ACTA ONCOLOGICA, 2018
VOL. 57, NO. 5, 595–603
https://doi.org/10.1080/0284186X.2017.1404635

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ORIGINAL ARTICLE

Accuracy of self-reported family history of cancer, mutation status and tumor characteristics in patients with early onset breast cancer

Annelie Augustinsson[a], Carolina Ellberg[a], Ulf Kristoffersson[b], Åke Borg[a] and Håkan Olsson[a,c]

[a]Department of Clinical Sciences in Lund, Oncology and Pathology, Lund University, Lund, Sweden; [b]Department of Laboratory Medicine, Clinical Genetics, Lund University and University Hospital, Lund, Sweden; [c]Department of Clinical Sciences in Lund, Cancer Epidemiology, Lund University, Lund, Sweden

ABSTRACT

Background: The main objectives of this study were to evaluate the concordance between self-reported and registry-reported information regarding family history of breast cancer (BC), ovarian cancer (OvC) and other types of cancer in first-degree relatives of patients with early onset BC, and to determine the frequency of mutation carriers and non-mutation carriers. The secondary objective was to describe tumor characteristics for each mutation group.

Material and methods: Between 1993 and 2013, 231 women who were ≤35 years old when diagnosed with BC were registered at the Oncogenetic Clinic at Skåne University Hospital in Lund, Sweden. Self-reported and registry-reported information regarding first-degree family history of cancer was collected together with information regarding tumor characteristics.

Results: Almost perfect agreement was observed between self-reported and registry-reported information regarding first-degree family history of BC ($\kappa = 0.92$) and OvC ($\kappa = 0.86$). Lesser agreement was observed between reports regarding family history of other types of cancer ($\kappa = 0.51$). Mutation screening revealed pathogenic germline mutations in 30.4%; 18.8% in *BRCA1*, 7.1% in *BRCA2* and 4.5% in other genes. Compared with other mutation groups, *BRCA1* mutation carriers were more likely to be diagnosed with high-grade, ER-, PR- and triple-negative tumors.

Conclusions: Our results demonstrate that physicians and genetic counselors can rely on self-reported information regarding BC and OvC in first-degree relatives. However, self-reported information regarding other types of cancer is not communicated as effectively, and there should be more focus on retrieving the correct information regarding family history of all tumor types. Furthermore, we observed that even though all BC patients fulfilled the criteria for genetic counseling and testing, a large number of patients diagnosed at ≤35 years of age did not receive genetic counseling at the Oncogenetic Clinic. This finding merits further elucidation.

ARTICLE HISTORY
Received 9 July 2017
Accepted 6 November 2017

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women, both worldwide and in Sweden. In 2014, 8023 women were diagnosed with invasive BC in Sweden, and less than 1.5% of them were younger than 35 years of age [1]. Although a BC diagnosis is relatively uncommon in young women, early onset BC tends to be diagnosed at a more advanced stage, be more aggressive, and have a poorer prognosis. The tumors are often characterized by high grade, large size and triple-negativity (estrogen receptor (ER) and progesterone receptor (PR) negativity and human epidermal growth factor receptor-2 (HER2) status that is not overexpressed) [2,3].

Several different factors have been associated with an increased risk for BC in women, and one of the major risk factors is a previous family history of BC. In familial BC, heredity is thought to be the dominant cause in approximately 25% of all BC. The majority of hereditary BC are caused by mutations in the high-penetrant *BRCA1* and *BRCA2* genes [4]. The risk of BC among *BRCA1* mutation carriers is more than 30 times as high as the risk among women in the general population at 40 years or younger, and 11 times as high among *BRCA2* mutation carriers of the same age [5]. These mutations also substantially increase the risk for other types of cancer, particularly ovarian cancer (OvC). Hereditary BC can also be caused by mutations in the *TP53* gene, which is also associated with early onset sarcomas and brain tumors. Other dominantly inherited, but less well-characterized, causes of hereditary BC with lower penetrance are mutations in the *PTEN*, *CDH1, CHEK2*, *PALB2, ATM, BRIP1* and the RAD51 genes. Models have also suggested that many of the sporadic cases of BC are caused by mutations in multiple low-penetrant genes, which seem to act multiplicatively [4,6,7].

Identifying a mutation in an early onset BC patient has implications on several levels regarding both treatment procedures and continued screening for contralateral BC and incident OvC. Regarding treatment procedures, *BRCA1* mutation carriers are candidates for targeted therapy with poly

CONTACT Annelie Augustinsson annelie.augustinsson@med.lu.se Department of Clinical Sciences in Lund, Oncology and Pathology, Lund University, Lund SE22185, Sweden

