MINI-REVIEW

Review of Selenium and Prostate Cancer Prevention

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Abstract

Prostate cancer is the most common malignancy in men in the United States. Surgery or radiation are sometimes unsatisfactory treatments because of the complications such as incontinence or erectile dysfunction. Selenium was found to be effective to preven prostate cancer in the Nutritional Prevention of Cancer Trial (NPC), which motivated two other clinical trials: the Selenium and Vitamin E Cancer Prevention Trial (SELECT) and a Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia. However, these two trials failed to confirm the results of the NPC trial and indicated that the selenium may not be preventive of prostate cancer. In this article we review the three clinical trials and discuss some different points which might be potential factors underlying variation in results obtained.

Keywords: Selenium - prostate cancer - prevention - clinical trials

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Introduction

Although the incidence and mortality of prostate cancer declined from 2000 to 2008 in the United States, the prostate cancer is still the most common cancer expected to occur and the second common causes of cancer death expected in men for 2012. It is estimated to account for 29% (241,740) of all newly diagnosed cancers in men and 9% (28,170) of all male cancer deaths (Siegel et al., 2012). The most common therapies for the prostate cancer at present are the surgical treatment or radiation. But the men undergoing those treatments may suffer from some complications such as incontinence and erectile dysfunction, and it will influence the quality of life and change the satisfaction of treatment (Sanda et al., 2008; Hu et al., 2009). Because of the important features of prostate cancer: late age of onset, slow to progress, and high incidence in men, it is regarded as an ideal candidate for chemoprevention. And since the selenium was found to be preventive to some cancers, especially the potential effect to prevent prostate cancer, it has got much interest to explore the relationship between the selenium and prostate cancer. The prevention of prostate cancer will have both economic and healthy benefits since per capita medicare spending for the prostate cancer is increasing which has been more than 10,000 dollars in the Unites States (Zhang et al., 2011) and the recent data suggest that many low-risk prostate cancer were over-treated (Silberstein and Parsons, 2010).

The selenium is a nonmetallic essential trace element to human health. The formulations include inorganic selenium such as selenite, selenate and organic selenium such as methylselenic acid and selenomethionine. It contributes to the human health by the enzymic function, redox function, and the effect to the immune response, etc. The dietary selenium intake recommended is 55μg/day by The American Recommended Dietary Allowance. The selenium-deficiency disease such as Keshan disease and Kashin-Beck disease have been identified. And since the 1970s the epidemiological studies have revealed an inverse relationship between the selenium level and cancer mortality (Rayman, 2000).

The Nutritional Prevention of Cancer Trial (NPC)

The selenium is found as a potential preventive element for the prostate cancer in the NPC trial (Clark et al., 1996; Clark et al., 1998; Duffield-Lillico et al., 2003). This trial was the first randomized, double-blind, placebo-controlled prevention trial designed to test and verify whether the nutrition supplement of selenium decrease the incidence of cancer (Clark et al., 1996). It enrolled a total of 1,312 at mean age of 63 years with a mean treatment of 4.5 years and a total follow-up of 6.4 years. The intervention agent used in this trial was 200 μg of selenium supplied as a 0.5g high-selenium brewer's yeast tablet by oral way (Clark et al., 1996). As the primary endpoint, the data analysis found no statistically significant differences in the incidence of basal or squamous cell carcinomas of the skin between the 2 groups, but the second analysis found a lower incidence of prostate cancer in the selenium group compared with the placebo group (Clark et al., 1998; Duffield-Lillico et al., 2003). This result pointed a possible preventive effect of the selenium to the prostate cancer which needed future trial to confirm.

