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Communication

Blood Iodine as a Potential Marker of the Risk of Cancer in BRCA1 Carriers

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Abstract: Breast cancer and ovarian cancer pose a significant risk for BRCA1 carriers, with limited risk-reduction strategies. While improved screening helps in the early detection of breast cancer, preventive measures remain elusive. Emerging evidence suggests a potential link between iodine levels and modulation of cancer risk, but comprehensive studies are scarce. We conducted a prospective study among 989 BRCA1 carriers to assess the association between blood iodine levels and breast and ovarian cancer risk. Using inductively coupled plasma mass spectrometry, we measured blood iodine levels and observed a negative association with breast cancer risk, with a significantly lower risk observed in quartile 4 (iodine > 38.0 µg/L) compared with quartile 1 (iodine < 30 µg/L) (HR = 0.49; 95%CI: 0.27–0.87; $p = 0.01$). Conversely, a suggestive increase in ovarian cancer risk was observed at higher iodine levels (HR = 1.91; 95%CI: 0.64–5.67; $p = 0.25$). No significant association was found between iodine levels and overall cancer risk. Our results suggest the potential of iodine to reduce breast cancer risk in BRCA1 carriers after prophylactic oophorectomy but require further validation and investigation of its effect on ovarian cancer risk and overall mortality. These findings highlight the need for personalized strategies to manage cancer risk in BRCA1 carriers.

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1. Introduction

BRCA1 (MIM# 113705), a tumor suppressor gene located on chromosome 17q21, plays an important role in breast and ovarian cancer risk/development [1–3]. The lifetime risk of breast cancer in BRCA1 carriers is approximately 70%, and the risk of ovarian cancer is approximately 40% [4,5]. It is estimated that, in Poland, there are 200,000 carriers of BRCA1 mutation, and so far, we have identified over 10,000 in our clinics [6]. BRCA1 mutation genetic testing began in 1995, and since then, we have gained a lot of knowledge about cancer prevention. Enhanced screening of BRCA1 carriers with MRI surveillance leads to early detection of breast cancer but does not reduce the risk. Preventive bilateral mastectomy and salpingo-oophorectomy are crucial recommendations and can drastically reduce the risk and improve survival at the cost of adverse effects associated with these procedures [7–13]. Age, reproductive history, hormonal therapies, and oral contraception are modifiers of breast and ovarian cancer risk. Other modifiers of cancer risk in BRCA1 carriers include microelements, of which, to date, only serum arsenic and blood lead levels have been proven to influence the risk [14,15]. The high number of BRCA1 carriers in the population, coupled with the lifetime risk of ovarian and breast cancer, presents a need to identify additional factors that can reduce the risk.

Iodine is an essential element required for the proper functioning of the human body and is associated with thyroid function [16]. Radioactive iodine can increase the risk of developing several types of cancer [17–19]. Information on non-radioactive sources of iodine and cancer risk is scarce, although it has been proposed that iodine might protect against breast, ovarian, and endometrial cancer [20–24]. Notable quantities of iodine are found in seaweed, fish, iodized salt, eggs, dairy products, poultry, and beef liver. Our study aims to assess the association between blood iodine levels and the risks of breast and ovarian cancer in a prospective study of healthy BRCA1 carriers.

2. Materials and Methods

Our cohort was representative of cohorts of BRCA1 carriers from cancer family clinics generally characterized by an increased proportion of familial breast and ovarian cases. Participants of the study were 1119 initially unaffected adult women with a BRCA1 mutation, of which 130 had only baseline data collected and were lost to follow-up (88.38% completed at least one follow-up generally performed every 2 years). All carriers received genetic testing and counseling between 2011 and 2017 at the Clinical Hospitals of Pomeranian Medical University in Szczecin, Poland, or at an associated hospital or outpatient clinic. At recruitment and later every 6 months all carriers had surveillance, including breast MRI and ultrasound (USG), mammography, transvaginal USG, and blood CA125 analysis. During the first study visit, each subject had a fasting blood sample taken for genetic testing for BRCA1 mutations and later for elements measurement. A total of 10 mL of peripheral blood was taken for analysis from all subjects into a vacutainer tube containing ethylenediaminetetraacetic acid (EDTA). Each blood sample was drawn between 8 am and 2 pm and stored at −80 °C until analysis.

Usually, patients with the mutation are offered the possibility to participate in other studies. The deleterious BRCA1 variant warranted the inclusion of participants in the study. Written informed consent was given by all participants. Medical records were reviewed for diagnosis date, age at enrollment (blood draw), ovary removal (yes/no), smoking status (current, former, never), contraceptive use (ever/never), diabetes (yes/no), dietary supplement use (ever/never), hormonal therapy (ever/never), and BMI (low/normal/fat/obesity). The study adhered to the Helsinki Declaration and received approval from the Ethics Committee of Pomeranian Medical University in Szczecin, documented under the number KB-0012/73/10 on 21 June 2010.

