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## REPORT

### Selenium

#### Important Health Benefits from an Overlooked Trace Mineral

By Julius G. Goepf, MD



When was the last time your doctor suggested that you supplement with selenium in an effort to prevent cancer? Scientists now know that this trace mineral has extraordinary value in fighting various cancers and other conditions involving oxidative stress and inflammation.<sup>1,2</sup>

Doctors assume that we get enough selenium through plant foods. Unfortunately, in many places in America and the rest of the world, including China and Russia, the soil is badly depleted of its selenium content because of acid rain, which can dramatically change the chemical composition of the soil. As a result, soil acidification alters the ability of the soil to bind with vital elements such as selenium for assimilation into edible plants.

#### SELENIUM'S UNIQUE BIOCHEMICAL PROPERTIES

What makes selenium unique? While scientists are still elucidating selenium's role in a multitude of biochemical processes, one of its chief attributes is serving as a component of specific proteins called selenoproteins. Almost all of these proteins are active in the defense against reactive oxygen species (free radicals), which fuel numerous diseases and the aging process itself through their damaging effects on DNA and proteins.

Selenoproteins and their antioxidant products scavenge cell-damaging free radicals. Selenium is the only mineral nutrient that has its own DNA code, which instructs the body's protein-synthesis "machinery" to incorporate selenium into its host proteins. Scientists interpret this unique attribute as evidence of selenium's fundamental importance to virtually all living things on Earth.<sup>3</sup>

Selenium is available from many dietary sources, including garlic, Brazil nuts, and certain vegetables; however, the amount of bioavailable selenium from these sources varies tremendously, depending on the soil and weather conditions where the plants are grown.<sup>4</sup> Foods containing selenium may also contain substances that limit selenium's bioavailability.<sup>5</sup> Therefore, selenium supplementation is often recommended as a way to assure a dependable, bioavailable supply of this nutrient.<sup>6</sup>

Selenium deficiency is increasingly associated with adverse health conditions and even life-threatening diseases. People who live in selenium-poor regions of the world suffer from dramatically increased rates of cancer, infections, and inflammatory diseases.<sup>1,7-9</sup> Fortunately, many of these conditions can be prevented and even reversed with selenium supplementation.<sup>10-13</sup> In this article, we will examine how oxidative stress can increase our vulnerability to inflammation, infection, cancer, and cardiovascular disease, and how selenium and the selenoproteins work to counteract oxidative stress, even in people without overt selenium deficiency.

#### SELENIUM PROTECTS AGAINST OXIDATIVE STRESS

Scientists now generally recognize that most disease processes produce their effects through chemically reactive molecules known as free radicals. Free radicals are composed mostly of reactive oxygen and nitrogen compounds. These reactive oxygen species initiate a destructive cycle fueled in part by the body's own defense mechanisms. They disrupt the normal structure of proteins and the genetic information encoded in DNA. This damage always results in the release of potent chemical messengers called cytokines. Cytokines trigger the inflammatory response in tissues, signaling immune and inflammatory cells to swarm the affected area.

This inflammatory reaction activates powerful factors deep within cell nuclei—such as nuclear factor-kappa beta (NFκB). These factors "translate" infection and inflammation into the uncontrolled cell replication that produces cancer.<sup>14</sup> Strong evidence also suggests that NFκB and related compounds are involved in the conversion of oxidative damage, stress, and inflammation into the stimuli that produce atherosclerosis and cardiovascular disease.<sup>15</sup>

Selenium not only scavenges reactive oxygen species before these free radicals can damage cells, but also regulates nuclear factor activities deep within the cells themselves.<sup>16</sup> For this reason, scientists now call selenium “one of the most promising agents” for the prevention and control of cancer.<sup>17</sup>

Laboratory evidence also supports selenium’s role in protecting cardiac muscle from the effects of reduced blood flow, or ischemia.<sup>18</sup> Under the extreme oxidative stress triggered by a severe infection, selenium has been shown to enhance the protective ability of intracellular antioxidant systems that use glutathione.<sup>19</sup> Moreover, selenium specifically inhibits the activation of NFκB, which in turn inhibits the release of inflammatory cytokines. In fact, in laboratory studies, a reduction of selenium has been shown to increase levels of these inflammatory molecules.<sup>20</sup> Research also shows that by reducing NFκB activity, selenium prevents the activation of inflammatory cells that contribute to vascular disease in type II diabetes.<sup>21</sup>



These laboratory findings underscore selenium’s promise in preventing and treating a wide array of human diseases, while reducing the cumulative oxidative damage that underlies many of the deleterious changes associated with aging.<sup>22</sup>

