Serum Iodine and Breast Cancer Risk: A Prospective Nested Case–Control Study Stratified for Selenium Levels

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ABSTRACT

Background: Iodine has been suggested to protect against breast cancer, but there are no epidemiologic studies on individual risk. An interesting finding is that in areas where the exposure to both selenium and iodine are high (e.g., Japan), the risk of breast cancer is lower than in areas where selenium is high and iodine low (e.g., United States), or in areas where both are low (e.g., Northern Europe). The aim of this study was to investigate the association between prediagnostic serum iodine levels and subsequent breast cancer risk, and to investigate if this potential association was modified by selenium levels.

Methods: The Malmö Diet and Cancer Study provided prediagnostic serum samples and the current analysis included 1,159 breast cancer cases and 1,136 controls. Levels of baseline serum iodine and selenium were analyzed. A logistic regression analysis yielded ORs with 95% confidence intervals adjusted for potential confounders.

Results: There was no evidence of an overall association between iodine levels and risk of breast cancer. Among women with high selenium levels (above the median), high iodine levels were associated with a lower risk of breast cancer; the OR for above versus below the median was 0.75 (0.57–0.99). The corresponding OR for women with low selenium was 1.15 (0.87–1.50), and the $P_{interaction}$ was 0.06.

Conclusions: The combination of high serum iodine levels and high selenium levels was associated with a lower risk of breast cancer.

Impact: A high iodine and selenium exposure may decrease the risk of breast cancer.

Introduction

Iodine has been suggested to protect against breast cancer, but there are no epidemiologic studies on individual risk. High iodine intake has been proposed to lead to a low risk of breast cancer in Japanese women (1–3), and an early correlation study indicated that a high iodine intake is protective (4). A study from Spain found an inverse association between iodine intake in different geographical areas and breast cancer mortality (5), but there have been no studies on iodine levels in individual women and breast cancer risk. Interestingly, a recent meta-analysis reported that women treated with radioactive iodine (RAI) for thyroid cancer had a relative risk of breast cancer of 0.61, as compared with patients with thyroid cancer not treated with RAI (6).

There is strong biological evidence of a potential protective effect from iodine regarding breast cancer. Iodine receptors, such as the sodium/iodide symporter (NIS), Pendrin, and the sodium/moncarboxylate transporter (SMCT), are present in breast tissue, which enables uptake of iodine (7). Iodine is necessary for normal breast development and iodine deficiency in rats causes breast atypia and dysplasia, which are reversible with iodine supplementation (8, 9). Iodine has also been proposed to act as an antioxidant to have antiproliferative effects and to stimulate apoptosis in breast tissue (3, 10, 11).

Iodine metabolism is closely related to selenium, for example, in the regulation of thyroid hormones, and selenium had also been implicated as a protective factor for breast cancer (9). Two early reviews (including 17 studies) reported no association between selenium and breast cancer risk (9, 12), and later, this was confirmed by a Cochrane analysis (13). Following this, we performed a study including more than 1,000 cases, confirming the findings in previous reviews (14). An interesting finding is that breast cancer mortality in the United States (on average low iodine and high selenium levels) and Europe (low iodine and low selenium) is about 4–5 times higher than in Japan where both selenium and iodine are high (2, 9, 15).

The aim of this study was to investigate the association between prediagnostic serum iodine levels and subsequent breast cancer risk, and to investigate if this potential association is modified by selenium levels.

Materials and Methods

The Malmö Diet and Cancer Study

The Malmö Diet and Cancer Study (MDCS) invited all men and women who were born between 1923 and 1950 and lived in Malmö, Sweden. Between 1991 and 1996, a total of 17,035 women were recruited, corresponding to a participation rate of 41%. The baseline examination included a questionnaire on sociodemographic data, lifestyle, reproductive factors, and medications. Everyone was measured concerning height and weight. Blood samples were drawn at baseline and they have been stored at −80°C (16). The questionnaire assessed most risk factors for breast cancer and menopausal status was constructed using information on menstrual bleedings and previous gynecologic surgery (14). A dietary assessment was performed through a modified dietary history method, using a 168-item dietary questionnaire, a 7-day menu book, and a 1-hour diet history interview (17).

