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EPIDEMIOLOGY

Determinants of genetic counseling uptake and its impact on breast cancer outcome: a population-based study

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Abstract Genetic counseling and *BRCA1/BRCA2* genes testing are routinely offered in a clinical setting. However, no data are available on the proportion of breast cancer patients with a positive family history undergoing genetic counseling. By linking databases of the Oncogenetics and Cancer Prevention Unit at the Geneva University Hospitals and the population-based Geneva Cancer Registry, we evaluated the uptake of genetic counseling among 1709 breast cancer patients with familial risk of breast cancer and the determinants of such a consultation process. We also studied the impact of genetic counseling on contralateral breast cancer occurrence and survival. Overall, 191 (11.2 %) breast cancer patients had genetic counseling; this proportion was 25.1 % within the high familial risk group. Recent period of diagnosis, early-onset breast cancer, female offspring, high familial risk, tumor size, and chemotherapy treatment were statistically significantly associated with genetic counseling uptake in multivariate analysis. More than 2 % of patients had developed contralateral metachronous breast cancer. An increased risk of contralateral breast cancer of borderline significance was found for patients who had genetic counseling versus those who had not (Cox model adjusted hazard ratio 2.2, 95 % confidence intervals 1.0–5.2, $P = 0.063$). Stratification by *BRCA1/BRCA2* mutation status showed that the occurrence of contralateral breast cancer was 8-fold higher among mutation carriers compared with non-carriers. Age-adjusted overall survival and breast cancer-specific survival were not significantly different between patients who underwent genetic counseling and those who did not. In conclusion, we observed a significant increase in the use of genetic counseling over time and found that breast cancer patients with high familial risk had more often genetic counseling than those with moderate familial risk. A more thorough evaluation of sociodemographic and clinical predictors to attend the cancer genetic unit may help improving the use of genetic counseling services for at-risk individuals at a population level.

Keywords Breast cancer · Familial · Genetic counseling · Second primary · Epidemiology · Cancer

Aurélie Ayme and Valeria Viassolo made an equal contribution to this study.

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Introduction

Positive family history is one of the strongest predictors of a woman's lifetime risk of developing breast cancer [1, 2].

BRCA1 and *BRCA2* are the two major susceptibility genes involved in hereditary predisposition to breast cancer [3, 4]. Genetic counseling and testing are now routinely offered to individuals with increased probability of carrying *BRCA1/BRCA2* mutations [5]. Therefore, breast cancer patients and their relatives dealing with the possibility of hereditary breast cancer risk have to face numerous decisions, including the choice of undergoing genetic counseling, testing for *BRCA1* and *BRCA2* mutations, screening, and prevention strategies such as chemoprevention and prophylactic surgery. Family history of breast cancer is also a well-established risk factor for contralateral breast cancer [6–10]. Carrying *BRCA1/BRCA2* germ-line mutations has been associated with a high risk of contralateral breast cancer with a 10-year risk ranging from 18 to 33 % for *BRCA1* mutation carriers and from 13 to 19 % for *BRCA2* mutation carriers [11–14]. To date, no study investigated the impact of genetic counseling among breast cancer patients with familial risk on breast cancer outcome.

Robust data exist on the uptake rate and determinants of *BRCA1/BRCA2* testing in families diagnosed with deleterious *BRCA1/BRCA2* mutations [15–20]. Rates of testing among first- and second-degree relatives of index cases ranged from 27 to 44 %, and testing decision was more frequent among females, first-degree relatives, individuals with personal history of cancer, and individuals with offspring [15–17, 19, 20]. On the contrary, little is known about the attendance rates and determinants of genetic counseling and testing in different populations, and the context according to personal and family history of breast cancer. In a systematic review evaluating the real and the hypothetical (defined as "being interested in testing") uptake of breast cancer genetic testing in individuals with personal or family breast cancer history, a few characteristics such as Ashkenazi Jewish heritage, older age, and married status were associated with genetic testing uptake [21]. However, studies differed in recruitment setting, assessment of family history of breast cancer and uptake definitions. In particular, none of the previous studies has evaluated on a population-based level, the effects of other potentially important characteristics such as social class, private or public sector of care, and tumor characteristics in genetic counseling attendance and the effect of such consultation on breast cancer outcome [21–24].

