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Nutritional and supranutritional levels of selenate differentially suppress prostate tumor growth in adult but not young nude mice

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Abstract

The inhibitory effect of oral methylseleninic acid or methylselenocysteine administration on cancer cell xenograft development in nude mice is well characterized; however, less is known about the efficacy of selenate and age on selenium chemoprevention. In this study, we tested whether selenate and duration on diets would regulate prostate cancer xenograft in nude mice. Thirty-nine homozygous NU/J nude mice were fed a selenium-deficient, Torula yeast basal diet alone (Se−) or supplemented with 0.15 (Se) or 1.0 (Se+) mg selenium/kg (as Na_2SeO_4) for 6 months in Experiment 1 and for 4 weeks in Experiment 2, followed by a 47-day PC-3 prostate cancer cell xenograft on the designated diet. In Experiment 1, the Se− diet enhanced the initial tumor development on days 11–17, whereas the Se+ diet suppressed tumor growth on days 35–47 in adult nude mice. Tumors grown in Se− mice were loosely packed and showed increased necrosis and inflammation as compared to those in Se and Se+ mice. In Experiment 2, dietary selenium did not affect tumor development or histopathology throughout the time course. In both experiments, postmortem plasma selenium concentrations in Se and Se+ mice were comparable and were twofold greater than those in Se− mice. Taken together, dietary selenate at nutritional and supranutritional levels differentially inhibit tumor development in adult, but not young, nude mice engrafted with PC-3 prostate cancer cells.

Keywords: Selenium; Age; Supranutrition; Xenograft; Nude mice; Prostate cancer

1. Introduction

Suboptimal selenium intake is implicated in viral infections, male infertility, depressed immunity and higher risk of cancer incidence [1,2]. Animal and clinical studies have established selenium as a chemoprevention agent, the efficacy of which depends on the stage of carcinogenesis and selenium formulation and dosages. In particular, methylseleninic acid and selenomethionine inhibit *in vitro* growth of prostate cancer cells (DU145, PC-3 and LNCaP) [3–8] and suppress tumorigenesis of DU145 and PC-3 cells in nude mice or in the TRAMP mouse model of spontaneous prostate cancer [9,10]. Although epidemiological studies have indicated an inverse association between prostate cancer incidence and body selenium status [11,12], selenomethionine alone (200 μg/day) did not decrease risks of prostate cancer incidence in the Selenium and Vitamin E Cancer Prevention trial prematurely terminated due to increased cancer risk by vitamin E and the potential complications of diabetes [13]. Nonetheless, supplementation of selenized yeast, a commercial yeast product by fermentation in selenium-enriched broth (Cypress Systems Inc, Fresno, CA, USA), at a dose of 200 μg/day significantly decreased prostate cancer incidence in skin cancer patients in the randomized Nutrition Prevention of Cancer trial [14]. The selenium chemoprevention was most efficient in those who entered the trial with suboptimal plasma selenium status. Taking the two clinical trials into consideration, the fact that 65%–80% of total selenium in the selenized yeast is selenomethionine [14] implicates selenium compounds other than selenomethionine as the effective species for selenium chemoprevention.

The anticarcinogenic activity of selenium is determined by chemical forms and bioavailability of selenium compounds [15–20]. Although mixed results exist, methyl-selenium compounds and selenite are generally considered as potent species of selenium chemoprevention. However, less is known about the effect of selenate, selenium deficiency and age on tumorigenesis. Since T cell immunity is linked to tumorigenesis and nude mice develop an age-dependent extrathymic T cell maturation [21], we hypothesized that dietary selenate may differentially regulate selenium chemoprevention in old and young nude mice. In the experiments described in this report, we examined the effect of dietary selenium deficiency, selenate supplementation and age on

Abbreviations: Se−, selenium-deficient; Se, selenium-adequate; Se+, selenium-supranutritional.

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tumorigenesis in nude mice engrafted with PC-3 human prostate cancer cells.