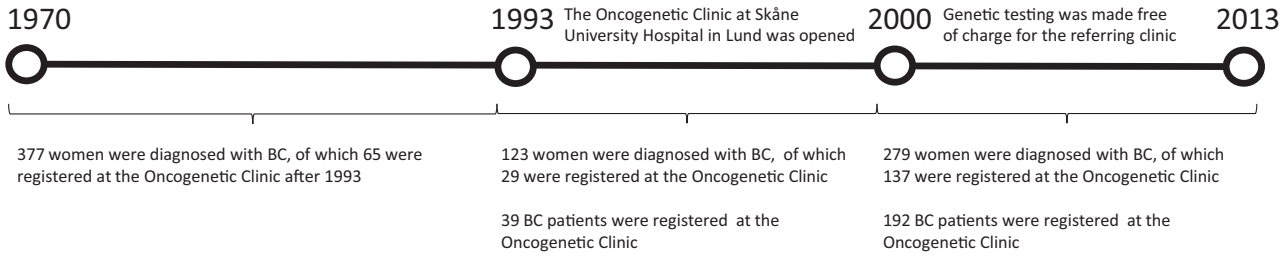

Figure 1. Timeline of when the 779 women aged 35 years or younger were diagnosed with primary BC in the South Swedish Health Care Region between 1 January 1970 and 31 December 2013, and when the 231 BC patients were registered at the Oncogenetic Clinic in Lund.

ADP-ribose polymerase (PARP) inhibitors and DNA damaging chemotherapy such as platinum agents. For patients with early onset BC who are either *BRCA1* or *BRCA2* mutation carriers, annual surveillance with MRI, in addition to mammography, is recommended due to the increased risk of contralateral BC compared with patients with sporadic BC. Prophylactic risk-reducing bilateral or contralateral mastectomy, as well as bilateral salpingo-oophorectomy, should be discussed and considered for the prevention of additional primary tumors. In addition, identifying family members carrying the same mutation will enable individual risk assessment and inclusion into surveillance programs for family members [8,9]. Because both treatment procedures and many screening and prevention strategies rely on mutation status, which in turn often rely on self-reported information regarding family history of cancer, accurate reporting of family history is crucial when risk stratifying BC patients. Inaccurate information could potentially also result in inaccurate care. The accuracy of self-reported family history of BC is considered to be quite precise among first-degree relatives, especially among younger probands. However, self-reports regarding other types of cancer tends to be less accurate [10]. In this study, we sought to validate the reporting of family history of cancer by patients diagnosed with BC at the age of 35 years or younger.

The main objectives of this study were to evaluate the concordance between self-reported and registry-reported information regarding family history of BC, OvC and other types of cancer in first-degree relatives of patients with early onset BC, to evaluate if there is a difference in agreement whether the self-reported information is reported by the young BC patient or by a relative, and to determine the frequency of mutation carriers and non-mutation carriers. The secondary objective was to describe tumor characteristics for each mutation group.

Material and methods

Study participants

The Oncogenetic Clinic at Skåne University Hospital in Lund was opened in 1993. The clinic is the only Oncogenetic Clinic in the South Swedish Health Care Region and serves the entire region, which contains approximately 20% of the total Swedish population, with regards to genetic counseling and testing. Prior to the year 2000, genetic testing was mostly research oriented. In the year 2000, funds facilitated genetic testing free of charge for the referring clinic, which enabled a more evenly distributed referral of individuals. Between 1 January 1970 and 31 December 2013, 779 women aged 35 years or younger were diagnosed with primary BC in the South Swedish Health Care Region, and 231 of the 779 BC patients were registered at the Oncogenetic Clinic (Figure 1). Of these 231 BC patients, 161 attended the genetic counseling sessions at the Oncogenetic Clinic themselves, and for 70 BC patients a relative (68 women and two men) attended the session at the clinic. All patients and/or relatives gave written informed consent for scientific follow-up within their families. The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained from the Ethical Review Board at Lund University, reference number 2013/673.

Data collection

As described in a previous article by Henriksson et al. [11], standardized questionnaires covering family history of all malignant types of cancer were sent to the BC patients or relatives before visiting the Oncogenetic Clinic in Lund. The completed questionnaires were returned to the clinic and pedigrees were constructed based on the self-reported information. At the counseling session at the clinic, another questionnaire covering risk factors for BC was given to the BC patients or relatives. This questionnaire was subsequently completed and returned to the clinic. Information regarding date of cancer diagnosis and tumor characteristics (type, size, histological grade, and ER, PR and HER2 expression status) of the primary BC was retrieved from the Southern Swedish Regional Tumor Registry and the OnkGen Register at Skåne University Hospital in Lund.

Personal identification numbers for all first-degree relatives of the 231 BC patients were extracted from the Population Registry, where all Swedish citizens are registered, and the Multi Generation Registry at Statistics Sweden. These numbers were matched with information at the Swedish Cancer Registry, which have an overall high completeness [12], at the National Board of Health and Welfare to obtain cancer diagnoses dates of diagnoses and tumor locations for the relatives. Migrants were included in the self-reported information but excluded in the registry-reported information due to lack of information on relatives.

Mutation screening

Information regarding mutation status was obtained from the OnkGen Register at Skåne University Hospital in Lund.