This study was approved by the regional ethical committee (Dnr 2015/283), and all participants signed a written informed consent at

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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baseline to allow collection of information and samples, as well as future follow-up (original ethical approval: LU 51–90).

Matching of cases and controls

Breast cancer cases, both invasive and cancer *in situ*, were identified by record linkage with The Swedish Cancer Registry up until the end of follow-up (December 31, 2013). There were 576 women who had been diagnosed with breast cancer prior to baseline examination and they were excluded from this analysis. The 1,186 women who had been diagnosed with breast cancer after baseline examination were considered as incident cases and they were included in this study. Cancer cases were described with regard to invasive/*in situ* status and the expression of hormone receptors. Estrogen receptor (ER) expression for cases in this cohort was assessed using IHC and this has been described in detail previously (18). For cases diagnosed up until 2004, this information was obtained by reanalyzing original tumor samples. Henceforth, this information was available from clinical notes and routine pathology reports. The cutoff for negative/positive status was 10%.

The selection of controls was based on two demands: to use a previous case–control dataset with additional important information, and the need to add new cases and controls, with the possibility to add information on genetic factors. Selection of the first set of controls in the MDCS was based on a previous study examining the association between breast cancer and vitamin D. That study included cases diagnosed up to December 31, 2005 ($n = 764$) and an equal number of controls identified using incidence density matching using age, menopausal status, and time of baseline examination as matching factors (19). Using incidence density matching, some individuals were used more than once, as control/case or as control/control. The selection resulted in 704 unique control individuals out of whom 694 remained free of breast cancer up until December 31, 2013. The second set of controls was selected from the MDCS cardiovascular cohort to get the same number of controls as the 1,186 cases. This subcohort includes 3,531 randomly selected women from the total MDCS cohort examined 1991–94. Of these, 2,615 were complete participants in MDCS without breast cancer up until December 31, 2013, and without being used previously as controls. In this group, 492 were randomly selected to get a total of 1,186 controls. The reason to select controls from the MDCS cardiovascular cohort was that they were planned to be genotyped.

Laboratory analyses

Serum analyses were performed by ALS Scandinavia AB, Luleå, Sweden, on samples collected at baseline, which had been stored at −80°C. Serum samples were analyzed by using single element standards, traceable to NIST, on ICP-SFMS (Thermo Element 2). An amount of 0.15 mL serum was diluted to 10 mL with an alkalic solution containing 0.1% NH3 and 0.005% EDTA/Triton-X. Reference material, Seronorm, was obtained from Sero AS (Lot 0608414) and two reference samples were added in each batch. CV for interbatch variation was 0.04 for iodine and 0.03 for selenium. Samples were analyzed in the order they had been collected, not related to case–control status. Following the initial analysis, 77 samples showed very high or extreme iodine levels, that is, above 1,000 μg/L. Following reanalysis of 14 samples confirming these levels, it was concluded that these high values were most likely caused by contamination when blood samples were drawn. It was, hence, decided to exclude these 77 individuals (27 cases and 50 controls) from further analysis. This is described in detail in Supplementary Methods and Materials. Some individuals (130 cases and 132 controls) had insufficient amount of biological material or the analysis failed.

Statistical analysis

Out of all 2,372 individuals (1,186 cases and 1,186 controls), 77 had extreme iodine values (see above) and they were excluded. Individuals with missing information on iodine levels were, however, kept and reported as a separate category. Hence, the final study population consisted of 1,159 cases and 1,136 controls.

The cohort was divided into quartiles based on serum iodine levels, for both cases and controls together, and with specific cutoffs for separate single baseline years (see Supplementary Methods and Materials). Selenium was handled in the same way using year-specific cutoffs to dichotomize the cohort into high (above the median) or low (below the median) selenium levels. Iodine quartiles were compared regarding established and potential risk factors for breast cancer, and for factors that may influence serum iodine/selenium levels. Potential differences were tested using a χ^2 test (excluding missing categories). An unconditional logistic regression analysis was used to obtain ORs with 95% confidence intervals (CI) for different quartiles, as compared with the first. Linear trends over quartiles was assessed, using the median value for each quartile in the model. A second model included established and potential risk factors for breast cancer, and factors that may influence serum iodine/selenium levels, that is, age at baseline, socioeconomic status, education, marital status, number of children, age at first childbirth, age at menarche, oral contraceptives, menopausal status, oophorectomy, hormone replacement therapy, smoking status, body mass index (BMI), alcohol consumption, and the month samples were collected. All factors were entered as categorical variables. Time between baseline examination and analysis, that is, storage time, was already accounted for by using year-specific cutoff levels. Missing values for covariates were handled as a separate category. Missing was a minor problem concerning included covariables, most factors having less than 2% of individuals with missing information. ORs were reported for the group with no information on iodine levels in order to examine if there was a systematic pattern concerning missing.