2.1. Measurement of Blood Iodine Level

Blood samples were collected from fasting individuals via venipuncture using the Vacutainer® System (product number 368381, Becton Dickinson, Plymouth, DEV, UK). The blood was then carefully aliquoted into new cryovials and frozen at −80 °C until it was analyzed.

The elemental composition of the samples was analyzed using inductively coupled plasma mass spectrometry (ICP-MS) with the NexION 350D instrument (PerkinElmer, Norfolk, VA, USA). Element determination was conducted in KED (Kinetic Energy Discrimination) mode, with rhodium serving as an internal standard to account for instrument drift and matrix effects. Specific parameters of the NexION 350D instrument used in the measurements can be provided upon request. For the analysis, blood samples were diluted 40-fold with a blank reagent (70 µL of blood to 2730 µL of buffer).

The blank reagent composed of high-purity water (>18 MΩ), TMAH (AlfaAesar, Kandel, Germany), Triton X-100 (PerkinElmer, Shelton, CT, USA), ethylenediaminetetraacetic acid (Merck, Darmstadt, Germany), and ethyl alcohol (Merck, Darmstadt, Germany). Calibration standards were created by diluting a 1000 µg/mL Iodine Standard stock solution (PerkinElmer Pure Plus, Shelton, CT, USA) with the blank reagent. The calibration method was matrix-matched, and the correlation coefficients for the calibration curve were always greater than 0.999.

The accuracy and precision of the measurements were assessed using certified reference materials (CRM): ClinChek® Plasmonorm Whole Blood Level 1 (Recipe, Munich, Germany) and Seronorm Whole Blood Level 2 (Sero, Norway). Technical details, including mass spectrometer acquisition parameters and plasma operating settings, are available upon request. The testing laboratory also participates in the independent external quality assessment scheme, QMEQAS (Quebec Multielement External Quality Assessment Scheme), organized by the Institut National de Santé Publique du Québec.

2.2. Statistical Analysis

All study subjects were allocated to one of four categories (quartiles) depending on their blood iodine level. The cumulative risks of breast and ovarian cancer were calculated from the age at blood draw to the age of diagnosis of breast or ovarian cancer, death from another cause, or last follow-up. For estimating the risk of ovarian cancer, women with oophorectomy prior to blood draw were excluded, and subjects with oophorectomy in the follow-up period were censored at the time of oophorectomy. For the analysis of breast cancer risk, oophorectomy was included as a time-dependent variable. To estimate the ten-year cumulative risk of ovarian cancer, patients were followed from blood draw to date of preventive oophorectomy, ovarian cancer, 10 years of follow-up, last follow-up, or death from another cause. Univariate and multivariate Cox proportional hazards regression analyses were performed to estimate risk ratios (HRs) for cancer risk. The following variables were included in the multivariate models: iodine level (quartile), year of birth, age at blood draw (<40 years, 40–49.9 years, ≥50 years), oral contraceptive use (yes/no), hormone replacement therapy use (yes/no), smoking history (current, former never), and BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0). SAS, version 9.4, was used for all statistical analyses.

3. Results

The study group consisted of 989 women with a diagnosed BRCA1 mutation. The women were unaffected at the time of inclusion in the study. The mean age of enrollment (blood draw) was 44.0 years. The mean follow-up was 7.52 years, during which 173 new cancers were reported in various organs (122 breast cancer cases, 29 ovarian cancer cases, and 23 cancers at other sites). We excluded 84 patients from the analyses due to missing data. Group characteristics are presented in Table 1.

Table 1. Group characteristics.

	Initially Unaffected (*n* = 989)
Age at enrollment (years)	
<50	775 (78.36%)
≥50	214 (21.64%)
mean	44.0
Smoking	
Never	720 (72.80%)
Ever	264 (26.69%)
Missing data	5 (0.51%)
Hormonal therapy	
Never	720 (72.80%)
Ever	263 (26.59%)
Missing data	6 (0.61%)
Oophorectomy	
No	413 (41.76%)
Yes	576 (58.24%)
Missing data	0 (0.00%)
Oral contraceptive use	
Never	501 (50.66%)
Ever	481 (48.64%)
Missing data	7 (0.70%)
Diabetes	
No	880 (88.98%)
Yes	62 (6.27%)
Missing data	47 (4.75%)
Body Mass Index (kg/m^2)	
<18.5	56 (5.66%)
18.5–24.9	553 (55.92%)
25.0–29.9	237 (23.96%)
≥30.0	95 (9.61%)
Missing data	48 (4.85%)
Dietary supplements usage	
Never	500 (50.56%)
Ever	489 (49.44%)
Missing data	0 (0.00%)
New cancer diagnosis	
Yes	172 (17.39%)
No	817 (82.61%)
New cancer site (*n* = 174)	
Breast	122 (70.11%)
Ovary	29 (16.67%)
Bladder	2 (1.15%)
Cervix	3 (1.72%)
Colon	2 (1.15%)
Kidney	1 (0.57%)
Leukemia	2 (1.15%)
Lung	3 (1.72%)
Pancreas	1 (0.57%)
Salivary gland	1 (0.57%)
Sarcoma	1 (0.57%)
Site unknown	1 (0.57%)
Skin	1 (0.57%)
Thyroid	3 (1.72%)
Urothelial	1 (0.57%)
Abdomen-CSU	1 (0.57%)