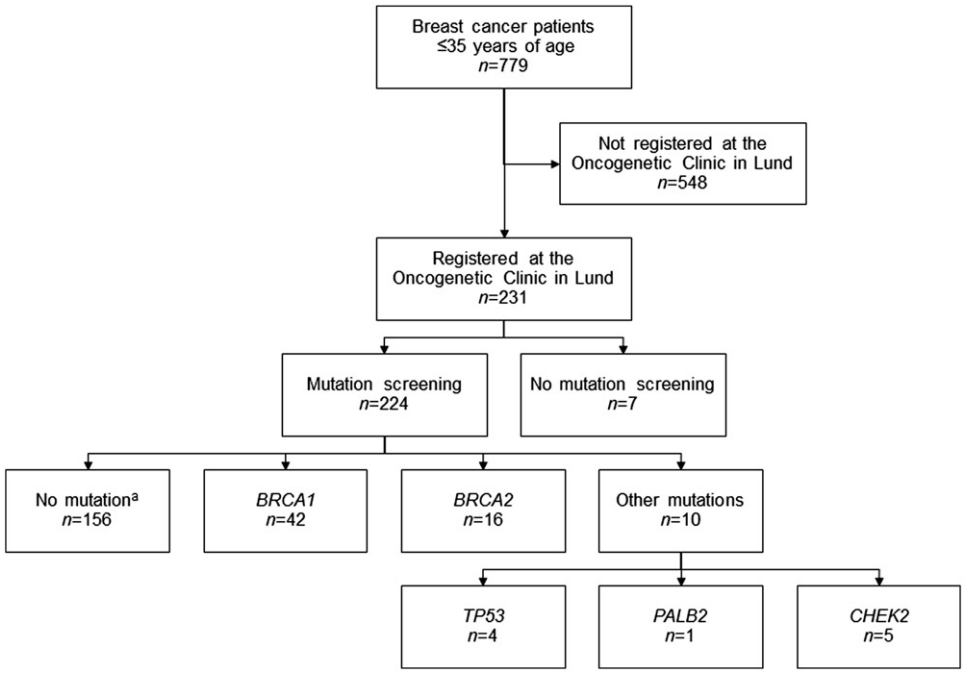

Figure 2. Flow chart of study inclusion and mutation status of the 224 BC patients who were mutation screened. [a]Including variants of uncertain significance in *BRCA1* ($n=6$), *TP53* ($n=2$), *CHEK2* ($n=1$), *PTEN* ($n=1$) and *CDH1* ($n=1$).

As described in previous articles [13,14], mutation screening was originally performed using protein truncation test (PTT), single-strand conformation polymorphism (SSCP) and denaturing high-performance liquid chromatography (DHPLC). Mutations were verified by sequencing. In 31 BC patients, for whom no mutations in *BRCA1* or *BRCA2* were found in previous screenings, a reanalysis was performed between the years 2012 and 2015. These BC patients had been re-remitted by physicians at the Oncogenetic Clinic in Lund for further investigation due to various reasons, e.g., a new incident BC-case in the BC patient's family, an inquiry from a relative, and/or a strong family history of cancer. The reanalysis was performed by using SureSelect (Agilent Technology, Santa Clara, CA, USA) and included the genes *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *STK11*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D*. Blood samples were sequenced using either Genome Analyzer II or Hiseq 2500 (Illumina, San Diego, CA, USA). Alignment was made with Novoalign and variants were detected with Unified Genotyper, GATK. Complementary Sanger sequencing was performed on all fragments/exons that did not have acceptable coverage.

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistical computing package version 22.0 (SPSS Inc., Chicago, IL). Cohen's kappa (κ) was performed to determine the agreement between self-reported and registry-reported information regarding first-degree relatives diagnosed with BC, OvC and other types of cancer. In addition, Fisher's exact test was performed to examine the association between tumor characteristics and the mutation status of the BC patients. These results were given as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was considered with a two-tailed p value of $<.05$.

Results

Study inclusion and mutation status of the BC patients are presented in Figure 2. Out of the 224 mutation screened BC patients, 30.4% tested positive for a pathogenic germline mutation; 18.8% in *BRCA1*, 7.1% in *BRCA2* and 4.5% in other genes (*CHEK2*, *PALB2* and *TP53*). Variants of uncertain significance were considered as mutation screened without findings (no mutation) in all tables and analyses. Thirty-seven of the 224 mutation screened BC patients were registered at the Oncogenetic Clinic between the years 1993 and 1999, when genetic testing was mostly research oriented. Out of these, 59.4% tested positive for a pathogenic germline mutation in *BRCA1* or *BRCA2*; 40.5% in *BRCA1* and 18.9% in *BRCA2*. Between the years 2000 and 2013, 187 of the 224 BC patients were mutation screened and 19.2% tested positive for a mutation in *BRCA1* or *BRCA2*; 14.4% in *BRCA1* and 4.8% in *BRCA2* (data not shown).

Age at BC diagnosis as well as self-reported and registry-reported first-degree family history of cancer in all BC patients and in relation to the mutation status of the BC patients are presented in Table 1. Germline mutations were found in 21.4% of BC patients diagnosed at the age of 25 years or younger, in 36.1% of patients diagnosed between 26 and 30 years of age and in 28.3% of patients diagnosed between 31 and 36 years of age. In relation to first-degree family history of cancer, 32.6% self-reported a family history of BC, 7.3% reported a family history of OvC and 26.6% reported a family history of other cancers. No family history of cancer was reported by 45.4%. The corresponding

Table 1. Age and first-degree family history of cancer in all BC patients and in relation to mutation status.