2. Materials and methods

2.1. Animals and diets

To study a role for selenate on prostate tumorigenesis, 39 male, homozygous NU/J nude mice were received from the Jackson Laboratory (Bar Harbor, ME, USA [22]) at 4 weeks of age. They were randomly assigned into three dietary groups based on the AIN-93G Torula yeast purified rodent diet (Dyets Inc., Bethlehem, PA, USA). Torula is a yeast species containing low level of selenium by nature. The basal (Se−) diet contains 30% Torula yeast and <0.03 ppm selenium by analysis (AOAC Method 986.15; Covance Laboratory, Madison, WI, USA). The basal diet was supplemented with 0.15 mg selenium/kg (selenium-adequate, Se) or 1.0 mg selenium/kg (selenium-supranutritional, Se+) as sodium selenate [23]. The mice spent 6 months on diets in Experiment 1 and 4 weeks in Experiment 2, followed by a 47-day PC-3 prostate cancer cell xenograft. The long-term feeding in Experiment 1 was chosen in an attempt to (a) deplete body selenium pool in the Se− mice, (b) increase anticarcinogenic efficacy of the Se+ diet without the possible confounding effect of selenium toxicity and (c) determine whether selenium chemoprevention can be modulated by partial extrathymic T cell maturation, which usually peaks at 32 weeks of age in nude mice [21]. The concentration of Se+ diet employed in this study is lower than that in the short-term (8 weeks) dietary supplementation study (4 mg/kg) in nude mice by Lin et al. [24]. Mice were kept under aseptic conditions in individually ventilated cages within a controlled-temperature (22°C) animal room utilizing a 12-h dark:light cycle. The bedding was irradiated, and the mice had *ad libitum* access to food and sterilized water. Our experiments were approved by the Institutional Animal Care and Use Committee at the University of Maryland, College Park, and were conducted in accordance with the National Institutes of Health guidelines for the care and use of experimental animals.

2.2. Human cancer cell xenograft

The PC-3 human prostate cancer cell line (American Type Culture Collection, Manassas, VA) was grown and maintained as described previously [25]. Cells at passages 23 to 26 were subcultured at a ratio of 1:4 every 3 days. The nude mice were engrafted with PC-3 prostate cancer cells as described previously [9], except that we injected subcutaneously on each side of the shoulder blade (left and right dorsal thoracic regions). Length, width and height of the tumors were measured every other day using a plastic ruler, and the volume was estimated using the following formula: length×width×height×0.5236 (mm^3), according to Lee et al. [29].

2.3. Necropsy

On day 47, all the mice were anesthetized with CO_2 and killed by exsanguination via cardiac puncture. Tumors were excised, blotted dry, weighed, fresh frozen in liquid nitrogen and stored in −80°C until analyses. Sections of tumor samples were fixed in 4% paraformaldehyde for histology processing.

2.4. Plasma selenium analysis

Blood was centrifuged at 4°C (1400*g* for 10 min), and plasma was removed and stored in −80°C. Plasma selenium was analyzed by a graphite furnace atomic absorption spectrophotometry with Zeeman-effect background correction [26].

2.5. Histopathology

Fixed tumor samples were embedded in paraffin, sectioned to 5 μm thick by microtome and stained with hematoxylin and eosin. Histopathological diagnoses of cell density, inflammation and necrosis were evaluated by a board-certified veterinary pathologist, Dr. Jerrold M. Ward, at Histoserv Inc. (Germantown, MD, USA). The evaluation was graded using the following scores: 1, minimal; 2, mild; 3, moderate; 4, severe.

2.6. Statistical analyses

Statistical analyses of the data were performed by Student's *t* test or analysis of variance using GraphPad Prism 5.03 software or SAS Version 9.1. Analysis of variance contrast analysis was performed to compare one group against the other two groups. Tukey's multiple comparison test was used to compare the differences between groups. The significance level was set at $P<.05$ unless indicated otherwise.