The main goals of the present study were to assess the proportion of breast cancer patients with a positive family history who decided to undergo genetic counseling in a population-based setting and to investigate the determinants of such a consultation process. We also investigated the impact of counseling uptake on breast cancer outcomes including contralateral tumor occurrence and survival. These issues were addressed by linking databases of the Oncogenetics and Cancer Prevention Unit at the Geneva University Hospitals and the population-based Geneva Cancer Registry in Switzerland.

Patients and methods

Oncogenetics and Cancer Prevention Unit and Geneva Cancer Registry databases

In 1994, a consultation unit providing cancer risk assessment, surveillance, and prevention recommendations was initiated by the Division of Oncology at the Geneva University Hospitals, Switzerland. It was formally set up as the Oncogenetics and Cancer Prevention Unit in 1996, and remained the only center providing genetic counseling for familial aggregation or hereditary breast cancer predisposition syndromes in the Geneva area. The counseling activity encompasses all levels of care (average, as well as moderate, and high cancer risk situations) and all types of familial cancer aggregation or hereditary cancer susceptibility syndromes. The cancer risk evaluation process involves the collection of personal and family history (at least for first-, second-, and third-degree relatives) and, whenever possible, confirmation of all cancer diagnoses through medical records. In case of personal or familial medical history suggestive of a hereditary cancer susceptibility syndrome, the possibility to undergo genetic testing is extensively discussed as part of the genetic counseling. Since 1994, more than 1,800 families have been seen at the Oncogenetics Unit and about 60 % of all probands consulted for breast cancer risk evaluation.

For the purpose of this study, 1,550 pedigrees of individuals (probands) who consecutively consulted the Oncogenetics and Cancer Prevention Unit between 1994 and 15 June 2012 were reviewed and all breast cancer diagnoses were registered. After having confirmed with the Geneva Cancer Registry that the residence of the patient and the site of breast cancer-related treatments were located in the Geneva Canton, a total of 469 individuals were retained for the study. Variables of interest included in this database are gender, date of birth, vital status, parity, date of breast cancer diagnosis, relationship with the family member attending genetic consultation, date of first consultation, carrying out *BRCA1/BRCA2* testing, date of blood sampling, and genetic testing result. For the carriers of pathogenic *BRCA1* or *BRCA2* mutations, information concerning preventive mastectomy and/or oophorectomy (realized or not, and when relevant, age at surgery) was also considered.

The population-based Geneva Cancer Registry has been described in detail elsewhere [25]. Briefly, the database contains information on all patients with cancer diagnosed in the resident population of the canton of Geneva since

1970. The Geneva Cancer Registry extracts information from various sources and is considered accurate [26]. Recorded data include sociodemographic information, history of breast and ovarian cancers in first- or second-degree relatives, tumor characteristics [27], hormone receptor status, stage of disease at diagnosis, treatment during the first 6 months after diagnosis, occurrence of other primary cancers, and survival status. The Cancer Registry regularly assesses survival. The index date refers to the date of diagnosis confirmation or the date of hospitalization when it preceded the diagnosis and was related to the disease. In addition to passive follow-up (routine examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office in charge of the registration of the resident population. Cause of death is systematically recorded and validated by consulting medical files or, when necessary, by sending a specific questionnaire to the patient's physician. Cause of death is coded according to the International Statistical Classification of Diseases and Related Health problems [28].

Variables of interest included in this database are patient characteristics (date of diagnosis, age at diagnosis, marital status, offspring, level of familial risk, social class, country of birth, sector of care), tumor characteristics (method of detection, stage, size, axillary node involvement, histological subtype, differentiation, hormone receptor status, and HER2 status), types of treatment (surgery, radiotherapy, chemotherapy, and hormonotherapy), and outcome.

Social class was regrouped in three levels: low (manual employees, skilled and unskilled workers), middle (non-manual employees and administrative staff), and high (professionals, executives, administrators, entrepreneurs) based on the patient's last occupation or, if unemployed, that of the spouse.

Breast cancer histology was classified as ductal carcinoma, lobular carcinoma, other and unknown (no microscopic confirmation). Staging was based on the pathologic tumor-node-metastasis (TNM) classification or, when absent, the clinical TNM classification [28]. Hormone receptor status was classified as positive ($\geq$1 % cells expressing receptors) or negative (<1 % cells expressing receptors). Treatment was classified as surgery (breast-conservative surgery, mastectomy), radiotherapy (yes, no), chemotherapy (yes, no), and hormonotherapy (yes, no).