A total of 573 of the women had a risk-reducing oophorectomy at a mean age of 45.2 years. A total of 204 of the women had the oophorectomy prior to the blood draw, and 369 women had the oophorectomy in the follow-up period.

The distribution of iodine levels in the cohort is shown in Figure 1.

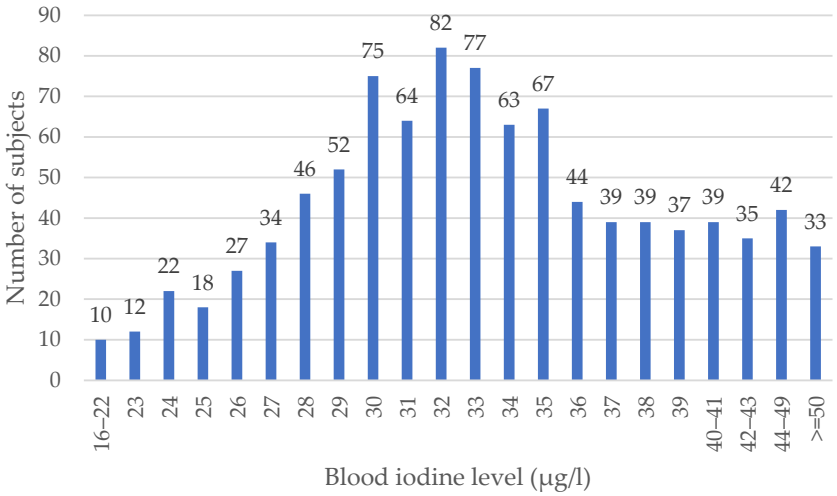

Figure 1. Distribution of iodine level in cohort of BRCA1 carriers (n = 989).

A significant negative association was observed between blood iodine levels and breast cancer risk (Table 2). Women with a blood iodine level greater than 38.0 µg/L had a significantly lower risk of breast cancer than women with blood iodine levels below 30 µg/L (quartile 4 vs. 1; HR = 0.49; 95%CI: 0.27–0.87; p = 0.01; Table 2). The crude and adjusted hazard ratios were similar. The mean iodine level was 33.22 µg/L for those who developed breast cancer and 35.40 µg/L for those who did not develop breast cancer (p = 0.004).

Table 2. Hazard ratio for breast cancer in relation to blood iodine level (quartile).

Variables	Breast Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Iodine level µg/L			
<30	33/240	1	1
30–34	31/237	0.86 (0.53–1.41) 0.56	0.89 (0.54–1.45) 0.63
34.1–38.0	32/240	0.90 (0.55–1.46) 0.65	0.90 (0.55–1.48) 0.68
>38.0	18/240	0.52 (0.29–0.92) 0.03	0.49 (0.27–0.91) 0.01
Total	114/957		
Year of birth			
≤1965	34/230	1	1
1965.01–1975	25/215	0.81 (0.48–1.35) 0.42	0.74 (0.31–2.05) 0.53
1975.01–1985	43/330	0.95 (0.61–1.50) 0.83	0.89 (0.25–3.22) 0.86
>1985	12/182	0.56 (0.29–1.08) 0.09	0.45 (0.11–2.01) 0.27
Age at blood draw			
≤40	59/549	1	1
40.01–50	26/208	1.12 (0.71–1.78) 0.62	1.62 (0.64–4.08) 0.31
>50	29/200	1.24 (0.79–1.94) 0.34	1.53 (0.42–5.66) 0.52
Oophorectomy			
No	27/393	1	1
Yes (time-dependent)	87/564	0.83 (0.57–1.21) 0.33	0.60 (0.36–0.99) 0.04

Table 2. *Cont.*

Variables	Breast Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Oral contraceptive use			
No	53/485	1	1
Yes	61/471	1.17 (0.81–1.69) 0.40	1.31 (0.88–1.94) 0.18
Hormone replacement therapy	83/697	1	1
No	31/259	0.87 (0.58–1.32) 0.51	0.83 (0.57–1.32) 0.43
Yes			
Smoking			
No	54/539	1	1
Current	33/215	1.60 (1.04–2.47) 0.03	1.59 (1.03–2.46) 0.04
Former	27/203	1.33 (0.84–2.12) 0.22	1.31 (0.82–2.09) 0.26
BMI at blood taken			
≤18.5	10/54	1.54 (0.79–2.99) 0.21	1.75 (0.89–3.45) 0.11
18.6–24.9	65/541	1	1
25.0–29.9	27/232	0.95 (0.61–1.49) 0.83	0.92 (0.57–1.47) 0.73
≥30	9/93	0.86 (0.43–1.73) 0.67	0.83 (0.40–2.71) 0.61
Missing	3/37		

* adjusted by all the variables listed in the left column.