3. Results

3.1. Effect of cancer cell xenograft and dietary selenium on body weight in nude mice

In Experiment 1, the mouse body weights were linearly decreased ($P<.05$) over the time course after PC-3 cancer cell xenograft in Se−, Se and Se+ adult mice, but they were not different between the dietary groups (Fig. 1A). In Experiment 2, mean body weights in young nude mice were linearly decreased throughout the time course in Se+ mice and were lower ($P<.05$) than those in Se− and Se mice during the time course (Fig. 2A).

3.2. Distinct impact of dietary selenium at nutritional and supranutritional levels on tumor growth in adult nude mice engrafted with PC-3 cancer cells

Overall, the xenograft had a 97% success rate as determined by the formation of at least one tumor per mouse over the time course. Interestingly, tumor volume increased in the first 2 weeks and reached a plateau on days 13–21 in Se−, Se and Se+ adult nude mice (Fig. 1B). Thereafter, tumor volumes remained largely steady in Se+ mice, while they increased significantly in Se− and Se mice. On days 41–45, mean tumor volumes were lower ($P<.05$) in Se+ than in Se− and Se mice. Consistently, the mean tumor weight was lower ($P<.05$) in Se+ mice than in Se− and Se mice (Fig. 1C). All the mice were sacrificed on day 47.

Analyses of the early tumor development demonstrated that tumor volumes were greater in Se− than in Se and Se+ adult nude mice on days 11–17, especially on day 11 ($P<.01$) (Fig. 1B boxout). Moreover, the number of tumors appeared to be greater in Se− than in Se and Se+ mice during the first 2 weeks after xenograft (Fig. 1D). Of note, one Se+ mouse developed two tumors of 70 and 40 mm^3, but they were regressed and completely disappeared by week 6. Taken together, supranutritional selenate greatly inhibits tumor growth at late stages, while selenium deficiency promotes tumorigenesis at early stages in adult nude mice engrafted with PC-3 cancerous cells.

3.3. Dietary selenium deficiency or selenate supplementation did not affect tumor growth in young nude mice engrafted with PC-3 cancer cells

In contrast, young nude mice on the Se−, Se and Se+ diets for 4 weeks prior to the xenograft exhibited comparable tumor volumes throughout the 47-day time course (Fig. 2B). Interestingly, tumor volumes in adult and young nude mice on day 46 were 120±36 vs. 270±69 mm^3 on Se− diet, 161±66 vs. 309±108 mm^3 on Se diet and 34±11 vs. 450±80 mm^3 on Se+ diet (Figs. 1B and 2B). The weight of the dissected tumors on day 47 (Fig. 2C) or tumor development in the first 3 weeks (Fig. 2D) was not significantly different between the dietary groups in young nude mice engrafted with PC-3 cancer cells.

3.4. Effect of dietary selenium status on plasma selenium concentrations in adult and young nude mice engrafted with PC-3 cancer cells

Next, we asked whether body selenium status was associated with tumorigenesis in the adult and young nude mice. Consistent with our previous results [27], plasma selenium concentration in postmortem mice was comparable between Se and Se+ adult (Fig. 3A) or young (Fig. 3B) nude mice. Compared to Se and Se+ diets, dietary selenium deficiency greatly reduced ($P<.01$) plasma selenium concentration in both adult and young nude mice. Plasma selenium level was greater ($P<.05$) in adult than in young nude mice (143±13 vs. 90±11 ng/ml) fed a Se− diet.