History of breast and ovarian cancers in first- or second-degree relatives is routinely recorded since 1990 [29]. Familial risk was categorized as high (at least 1 first-degree relative with breast/ovarian cancer diagnosed before the age of 50 years, or at least 2 first-degree relatives with breast/ovarian cancer at any age, or at least three cases of breast/ovarian cancer among first- or second-degree relatives), low (no affected first- or second-degree relatives with breast/ovarian cancer), or moderate (all other known family histories) according to a previous study of our group [29].

For the purpose of the current study, we identified all women with a first invasive breast cancer and a moderate or high familial risk recorded between 1990 and 2010 at the Geneva Cancer Registry ($n = 1784$). Linkage of this database with the one of Oncogenetics and Cancer Prevention Unit ($n = 469$) led us to exclude 203 individuals from the latter (9 male patients, 11 breast cancer patients diagnosed before 1990, 33 patients with in situ carcinoma and 150 patients classified as low familial risk). Finally, 75 women who had not themselves undergone genetic counseling were excluded from both databases.

Statistical analysis

We compared patient, tumor, and treatment characteristics among women who had genetic counseling versus women who had not using the Chi square test of heterogeneity. To assess which variables were independently associated from genetic consultation, we performed an unconditional logistic regression including in the model variables significantly associated in univariate analyses. Breast cancer patients who had genetic counseling were considered as cases and those who had not as controls.

Patients were followed for occurrence of metachronous contralateral breast cancer or death until December 31, 2010. Metachronous contralateral breast cancers were defined as all invasive breast cancers occurring after 6 months following the first breast cancer. Cumulative risks for developing metachronous contralateral breast cancer after the first breast cancer were calculated by using the Kaplan–Meier product-limit method and were compared between patients with and without genetic counseling by using the log-rank test. Cox proportional hazards regression was used to calculate hazard ratios and their 95 % confidence intervals (95 % CI). Observations were censored at the time of contralateral breast cancer, or death, whichever occurred first. Patients with synchronous contralateral cancer at the time of first breast cancer ($n = 34$) or having had a prophylactic bilateral mastectomy ($n = 43$) were excluded from this analysis.

We also evaluated the breast cancer-specific survival defined as the interval between the date of diagnosis and the date of death from breast cancer, and the overall survival defined as the interval between the date of diagnosis and the date of death from any cause. We used Cox regression models to evaluate the impact on survival of having genetic counseling.

All tests were two-sided. Statistical significance was established at $P < 0.05$. Analyses were performed using SPSS software (version 15.0.1, SPSS Inc. Chicago, IL, USA).

Results

The studied cohort included 1,709 breast cancer patients with moderate or high familial risk, 191 (11.2 %) had genetic counseling, and 1,518 (88.8 %) never had one. The mean duration of follow-up was not significantly different between patients who underwent genetic counseling and those who did not (79 months and 86 months, respectively; $P = 0.095$). Among the 191 patients who had genetic counseling, 119 (62.3 %) underwent *BRCA1/BRCA2* genetic testing. Out of this group, pathogenic mutations were identified in 23 (19.3 %) patients, whereas the remaining 96 patients had non-informative testing results. Fifteen patients carried a *BRCA1* mutation and eight patients a *BRCA2* mutation.