We observed an increased risk of ovarian cancer according to iodine levels in the BRCA1 carriers (Table 3). Those who had an iodine level above the median (34 µg/L) had a higher risk of ovarian cancer relative to those with a level below the median (crude HR = 2.15; 95%CI: 0.75–6.18; $p = 0.16$). This was not attenuated in the multivariate model (adjusted HR = 1.91; 95%CI: 0.64–5.67; $p = 0.25$). The mean iodine level was 50.56 µg/L for those who developed ovarian cancer and 34.71 µg/L for those who did not develop ovarian cancer ($p = 0.25$).

Table 3. Hazard ratio for ovarian cancer in relation to blood iodine level (quartile).

Variables	Ovarian Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Iodine level µg/L			
<30	5/188	1	1
30–34	1/188	0.18 (0.02–1.50) 0.12	0.17 (0.02–1.42) 0.10
34.1–38.0	9/189	1.69 (0.67–5.05) 0.35	1.47 (0.48–4.52) 0.50
>38	11/189	2.15 (0.75–6.18) 0.16	1.91 (0.64–5.67) 0.25
Total	26/754		
Year of birth			
≤1965	9/95	1	1
1965.01–1975	8/156	0.49 (0.20–1.22)0.13	1.01 (0.06–16.4) 1.00
1975.01–1985	8/321	0.25 (0.10–0.64)0.003	0.42 (0.02–9.52) 0.59
>1985	1/182	0.06 (0.01–0.50)0.006	0.09 (0.00–3.36) 0.19
Age at blood draw			
≤40	12/539	1	1
40.01–50	5/124	1.53 (0.55–4.23) 0.42	0.57 (0.14–2.47) 0.45
>50	9/91	4.49 (1.99–10.1) 0.0003	1.09 (0.05–1.97) 0.62
Oral contraceptive use	16/359	1	1
No	10/394	0.54 (0.25–1.14) 0.10	0.80 (0.32–1.97) 0.62
Yes			

Table 3. *Cont.*

Variables	Ovarian Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Hormone replacement therapy	23/601	1	1
No	3/152	0.40 (0.12–1.32) 0.13	0.35 (0.11–1.25) 0.11
Yes			
Smoking			
No	11/436	1	1
Current	6/170	1.46 (0.58–3.71) 0.42	1.30 (0.48–3.56) 0.60
Former	9/148	2.53 (1.09–5.85) 0.03	2.09 (0.84–5.21) 0.12
BMI at blood taken			
≤18.5	0/49	0	0
18.6–24.9	13/448	1	1
25.0–29.9	8/157	1.83 (0.76–4.42) 0.18	1.26 (0.50–3.17) 0.62
≥30	4/64	2.32 (0.76–7.13) 0.14	1.23 (0.37–4.02) 0.74
Missing	1/36		

* adjusted by all the variables listed in the left column.

There were 240 women who had an iodine level below 34.0 μg/L (lowest quartile). In this quartile, there were 5 ovarian cancer cases and 33 breast cancer cases (38 cases in total). There were 240 women who had an iodine level above 38.0 μg/L (highest quartile). In this quartile, there were 11 ovarian cancer cases and 18 breast cancer cases (29 cases in total).

The results of the analysis between iodine level and the risk of any cancer are presented in Table 4. The association with iodine was not significant.

Table 4. Hazard ratio for all cancers associated with blood iodine level.

Variables	All Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Iodine level μg/L			
<30	43/240	1	1
30–34	35/237	0.67 (0.43–1.05) 0.08	0.68 (0.44–1.07) 0.10
34.1–38.0	49/240	0.98 (0.65–1.48) 0.92	1.00 (0.66–1.52) 0.99
>38	35/240	0.80 (0.51–1.25) 0.33	0.79 (0.51–1.25) 0.32
Total	162/957		
Year of birth			
≤1965	54/230	1	1
1965.01–1975	39/215	0.84 (0.56–1.27) 0.40	1.40 (0.57–3.46) 0.46
1975.01–1985	54/330	0.83 (0.57–1.21) 0.32	1.81 (0.58–6.68) 0.31
>1985	15/182	0.62 (0.35–1.11) 0.11	1.16 (0.34–3.98) 0.81
Age at blood draw			
≤40	77/549	1	1
40.01–50	36/208	1.14 (0.77–1.70) 0.51	1.53 (0.73–3.22) 0.26
>50	49/200	1.41 (0.98–2.02) 0.06	2.41 (0.77–7.70) 0.13
Oral contraceptive use			
No	83/485	1	1
Yes	79/471	0.92 (0.68–1.26) 0.61	1.01 (0.73–1.42) 0.94
Hormone replacement therapy	122/697	1	1
No	50/259	0.67 (0.47–0.96) 0.03	0.61 (0.41–0.89) 0.01
Yes			