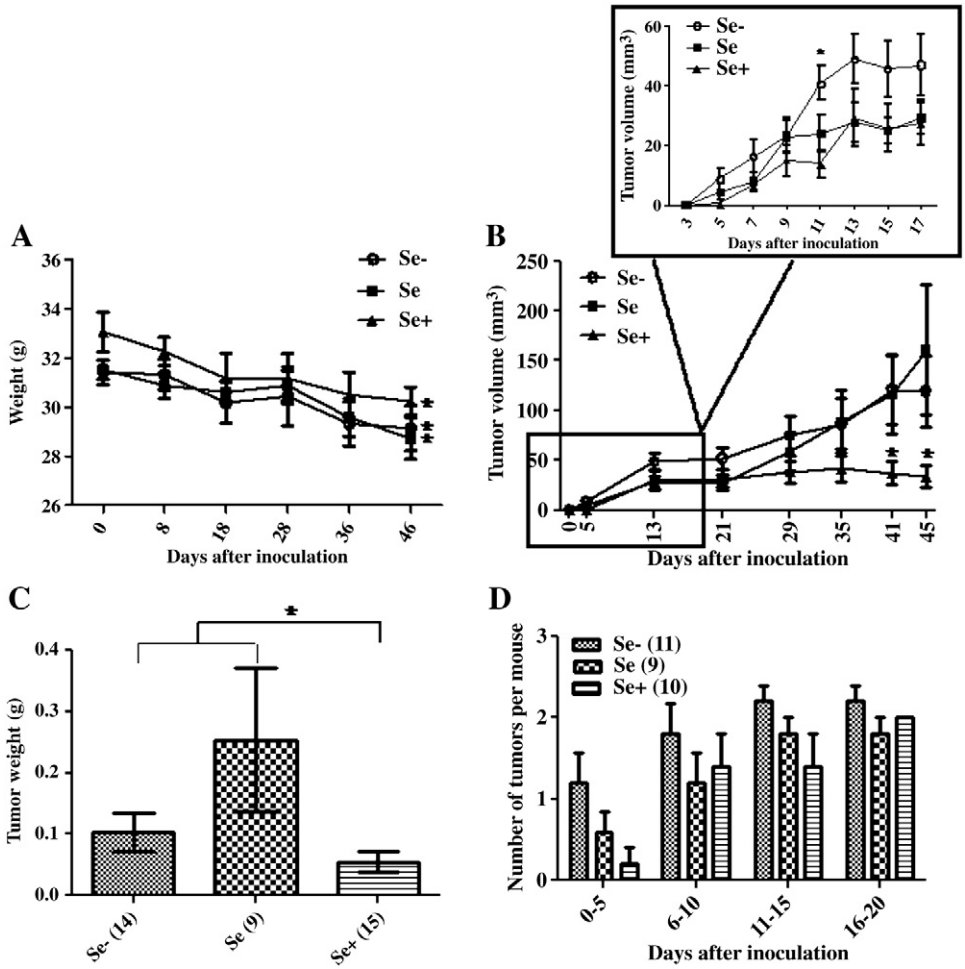

Fig. 1. Effect of dietary selenium status on tumorigenesis in male adult nude mice subcutaneously engrafted with PC-3 cells.(A) Body weight of adult nude mice fed a selenium-deficient (Se−) or the basal diet supplemented with selenium at 0.15 mg/kg (Se) or 1.0 mg/kg (Se+) during the 7-week time course. *A linear decrease (P<.05) from 0 to 46 days. Values are means±SE (n=5). (B) Time course of the mean tumor volume. Values are means±SE (n=5). *P<.01, Se+ vs. Se or Se− mice on days 41 and 45. In the boxout highlighting days 0–17: *P<.05, Se− vs. Se or Se+ mice. (C) Postmortem mean tumor weight. Values are means±SE. *P<.05. (D) Average tumor numbers per mouse during the first 3 weeks after the PC-3 cells xenograft. Values are means±SE (n=4–5). The total number of tumors is shown in the parentheses.

3.5. Distinct impact of dietary selenium status on tumor histopathology in adult and young nude mice engrafted with PC-3 cancer cells

We observed that tumors were softer in appearance in Se− mice, while they were more solid in Se+ adult mice (Fig. 4A). This was verified by histological examination of tumor sections (Supplemental Figures 1 and 2). Compared to Se and Se+ adult mice, tumors grown in Se− adult mice appeared to exhibit greater areas of loosely compacted cells and increased (P<.05) inflammation and necrosis (Figs. 4B and 4C). Blinded scoring (with 4 being the most severe) of the sections for inflammation, an event promoting tumor growth, gave mean values of 1.8, 1.0 and 1.0 for Se−, Se and Se+ mice, respectively. For necrosis, the scores were 1.2, 1.0 and 0.5, respectively. Tumors that developed in adult nude mice on the 8-month Se+ diet exhibited increased cell density and decreased inflammation and necrosis. In contrast, dietary selenium status did not significantly affect the histopathology, including inflammation and necrosis, of tumors that developed in young nude mice that were on the selenium diets for 3 months. Tumors that developed in Se− and Se young nude mice showed increased areas of hyalinized stroma, a feature of aberrant deposition of basement membrane material produced by tumor cells (Supplemental Figure 3). Taken together, dietary selenium differentially affects the histopathology of tumors that developed in adult and young nude mice.