	All *n* = 231 *n* (%)	No mutation[a] *n* = 156 *n* (%)	*BRCA1* *n* = 42 *n* (%)	*BRCA2* *n* = 16 *n* (%)	Other mutations[b] *n* = 10 *n* (%)	No mutation screening *n* = 7 *n* (%)
Age at BC diagnosis						
≤25 years	14 (6.1)	11 (7.1)	2 (4.8)	0 (0.0)	1 (10.0)	0 (0.0)
26–30 years	75 (32.5)	46 (29.5)	13 (31.0)	7 (43.8)	6 (60.0)	3 (42.9)
31–35 years	142 (61.5)	99 (63.5)	27 (64.3)	9 (56.3)	3 (30.0)	4 (57.1)
Median years (range)	32.6 (17.7–36.0)	32.8 (17.7–36.0)	32.1 (21.3–36.0)	32.1 (27.7–35.5)	28.7 (25.5–34.8)	33.0 (27.3–35.5)
Self-reported family history						
No family history	99 (45.4)	82 (55.8)	8 (20.0)	4 (26.7)	2 (22.2)	3 (42.9)
BC	50 (22.9)	25 (17.0)	13 (32.5)	5 (33.3)	4 (44.4)	3 (42.9)
OvC	8 (3.7)	1 (0.7)	6 (15.0)	0 (0.0)	0 (0.0)	1 (14.3)
BC and OvC	3 (1.4)	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other cancer	37 (17.0)	26 (17.7)	4 (10.0)	5 (33.3)	2 (22.2)	0 (0.0)
BC and other cancer	16 (7.3)	11 (7.5)	3 (7.5)	1 (6.7)	1 (11.1)	0 (0.0)
OvC and other cancer	3 (1.4)	1 (0.7)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
BC, OvC and other cancer	2 (0.9)	1 (0.7)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	13	9	2	1	1	0
Registry-reported family history						
No family history	86 (40.6)	72 (50.0)	6 (16.2)	3 (18.8)	3 (33.3)	2 (33.3)
BC	37 (17.5)	18 (12.5)	11 (29.7)	5 (31.3)	3 (33.3)	0 (0.0)
OvC	3 (1.4)	0 (0.0)	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
BC and OvC	4 (1.9)	0 (0.0)	4 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)
Other cancer	53 (25.0)	37 (25.7)	6 (16.2)	6 (37.5)	2 (22.2)	2 (33.3)
BC and other cancer	26 (12.3)	15 (10.4)	6 (16.2)	2 (12.5)	1 (11.1)	2 (33.3)
OvC and other cancer	2 (0.9)	1 (0.7)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
BC, OvC and other cancer	1 (0.5)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	19	12	5	0	1	1

[a]Mutation screened without findings, including variants of uncertain significance in *BRCA1*, *TP53*, *CHEK2*, *PTEN* and *CDH1*.
[b]Carriers of other types of mutations are presented in Figure 2.

Table 2a. The accuracy of reported information regarding first-degree family history of cancer for all BC patients as well as for the mutation groups no mutation[a], *BRCA1* and *BRCA2*.

		Sensitivity		Specificity		
	κ	Number/total	%	Number/total	%	*p*
No family history						
All	0.70	98/121	81.0	73/80	91.3	<.001
No mutation[a]	0.70	53/70	75.7	63/67	94.0	<.001
BRCA1	0.60	27/30	90.0	4/5	80.0	<.001
BRCA2	0.44	10/12	83.3	2/3	66.7	.080
BC						
All	0.92	61/64	95.3	133/137	97.1	<.001
No mutation[a]	0.92	31/32	96.9	102/105	97.1	<.001
BRCA1	0.83	18/20	90.0	14/15	93.3	<.001
BRCA2	1.00	6/6	100.0	9/9	100.0	<.001
OvC						
All	0.86	10/10	100.0	188/191	98.4	<.001
No mutation[a]	0.80	2/2	100.0	134/135	99.3	<.001
BRCA1	0.92	8/8	100.0	26/27	96.3	<.001
BRCA2	N/A	N/A	N/A	15/15	100.0	N/A
Other cancer						
All	0.51	41/77	53.2	117/124	94.4	<.001
No mutation[a]	0.55	29/52	55.8	81/85	95.3	<.001
BRCA1	0.51	6/12	50.0	22/23	95.7	.001
BRCA2	0.60	5/7	71.4	7/8	87.5	.020

[a]Mutation screened without findings, including variants of uncertain significance in *BRCA1*, *TP53*, *CHEK2*, *PTEN* and *CDH1*.

registry-reported information was 31.6 (BC), 4.7 (OvC), 38.7 (other cancer) and 41.0% (no family history), respectively.

The accuracy of reported first-degree family history of cancer for all BC patients as well as for the mutation groups No mutation, *BRCA1* and *BRCA2* is presented in Table 2a. Almost perfect agreement between self-reported and registry-reported information regarding first-degree family history of BC ($\kappa = 0.92$) and OvC ($\kappa = 0.86$) was observed when analyzing all 231 BC patients. In addition, both high sensitivity and high specificity were observed regarding reported family history of BC (95.3 and 97.1%, respectively) and OvC (100.0 and 98.4%, respectively). However, lesser agreement was observed between reports regarding family history of other types of cancer ($\kappa = 0.51$). The specificity of reported family history of other types of cancer was high (94.4%), while sensitivity was lower (53.2%). All the above mentioned results regarding accuracy of reported history of cancer were statistically significant.

