Short Communication

Increased Rates of Chromosome Breakage in BRCA1 Carriers Are Normalized by Oral Selenium Supplementation

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Abstract

Women who are born with constitutional heterozygous mutations of the *BRCA1* gene face greatly increased risks of breast and ovarian cancer. The product of the *BRCA1* gene is involved in the repair of double-stranded DNA breaks and it is believed that increased susceptibility to DNA breakage contributes to the cancer phenotype. It is hoped therefore that preventive strategies designed to reduce chromosome damage will also reduce the rate of cancer in these women. To test for increased mutagenicity of cells from *BRCA1* carriers, the frequency of chromosome breaks was measured in cultured blood lymphocytes following *in vitro* exposure to bleomycin in female *BRCA1* carriers and was compared with noncarrier relatives. The frequency of chromosome breaks was also measured in *BRCA1* carriers following oral selenium supplementation. Carriers of *BRCA1* mutations showed significantly greater mean frequencies of induced chromosome breaks per cell than did healthy noncarrier relatives (0.58 versus 0.39; $P < 10^{-4}$). The frequency of chromosome breaks was greatly reduced following 1 to 3 months of oral selenium supplementation (mean, 0.63 breaks per cell versus 0.40; $P < 10^{-10}$). The mean level of chromosome breaks in carriers following supplementation was similar to that of the noncarrier controls (0.40 versus 0.39). Oral selenium is a good candidate for chemoprevention in women who carry a mutation in the *BRCA1* gene. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1302–6)

Introduction

Women who carry a mutation of the *BRCA1* gene face a lifetime risk of breast cancer of ~80% and a lifetime risk of ovarian cancer of ~40% (1). Men who carry a BRCA1 mutation seem at elevated risk for breast and prostate cancer (2). The *BRCA1* gene product is involved in the maintenance of the integrity of the human genome and functions in conjunction with BRCA2 and RAD51 to repair double-stranded DNA breaks through the mechanism of homologous recombination (3). Deficiencies in the ability to repair double-stranded DNA breaks lead to an increase in the formation of gross chromosome rearrangements. Structural chromosomal aberrations seem in excess both in BRCA1-deficient mouse cells (4) and in BRCA1-deficient cancer cells (5). BRCA1 serves multiple functions, including DNA damage response (3), nucleotide excision repair (6), and protection against oxidative stress (7). It is not yet clear to what extent each of these contributes to the cancer susceptibility phenotype of *BRCA1* heterozygotes. Nevertheless, it is believed that the chromosomal instability of BRCA1-deficient cells contributes to their tendency to undergo neoplastic transformation (3). Strategies to reduce the frequency of chromosome breaks, therefore, may result in a reduction in the cancer risk. Selenium has several anticancer properties, including protection against oxidative damage and enhancing nucleotide excision repair (8).

One of the most commonly used cytogenetic tests for the assessment of chromosome instability is the *in vitro* bleomycin assay (9). This is a simple and reproducible assay that measures induced chromosome breaks. Patient lymphocytes are cultured in the presence of bleomycin, a known mutagenic agent that typically induces double-strand breaks (similar to those induced by ionizing radiation). The mean number of chromosomal breaks per cell is then measured after bleomycin exposure. The assay has been used to study susceptibility to various types of cancer (9, 10). Using this technique, we explored the possibility that oral selenium supplementation may reduce the formation of induced chromosome breaks in female *BRCA1* carriers.

Materials and Methods

Study Subjects. Female study subjects were recruited from among the attendees of a single familial cancer clinic of the Hereditary Cancer Centre of the Pomeranian Academy of Medicine in Szczecin, Poland. Women were referred to this clinic because of a family history of breast or ovarian cancer. The women who participated in this study had previously been offered and had consented to genetic testing. There were two phases to this study involving two groups of women. The first group of women was recruited for the purpose of comparing the frequencies of chromosome breaks in *BRCA1* carriers and noncarriers. Case women were recruited from among those who had been found to be carriers of a deleterious mutation in the *BRCA1* gene. Control subjects were recruited from among the family members of the carriers (cases) but who had been determined not to carry the deleterious mutation. It was possible to generate 26 case-control pairs. In 20 instances, the control relative was the sister of the case and in six instances, she was a more distant relative. Only healthy women were invited to participate in this study; women with a past history of breast, ovary, or other

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forms of cancer were excluded. Each woman provided a blood sample at some time between February 2001 and January 2002.