Determinants of genetic counseling uptake

Characteristics of the entire patients' cohort are presented in Table 1. Genetic counseling uptake increased from 8.4 % (20/238) for patients diagnosed in 1990–1994 to 16.3 % (91/560) for those diagnosed in 2005–2010, whichever was the date of genetic consultation. Among high familial risk patients, 25.1 % (94/374) had genetic counseling versus 7.3 % (97/1335) of patients belonging to moderate-risk group ($P < 0.001$). Compared to patients without genetic counseling, those who underwent genetic counseling were significantly younger (mean, 49.5 years vs 60.0 years, $P < 0.001$), of higher social class ($P = 0.036$), had more often female offspring ($P < 0.001$) and a higher familial risk ($P < 0.001$). Statistically, significant differences in family history between patients who underwent genetic counseling and those who did not were noted: 53.9 % of counseled patients versus 24.8 % of uncounseled patients had two or more first- or second-degree relatives affected by breast/ovarian cancer ($P < 0.001$); these figures were 14.1 and 4.6 %, respectively, when considering affected first-degree relatives only ($P < 0.001$). Patients who had genetic counseling had significantly more often tumors of smaller size ($P = 0.001$) and received more often chemotherapy ($P < 0.001$) than uncounseled patients. To assess which variables were independently associated with the uptake of genetic counseling, we included in a logistic regression model all variables significantly linked to genetic counseling attendance in univariate analyses (i.e., period of diagnosis, age at diagnosis, social class, female offspring, familial risk, tumor size, and chemotherapy). Patients with a significantly higher probability of having genetic counseling were those diagnosed in 2005–2010 compared to those diagnosed in 1990–1994 (odds ratio [OR] 2.2, 95 % CI 1.2–4.0), those with female offspring versus those without (OR 2.0, 95 % CI 1.4–2.9), those with high familial risk versus those with moderate familial risk (OR 5.1, 95 % CI 3.6–7.1), and those with versus without chemotherapy (OR 1.8, 95 % CI 1.2–2.6) (Table 2). By contrast, the ORs for genetic counseling use were significantly decreased for patients aged 50–69 years (OR 0.4, 95 % CI 0.3–0.5) or aged 70 years or more (OR 0.1, 95 % CI 0.1–0.3) compared with patients under 50 years of age. We performed sensitive analyses by adding in the model the four variables found with a P value between 0.05 and 0.10 in univariate analysis (i.e., method of breast cancer detection, tumor differentiation, surgery, and radiotherapy) and also using a backward stepwise logistic regression including all the 21 parameters studied in Table 1. The results were unchanged or were not modified. None of the interactions tested was significant: the P values were 0.93 for interaction between social class and age, 0.97 for interaction between tumor size and chemotherapy, 0.96 for interaction between tumor size and radiotherapy, and 0.46 for interaction between tumor size and surgery.

Impact of genetic counseling uptake on breast cancer outcome

In total, 1,632 patients with a previous unilateral breast cancer diagnosis were included in the analysis of contralateral metachronous breast cancer. Among the 191 patients who underwent genetic counseling, ten women were excluded (four had synchronous bilateral breast cancer and six had contralateral preventive mastectomy associated to primary breast surgery). A total of 36 patients (2.2 %) had developed a contralateral invasive breast cancer in a median period of 2,363 days (range 430–5,984). The hormonal status of both first and second breast tumors was known for 24 of these 36 patients. A moderate agreement was found for the estrogen receptor status (kappa = 0.44, $P = 0.028$) whereas no agreement between the first and second tumors was observed for the progesterone receptor status (kappa = 0.08, $P = 0.63$). Table 3 shows patient, tumor, and treatment characteristics significantly associated with metachronous contralateral breast cancer occurrence in a univariate analysis. Genetic counseling use, diagnosis of cancer in the earlier periods, younger age at diagnosis, high familial risk, larger tumor size, mastectomy, lack of estrogen receptor of the first tumor, the absence of hormonotherapy (which is linked to estrogen receptor status) appeared as risk factors for the development of metachronous contralateral breast cancer in our study. Cumulative risks for developing metachronous contralateral breast cancer after the first diagnosis were significantly different between patients who underwent a genetic consultation versus those who did not (logrank test $P < 0.001$, Fig. 1). The delay for contralateral breast cancer occurrence was similar for patients with

Table 1 Characteristics of breast cancer patients with increased familial risk according to uptake of genetic counseling