The analyses were also performed stratified for high/low selenium levels. Following quartile analyses, a threshold effect was suggested, and analyses were also performed using iodine as a dichotomized factor. An interaction term for iodine quartile (high/low category) and selenium category was included in the logistic regression model and tested using the Wald statistic.

Finally, we performed several sensitivity analyses concerning the main findings, that is, iodine levels analyzed as a dichotomized factor and stratified for selenium levels. The first analysis excluded all cases that got breast cancer within two years from baseline examination. The second analysis excluded *in situ* cases ($n = 98$), and a third analysis was stratified for ER status. A fourth analysis included potential confounders related to diet that has been suggested as potential risk factors for breast cancer, that is, vitamin D, beta-carotene, and calcium (20). Dietary factors were classified into quintiles and the model was also adjusted for total energy intake. A set of subgroup analyses were explorative and not based on an *a priori* hypothesis. Hence, a fifth analysis was made separately for pre-/perimenopausal and postmenopausal women. A sixth model was stratified for age at diagnosis and we used 55 years of age at a cutoff as we previously had used this cutoff to define postmenopausal status where other information was missing (19). Older women were divided into 55–65 and above 65 years of age, given that median age at diagnosis was 65.9 years. Samples were taken before diagnosis and a final sensitivity analysis dichotomized

cases according to the time between baseline and time of diagnosis, using the median. All *P* values were two-sided and a *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS v24.0.

Results

Iodine serum levels were slightly higher in older women. Other factors statistically significantly associated with iodine levels were menopausal status, use of hormone replacement therapy (HRT), and alcohol consumption (**Table 1**).

There was no statistically significant overall association between iodine levels and risk of breast cancer (**Table 2**). Among women with high selenium levels (above the median), high iodine levels were associated with a lower risk of breast cancer; the adjusted OR for above versus below the median was 0.75 (0.57–0.99). The quartile analysis showed a similar pattern, with a relatively low risk in quartile 3 and 4 as compared with the first, but these associations were not statistically significant. There were no corresponding associations among women with low selenium levels. The *P* value for interaction ($P_{interaction}$), comparing the iodine-associated risk in women with high versus low selenium levels was 0.06 (0.04 in the crude analysis; **Table 2**).

In the sensitivity analysis excluding cases during the first two years following baseline, all ORs were very similar to the main analysis (Supplementary Table S1). The same was observed when *in situ* cases were excluded. The analysis including only ER-positive cases was similar to the main analysis but the analysis on ER-negative cases showed ORs close to unity and broad CIs. All ORs were also similar when the analyses were adjusted for dietary factors (Supplementary Table S1). Menopausal status at baseline did not seem to affect the overall association between iodine and breast cancer. If anything, the negative association in women with high selenium levels was slightly stronger among postmenopausal women (Supplementary Table S2). Age at diagnosis and time between baseline and breast cancer diagnosis covaries. In women with low selenium levels, there was a statistically significant positive association between high iodine levels and breast cancer for cases diagnosed relatively early. If anything, the negative association between iodine and breast cancer among women with high selenium levels was somewhat stronger in women diagnosed later during follow-up or at high age (Supplementary Table S2).

Discussion

Our study found that among women with high selenium levels, high iodine levels were associated with a risk of breast cancer that was about 25% lower than among women with low iodine levels. This is in line with the hypothesis that the combination of high iodine and high selenium levels, as seen in Japanese women, can be related to a low risk of breast cancer (2, 9).

Our descriptive analysis found that age, postmenopausal status, use of HRT and a relatively modest alcohol consumption was positively associated with iodine levels. Age, menopausal status, and HRT are tightly related. Moreover, in the current cohort, older women drink less alcohol (data now shown). There are, to our knowledge, a very small number of previous studies on determinants for iodine status, but a recent study has reported that serum iodine increases with age (21), and this is in line with our study.