Table 4. *Cont.*

Variables	All Cases/ Total	Univariate HR (95%CI) P	Multivariate * HR (95%CI) P
Smoking			
No	78/539	1	1
Current	41/215	1.42 (0.98–2.08) 0.07	1.40 (0.95–2.06) 0.09
Former	43/203	1.47 (1.01–2.14) 0.04	1.37 (0.93–2.00) 0.11
BMI at blood taken			
≤18.5	10/54	1.15 (0.60–2.22) 0.67	1.16 (0.59–2.25) 0.67
18.6–24.9	86/541	1	1
25.0–29.9	43/232	1.11 (0.77–1.60) 0.59	0.95 (0.64–1.40) 0.80
≥30	19/93	1.49 (0.90–2.44) 0.12	1.27 (0.76–2.13) 0.37
Missing	4/37		

* adjusted by all the variables listed in the left column.

4. Discussion

In our study, we observed a significant association between a relatively high blood iodine level and a reduced risk of breast cancer (quartile 4 vs. quartile 1; HR = 0.49; 95%CI: 0.27–0.87; $p = 0.01$).

There was a suggestion of an increased risk of ovarian cancer associated with a high iodine level, but this was not statistically significant. Overall, the risk of all cancers combined was not associated with the serum iodine level.

Iodine deficiency as a cause of breast cancer has been a subject of interest. In Japan, a low incidence of breast cancer has been correlated with high consumption of dietary iodine, and adoption of a Western diet is associated with higher breast cancer risk [21–23,25,26]. Another study reported the effect of high dietary iodine intake on reducing the risk of breast, ovarian, and endometrial cancers [24]. However, only one previous study correlated serum iodine levels with breast cancer risk, performed in Sweden by Manjer et al. [20]. There was no association observed between iodine levels and breast cancer risk. A modest reduction in risk was found for the subgroup of women with high iodine and high selenium levels. However, to the best of our knowledge there is no prospective data about BRCA1 mutation carriers or the correlation between blood iodine level and cancer risk. A previous report from our center on selenium [27] and the aforementioned work, together with our results, are laying the groundwork for further studies of the effects of selenium and iodine on breast cancer risk, which we plan to examine in the future.

So far, most studies of iodine have been focused on its role in thyroid function. According to the WHO, a daily iodine intake of 150–299 µg is needed for the normal functioning of the thyroid [28]. In addition to the thyroid, other organs, such as breasts, the ciliary body of the eye, gastric mucosa, lacrimal and salivary glands, nervous system, ovaries, pancreas, placenta, prostate, skin, thymus, and uterus, also participate in iodine uptake [29]. Some researchers report that iodine may also have anti- and pro-inflammation functions [30–32]. Furthermore, a daily iodine intake of 1 mg or higher was linked to the antioxidant properties of this element [33,34]. Even higher doses of 1 to 6 mg of iodine intake a day were reported to have an improved outcome in fibrocystic breast disease at the cost of a high rate of side effects such as changes in the thyroid indices, acne, and short periods of increased pain [35].

There is a biological basis for the potential preventive effect of iodine on breast cancer. Iodine is crucial for physiological breast development—breast tissue contains iodine receptors (NIS), pendrin, and sodium-monocarboxylate transporter (SMCT). Precancerous lesions (breast dysplasia) can be caused in mice by iodine deficiency. Antioxidant, antiproliferative, and apoptotic effects in breast tissue are associated with iodine activity [23,33,36–38].

In studies on mice, it has been observed that iodine deficiency causes "hyperresponsiveness" to estradiol [37]. The higher sensitivity of BRCA1 carriers to iodine may be

age-related, as the average age of breast cancer diagnosis is 45 years when there is high estradiol activity. In the study by Manjer et al., 25% of women were of age < 50 years, and in our cohort almost 70% were younger than 50 years [20].

Our study has several limitations. This is the first study of the effects of iodine on breast cancer risk in BRCA1 carriers, and the results should be validated in other populations. It may be that our data will not be relevant for other geographical regions and ethnic groups. Further studies should also consider interactions with other elements.