4. Discussion

Although nude mice have been employed to assess the efficacy of selenium compounds on the development of tumor xenograft [24], little is known about the effect of age or selenate on selenium chemoprevention. Moreover, previous studies on selenium chemoprevention highlighted supranutritional selenium in organic forms [28,29]. Here, we provide evidence that the inorganic sodium selenate at a nutritional level can suppress tumor incidence in the first 2 weeks, whereas supranutritional selenate inhibits tumor growth in week 6 after PC-3 prostate cancer xenograft. Intriguingly, this pattern of selenium chemoprevention occurs in old but not young nude mice.

Why does selenate chemoprevention occur in adult but not young nude mice? Interestingly, the athymic nude mice intrinsically develop age-dependent extrathymic T cell maturation, which usually peaks at 32 weeks of age [21]. Given the time frame, it is possible that selenate or its metabolites are involved in modulating extrathymic T cell maturation after xenograft in adult but not young mice. In fact, dietary selenium is known to up-regulate CD25-expressed T cells, an indicator of T cell activation, in humans and mice [30-33]. In contrast, dietary selenium deficiency promotes tumorigenesis at the onset of tumor development (days 11–17), which is consistent with the observation that dietary selenium deficiency does not affect the weight of full-blown tumors [24].

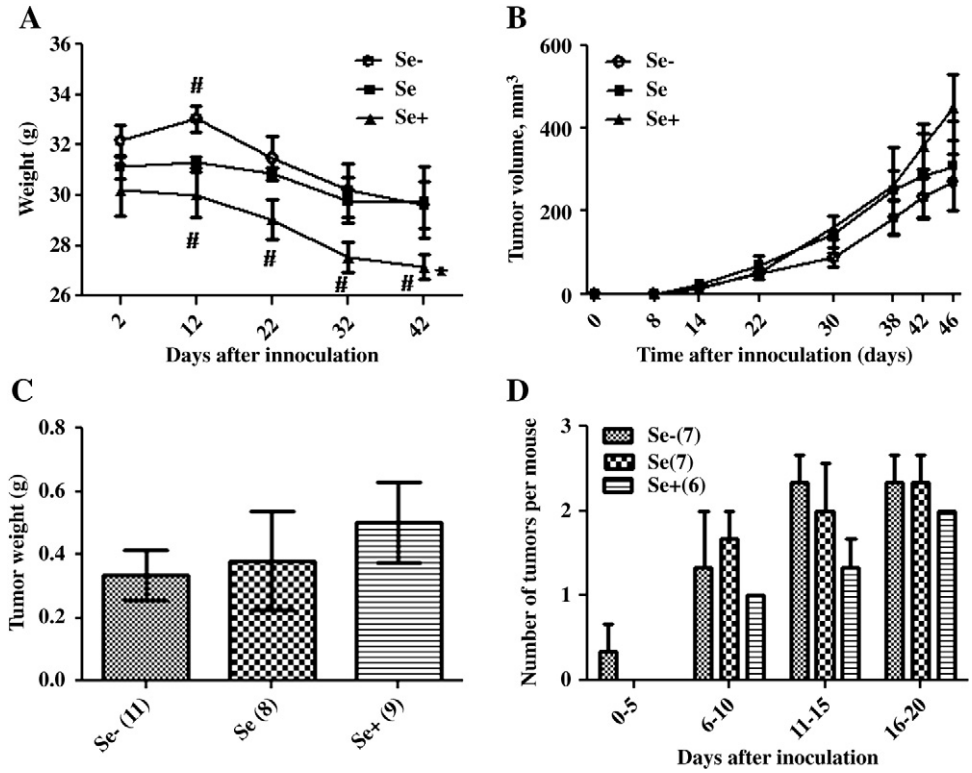

Fig. 2. Effect of dietary selenium status on tumorigenesis in male young nude mice subcutaneously engrafted with PC-3 cells. (A) Body weight of young nude mice fed a selenium-deficient (Se−) or the basal diet supplemented with selenium at 0.15 mg/kg (Se) or 1.0 mg/kg (Se+) during the 7-week time course. *A linear decrease ($P<.05$) from 0 to 42 days. #$P<.05$, compared to Se mice. Values are means±SE ($n=3$). (B) Time course of the mean tumor volume. Values are means±SE ($n=3$). (C) Postmortem mean tumor weight. Values are means±SE. (D) Average tumor numbers per mouse during the first 3 weeks after the PC-3 cells xenograft. Values are means±SE ($n=3$). The total number of tumors is shown in the parentheses.