Then two large clinic trials-The Selenium and Vitamin

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E Cancer Prevention Trial (SELECT) and Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia (SWOG S9917) motived by the NPC trial were launched and tried to confirm the preventive effect of selenium to the prostate cancer.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The SELECT designed to be a phase III, randomized, prospective, double-blind study with an enrollment of 32,400 men and an intended follow-up of up to 12 years. It was planned to started in 2001 with final results anticipated in 2013 and investigate whether selenium (200 μg/day from L-selenomethionine) and vitamin E(400 IU/day of all-rac-α-tocopheryl acetate) alone and in combination can reduce the risk of prostate cancer among healthy men. The target population include non–African American men at least 55 years of age and African American men at least 50 years of age, with a serum PSA (prostate specific antigen) no more than 4 ng/ml and not suspect of the prostate cancer in the DRE (digital rectal examination). The primary endpoint for the trial is the clinical incidence of prostate cancer, determined by a recommended routine clinical management, including yearly DRE and serum PSA level. Secondary endpoints include prostate cancer-free survival, all-cause mortality, and the incidence and mortality of other cancers or diseases potentially caused by the chronic use of selenium and vitamin E (Lippman et al., 2005). A total of 35,533 men were accrued at 427 participating sites in the United States, Canada, and Puerto Rico from August 22, 2001 to June 24, 2004. The participants have approximately median age of 62.5 years (range, 58.0-68.0 years), a mean rate at 79% of white people and 12% of African American, and prestudy baseline of serum selenium was approximately 136μg/L. They were randomized in 4 groups (placebo, vitamin E, selenium, and selenium + vitamin E) and well balanced with respect to the age, race, situation of the education, serum PSA level and smoking status (Lippman et al., 2009). On September 15, 2008, the SELECT trial was discontinued by the independent data and safety monitoring committee because the second formal interim analysis demonstrated that there was no evidence of benefit from the selenium or vitamin E for the incidence of prostate cancer between the trial groups. The median overall follow-up was 5.46 years (range, 4.17-7.33 years), and the rates of prostate cancer for the 4 group were: placebo, 416 cases [4.43%]; selenium, 432 cases [4.56%]; vitamin E, 473 cases [4.93%]; selenium +vitamin E, 437 cases [4.56%]. There was no statistically significant differences found in the rate of prostate cancer between the 4 groups but a statistically nonsignificant increase in prostate cancer in the vitamin E-alone group (P=0.09) and a statistically nonsignificant increase in type 2 diabetes mellitus (P=0.08) occurred in the selenium-alone group. So the SELECT ended with result demonstrating that selenium (200 μg/day from L-selenomethionine) and vitamin E (400 IU/day of all-rac-α-tocopheryl acetate) alone or in combination have no effect on the primary prevention of prostate cancer in the healthy population (Lippman et al., 2009).

The Phase III Trial of Selenium to Prevent Prostate Cancer in Men with High-grade Prostatic Intraepithelial Neoplasia: SWOG S9917

High-grade prostatic intraepithelial neoplasia (HGPIN) was believed as the potential premalignant lesion with high risk for progression to prostate cancer. This trial focused on the men at elevated risk of prostate cancer identified by the prestudy biopsy of HGPIN. It extended the SELECT which focused on the average risk men to the prostate cancer. It is a double-blind, randomized, placebo-control trial of selenium 200μg/day as selenomethionine in men with HGPIN. The primary endpoint was the progression of HGPIN to the prostate cancer. An end-of-study prostate biopsy, within a window of ±90 days, was planned for the participants who were not diagnosed with prostate cancer during the 3 years of the trial (Marshall et al., 2011). This trial was started in 2000 and closed in 2006. The eligibility criteria were: age no less than 40 years; digital rectal examination; confirmed of the HGPIN by biopsy; the PSA no more than 10 ng/ml; and American Urological Association symptom score less than 20. The exclusion criteria were: diagnosis of any other cancer (other than nonmelanoma skin cancer) within 5 years prior to the trial registration; taking selenium supplements containing more than 50 mg/d within 30 days prior to registration; and taking finasteride or other 5-a reductase inhibitors (Marshall et al., 2011). Finally the trial enrolled a total of 619 men, and 423 men with HGPIN were randomized to the selenium arm of 212 and placebo arm of 211 men. The primary analysis involved the 135 men (63.7%) of the selenium arm and 134 men (63.5%) of the placebo arm with an endpoint status known through an interim biopsy or a biopsy taken at ±90 days of the end of study. The comparison of the incidence of prostate cancer between the 2 arms were 48 cases (35.6%) on selenium versus 49 cases (36.6%) on placebo (P=0.73). The 2 arms had a similar rate diagnosis of prostate cancer. End-up-study prostate biopsy were negative in 64.4% of selenium arm and 63.4% of placebo arm. Also an extra-analysis that widened the window of the end-up-biopsy to ±180 days increasing the proportion of biopsy confirmed endpoint still found a similar rate of prostate cancer in the 2 arms (P=0.90). So there is no appreciable or statistically significant association between selenium treatment and a prostate cancer diagnosis (P=0.73) while subset analyses showed a nonsignificantly reduced prostate cancer risk (RR=0.82; 95% CI: 0.40–1.69) in selenium versus placebo patients in the lowest quartile of baseline selenium level (<106 ng/mL) (Marshall et al., 2011).