	Genetic counseling		P^a
	Yes, $n = 191$ No. (%)	No, $n = 1,518$ No. (%)	
Patient characteristics			
Period of cancer diagnosis			<0.001
1990–1994	20 (11)	218 (14)	
1995–1999	27 (14)	380 (25)	
2000–2004	53 (28)	451 (30)	
2005–2010	91 (48)	469 (31)	
Age at diagnosis, years			<0.001
<50	98 (51)	348 (23)	
50–69	82 (43)	811 (53)	
≥70	11 (6)	359 (24)	
Marital status			0.971
Ever married	162 (85)	1,286 (85)	
Never married	29 (15)	232 (15)	
Female offspring[b]			<0.001
No	68 (36)	858 (57)	
Yes	123 (64)	660 (44)	
Familial risk			<0.001
Moderate	97 (51)	1,238 (82)	
High	94 (49)	280 (18)	
Social class			0.036
High	51 (29)	276 (20)	
Medium	97 (55)	834 (61)	
Low	30 (17)	253 (19)	
Unknown	13 (–)	155 (–)	
Country of birth			0.591
Switzerland	98 (51)	824 (54)	
Southern Europe	52 (27)	363 (24)	
Other	41 (22)	331 (22)	
Sector of care			0.297
Private	90 (47)	776 (51)	
Public	101 (53)	742 (49)	
Tumor characteristics			
Method of detection			0.071
Symptoms	34 (18)	358 (24)	
Breast self-examination	73 (38)	477 (31)	
Clinical screening	10 (5)	125 (8)	
Mammography	74 (39)	558 (37)	
Stage			0.980
I	80 (43)	630 (43)	
II	81 (43)	634 (43)	
III	21 (11)	168 (11)	
IV	5 (3)	48 (3)	
Unknown	4 (–)	38 (–)	
Axillary node			0.130
Negative	101 (54)	883 (60)	
Positive	86 (46)	594 (40)	
Unknown	4 (–)	41 (–)	

Table 1 continued

	Genetic counseling		P^a
	Yes, $n = 191$ No. (%)	No, $n = 1,518$ No. (%)	
Histological subtype			0.436
Ductal	160 (84)	1,218 (80)	
Lobular	23 (12)	207 (14)	
Other	8 (4)	93 (6)	
Differentiation			0.051
Good	47 (26)	397 (28)	
Moderate	81 (44)	707 (50)	
Poor	56 (30)	318 (22)	
Unknown	7 (–)	96 (–)	
Size, mm			0.001
1–20	121 (78)	858 (65)	
21–40	23 (15)	379 (29)	
>40	11 (7)	90 (7)	
Unknown	36 (–)	191 (–)	
Estrogen receptor status[c]			0.204
Positive	141 (84)	1,106 (87)	
Negative	27 (16)	159 (13)	
Unknown	23 (–)	253 (–)	
Progesterone receptor status[c]			0.429
Positive	125 (74)	979 (77)	
Negative	43 (26)	290 (23)	
Unknown	23 (–)	249 (–)	
HER2 receptor status[d]			0.446
Positive	20 (16)	137 (19)	
Negative	103 (84)	578 (81)	
Unknown	68 (–)	803 (–)	
Treatment characteristics			
Surgery			0.096
No	4 (2)	89 (6)	
Mastectomy	51 (27)	393 (26)	
Breast conserving	136 (71)	1,036 (68)	
Radiotherapy			0.096
No	32 (17)	334 (22)	
Yes	159 (83)	1,184 (78)	
Chemotherapy			<0.001
No	74 (39)	920 (61)	
Yes	117 (61)	598 (39)	
Hormonotherapy			0.966
No	53 (28)	419 (28)	
Yes	138 (72)	1,099 (72)	

[a] χ^2 test of heterogeneity

[b] Extracted from the Cantonal Population Office

[c] Recorded since 1995

[d] Recorded since 2001

genetic counseling and for those without genetic counseling (2,550 and 3,194 days, respectively; $P = 0.298$). In a Cox model accounting for other variables significantly associated with contralateral breast cancer occurrence (i.e., period of diagnosis, age at diagnosis, familial risk, tumor size, breast surgery and hormonotherapy), the risk (hazard ratio [HR]) for a contralateral breast cancer for patients with versus without genetic counseling was 2.2 (95 % CI 1.0–5.2, $P = 0.063$). Further adjustment on other potential determinants of metachonous breast cancer, including

Table 2 Adjusted odds ratio (OR) for the uptake of genetic counseling

Variables	Adjusted OR[a] (95 % CI)	$P_{(heterogeneity)}$
Period of diagnosis		
1990–1994	1 (Reference)	0.001
1995–1999	0.8 (0.4–1.6)	
2000–2004	1.3 (0.7–2.5)	
2005–2010	2.2 (1.2–4.0)**	
Age at diagnosis, years		
<50	1 (Reference)	<0.001
50–69	0.4 (0.3–0.5)***	
≥70	0.1 (0.1–0.3)***	
Social class		
High	1 (Reference)	0.406
Medium	0.8 (0.5–1.2)	
Low	0.7 (0.4–1.2)	
Female offspring		
No	1 (Reference)	<0.001
Yes	2.0 (1.4–2.9)***	
Familial risk		
Moderate	1 (Reference)	<0.001
High	5.1 (3.6–7.1)***	
Tumor size, mm		
1–20	1 (Reference)	0.004
21–40	0.4 (0.3–0.7)**	
>40	0.9 (0.4–1.9)	
Chemotherapy		
No	1 (Reference)	0.004
Yes	1.8 (1.2–2.6)**	