Moreover, combined selenium and vitamin E deficiency has been shown to depress T cell-mediated cytotoxicity in rats after 7 weeks on the diet [34]. These results suggest that selenoproteins at the nutritional level may mediate T cell immunity and protect against tumorigenesis at an early stage. In a mouse model of selenoprotein deficiency specific in the immune system, T cell maturation was compromised due to defective T cell receptor stimulation and increased oxidative stress [35]. Alternatively, selenium bioavailability may differ in adult and young nude mice after xenograft. Sunde et al. [20] demonstrated a differential effect of methionine on selenomethionine and selenite bioavailability in adult and young rats. Future studies should profile the complete T cell population, T cell activation and the bioavailability of various selenium compounds during tumorigenesis under various dietary selenium levels.

Our results indicate that selenate supplementation was well tolerated. Because body weights did not drop in age-matched adult nude mice without xenograft (data not shown), the body weight reduction was attributed to the xenograft instead of aging or the Se+ diet. We would like to point out that the body weight decrease in the engrafted young nude mice was the greatest on the Se+ diet, which could be one of the reasons for the lack of selenium chemoprevention in the mice. As discussed above, young nude mice do not develop extrathymic T cell immunity, and selenium can stimulate T cell immunity [21,30-33]. Thus, it is also possible that a weakened immune response in young nude mice may veil the otherwise selenium chemoprevention through stimulation on T cell immunity. In addition, the immunodeficient young nude mice may be highly susceptible to the Se+ diet, resulting in the body weight decrease (~10%) and repressed tumor suppression by supranutritional selenium.

Consistent with our previous result [27], plasma selenium, a reliable indicator of body selenium status, reached a plateau at the

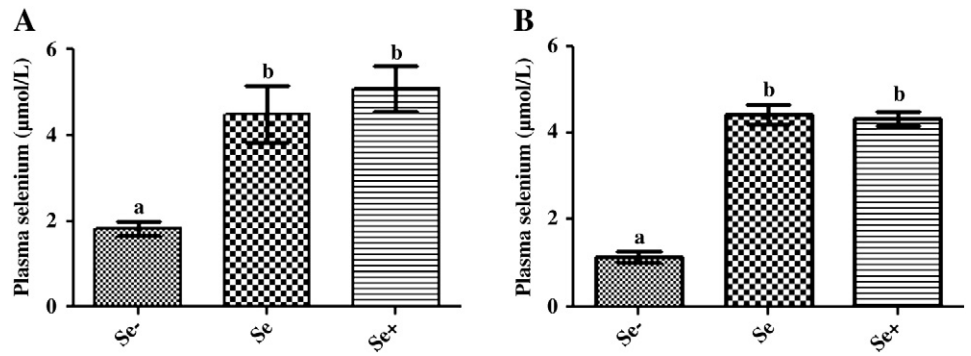

Fig. 3. Effect of dietary selenium on plasma selenium concentration in the postmortem adult (A) and young (B) nude mice after the xenograft. Bars not sharing a common letter are different ($P<.05$). Values are means±SE ($n=3$–5).