Table 2b. The accuracy of reported information regarding first-degree family history of cancer in relation to information provider.

		Sensitivity		Specificity		
	κ	Number/total	%	Number/total	%	*p*
No family history						
BC patients	0.73	60/75	80.0	62/66	93.9	<.001
Relatives	0.54	38/46	82.6	11/14	78.6	<.001
BC						
BC patients	0.93	36/38	94.7	101/103	98.1	<.001
Relatives	0.90	25/26	96.2	32/34	94.1	<.001
OvC						
BC patients	0.92	6/6	100.0	134/135	99.3	<.001
Relatives	0.78	4/4	100.0	54/56	96.4	<.001
Other cancer						
BC patients	0.56	28/50	56.0	87/91	95.6	<.001
Relatives	0.41	13/27	48.1	30/33	90.9	.001

The accuracy of reported first-degree family history of cancer in relation to the provider of information is presented in Table 2b. As previously described, out of the 231 BC patients, 161 had themselves been attending the genetic counseling sessions at the Oncogenetic Clinic. However, for 70 BC patients, it was a relative who had been attending the session at the clinic. Of these 70 BC patients, 42 were diagnosed with BC prior to the year 1993, when the Oncogenetic Clinic was opened, and 28 were diagnosed between 1993 and 2013. Regarding the relationship status of the information-providing

Table 3. Tumor characteristics in all BC patients and in relation to mutation status.

	All *n* = 231 *n* (%)	No mutation[a] *n* = 156 *n* (%)	*BRCA1* *n* = 42 *n* (%)	*BRCA2* *n* = 16 *n* (%)	Other mutations[b] *n* = 10 *n* (%)	No mutation screening *n* = 7 *n* (%)
Tumor size (mm)						
Median (range)	20.0 (1–90)	20.0 (1–90)	20.0 (5–90)	20.5 (3–50)	19.0 (7–51)	19.5 (14–20)
Missing	72	56	5	4	4	3
Tumor type						
Invasive ductal carcinoma	144 (74.6)	95 (74.8)	30 (76.9)	11 (68.8)	6 (75.0)	2 (66.7)
Invasive lobular carcinoma	4 (2.1)	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medullary carcinoma	11 (5.7)	6 (4.7)	4 (10.3)	0 (0.0)	0 (0.0)	1 (33.3)
Comedo carcinoma	6 (3.1)	3 (2.4)	1 (2.6)	2 (12.5)	0 (0.0)	0 (0.0)
Ductal carcinoma *in situ*	11 (5.7)	10 (7.9)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Other types of carcinoma	8 (4.1)	6 (4.7)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown invasive carcinoma	9 (4.7)	3 (2.4)	2 (5.1)	3 (18.8)	1 (12.5)	0 (0.0)
Missing	38	29	3	0	2	4
Tumor grade						
1	3 (2.7)	2 (2.4)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
2	36 (32.1)	33 (40.2)	1 (4.8)	1 (16.7)	1 (50.0)	0 (0.0)
3	73 (65.2)	47 (57.3)	20 (95.2)	4 (66.7)	1 (50.0)	1 (100.0)
Missing	119	74	21	10	8	6
ER status						
Positive	70 (45.5)	53 (54.6)	3 (9.1)	8 (61.5)	5 (71.4)	1 (25.0)
Negative	84 (54.5)	44 (45.4)	30 (90.9)	5 (38.5)	2 (28.6)	3 (75.0)
Missing	77	59	9	3	3	3
PR status						
Positive	68 (44.4)	55 (57.3)	1 (3.0)	7 (53.8)	4 (57.1)	1 (25.0)
Negative	85 (55.6)	41 (42.7)	32 (97.0)	6 (46.2)	3 (42.9)	3 (75.0)
Missing	78	60	9	3	3	3
HER2 status						
Positive	34 (34.3)	28 (37.8)	0 (0.0)	1 (16.7)	5 (100.0)	0 (0.0)
Negative	65 (65.7)	46 (62.2)	13 (100.0)	5 (83.3)	0 (0.0)	1 (100.0)
Missing	132	82	29	10	5	6
Triple-negative tumors						
Yes	30 (31.3)	18 (25.4)	10 (76.9)	1 (16.7)	0 (0.0)	1 (100.0)
No	66 (68.8)	53 (74.6)	3 (23.1)	5 (83.3)	5 (100.0)	0 (0.0)
Missing	135	85	29	10	5	6

[a]Mutation screened without findings, including variants of uncertain significance in *BRCA1*, *TP53*, *CHEK2*, *PTEN* and *CDH1*.
[b]Carriers of other types of mutations are presented in Figure 2.

relatives; 48 were first-degree, 10 were second-degree and seven were third-degree relatives. The relationship status was unknown for five of the relatives. The agreement between self-reported and registry-reported information regarding family history of BC was almost perfect in relation to both BC patients ($\kappa = 0.93$) and relatives ($\kappa = 0.90$). However, regarding reports of no family history of cancer, lesser agreement was observed in relation to relatives ($\kappa = 0.54$) compared with BC patients ($\kappa = 0.73$). The sensitivity regarding reports of no family history of cancer was similar in relation to relatives and BC patients (82.6 and 80.0%, respectively), while specificity was lower in reports by relatives compared with BC patients (78.6 and 93.9%, respectively). In addition, lesser agreement was observed between reports of family history of other types of cancer in BC patients ($\kappa = 0.56$) and in relatives ($\kappa = 0.41$). The specificity of reported family history of other types of cancer was high (95.6 and 90.9%, respectively), while sensitivity was lower (56.0 and 48.1%, respectively). All the above mentioned results regarding accuracy of reported history of cancer, in relation to information provider, were statistically significant.