[a] Adjusted for all other variables

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3 Factors associated with occurrence of metachronous contralateral breast cancer

Variables	*n*	Metachronous contralateral breast cancer *n* (%)	P^a
Genetic counseling			
No	1,451	26 (1.8)	0.001
Yes	181	10 (5.5)	
Period of diagnosis			
1990–1994	229	9 (3.9)	0.001
1995–1999	386	15 (3.9)	
2000–2004	482	10 (2.1)	
2005–2010	535	2 (0.4)	
Age at diagnosis, years			
<50	426	15 (3.5)	0.021
50–69	857	19 (2.2)	
≥70	349	2 (0.6)	
Familial risk			
Moderate	1,278	22 (1.7)	0.011
High	354	14 (4.0)	
Tumor size, mm			
1–20	945	15 (1.6)	0.022
21–40	377	9 (2.4)	
>40	94	6 (6.4)	
Unknown	216	6 (2.8)	
Surgery			
No	91	0 (0.0)	0.044
Mastectomy	384	14 (3.6)	
Breast conservation	1,157	22 (1.9)	
Hormonotherapy			
No	452	18 (4.0)	0.002
Yes	1,180	18 (1.5)	

[a] χ^2 test of heterogeneity; univariate analysis

social class, sector of care, method of breast cancer detection, tumor differentiation, surgery, and radiotherapy, yielded a HR 2.0 (95 % CI 0.9–4.9, $P = 0.108$).

Among the 181 patients who benefited from genetic counseling included in the analysis of contralateral metachronous breast cancer, 111 (61.3 %) performed genetic testing and 18 of them (16.2 %) carried *BRCA1/BRCA2* germ-line mutations. Stratification by *BRCA1/BRCA2* mutation status showed that the occurrence of contralateral breast cancer was 8-fold higher among mutation carriers than among non-carriers (33 vs 4 %, $P < 0.001$). The risk of developing a contralateral breast cancer for patients with versus without *BRCA1/BRCA2* mutations was significantly higher (crude HR 10.5, 95 % CI 2.9–38.5, $P < 0.001$).

The overall survival did not significantly differ between patients who underwent genetic counseling and those who did not (age-adjusted HR 0.8, 95 % CI 0.5–1.3, $P = 0.906$). Similarly, breast cancer-specific survival was not significantly different between the two groups (age-adjusted HR 0.8, 95 %CI 0.5–1.4, $P = 0.484$).

Discussion

To our knowledge, this is the first population-based study assessing the rate of genetic counseling uptake among breast cancer patients with a positive family history and to demonstrate the impact of such counseling on breast cancer outcome. This study has been carried out with the support of the Oncogenetics and Cancer Prevention Unit, which is the only center providing genetic consultation since 1994 for breast cancer familial aggregation or hereditary predisposition syndromes, and the Geneva Cancer Registry, which is the oldest registry in Switzerland to collect and analyze cancer data for the entire population of Geneva. In Switzerland, modalities of breast cancer treatment are

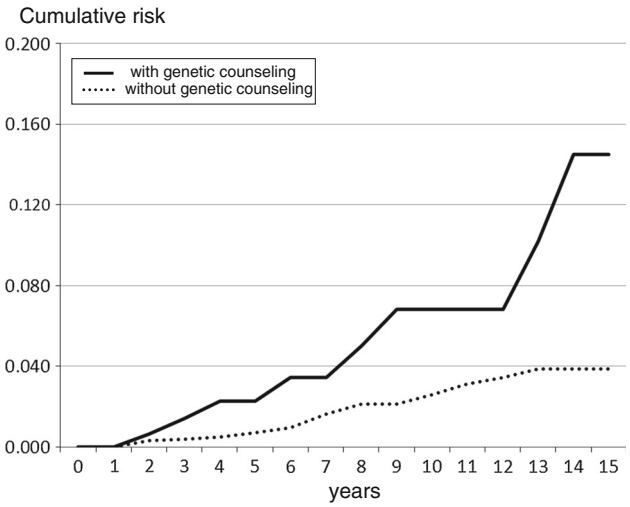

Fig. 1 Cumulative risk for metachronous contralateral breast cancer according to uptake of genetic counseling

Curves were calculated using the Kaplan-Meier method; logrank test P<0.001.

