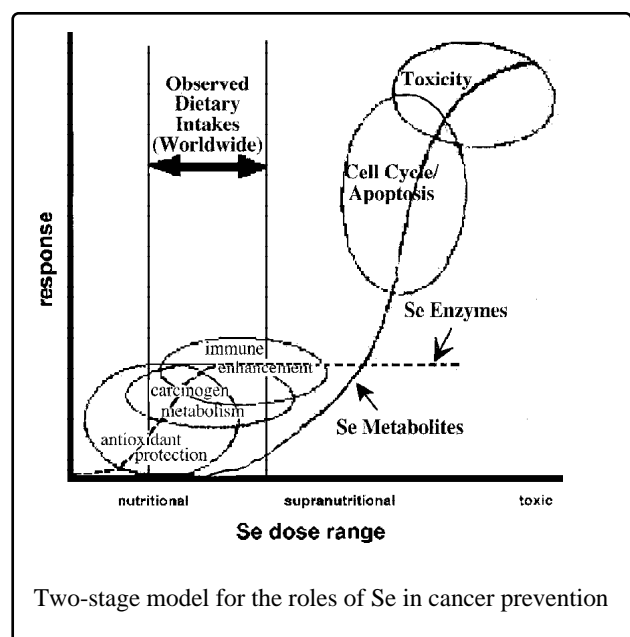


Figure 4 • From Combs and Gray, 1998, in the author's opinion this is the best diagrammatic representation of all the nutritional affects of selenium representing deficiency, metabolism of carcinogens, immunity, carcinostatic activity and overt toxicity. It demonstrates worldwide dietary intake, enzyme and protein saturation and the important selenium metabolites which cause chemoprevention whose effects shall be discussed in Part 2

generation by these different selenium compounds of reactive free radical species³³. As the hypothesis to be outlined and explored in Part 2 of this article, it is free radical generation by selenium compounds, not antioxidant activity, that appears to be the common unifying and underlying event in cancer cells that imparts selenium's unique carcinostatic activity.

Conclusions, Part 1: Selenium is an essential dietary nutrient for most animals and humans, which is incorporated into twelve or more known proteins or enzymes as an amino acid, selenocysteine. Most, but not all selenium from selenium compounds can be efficiently incorporated into selenocysteine. The major dietary forms of selenium are L-selenomethionine from cereal and animal protein and L-selenocysteine from animal protein. Fruits and vegetables generally contain very low levels of selenium. At supranutritional levels of dietary selenium by way of supplementation, most but not all selenium compounds can reduce the incidence of naturally occurring, viral or chemically induced cancer in both animals and humans. This empirical effect of selenium chemoprevention of cancer depends upon the dietary supplemental dose and chemical form of selenium ingested. Selenium's dietary chemoprevention effect quantitatively lies between ingestion of amounts of selenium that fulfills its essential role in enzymes and proteins and amounts that may express overt toxicity. A common characteristic of all selenium compounds that express significant experimental carcinostatic activity in vitro or in vivo is their interaction with thiols and the generation of free radical species.

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The Tables and Figures and the attached commentary of the author have been selected from the literature to elucidate statements made in the text

COMING IN PART 2...

Mechanisms for the Carcinostatic Activity of Selenium Compounds

THE VIEWS EXPRESSED IN THE ARTICLES PUBLISHED IN THE BULLETIN ARE THOSE OF THE AUTHORS, NOT NECESSARILY THOSE OF THE STDA