A second group of *BRCA1* carriers was recruited from this clinic for the purpose of studying the effect of selenium supplementation on frequencies of chromosome breaks. Thirty-five women with *BRCA1* mutations agreed to participate in this phase of the study. Blood samples were taken before the onset of selenium supplementation, and again at a time from 1 to 3 months following the start of daily selenium supplementation. Because the two studies were conducted at different times and because of the availability of suitable controls, and because of willingness to participate, there was little overlap in the study subjects between the two groups of carrier subjects. Only six carrier women participated in both phases of the study.

Bleomycin Assay. Chromosome sensitivity to bleomycin was measured according to the method of Hsu et al. (9) Bleomycin (Nippon-Kayuka, Tokyo, Japan) was added to the cell culture 5 hours before the end of the culture at a concentration of 0.03 IU/mL. Conventional harvesting and Giemsa staining were made. For each subject, 100 consecutive euploid cells in metaphase were read (cells with overlapping chromosomes were excluded). Each chromatid aberration (excluding gaps) was scored as one breakpoint and each exchange-type aberration was scored as two breakpoints. The total number of breakpoints per 100 cells was recorded for each subject. Reading of coded slides was done blindly by one of us (E.K.) For 20 randomly selected cases, the counts were determined independently by two cytogenetic technicians with good agreement.

Selenium Supplementation. An oral selenium solution was provided to the study subjects which contained 690 μg of pure selenium, in the form of sodium selenite (Na_2SeO_3) per mL of 70% ethanol. Subjects were requested to consume 0.2 mL of the solution twice daily. Among the *BRCA1* carriers ($n = 32$), this level of supplementation resulted in an increase in the mean serum selenium from 56.7 ± 12.7 to 90.2 ± 17.6 ng/mL ($P < 0.001$). Selenium levels were not measured in the noncarrier controls.

Statistical Analysis. The mean number of breaks per cell was calculated after inspection of 100 cells. The paired *t* test was used to compare the pre- and post-supplementation selenium levels and numbers of chromosome breaks. The nonparametric sign test was also used to the mean number of chromosome breaks in cases and controls. The frequency of chromosome breaks was also tested for possible correlation with patient age using the Pearson correlation coefficient. To ensure that there was no significant variation in the frequencies of chromosome breaks associated with the date of testing, a comparison of chromosome breaks was made among carriers with date of testing.

Results

In the first phase of the study, we compared the frequency of chromosome breaks in a panel of 26 unaffected *BRCA1* carriers with a matched group of healthy controls. The most common mutation was the Polish founder mutation 5382 insC (16 carriers), but there were 10 women with other *BRCA1* mutations. For each carrier, a single healthy noncarrier relative was available; these control women had been tested for and found not to carry the deleterious mutation identified in the family. Twenty of the controls were sisters of the cases and six were more distant relatives. The mean age of the carriers was 35.3 years (range, 18-58 years) and the mean age of the noncarrier controls was 35.7 years (range, 20-61 years).

The mean number of chromosome breaks per cell was 0.58 for the carriers (range, 0.34-0.73) and was 0.39 for the controls (range, 0.28-0.62; Table 1; $P < 0.0001$ for difference). For 23 pairs, the value for the carrier exceeded that for the related control; for two pairs, the control value was the higher of the two; and for one pair, the two values were equal ($P < 0.0001$; sign test). The distribution of chromosome breaks among *BRCA1* carriers and noncarriers is presented in Fig. 1.