Additionally, our studies need to be extended to include the influence of iodine on all-cause mortality—there are suggestions that iodine deficiency is associated with more aggressive breast cancers [23,38]. It is also important to extend our findings of iodine levels on ovarian cancer risk to ensure that iodine supplements do not increase the risk of ovarian cancer. If confirmed, patients would have to adhere to different iodine diets depending on their mastectomy and oophorectomy status. At present, our data suggests that an iodine-rich diet or supplementary iodine may be indicated for women with a BRCA1 mutation who have had a preventive salpingo-oophorectomy and who have two breasts intact. We must also note that at this point, these results concern only BRCA1 carriers; further studies with a BRCA1-negative cohort are needed to assess whether we can apply the same correlation to a general population.

5. Conclusions

This is the first study to demonstrate an association between blood iodine levels in BRCA1 carriers and breast and ovarian cancer risk. The risk for breast cancer was decreased, but the risk for ovarian cancer presented a positive trend with increasing iodine levels. It is important to further study the association observed between iodine levels and cancer. The results of this suggest a potential for reduction in breast cancer risk in BRCA1 carriers using iodine but should only be considered after preventive oophorectomy.

6. Patents

A patent application (P.447790) has been submitted to the Patent Office of the Republic of Poland based on the results presented in the following communication.

Author Contributions: Conceptualization, A.K., M.M. and J.L.; methodology, W.M., R.D., M.B., P.B. and P.S.; software, P.B., M.B. and P.S.; validation, W.M. and R.D.; formal analysis, P.B., M.B., P.S. and J.L.; investigation, A.K., M.M., W.M. and R.D.; resources, J.L., C.C., T.D., T.H., J.G., M.S. (Marek Szwiec), M.S.-N., D.G., A.P., A.J. (Andrzej Jasiewicz), T.K., J.T.-S., E.K.-K., M.S. (Monika Siołek), R.W., R.P. and J.J.-T.; data curation, A.K., M.M., W.M., R.D., K.S., P.B., P.S., M.B., J.L., C.C., T.D., T.H., J.G., M.R.L. and A.J. (Anna Jakubowska); writing—original draft preparation, A.K., M.M., A.C., J.L., S.A.N. and R.J.S.; writing—review and editing, A.K., M.M., S.A.N. and J.L.; visualization, A.K., M.M. and J.L.; supervision, J.L. and S.A.N.; project administration, J.L.; funding acquisition, C.C., T.H., J.G., T.D., M.R.L. and A.J. (Anna Jakubowska). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This research was carried out in compliance with the Declaration of Helsinki and received approval from the Ethics Committee of the Pomeranian Medical University in Szczecin, Poland (reference number KB-0012/73/10; 26 June 2010).

Informed Consent Statement: Informed consent was obtained from all study subjects.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy.

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Conflicts of Interest: Author J.L., W.M., R.D., P.B., J.G., C.C. and T.H. were employed by the company Read-Gene SA, Grzepnica, ul. Alabastrowa 8, 72-003 Dobra, Poland. The remaining authors declare