Clinical tumor characteristics in all BC patients and in relation to mutation status are listed in Table 3. As expected, medullary carcinoma was more common among *BRCA1* mutation carriers. Compared with BC patients who were screened without findings and *BRCA2* mutation carriers, *BRCA1* mutation carriers were more likely to be diagnosed with high-grade as well as ER-, PR- and triple-negative tumors (Table 4).

Of the 779 patients diagnosed with BC before age 36, all fulfilled the Swedish national guidelines for consideration for genetic counseling and testing. However, only 231 BC patients attended genetic counseling and 548 did not. Of the BC patients diagnosed prior to the year 2000, 94 (18.8%) attended genetic counseling and 406 (81.2%) did not, and of the BC patients diagnosed during/after 2000, 137 (49.1%) attended genetic counseling and 142 (50.9%) did not. Out of these 142 BC patients, five were diagnosed before the age of 25 years, 29 were diagnosed between 26 and 30 years and 108 were diagnosed between 31 and 36 years. Of the five BC patients diagnosed before age 25, four were diagnosed after 2010 (Table 5).

Discussion

In this study, we evaluated the concordance between self-reported and registry-reported information regarding family history of BC, OvC and other types of cancer in first-degree relatives of patients with early onset BC. We found that young BC patients accurately self-reported information regarding both BC and OvC in first-degree relatives. We also determined the frequency of mutation carriers and

Table 4. Association between tumor characteristics in relation to BC patients' mutation status.

	BRCA1 vs. no mutation[a]		*BRCA2* vs. no mutation[a]		*BRCA1* vs. *BRCA2*	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Tumor grade						
1 and 2	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
3	14.9 (1.91–116)	.010	1.49 (0.26–8.60)	.501	10.0 (0.72–139)	.115
ER status						
ER positive	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
ER negative	12.0 (3.44–42.1)	<.001	0.75 (0.23–2.47)	.435	16.0 (3.14–81.7)	.001
PR status						
PR positive	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
PR negative	42.9 (5.63–327)	<.001	1.15 (0.36–3.68)	.521	37.3 (3.86–361)	<.001
HER2 status						
HER2 positive	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
HER2 negative	N/A	N/A	3.04 (0.34–27.4)	.287	N/A	N/A
Triple-negative						
No	1.00 (ref.)	–	1.00 (ref.)	–	1.00 (ref.)	–
Yes	9.82 (2.43–39.7)	.001	0.59 (0.06–5.38)	.538	16.7 (1.36–204)	.024

[a]Mutation screened without findings, including variants of uncertain significance in *BRCA1*, *TP53*, *CHEK2*, *PTEN* and *CDH1*.

Table 5. The frequency of BC patients registered vs. not registered at the Oncogenetic Clinic in relation to age and year of BC diagnosis.

	All *n* = 779		≤25 years *n* = 43		26–30 years *n* = 192		31–35 years *n* = 544	
	Registered *n* (%)	Not registered *n* (%)	Registered *n* (%)	Not registered *n* (%)	Registered *n* (%)	Not registered *n* (%)	Registered *n* (%)	Not registered *n* (%)
Year of BC diagnosis								
1970–1989	55 (16.5)	278 (83.5)	2 (10.5)	17 (89.5)	21 (25.0)	63 (75.0)	32 (13.9)	198 (86.1)
1990–1994	22 (27.2)	59 (72.8)	1 (20.0)	4 (80.0)	9 (45.0)	11 (55.0)	12 (21.4)	44 (78.6)
1995–1999	17 (19.8)	69 (80.2)	1 (25.0)	3 (75.0)	4 (22.2)	14 (77.8)	12 (18.8)	52 (81.3)
2000–2004	37 (42.0)	51 (58.0)	3 (100.0)	0 (0.0)	8 (34.8)	15 (65.2)	26 (41.9)	36 (58.1)
2005–2009	53 (53.0)	47 (47.0)	3 (75.0)	1 (25.0)	17 (70.8)	7 (29.2)	33 (45.8)	39 (54.2)
2010–2013	47 (51.6)	44 (48.4)	4 (50.0)	4 (50.0)	16 (69.6)	7 (30.4)	27 (45.0)	33 (55.0)

non-mutation carriers, and described tumor characteristics for each mutation group. The observed frequency of mutation carriers was higher than expected. Furthermore, we observed that even though all patients fulfilled the criteria for genetic counseling and testing, a large number of patients who were diagnosed with BC before 36 years of age did not receive genetic counseling at the Oncogenetic Clinic.