In conclusion, this trial extended the finding of the SELECT trial and showed the selenium do not prevent prostate cancer in the selenium-replete men while finding that the selenium-deficient men might benefit from the selenium supplement.

Discussion Points

Although the SELECT and HGPIN trial have showed

that the selenium do not lower the incidence of prostate cancer which is opposite to the result of the NPC trial, it's too early to conclude that the selenium is not preventive to prostate cancer because Hurst et al found a decreased risk of prostate cancer appears to be associated with a relatively narrow range of selenium status from a systematic review and meta-analysis (Hurst et al., 2012). The differences among the 3 trials above which might be the potential influence to the results are worthy to discuss.

The formulation and dose of the selenium used in the SELECT and HGPIN trial was the selenomethionine by 200μg/day, while the high-selenium brewer's yeast by 0.5g/day used in NPC trial (Clark et al., 1996; Lippman et al., 2009). A.L.Sabichi et al have showed that the oral supplementation of the selenomethionine can increase the selenium concentration in the prostate tissue (Sabichi et al.,2006), and JH Wake found the treatment with selenomethionine had a inhibitory effect on clone derived from a human prostate cancer cell line (Ware et al., 2006). However the research of Nur Özten et al. (2010) suggested that selenomethionine and α-tocopherol supplementation does not prevent prostate carcinogenesis in an animal model, and in vivo data by ZHANG supported selenomethionine is ineffective by the daily oral administration for inhibition human PC-3 xenograft growth in athymic nude mice and demonstrated the metabolic and biological differences between Se compounds (Zhang et al., 2011). So we need more explorations on the human effect of selenium, and the failure of selenomethionine in the SELECT trial cannot be equated to the other Se forms as "ineffective" for prostate cancer (Zhang et al., 2011).

The participants who benefited from selenium administration in the NPC trial had a lower median baseline selenium levels at 113ng/mL vs 135ng/mL in the SELECT (Clark et al., 1996; Lippman et al., 2009) while the HGPIN trial enrolled the men with a mean baseline selenium level >135 ng/mL (Marshall et al., 2011). The HGPIN trial also found a nonsignificantly reduced prostate cancer risk in selenium versus placebo patients in the lowest quartile of baseline selenium level (<106 ng/mL), which support the result of the NPC trial (Marshall et al., 2011). Veda Diwadkar-Navsariwala et al found that selenoprotein levels can influence prostate cancer development, and low dietary selenium intake can result in reduced levels of selenoproteins and increased cancer risk (Diwadkar-Navsariwala, 2006). That may explain why the selenium supplementation can reduce the risk of prostate cancer in the selenium-deficient group.

Besides, other factors such as the race, smoking status and interaction between vitamin E and selenium etc may also impact the result of the trials. The African American men have among the highest prostate cancer risks in the world (Hsing and Chokkalingam, 2006), the SELECT had very high rate of participation of African American men (13%) while the NPC is unclear (Clark et al., 1996; Lippman et al., 2009). The smoking status, which may be a risk factor to prostate cancer (Grundmark et al., 2011), were also different in the SELECT and NPC trial (Clark et al., 1996; Lippman et al., 2009). Further, some limitation in the NPC trial have been reported recently, such as the prostate cancer was not the primary endpoint of the NPC trial, the treatment and placebo subjects did not have an equal opportunity to have a biopsy for diagnosis of the prostate cancer, although the investigators attempted to adjust the differences between the 2 arms, it did not appear to eliminate the influence (Duffield-Lillico et al., 2003).

Also, the toxic effect of the selenium supplementation should be considered in the future study because both the NPC trial and SELECT found an elevated risk of the diabetes in the selenium group compared with the placebo group (Clark et al., 1996; Lippman et al., 2005).

Finally, the selenium biology in the human body is not totally clear now, it is important to understand fully the proper biology of selenium. Getting more information and knowledge on those mechanisms may be helpful in designing future studies on the prevention of selenium for prostate cancer.

Conclusions

At present, selenium is not identified to be effective to the primary prevention of prostate cancer, and the selenium supplementation is not recommended to the men risky to prostate cancer clinically. Although the SELECT and HGPIN trial failed to prove the effect of selenium to prostate cancer prevention, they would not be the end of the research in this field. More in vitro and in vivo trials are needed, such as the research focusing on the different forms of selenium and other target population or area. In addition, the researches on the biology and metabolism of selenium are very important to a better understanding of the mechanism for cancer prevention of selenium. The application of selenium supplementation may change the prevention and management of prostate cancer in future.

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