In the second phase of the study, *BRCA1* mutation carriers were offered selenium supplementation. Thirty-five carrier women volunteered for this phase of the study (selenium supplementation was not offered to noncarriers). A second blood sample was taken at a time from 1 to 3 months after commencement of selenium and the bleomycin test was repeated. After a mean of 1.5 months of selenium supplementation, the mean serum levels of selenium rose from 56.7 to 90.2 ng/mL ($P < 0.001$). For 94% of the women, the second selenium level exceed the first, indicating a high level of compliance with the intervention. Before selenium supplementation, the mean number of induced chromosome breaks per cell was 0.63 (range, 0.42-0.81) and after selenium supplementation the mean number of chromosome breaks per cell was reduced from 0.63 to 0.40 (range, 0.27-0.60). In every case, the post-supplementation level of chromosome breaks showed a decline from the baseline level (Table 2) and the mean difference was highly significant ($P < 0.001$).

Discussion

In the first phase of this two-part study, we observed that the lymphocytes from heterozygous carriers of deleterious mutations of the *BRCA1* gene show an elevated frequency of chromosome breaks after exposure to bleomycin *in vitro* compared with noncarriers. In the second part of the study, we have shown that in most cases, these elevated levels can be reduced to normal with oral selenium supplementation.

Table 1. Comparison of chromosome breaks (per cell) in BRCA1 carriers and matched controls

Case ID	Case (carrier)		Control (noncarrier)	
	Age	Chromosome breaks per cell	Age	Chromosome breaks per cell
1	22	0.58	22	0.41
2	43	0.61	54	0.55
3	29	0.34	33	0.44
4	39	0.51	36	0.62
5	21	0.48	31	0.31
6	24	0.57	20	0.49
7	45	0.60	51	0.40
8	47	0.52	55	0.52
9	51	0.61	29	0.44
10	24	0.66	22	0.42
11	48	0.57	28	0.35
12	24	0.65	29	0.28
13	23	0.65	22	0.42
14	31	0.73	29	0.46
15	31	0.52	34	0.32
16	23	0.52	38	0.36
17	44	0.59	35	0.36
18	59	0.48	58	0.30
19	53	0.54	61	0.29
20	58	0.59	50	0.34
21	44	0.51	46	0.38
22	22	0.67	27	0.45
23	34	0.60	30	0.28
24	34	0.71	36	0.41
25	18	0.59	21	0.28
26	27	0.64	31	0.35
Mean	35.3	0.58	35.7	0.39

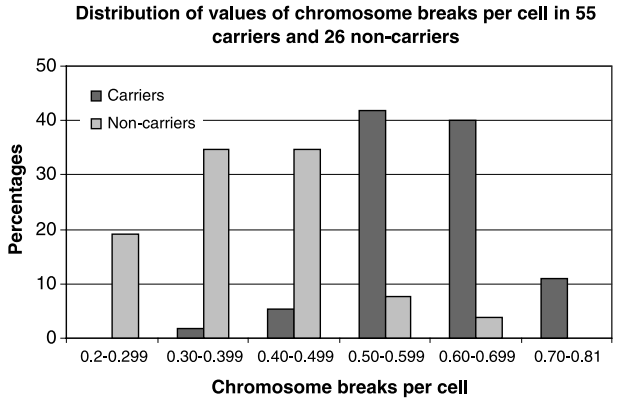

Figure 1. Distribution of chromosome breaks in carriers of BRCA1 mutations and in noncarriers. All 56 carriers are included. The values for carriers are those measured before selenium supplementation.

Although our sample size was small, our results were highly significant; in every case, selenium supplementation resulted in a reduced frequency of chromosome breaks.

It is likely that the observed difference between carriers and noncarriers is due to the functional consequences of the *BRCA1* mutation; however, alternate explanations must be considered. The cases and controls were matched within families and neither were affected with cancer. The mean (absolute) age difference between the case and her matched control was about 6 years, but the mean ages of the groups differed by <1 year. This difference is relatively small and in our study group there was no significant correlation between the age at testing and the observed number of chromosome breaks; the number of chromosome breaks declined slightly with age ($r = -0.16$; $P = 0.35$). Previously, Gu et al. showed that neither age, sex, nor smoking status were significantly correlated with the frequency of bleomycin-induced breaks in 56 healthy individuals (11). Nor could the difference in the pre- and post-supplementation chromosome breaks levels could be accounted for by variation in the assay with the date of testing. The samples for cytogenetic analyses were processed in batches, and each batch contained a mix of pre- and post-supplemented samples. In addition, no trend was observed between the observed frequencies of breaks and date of testing. The median date of testing of the pre-supplementation patients occurred in September 2001 and the median date of testing of the post-supplementation testing occurred in October 2001. The mean number of breaks among the first 18 women tested (pre-supplementation) was 0.60 per cell and among the last 17 women tested was 0.66 breaks per cell. Similarly, after supplementation, the levels for the women in these groups was 0.36 and 0.43, respectively. This argues against the possibility that the assay detected fewer breaks with time.