## SELENIUM COMBATS INFLAMMATORY AND INFECTIOUS DISEASES

The recognition of selenium’s ability to prevent oxidative damage has fueled research into how selenium influences various chronic inflammatory conditions. For example, in a study of 70 patients with rheumatoid arthritis, selenium concentrations were found to be significantly lower than in a healthy population. When the subjects were given selenium or placebo for three months, the selenium-supplemented group showed fewer tender or swollen joints and less morning stiffness than did the control group. The supplemented patients also required less cortisone and nonsteroidal anti-inflammatory drugs (NSAIDs) than did the controls, and demonstrated a reduction in laboratory indicators of inflammation. No side effects of selenium supplementation were noted.<sup>23</sup>

Selenium has shown great promise in the treatment of autoimmune thyroiditis as well.<sup>24</sup> In a recent study, 48 patients with elevated levels of an antibody to thyroid enzymes were given selenium daily for three months, while 40 patients received placebo. Serum levels of the antibody dropped significantly in the supplemented group compared to the placebo group, demonstrating that selenium suppressed the autoimmune attack on these patients’ thyroid glands.<sup>25</sup> Similar reductions in measures of autoimmune inflammatory response have been shown in other studies of selenium alone or in combination with other antioxidants.<sup>26-28</sup>

Many other autoimmune conditions are associated with low selenium levels, including autoimmune hepatitis and diabetes.<sup>29-32</sup> Preliminary trials have demonstrated a protective effect of selenium supplementation against both hepatitis C and alcoholic hepatitis; both conditions involve a substantial inflammatory component that is thought to be mitigated by the actions of selenoproteins.<sup>33,34</sup>

## FOUR DIFFERENT FORMS OF SELENIUM

Selenium is available in a number of different forms for supplementation, and each has slightly different uses and benefits. Ideally, a good supplement should contain all four of the following forms of selenium for broad-spectrum protection.

- In the form of the salt, sodium selenite, selenium has been used to reduce post-operative swelling that is related to the increased free radical stresses produced by surgery.<sup>69</sup> Related beneficial effects are seen when sodium selenite is used to protect against radiation treatment-induced swelling and inflammation.<sup>70,71</sup> Sodium selenite has also demonstrated dramatic immune-boosting function in patients with borderline low selenium status.<sup>72</sup>
- The natural metabolite of selenium, selenodiglutathione, contains a selenium ion bonded to two molecules of the potent antioxidant glutathione. This compound appears to be heavily involved in the cancer chemoprotective effects of selenium,<sup>73-76</sup> as demonstrated by its ability to stimulate apoptosis, the programmed cell death the body uses to purge itself of incipient cancers.<sup>77,78</sup>
- The selenium-containing amino acid, L-selenomethionine, is an essential component of the selenoproteins involved in controlling autoimmune diseases.<sup>79</sup> It is also selectively accumulated in prostate tissue, where it has been shown to have cancer-fighting activity.<sup>80</sup> As a component of an “antioxidant cocktail,” L-selenomethionine can increase brain blood flow and scores on psychological testing in elderly people.<sup>81</sup>
- Another selenium-containing amino acid complex, Se-methylselenocysteine, has especially great potential in the treatment of established cancers,<sup>82</sup> where it has been shown to radically enhance the effects of traditional chemotherapy drugs while protecting against their toxicity.<sup>83</sup> In one study, drug treatment alone was curative in only 30% of animals bearing human squamous cell carcinoma of the head and neck; that rate rose to 100% with the addition of methylselenocysteine.<sup>84</sup>

Severe infection imposes some of the most concentrated oxidative stress of all human diseases. Selenium has shown important benefits for those with septic shock, one of the most troubling killers of people with infections, compromised immune systems, or those confined to the hospital. Now known as systemic inflammatory response syndrome, or SIRS, overwhelming infection leads to runaway release of cytokines and other inflammatory mediators, ultimately causing a dramatic failure of multiple organs and bodily systems.<sup>19</sup> This condition, formerly known as “septic shock,” has yielded dramatically to the inclusion of selenium in treatment protocols, as evidenced by two remarkable studies published in 1999.

When 21 intensive-care patients with SIRS were given high-dose selenium (beginning at 535 mcg per day), their selenium and glutathione peroxidase levels normalized within three days; by contrast, selenium and glutathione peroxidase levels remained low in 21 control patients who received only “normal” amounts of selenium. Scores on a scale of physiological function were significantly better in the supplemented group than in the controls, and hemodialysis because of acute kidney failure was needed in only 3 of the 21 supplemented patients, compared to 9 of the 21 control patients.<sup>35</sup> A similar study of 34 children with SIRS demonstrated markedly elevated activity of antioxidant enzymes in the selenium-supplemented group, with markers of lipid peroxidation and cell membrane destruction falling dramatically compared to controls.<sup>36</sup>

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#### SELENIUM SHOWS PROMISE IN PREVENTING CANCER

Selenium's antioxidant properties have spurred great interest in its potential to prevent cancer. This is not surprising, given our increasing awareness that cancer is caused and promoted by the same cascade of events—oxidative stress and cytokine release—that produces the autoimmune and other inflammatory conditions just discussed.