This is the first study ever on the association between serum iodine levels and breast cancer risk using individually measured iodine levels among cases and controls. Our study is, moreover, prospective using prediagnostic serum iodine levels. Previous studies comparing incidence rates of breast cancer with iodine status in different populations have suggested a protective effect from iodine (1, 2, 4, 9). An ecological study from Spain found an inverse association between iodine intake in different geographical areas and corresponding breast cancer mortality (correlation coefficient = 0.44). The study found that areas with a low iodine status had a relative risk of 1.87 relating to breast cancer mortality as compared with high iodine areas (5). Our study did not, however, find an overall association between iodine levels and breast cancer risk.

Results from studies of women who have undergone RAI treatment for thyroid disease are problematic to interpret as the potential association between iodine and breast cancer risk may be caused by confounding by indication, nonphysiologic doses, and selection of study participants. However, they may offer some indirect evidence. The meta-analysis mentioned above reported that women treated with RAI for thyroid disease have a decreased risk of breast cancer (6). This was also found in a study by Ahn and colleagues (22) and in a study by Kuo and colleagues (23); however, in the former study only statistically significant following high-dose treatment (hazard ratio 0.17 for RAI vs. not), and in the latter only statistically significant in the univariable analysis.

Some methodologic issues have to be considered. Serum samples had been stored for about 20 years and it is not known to what extent iodine levels may have changed during storage, for example, due to degradation or evaporation of the sample. We handled this by using separate cutpoints for different calendar years. The inter-batch coefficient of variation for the iodine analysis was 0.04, which strengthens the reliability of our measurements. Concerning our endpoint, incident breast cancer, The Swedish Cancer Registry was used to identify cases, a registry with a high validity and completeness (24). The participation rate in the MDCS was 41%, but previous analyses have shown that participants are similar to the overall background population regarding factors like socioeconomy, BMI, and smoking (16) and this increases the generalizability of the results. A weakness of our study design is that we used two different types of selection criteria for our control group; some were matched and some were randomly selected. However, matching factors was adjusted for in the analyses, which ought to have limited this potential problem.

Several sensitivity analyses were performed. There was nothing to suggest that subclinical disease had affected the results, given similar results when cases diagnosed within two years following baseline were excluded. Similarly, all results were very similar when *in situ* cases were excluded, when the analysis only included ER-positive cases, and when the model was adjusted for dietary factors. The analysis in relation to ER-negative cases included few cases and had a limited statistical power. We had no *a priori* hypothesis on a potential modifying effect of menopausal status, age at diagnosis, or time of follow-up. Only including cases diagnosed during the first half of the follow-up period, the finding of a positive association between iodine and breast cancer risk in women with low selenium levels was not expected given the hypothesis. Because of the large number of additional analyses, a type I error is difficult to exclude.

Iodine receptors such as NIS and Pendrin are expressed during lactation and in breast cancer, but are not seen in normal breast tissue. On the other hand, SMCT is seen in normal breast tissue but not in breast cancer (7). During lactation, iodine is incorporated in the breast into iodoproteins and iodolipids which have been suggested to have antiproliferative effects (9). There is also some evidence that iodine *per se* may act as an antioxidant (10), and that iodine may have antiproliferative and apoptotic effects (3, 11). Interestingly, the iodine receptor SMCT functions as a tumor suppressor (7), which may delay tumor progression. That iodine receptors may affect breast cancer

Table 1. Established and potential risk factors for breast cancer in relation to quartiles (Q) of serum iodine levels.