There were two phases to this study. Ideally, we would have used the same cases and controls in the two phases. However, this was impractical because the first phase was completed before the development of the protocol for the second phase and only six carriers were enrolled in both phases. We did not offer selenium supplementation to controls because we did not feel the intervention was justified in women who were not at increased risk of cancer and who showed normal levels of chromosome breakage.

In this pilot study, we did not measure the relationship between chromosome breaks and breast cancer risk and this will be the subject of a future investigation. In a previous small study (12), the mean number of chromosome breaks per cell was higher in 11 patients with familial breast cancer (0.63) than in 22 healthy controls (0.28; $P < 0.001$). Unaffected relatives of the cases had an intermediate value (0.37 breaks per cell). These authors propose that familial breast cancer clustering may be due in part to chromosome instability, but BRCA testing was not done. There is little evidence to date to suggest a relationship between indices of genomic instability and the risk of sporadic (nonfamilial) breast cancer cases. In an early study, Hsu et al. found no difference in the frequency of bleomycin-induced chromosome breaks between unselected beast cancer patients and healthy controls (9). However, Scott et al. (13) observed that 21 of 50 unselected breast cancer patients exhibited structural chromosome damage in irradiated lymphocytes compared with 7 of 74 healthy controls ($P < 10^{-4}$). In a small study, Barrios et al. (14) found the frequency of chromosomal aberrations per cell to be higher in lymphocytes taken from breast cancer patients than from healthy controls. It has been proposed that direct mutagenic effects of estrogen may contribute to breast cancer incidence, but this hypothesis has not been proven (15).

Several other studies have reported a correlation between the level of chromosome breaks and cancer susceptibility. In a cohort study of 3,182 workers exposed to mutagens, the frequency of chromosomal aberrations at baseline predicted subsequent cancer risk (16). Several case-control studies have been conducted in populations where exposure to mutagenic carcinogens is common (e.g., lung cancer and head and neck cancer; refs. 17-22); however, an important etiologic role for mutagens in breast cancer has not yet been clearly defined.

The value of selenium as a chemopreventive agent is based upon the assumption that bleomycin-induced breaks in cell culture are representative of the type of chromosome

Table 2. Comparison of chromosome breaks (per cell) in BRCA1 carriers before and after selenium supplementation

Case ID	Before selenium supplementation	After selenium supplementation
12	0.65	0.60
15	0.52	0.40
18	0.48	0.36
24	0.71	0.49
25	0.59	0.30
26	0.64	0.39
27	0.63	0.29
28	0.66	0.44
29	0.66	0.32
30	0.42	0.33
31	0.55	0.32
32	0.65	0.38
33	0.67	0.37
34	0.65	0.30
35	0.55	0.32
36	0.60	0.32
37	0.74	0.43
38	0.55	0.43
39	0.61	0.27
40	0.57	0.36
41	0.59	0.27
42	0.65	0.44
43	0.62	0.34
44	0.67	0.52
45	0.67	0.50
46	0.63	0.58
47	0.77	0.42
48	0.57	0.32
49	0.62	0.31
50	0.58	0.46
51	0.70	0.52
52	0.59	0.34
53	0.71	0.47
54	0.81	0.51
55	0.65	0.45
Mean	0.63	0.40

damage that occurs *in vivo*, and that genetic instability in *BRCA1* carriers is related to carcinogenesis. One of the functions of BRCA1 is to repair double-stranded DNA breaks through homologous recombination, but it is not clear if this is the critical function which, when impaired, leads to carcinogenesis. It has also recently been shown that BRCA1 up-regulates multiple genes involved in the antioxidant response and thereby helps protect cells against oxidative stress (7). Selenium is known to protect against oxidative damage, induces apoptosis, and has also been found to assist in nucleotide excision repair (8). It may be that *BRCA1* carriers are particularly sensitive to oxidative stress and that this sensitivity may be mitigated by dietary selenium.