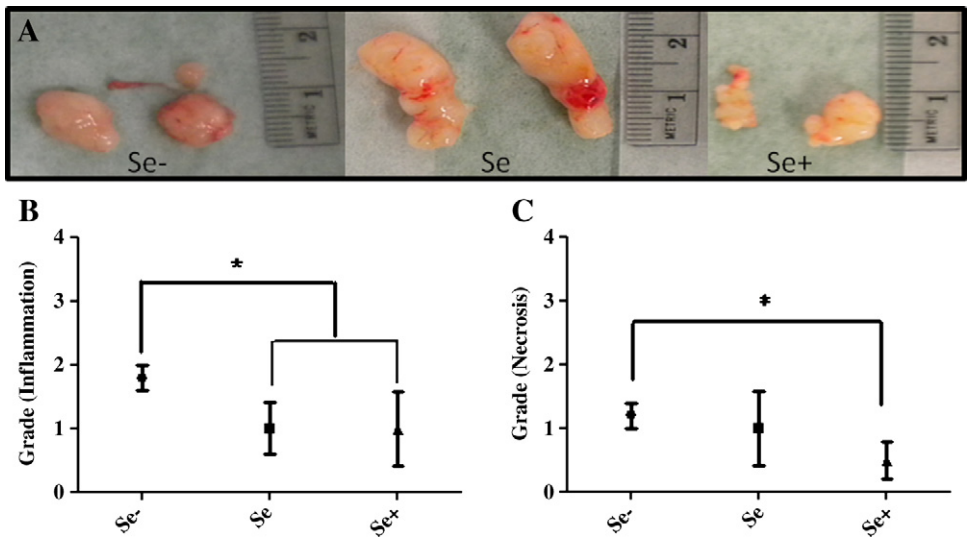

Fig. 4. Representative pictures of tumors from adult nude mice among the different dietary groups (Se−, Se and Se+) are shown in (A). Blinded scores of histological examination of tumor inflammation (B) and necrosis (C) in PC-3-cell-engrafted adult nude mice fed a Se−, Se or Se+ diet. Values are means±SE (n=4–5). *P=.05.

nutritional level of selenium in both young and adult nude mice. Thus, body selenium status does not seem to be directly correlated with the suppression of tumor growth offered by supranutritional selenate. Rather, selenium metabolites generated by supranutritional selenium are known to confer selenium chemoprevention [36]. Interestingly, tumors in nude mice fed Se+ diet are solid and pale in appearance (Fig. 4A), which is accompanied with reduced necrosis inside the tumors as evidenced by histopathology analysis (Supplemental Figure 2). Based on these observations, it is conceivable that selenium at the supranutritional levels may inhibit prostate tumorigenesis through the suppression of angiogenesis. In agreement with this hypothesis, selenium compounds, in combination with other chemopreventive agents, have been shown to suppress angiogenesis in mouse models of cancer [36–38]. Since blood vessels are present mainly in the outer surface of a tumor, increased angiogenesis would deplete nutrient supplies to cells inside the tumors, resulting in increased cell death in the softer Se− tumors.

To our knowledge, the long-term effect of dietary selenium on chemoprevention has not been studied. Selenate was chosen due to its low toxicity and enhanced absorption rate in the small intestine [39]. The duration on the selenium diet may explain the inconsistent results on selenium chemoprevention in the literature. As shown by Finley and Davis [23], chemical-induced precancerous colon lesions are attenuated in weanling rats fed with selenium-enriched broccoli for 11 weeks. In contrast, Lin et al. showed no effect of dietary selenite deficiency or excess (4 mg selenium/kg) on tumor development when weanling nude mice were fed with the diets for 4 weeks prior to entering a mammary tumor xenograft experiment [24]. All in all, our results provide the first evidence of selenate being an antitumorigenic agent suitable for long-term intake at supranutritional level (1 mg/kg).

Supplementary data to this article can be found online at doi:10.1016/j.jnutbio.2011.06.001.

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