Our study exhibited higher frequencies of first-degree relatives diagnosed with BC and OvC in BC patients with early onset BC than the majority of previously published studies [2,15,16] have done. However, our findings correspond well with the results reported by Loman et al. that approximately 30% of the BC diagnosed patients aged ≤40 years in the South Swedish Health Care Region had at least one first-degree relative diagnosed with BC or OvC [17]. Because of this, and of reliable data from the National Cancer Registry, we believe that the frequency of first-degree relatives diagnosed with BC and OvC presented in this article might be close to the true rates in the population.

The agreement between self-reported and registry-reported information regarding first-degree family history of BC in our study was almost perfect. This result is concordant with observations from previously published studies by Verkooijen et al. [18] and Ziogas and Anton-Culver [10]. Therefore, our conclusion is that BC patients with early onset BC and/or relatives of young BC patients have correct information regarding family history of BC in first-degree relatives and accurately report this information to the physician. In addition, the agreement between self-reported and registry-reported information regarding family history of OvC in our study was almost perfect. This contradicts the results from the previously published studies by Verkooijen et al. and Ziogas and Anton-Culver, where lower agreement ($\kappa = 0.66$) and lower sensitivities (66.7 and 83.3%, respectively) regarding reported family history of OvC were observed. However, both our study and the study by Verkooijen et al. comprised a small number of patients reporting a family history of OvC, which makes it difficult to draw strong conclusions. One explanation to the high accuracy of reports regarding OvC in first-degree family members in our study might be that oncologists at Skåne University Hospital in Lund, in addition to being physicians, most often are researchers. Hence, they have been aware of the risk of both BC and OvC in families with BRCA mutations for a long period of time. Regarding other types of cancer, the result in our study is concordant with the findings reported by Ziogas and Anton-Culver, exhibiting lesser accuracy in reported family history in first-degree relatives. In our study, both BC patients and relatives statistically significant underreported the family history of other types of cancer, indicating that information regarding other types of cancer in first-degree relatives is not communicated as effectively. This might be due to a number of reasons. Perhaps certain types of cancer are less openly discussed in families, and even if cancer history is shared within families, the information may not always be accurate or may simply be forgotten. Because physicians might be focusing on retrieving information regarding family history of BC and OvC when assessing the need for genetic

counseling and testing, it is worth considering that diagnosis of hereditary BC is more extensive than simply mutations in the *BRCA1* and *BRCA2* genes. Other types of cancer should not be neglected, as some germline mutations (e.g., *TP53*) lead to an increased susceptibility to a variety of cancers [19,20]. Therefore, moving forward, more focus should be placed on retrieving the correct information on family history of all tumor types when determining the need for genetic counseling and testing.

For 70 out of the 231 BC patients registered at the Oncogenetic Clinic, information regarding family history was provided by a relative and not by the patient. One explanation for this is that some of the BC patients were diagnosed several years prior to the opening of the Oncogenetic Clinic in Lund. However, the information of first-degree family history of cancer reported by relatives was almost as accurate as the information reported by the BC patients, indicating that relatives are a good substitute for information regarding family history of cancer when BC patients are not themselves able to.

Even though substantial amounts of data regarding tumor characteristics were missing (mostly due to the number of BC patients diagnosed before clinical use of ER, PR and HER2), our findings correspond well to previously described characteristics of early onset BC, such as a high prevalence of both high-grade [21] and triple-negative tumors in *BRCA1* mutation carriers [7,22]. In addition, the *BRCA1* mutation carriers had a high frequency of medullary carcinoma, which also corresponds well to previously described tumor characteristics in *BRCA1* mutation carriers [7,22].

There is no commonly agreed-upon age limit regarding the definition of early onset BC. However, in this study we chose to include BC patients who were diagnosed at 35 years or younger due to the Swedish national guidelines for considering referral of patients for genetic counseling and testing, in which this age cut off is a key criterion. If this criterion is met, the probability of detecting a mutation related to BC is high [23]. In the first international consensus guidelines for BC in young women, Partridge et al. stated that 10–15% of BC patients diagnosed before 35 years of age will harbor a *BRCA1* or *BRCA2* mutation [9]. In our study, the prevalence of *BRCA1* and *BRCA2* mutation carriers among the patients with early onset BC was much higher (25.9%). The most plausible explanation for the high prevalence in our study is that the BC patients had a more pronounced family history of cancer and thereby increased their probability of being referred by the physicians. When the Oncogenetic Clinic in Lund was opened in 1993, the first BC patients eligible for genetic testing had a very pronounced family history of BC as well as a high penetrance of cancer at an early age. Prior to the year 2000, genetic testing at the Oncogenetic Clinic in Lund was mostly research oriented and out of the 37 BC patients who were tested between 1993 and 1999, 59.4% harbored a *BRCA1* or *BRCA2* mutation. After the year 2000, when a more evenly distributed recruitment was enabled by funds that facilitated genetic testing free of charge for the referring clinic, 19.2% of the tested BC patients harbored a *BRCA1* or *BRCA2* mutation. This prevalence of *BRCA1* and *BRCA2* mutation carriers is still higher than previously reported, and another explanation might be that at-risk family members have higher awareness of the hereditary aspects of BC and, therefore, more often referred themselves [11]. However, a complete mutation testing of all 779 patients is needed to determine the true prevalence of germline mutation carriers. Furthermore, it should be noted that the true prevalence of mutation carriers of other known predisposing genes than *BRCA1* and *BRCA2* in our study is unknown, and that the frequency could be higher than reported.