Many studies have evaluated the potential chemopreventive properties of selenium compounds. In a randomized trial designed to evaluate skin cancer prevention, patients who received selenium supplementation experienced declines in the rates of cancer of the prostate, colon, and lung (23). In an update of this prospective study, Duffield-Lillico et al. (24) observed a decrease in the overall cancer rate (relative risk, 0.75; 95% confidence interval, 0.58-0.97) but not in the incidence of breast cancer (relative risk, 1.82; 95% confidence interval, 0.62-6.01). In general, no consistent relationship has been seen between either dietary intake or tissue levels of selenium intake and breast cancer risk in case-control and cohort studies. For example, in the large Nurses' Health Study, there was no correlation between toenail selenium levels and subsequent risk of breast cancer (25). However, this may not necessarily be the case for breast cancers in *BRCA1* carriers. It is likely that the risk factors for breast cancer in *BRCA1* carriers are different than for sporadic cancer and that DNA stability and repair is more important for hereditary breast cancer than for cancer in noncarriers. It is of interest that the other genes involved in hereditary susceptibility to breast cancer, such as *BRCA2*, *CHEK2*, *p53*, *NBS1*, *ATM*, and *Rad51* also participate in the DNA damage response pathway (refs. 3, 26-30) and selenium may be a candidate preventive agent in these syndromes as well.

We chose to give selenium as selenium selenite (inorganic selenium). This preparation is easily dissolved, has high bioavailability, and was effective in preventing chemically induced breast cancer in mice (31). Our daily dose of supplemental selenium was 276 μg. This is slightly lower than the recommended upper dose of 400 μg recommended by the WHO in 1996 and is approximately one third of the daily mean marginal level of safe selenium intake (32). Our study was conducted in Poland, where mean serum selenium levels are lower than in other countries in Europe, the United States, and Australia. The mean level before supplementation in our study subjects was 56 ng/mL, which is lower than the level deemed to meet nutritional requirements. Selenium levels in soil and forage crops differ significantly from country to country and it may be that the results of this experiment would be less dramatic in a country where mean selenium levels are higher.

Liu et al. observed that dietary selenium (as sodium selenite) profoundly inhibited rates of mammary carcinogenesis in 7,12-dimethylbenz(a)anthracene–treated mice (31). This mouse model may not adequately represent the majority of human sporadic breast cancers (where the role of mutagenic carcinogens is uncertain) but may be relevant for hereditary syndromes in which the breast cancers show genomic instability. Foray et al. (33) reported a diminished capacity of immortalized lymphocytes from *BRCA1* carriers to repair double-stranded DNA breaks and an increase in the number of micronuclei. These observations were not confirmed by Nieuwenhuis et al. (34) who found that fibroblasts from *BRCA1* carriers did not show a greater frequency of unrepaired double-stranded DNA breaks following exposure to radiation than fibroblasts derived from noncarrier controls. The mechanism by which selenium reduces the frequency of chromosome breaks in *BRCA1* carriers is unclear, but it is likely that selenium reduces the frequency of double-stranded breaks, as opposed to correcting the capacity of the cells to repair broken strands of DNA. We did not offer selenium supplementation to healthy controls; future studies of this type may help to resolve this question.

In general, tumor cells from women with *BRCA1* mutations will have lost both functional copies of the *BRCA1* gene; however, the present study indicates that there may be a subclinical phenotype at the cellular level associated with the loss of a single copy of BRCA1. We did not confirm that that the cells with chromosome breaks in our study have an intact *BRCA1* allele; however, because of the high frequency of involved cells observed in both cases and in controls, this is likely to be the case. This data suggests that there may be a mutator phenotype associated with loss of a single copy of BRCA1.

Our study was small and was limited to women with *BRCA1* mutations. It is important that these results be replicated before selenium is offered to high-risk patients. Ultimately, it is hoped to show a reduction in breast cancer incidence in *BRCA1* carriers associated with selenium supplementation.

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