that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Newman, B.; Austin, M.A.; Lee, M.; King, M.C. Inheritance of Human Breast Cancer: Evidence for Autosomal Dominant Transmission in High-Risk Families. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 3044–3048. [CrossRef]
2. Easton, D.F.; Bishop, D.T.; Ford, D.; Crockford, G.P. Genetic Linkage Analysis in Familial Breast and Ovarian Cancer: Results from 214 Families. The Breast Cancer Linkage Consortium. *Am. J. Hum. Genet.* **1993**, *52*, 678–701.
3. Ford, D. Risks of Cancer in BRCA1-Mutation Carriers. *Lancet* **1994**, *343*, 692–695. [CrossRef]
4. Kuchenbaecker, K.B.; Hopper, J.L.; Barnes, D.R.; Phillips, K.-A.; Mooij, T.M.; Roos-Blom, M.-J.; Jervis, S.; van Leeuwen, F.E.; Milne, R.L.; Andrieu, N.; et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* **2017**, *317*, 2402. [CrossRef]
5. Li, S.; Silvestri, V.; Leslie, G.; Rebbeck, T.R.; Neuhausen, S.L.; Hopper, J.L.; Nielsen, H.R.; Lee, A.; Yang, X.; McGuffog, L.; et al. Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants. *J. Clin. Oncol.* **2022**, *40*, 1529–1541. [CrossRef]
6. Górski, B.; Cybulski, C.; Huzarski, T.; Byrski, T.; Gronwald, J.; Jakubowska, A.; Stawicka, M.; Gozdecka-Grodecka, S.; Szwiec, M.; Urbański, K.; et al. Breast Cancer Predisposing Alleles in Poland. *Breast Cancer Res. Treat.* **2005**, *92*, 19–24. [CrossRef]
7. Narod, S.A. Choices for Cancer Prevention for Women with a BRCA1 Mutation? A Personal View. *Hered. Cancer Clin. Pract.* **2023**, *21*, 26. [CrossRef]
8. Kotsopoulos, J.; Lubinski, J.; Gronwald, J.; Menkiszak, J.; McCuaig, J.; Metcalfe, K.; Foulkes, W.D.; Neuhausen, S.L.; Sun, S.; Karlan, B.Y.; et al. Bilateral Oophorectomy and the Risk of Breast Cancer in BRCA1 Mutation Carriers: A Reappraisal. *Cancer Epidemiol. Biomark. Prev.* **2022**, *31*, 1351–1358. [CrossRef]
9. Finch, A.P.M.; Lubinski, J.; Møller, P.; Singer, C.F.; Karlan, B.; Senter, L.; Rosen, B.; Maehle, L.; Ghadirian, P.; Cybulski, C.; et al. Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a BRCA1 or BRCA2 Mutation. *J. Clin. Oncol.* **2014**, *32*, 1547–1553. [CrossRef]
10. Mavaddat, N.; Antoniou, A.C.; Mooij, T.M.; Hooning, M.J.; Heemskerk-Gerritsen, B.A.; Noguès, C.; Gauthier-Villars, M.; Caron, O.; Gesta, P.; Pujol, P.; et al. Risk-Reducing Salpingo-Oophorectomy, Natural Menopause, and Breast Cancer Risk: An International Prospective Cohort of BRCA1 and BRCA2 Mutation Carriers. *Breast Cancer Res.* **2020**, *22*, 8. [CrossRef]
11. Domchek, S.M. Association of Risk-Reducing Surgery in Mutation Carriers with Cancer Risk and Mortality. *JAMA* **2010**, *304*, 967. [CrossRef]
12. Metcalfe, K.; Lynch, H.T.; Foulkes, W.D.; Tung, N.; Kim-Sing, C.; Olopade, O.I.; Eisen, A.; Rosen, B.; Snyder, C.; Gershman, S.; et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. *JAMA Oncol.* **2015**, *1*, 306. [CrossRef]
13. Heemskerk-Gerritsen, B.A.M.; Jager, A.; Koppert, L.B.; Obdeijn, A.I.-M.; Collée, M.; Meijers-Heijboer, H.E.J.; Jenner, D.J.; Oldenburg, H.S.A.; van Engelen, K.; de Vries, J.; et al. Survival after Bilateral Risk-Reducing Mastectomy in Healthy BRCA1 and BRCA2 Mutation Carriers. *Breast Cancer Res. Treat.* **2019**, *177*, 723–733. [CrossRef]
14. Marciniak, W.; Matoušek, T.; Domchek, S.; Paradiso, A.; Patruno, M.; Irmejs, A.; Roderte, I.; Derkacz, R.; Baszuk, P.; Kuświk, M.; et al. Blood Arsenic Levels as a Marker of Breast Cancer Risk among BRCA1 Carriers. *Cancers* **2021**, *13*, 3345. [CrossRef]
15. Kiljańczyk, A.; Matuszczak, M.; Marciniak, W.; Derkacz, R.; Stempa, K.; Baszuk, P.; Bryśkiewicz, M.; Lubiński, K.; Cybulski, C.; Dębniak, T.; et al. Blood Lead Level as Marker of Increased Risk of Ovarian Cancer in BRCA1 Carriers. *Nutrients* **2024**, *16*, 1370. [CrossRef]
16. Cao, L.-Z.; Peng, X.-D.; Xie, J.-P.; Yang, F.-H.; Wen, H.-L.; Li, S. The Relationship between Iodine Intake and the Risk of Thyroid Cancer. *Medicine* **2017**, *96*, e6734. [CrossRef]
17. Gronich, N.; Lavi, I.; Rennert, G.; Saliba, W. Cancer Risk After Radioactive Iodine Treatment for Hyperthyroidism: A Cohort Study. *Thyroid* **2020**, *30*, 243–250. [CrossRef]
18. Holm, L.-E.; Hall, P.; Wiklund, K.; Lundell, G.; Berg, G.; Bjelkengren, G.; Cederquist, E.; Ericsson, U.-B.; Hallquist, A.; Larsson, L.-G.; et al. Cancer Risk after Iodine-131 Therapy for Hyperthyroidism. *JNCI J. Natl. Cancer Inst.* **1991**, *83*, 1072–1077. [CrossRef]
19. Kim, K.J.; Kim, K.J.; Choi, J.; Kim, N.H.; Kim, S.G. Linear Association between Radioactive Iodine Dose and Second Primary Malignancy Risk in Thyroid Cancer. *JNCI J. Natl. Cancer Inst.* **2023**, *115*, 695–702. [CrossRef]
20. Manjer, J.; Sandsveden, M.; Borgquist, S. Serum Iodine and Breast Cancer Risk: A Prospective Nested Case–Control Study Stratified for Selenium Levels. *Cancer Epidemiol. Biomark. Prev.* **2020**, *29*, 1335–1340. [CrossRef]
21. Venturi, S. Is There a Role for Iodine in Breast Diseases? *Breast* **2001**, *10*, 379–382. [CrossRef] [PubMed]
22. Smyth, P.P. The Thyroid, Iodine and Breast Cancer. *Breast Cancer Res.* **2003**, *5*, 235. [CrossRef]
23. Rappaport, J. Changes in Dietary Iodine Explains Increasing Incidence of Breast Cancer with Distant Involvement in Young Women. *J. Cancer* **2017**, *8*, 174–177. [CrossRef] [PubMed]
24. Stadel, B.V. Dietary iodine and risk of breast, endometrial, and ovarian cancer. *Lancet* **1976**, *307*, 890–891. [CrossRef]
25. Minami, Y.; Takano, A.; Okuno, Y.; Fukao, A.; Kurihara, M.; Hisamichi, S. Trends in the Incidence of Female Breast and Cervical Cancers in Miyagi Prefecture, Japan, 1959–1987. *Jpn. J. Cancer Res.* **1996**, *87*, 10–17. [CrossRef]
26. Tominaga, S.; Kuroishi, T. An Ecological Study on Diet/Nutrition and Cancer in Japan. *Int. J. Cancer* **1997**, *71* (Suppl. 10), 2–6. [CrossRef]