To date, more than 100 animal studies have investigated selenium's effects on the mechanisms responsible for initiating cancer. In the overwhelming majority of these studies, selenium reduced tumor incidence and tissue changes that lead to cancer.<sup>8,37</sup> The high incidence of various cancers in selenium-deficient regions of the world strongly supports a cancer-preventive role for selenium in humans as well, and epidemiological studies have demonstrated reductions in the rates of, and mortality from, all cancers in populations receiving selenium supplementation.<sup>38</sup>

#### SELENIUM PREVENTS AND SLOWS PROSTATE CANCER

Additional studies of selenium's effects in helping to prevent specific cancers have yielded results that are even more positive.

One of the most dramatic of these was the unexpected outcome of a study designed to examine selenium's impact on skin cancer.<sup>39</sup> This study of 1,312 individuals who received 200 mcg of selenium daily or a placebo showed no effect against skin cancer, but demonstrated "striking" results in preventing prostate cancer, the most common cancer in American men.<sup>40,41</sup> The overall risk of prostate cancer was almost 50% lower in the supplemented group than in the controls, though the result was significant only in men who had relatively low prostate-specific antigen (PSA) levels and low initial selenium levels.

This result prompted a re-analysis of data from the SU.VI.MAX study, with a specific look at prostate cancer.<sup>42</sup> Within that group, 5,141 men took the selenium-containing supplement or placebo for eight years, and biochemical markers of prostate disease were measured at the beginning and end of the study. Overall, a slight reduction in prostate cancer risk was reported; however, among men who had normal PSA levels at the study's outset, a significant risk reduction of nearly 50% was recorded.



A 2005 study focusing on selenium's effects in preventing prostate cancer dramatically confirmed this protective effect.<sup>43</sup> Forty-eight patients with early prostate cancer took selenium, vitamin E, both L-selenomethionine and vitamin E, or a placebo for three to six weeks before undergoing prostatectomy (removal of the prostate). Levels of cancer markers were measured and compared with 29 healthy control subjects. The startling result was a change in classification from cancerous to healthy in the serum markers of disease in the men who took supplements compared to those who did not.

In addition to its clear role in preventing prostate cancer, selenium may slow the progression of already established prostate cancer. In a six-week trial, 37 men with prostate cancer and increasing PSA levels were given either a placebo or an antioxidant supplement containing selenium, plant estrogens, and other antioxidants.<sup>44</sup> In the supplemented group, male hormone levels (known to stimulate prostate cancer growth) were lower during treatment. In addition, free PSA levels rose during treatment with the placebo, but decreased during antioxidant supplementation.

These studies, along with recent findings that selenium is selectively concentrated in prostate tissue,<sup>45</sup> strongly support a role for selenium supplementation in both preventing and slowing the progression of prostate cancer.

#### SELENIUM PROTECTS AGAINST LUNG CANCER

Lung cancer is the most common cause of cancer death in the world.<sup>46</sup> The previously mentioned skin cancer study also demonstrated that selenium supplementation reduced rates of lung and colorectal cancers.<sup>39</sup> Lung cancer is associated with antioxidative stress and low levels of antioxidants, including selenium.<sup>47</sup> A 1993 study demonstrated a 50% reduction in lung cancer occurrence in people with the highest dietary selenium intake compared to those with the lowest intake.<sup>48</sup> This finding is

supported by a more recent study of more than 27,000 male smokers who were followed for nearly 15 years. In this study, researchers found that lung cancer risk was significantly lower in patients who had the highest intake of antioxidant vitamins and selenium.<sup>49</sup>

Selenium supplementation was highly effective in preventing lung cancer in a region of China where very low natural selenium concentrations contribute to some of the world's highest rates of lung cancer. Forty Chinese tin miners were randomly assigned to receive either 300 mcg of selenium or a placebo daily for one year. As expected, selenium blood levels rose dramatically in the supplemented miners, while serum levels of the antioxidant enzyme glutathione peroxidase increased by 156%. At the same time, levels of lipid peroxide (a measure of cell membrane damage that leads to cancer) were reduced by 75% in the supplemented group, and there was laboratory evidence of protection from DNA damage, another prerequisite for cancer formation.<sup>50</sup>