Category	Q1 ($n = 506$)	Q2 ($n = 509$)	Q3 ($n = 512$)	Q4 ($n = 506$)	*P*	Missing ($n = 262$)
	Column %					Column %
Age						
≤50	25.7	25.5	22.7	20.6	$P < 0.001$	13.4
>50–≤55	29.1	24.6	25.4	18.0		16.4
>55–≤60	20.0	20.8	18.8	21.7		17.9
>60	25.3	29.1	33.2	39.7		52.3
Socioeconomic index						
Manual	33.6	36.3	36.1	37.5	$P = 0.79$	38.9
Nonmanual	60.1	56.2	55.7	54.7		56.9
Employer	5.9	6.5	6.4	7.1		3.8
Education						
≤9 years	62.3	67.4	70.1	69.2	$P = 0.13$	79.4
10–12 years	9.7	6.7	6.8	7.1		6.5
University	27.9	25.5	23.0	23.3		14.1
Married or cohabiting						
No	32.0	33.6	30.5	35.0	$P = 0.45$	29.8
Yes	68.0	66.4	69.5	65.0		70.2
Parity						
0	13.4	13.9	13.7	12.8	$P = 0.79$	12.2
1	19.6	18.7	20.9	19.6		22.5
2	43.1	45.0	42.4	43.5		40.1
3	15.4	14.7	17.8	15.2		17.2
≥4	5.5	5.9	3.1	5.5		5.3
Missing	3.0	1.8	2.1	3.4		2.7
Age at first childbirth						
≤20	17.2	15.5	16.2	17.2	$P = 0.61$	18.3
>20–≤25	31.6	33.4	37.1	36.0		35.1
>25–≤30	23.9	27.1	22.9	21.1		22.9
>30	10.7	8.3	8.0	9.5		8.8
Nulliparous	13.4	13.9	13.7	12.8		12.2
Missing	3.2	1.8	2.1	3.4		2.7
Age at menarche						
≤12	21.9	23.0	23.8	20.9	$P = 0.85$	21.0
>12–≤14	53.0	51.3	52.1	52.8		54.6
>14	24.3	25.3	22.7	26.3		22.5
Ever use of oral contraceptives						
No	44.9	46.4	52.1	50.0	$P = 0.08$	53.8
Yes	55.1	53.6	47.9	50.0		45.8
Menopausal status						
Pre	30.6	30.8	25.8	22.7	$P < 0.001$	15.3
Peri	11.3	9.0	7.8	6.7		3.8
Post	58.1	60.1	66.4	70.6		80.9
Oophorectomy bilateral						
No	98.6	98.4	98.8	97.8	$P = 0.61$	98.1
Yes	1.4	1.6	1.2	2.2		1.9
HRT, use at baseline						
No	79.6	81.1	74.8	70.8	$P < 0.001$	80.9
Yes	20.2	18.5	25.0	29.1		18.7
Smoker						
Never	46.0	41.8	42.2	40.7	$P = 0.51$	45.4
Current	27.5	28.3	26.4	28.1		26.7
Ex	26.3	29.9	31.4	31.2		27.9
BMI						
<20	4.5	4.3	5.5	6.5	$P = 0.33$	3.8
≥20–<25	52.4	47.9	45.9	46.6		42.7
≥25–<30	33.8	34.6	35.4	34.2		34.7
≥30	9.3	13.2	13.3	12.5		18.7
Alcohol consumption						
Zero	3.8	5.5	7.4	9.5	$P < 0.001$	8.8
<15 g/day	62.1	64.8	62.7	64.4		64.5
15–30 g/day	19.2	16.5	12.1	10.7		10.7
>30 g/day	4.7	2.6	2.9	3.2		3.4
Infrequent	10.3	10.6	14.6	12.3		12.6

Note: Missing data not presented if a factor had <2% missing in all quartiles.

Table 2. Iodine levels and breast cancer risk, overall and stratified for selenium levels.

Iodine level	Iodine[b] (μg/L)	All			Low selenium[b] (≤92.0 μg/L)			High selenium[b] (≥88.0 μg/L)				
		Cases/controls	OR (95% CI)	OR[a] (95% CI)	Cases/controls	OR (95% CI)	OR[b] (95% CI)	Cases/controls	OR (95% CI)	p_I	OR[b] (95% CI)	p_I
Q1	≤61.6	254/252	1	1	155/164	1	1	99/88	1		1	
Q2	58.1–70.9	271/238	1.13 (0.88–1.45)	1.16 (0.90–1.50)	135/124	1.15 (0.83–1.60)	1.15 (0.82–1.64)	136/114	1.06 (0.73–1.55)	*0.75*	1.06 (0.70–1.59)	*0.64*
Q3	65.5–82.2	253/259	0.97 (0.76–1.24)	0.97 (0.75–1.26)	124/118	1.11 (0.80–1.55)	1.20 (0.83–1.72)	129/141	0.81 (0.56–1.18)	*0.22*	0.78 (0.52–1.17)	*0.19*
Q4	≥73.2	251/255	0.98 (0.76–1.25)	1.01 (0.78–1.30)	106/88	1.27 (0.89–1.82)	1.26 (0.86–1.85)	145/167	0.77 (0.54–1.11)	*0.05*	0.78 (0.52–1.16)	*0.08*
	P_{trend}	1,029/1,004	*0.57*	*0.68*	520/494	*0.21*	*0.24*	509/510	*0.06*	—	*0.10*	—
	Missing vs. Q1	130/132	0.98 (0.72–1.32)	1.01 (0.74–1.39)	—	—	—	—	—	—	—	—
Low	≤70.9	525/490	1	1	290/288	1	1	235/202	1		1	
High	≥65.6	504/514	0.92 (0.77–1.09)	0.92 (0.76–1.10)	230/206	1.11 (0.87–1.42)	1.15 (0.87–1.50)	274/308	**0.76 (0.60–0.98)**	***0.04***	**0.75 (0.57–0.99)**	*0.06*