27. Narod, S.A.; Huzarski, T.; Jakubowska, A.; Gronwald, J.; Cybulski, C.; Oszurek, O.; Dębniak, T.; Jaworska-Bieniek, K.; Lener, M.; Białkowska, K.; et al. Serum Selenium Level and Cancer Risk: A Nested Case-Control Study. *Hered. Cancer Clin. Pract.* **2019**, *17*, 33. [CrossRef] [PubMed]
28. WHO Progress towards the Elimination of Iodine Deficiency Disorders (IDD). Available online: https://iris.who.int/handle/10665/65931 (accessed on 14 May 2024).
29. De la Vieja, A.; Santisteban, P. Role of Iodide Metabolism in Physiology and Cancer. *Endocr. Relat. Cancer* **2018**, *25*, R225–R245. [CrossRef]
30. Moore, K.; Thomas, A.; Harding, K.G. Iodine Released from the Wound Dressing Iodosorb Modulates the Secretion of Cytokines by Human Macrophages Responding to Bacterial Lipopolysaccharide. *Int. J. Biochem. Cell Biol.* **1997**, *29*, 163–171. [CrossRef]
31. Bilal, M.Y.; Dambaeva, S.; Kwak-Kim, J.; Gilman-Sachs, A.; Beaman, K.D. A Role for Iodide and Thyroglobulin in Modulating the Function of Human Immune Cells. *Front. Immunol.* **2017**, *8*, 1573. [CrossRef]
32. Venturi, S.; Venturi, M. Iodine in Evolution of Salivary Glands and in Oral Health. *Nutr. Health* **2009**, *20*, 119–134. [CrossRef] [PubMed]
33. Winkler, R.; Griebenow, S.; Wonisch, W. Effect of Iodide on Total Antioxidant Status of Human Serum. *Cell Biochem. Funct.* **2000**, *18*, 143–146. [CrossRef]
34. Alfaro, Y.; Delgado, G.; Cárabez, A.; Anguiano, B.; Aceves, C. Iodine and Doxorubicin, a Good Combination for Mammary Cancer Treatment: Antineoplastic Adjuvancy, Chemoresistance Inhibition, and Cardioprotection. *Mol. Cancer* **2013**, *12*, 45. [CrossRef] [PubMed]
35. Ghent, W.R.; Eskin, B.A.; Low, D.A.; Hill, L.P. Iodine Replacement in Fibrocystic Disease of the Breast. *Can. J. Surg.* **1993**, *36*, 453–460.
36. Poole, V.L.; McCabe, C.J. Iodide Transport and Breast Cancer. *J. Endocrinol.* **2015**, *227*, R1–R12. [CrossRef] [PubMed]
37. Mendieta, I.; Nuñez-Anita, R.E.; Nava-Villalba, M.; Zambrano-Estrada, X.; Delgado-González, E.; Anguiano, B.; Aceves, C. Molecular Iodine Exerts Antineoplastic Effects by Diminishing Proliferation and Invasive Potential and Activating the Immune Response in Mammary Cancer Xenografts. *BMC Cancer* **2019**, *19*, 261. [CrossRef]
38. Cann, S.A.; van Netten, J.P.; van Netten, C. Hypothesis: Iodine, Selenium and the Development of Breast Cancer. *Cancer Causes Control* **2000**, *11*, 121–127. [CrossRef]

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