Moreover, results from the US Nutritional Prevention of Cancer Trial demonstrated a statistically significant reduction in lung cancer incidence with selenium supplementation, with 200 mcg per day cutting the incidence of cancer by nearly 50%.<sup>51</sup> A later re-analysis with additional data showed the effect to be most significant in people with low baseline selenium levels, again suggesting that supplementation is preventive when initiated early.<sup>37</sup>

## SELENIUM GUARDS AGAINST COLON CANCER

Selenium supplementation has also shown effectiveness in preventing colorectal cancer, the third most common cause of cancer death in the US.<sup>52</sup> Glutathione peroxidase, a selenium-containing antioxidant enzyme, is genetically defective in a significant percentage of patients with colon cancer.<sup>53</sup> Selenium actually activates the DNA repair mechanisms that help cells protect themselves against colon and other cancers,<sup>54</sup> while inducing programmed cell death (apoptosis) in cancerous tissue.<sup>55</sup> In an animal model of cancer, selenium-containing broccoli in the diet of laboratory rats protected the animals against chemically induced mammary and colon cancers.<sup>56</sup>

After demonstrating that patients with colon cancer routinely have selenium deficiencies, and that levels of vital antioxidant enzymes could be increased with selenium supplementation, one research team concluded, "If prospective trials confirm that selenium supplementation reduces colon cancer incidence rates, it may be concluded that selenium supplementation should be recommended for patients at risk."<sup>57</sup>

Such confirmation is now beyond doubt. In a 1996 study of 44 patients with colon cancer, half were randomly assigned to receive selenium supplements and half were given a placebo. All the subjects had their tumors surgically removed, and all had abnormally low selenium levels at baseline. The selenium-supplemented patients demonstrated significant increases in anti-cancer immune system cells compared to levels in control patients, suggesting that selenium supplementation boosts cell-mediated immunity.<sup>58</sup>

More dramatic, unexpected evidence of selenium's cancer-preventive properties comes from a 2006 study. Seeking to determine the maximum tolerable dose of the anti-cancer drug irinotecan, researchers administered a massive dose of selenomethionine (containing 2200 mcg of selenium) to protect against the drug's toxicity.<sup>59</sup> Selenium supplementation was begun one week before the first dose of irinotecan was administered to colon cancer patients who had previously not responded to chemotherapy. This small study of highly drug-resistant patients produced unexpected responses (one patient out of six showed a partial response to treatment) and disease stabilization. No adverse effects of the high dose were reported. The scientists recommended further study of high-dose selenomethionine to determine the most protective serum concentrations of selenium.

## CARDIOVASCULAR DISEASES, ATHEROGENESIS, AND THE METABOLIC SYNDROME

The exciting evidence for selenium's effectiveness in preventing inflammatory diseases and cancer has led scientists to explore its protective effects against other conditions involving oxidative damage. Many of these conditions were previously considered to be "natural" consequences of aging. With the discovery that atherosclerosis, cardiovascular disease, hypertension, obesity, and type II diabetes—components of the so-called "metabolic syndrome—are all caused or exacerbated by oxidant stress,<sup>60</sup> selenium may prove to have a valuable preventive and therapeutic role in these conditions as well.

Patients with acute myocardial infarction (heart attack) have been shown to have lower levels of selenium in their plasma, red blood cells, and urine compared to control subjects.<sup>61</sup>

Selenium concentrations are also low in some patients with endothelial dysfunction, the inflammatory-mediated precursor to atherosclerosis and hypertension. Supplementation with selenium has been shown to reverse specific chemical markers of endothelial dysfunction.<sup>62</sup> In addition, selenium may help protect against congestive heart failure.<sup>63,64</sup>

Oxidative stress is both a cause and consequence of chronic renal failure. Patients who suffer from this condition experience



exceptionally high levels of cardiovascular disease and death,<sup>65</sup> as well as impaired immune function.<sup>66</sup> Selenium levels are markedly reduced in these patients.<sup>67</sup> Selenium deficiency is especially pronounced in patients on kidney dialysis, who lose considerable amounts of selenium during the dialysis process. This renders them even more vulnerable to further oxidative damage to their cardiovascular systems.<sup>65</sup> Selenium supplementation in dialysis patients has been used successfully to reduce oxidative stress,<sup>68</sup> and has actually been shown to improve immune function as well.<sup>66</sup>

## CONCLUSION

A review of recent research findings suggests that scientists have only begun to tap selenium's potential as a vital antioxidant mineral.

As scientists continue to discover the many ways in which oxidative stress is related to inflammation and its destructive consequences—from atherosclerosis to prostate, lung, colon, and other cancers—the disease-preventive powers of selenium are likely to receive even greater scrutiny. For now, all health-conscious adults would be well advised to incorporate this vital mineral nutrient in their daily supplement regimen as part of a comprehensive disease-prevention program.

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