Note: Italics are used to distinguish *P* values for trend from other results.

[a]Adjusted for age at baseline, socioeconomic status, education, marital status, parity, age at first childbirth, age at menarche, oral contraceptives, menopausal status, oophorectomy, HRT, smoking status, BMI, alcohol consumption, and calendar month samples were collected. All entered as categorical variables.

[b]Categorizations of quartiles (Q) and medians were year-specific and absolute values may overlap. The year-specific median was used to classify selenium as low/high. p_I is the *P* value in the interaction analysis comparing association between iodine levels and breast cancer risk in women with high versus low selenium levels. Some women had no data on selenium levels, which is why numbers in stratified analyses do not equal the total.

development is indirectly suggested by the finding that metastatic breast cancer has relatively low levels of NIS (25).

Considering breast tissue specifically, experimental studies have shown that iodine deficiency leads to dysplasia and the gland becomes highly sensitive to estradiol (8, 26), factors that would increase cancer risk. Indeed, Kilbane and colleagues reported that breast tumors had a lower tissue content of iodine as compared with normal tissue (27). Experimental studies have also shown that iodine, for example, in seaweed, given to rats with breast cancer leads to a reduction in tumor size and delays tumor development (28). In line with this, seaweed also induces apoptosis in human breast cancer cell lines (29).

Selenium, in relation to breast cancer, has been studied in a large number of studies, showing no clear association with risk (9, 12, 13). However, there are well-known biological mechanisms that in theory may lead to a protective effect in relation to breast cancer. Selenium exerts many important effects through the action of selenoenzymes, many of which are potent antioxidants. They may also regulate transcription, cell proliferation, and apoptosis, and selenium may also improve the immune response (15). Concerning selenium, it has been suggested that it is the combination with high iodine that may lower the risk of breast cancer (2, 9). This hypothesis is mainly based on ecologic studies comparing different geographical areas, often using Japan as an example. If true, there are several reasons why women with a combination of high iodine and high selenium levels have a decreased risk of breast cancer. It may simply be an additive effect that leads to an effect large enough to be observed. Considering serum selenium, we found no association with risk and this is in line with a previous Cochrane review (13, 14). For iodine, there are no previous case–control or cohort studies, and the current study did not support an overall risk. Given the results in this study, it is possible that there is a true biological interaction between iodine and selenium, but the mechanisms are not clear. It has been suggested that iodine deficiency leads to changes in the breast such as atypia, dysplasia, and even neoplasia. Low iodine levels also seem to increase the sensitivity to estrogens (1, 9). Such factors may not necessarily increase the risk of breast cancer, but in the absence of a protective effect from selenium this combination may define women with a high risk, that is, high iodine in combination with high selenium may be protective. Future experimental studies are needed to investigate this further.

Following that a combination of high iodine/selenium was associated with a 25% lower risk of breast cancer, we conclude that it is important to further investigate if the combination of high iodine and selenium levels may be protective with regard to breast cancer. An important aspect is that our study is the first on this topic, and the result has to be replicated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Manjer, S. Borgquist

Development of methodology: J. Manjer

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Manjer, S. Borgquist

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Manjer

Writing, review, and/or revision of the manuscript: J. Manjer, M. Sandsveden, S. Borgquist

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Manjer, M. Sandsveden

Study supervision: J. Manjer

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