All the 779 patients, aged 35 years or younger when diagnosed with primary BC in the South Swedish Health Care Region, fulfilled the Swedish national guidelines for consideration of genetic counseling and testing. However, approximately half of the early onset BC patients who were diagnosed during/after the year 2000, when genetic screening was implemented into clinical care, did not receive genetic counseling and testing. It should be noted that the lower age limit was altered from 30 to 35 years during the follow-up period of this study. This change was successively initiated due to altered praxis and was formally altered in the national guidelines in 2012 [23]. Still, after the year 2010, slightly over one third of the BC patients diagnosed at the age of 30 years or younger did not receive genetic counseling and testing. Furthermore, it should be emphasized that in the youngest BC patient group ($\leq$25 years when diagnosed), only half of the BC patients had been registered at the Oncogenetic Clinic. In a study from 2015, Rosenberg et al. reported that 87% out of 897 women aged 40 years or younger at BC diagnosis had participated in BRCA-testing within one year post-diagnosis, with the frequency of testing increasing from 77 to 95% between 2006 and 2013 [24]. One explanation for the discrepancy between the results in our study and the study by Rosenberg et al. might be that a higher frequency of BC patients in our study chose not to attend, being reluctant to know about any mutations, even though they were offered a referral to the Oncogenetic Clinic by a physician. Another explanation could be that the physicians did not offer a referral for genetic counseling and testing to the BC patients due to lack of information or lack of knowledge. However, equivalent to what Nilsson et al. concluded in a previous article [25], there is room for improvement regarding the referral rate to the Oncogenetic Clinic.

In relation to the mutation prevalence of the 548 BC patients who did not attend genetic counseling and testing, two scenarios can be considered. One is that the BC patients who never attended genetic counseling reported less family history of BC and OvC, and were, therefore, not remitted by the physicians. The other is that the family history of BC and OvC and the mutation prevalence was similar in the two populations. In the first scenario, the young age at BC diagnosis is in itself one of the key criteria for considering referral for genetic counseling and testing. However, if none of these BC patients reported any family history of BC or OvC, this might be the reason why they were not referred. If we suppose that none of the 548 BC patients who did not attend genetic counseling and testing had any germline mutations, 8.7% of the 779 BC patients would have been mutation carriers (when excluding the seven BC patients in our study who were not mutation tested). However, it seems unlikely

that none of these BC patients harbored a germline mutation. In the second scenario, if the BC patients who were not registered at the Oncogenetic Clinic had the same prevalence of family history of BC and OvC as the registered BC patients, one could assume that the same prevalence of mutation carriers would also exist within this population. If this was the case, 166 mutation carriers would have been missed: nine BC patients aged 25 years or younger, 35 BC patients aged 26–30 years and 122 BC patients aged 31–35 years. Ideally, all mutation carriers within families with hereditary BC should be identified within the healthcare system and should subsequently be offered a referral to the Oncogenetic Clinic. However, half of the patients diagnosed with early onset BC between the years 2000 and 2013 have not attended genetic counseling and testing. The reason why this group of patients with early onset BC did not attended genetic counseling must be further elucidated.

Another limitation that should be considered in the interpretation of the findings in this study is that the number of observed BC patients was relatively small. However, we were able to include all the 231 women diagnosed with BC before 36 years of age who were registered at the Oncogenetic Clinic at Skåne University Hospital in Lund, which is a relatively small subgroup of women with BC. In addition, because all patients diagnosed with early onset BC in the South Swedish Health Care Region, which contains approximately 20% of the total Swedish population, would be referred to the Oncogenetic Clinic at Skåne University Hospital in Lund, this study population can be considered population-based.

Conclusions

Our results demonstrate that physicians and genetic counselors can rely on self-reported information regarding BC and OvC in first-degree relatives. However, self-reported information regarding other types of cancer in first-degree relatives is not communicated as effectively, and more focus should be placed on retrieving the correct information regarding family history of all tumor types. The prevalence of *BRCA1* and *BRCA2* mutation carriers among the patients with early onset BC was high, and a high prevalence of medullary, high-grade and triple-negative tumors were found in *BRCA1* mutation carriers. We also found that even after the year 2000, when genetic screening was implemented into clinical care, half of the BC patients diagnosed at the age of 35 years or younger were still not referred for genetic counseling and testing. This finding merits further elucidation.

Acknowledgments

We wish to thank Karin Henriksson, manager at the OnkGen Register at Skåne University Hospital in Lund.

Ethical standards

The study was carried out according to national legislation and was approved by the Ethical Review Board at Lund University. Written informed consent was obtained from all patients.

Disclosure statement

The authors declare that they have no conflict of interest.

Funding

This study was supported by the European Research Council under Advanced Grant ERC-2011-294576, the Swedish Cancer Society, the Hospital Funds of Skåne University Hospital and the Mrs. Berta Kamprad Foundation.

ORCID

Annelie Augustinsson http://orcid.org/0000-0003-3415-0536
Carolina Ellberg http://orcid.org/0000-0001-7297-0645
Åke Borg http://orcid.org/0000-0002-5793-132X
Håkan Olsson http://orcid.org/0000-0002-8794-9635

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