Genetic counseling	0-3 years		4-7 years		8-11 years		12-15 years	
	n	*Obs*	*n*	*Obs*	*n*	*Obs*	*n*	*Obs*
No	1451	5	1082	10	656	7	330	2
Yes	181	2	119	2	66	2	33	2

n is the number of persons at risk at the beginning of the period of follow-up. *Obs* is the number of observed cases of metachronous contralateral breast cancer during the period of follow-up.

This figure did not include 4 cases of metachronous contralateral breast cancer occurring after a follow-up period of over 15 years (2 in the group with genetic counselling and 2 in the group without genetic counselling) because of the small number of persons remaining at risk.

chosen by a multidisciplinary staff including surgeons, chemo- and radiotherapists according to the international clinical guidelines. Procedures are the same in the public and the private sectors of care. Accordingly, all patients are offered the same options of treatment at first issue. Globally, 11.2 % of breast cancer patients that could potentially benefit from genetic counseling were effectively seen at the Oncogenetics and Cancer Prevention Unit. The geographic dispersal of some of the families and the cosmopolitan characteristics of the Geneva population with an important turn-over may partially explain this low proportion of uptake compared to less mobile populations. It is possible that some of breast cancer patients sought counseling somewhere out of the Geneva canton, so that 11.2 % would be a conservative estimate. Approximately, one out of four high familial risk breast cancer patients underwent genetic counseling. In our opinion, this is an important result since consultation process, genetic analysis, and specific surveillance/preventive measures are mostly addressed to high- rather than moderate-breast cancer risk patients. Our data are consistent with previous studies that found a statistically significant association between having a positive family history and hypothetical or real uptake of *BRCA1/BRCA2* genetic testing [21, 30, 31].

In this study, we showed that recent period of breast cancer diagnosis, young age at diagnosis, female offspring, and high familial risk were statistically significant determinants of genetic counseling uptake. The increasing use of genetic counseling over time has previously been reported [32]. This is not surprising considering the better knowledge on prevalence and penetrance of *BRCA1/BRCA2* mutations [14, 33–38], the impact of risk management recommendations on breast cancer prevention and mortality [39, 40], and the growing interest in genetics showed by physicians and general population. Therefore, it is anticipated that a higher proportion of breast cancer patients and their relatives will benefit from appropriate clinical recommendations in the future. Early-onset breast cancer is a criterion to refer patients to genetic counseling [41–43]. Thus, it was expected that breast cancer patients

diagnosed before 50 years of age were more likely to undergo genetic counseling than patients diagnosed after 50 years of age. The association between genetic counseling uptake and female offspring found in our study is in agreement with results from previous studies on predictive *BRCA1/BRCA2* genetic testing [15–20]. These studies showed that one of the currently reported motivations to undergo genetic counseling is to determine the cancer risk of the offspring, which may in the future have an impact on their clinical surveillance.

With regard to a possible association between social class levels and use of genetic counseling, we cannot exclude that patients belonging to lower socio-economic classes could be less concerned by genetic counseling and medical screening than individuals of higher social level. Of note, this type of medical consultation, as well as the cost of testing for most of the cancer genetic predisposition syndromes, is covered by the mandatory health insurance system for all Swiss citizens. Consequently, in our opinion, genetic counseling-related costs *per se* would not or little influence the decision to uptake genetic counseling. The fact that genetic counseling uptake was higher among patients with high social level could be related to a more effective communication process between the physicians and their patients. Noteworthy, receiving chemotherapy treatment was another factor associated with the uptake of genetic counseling. This result could reflect a particular awareness about genetic and familial risk of medical oncologists compared to other physicians [44]. It could also reflect a heightened awareness regarding more adequate or more complete cancer treatment among breast cancer patients with affected family members who underwent genetic counseling.

We found a twofold higher risk of metachronous contralateral breast cancer among patients with genetic counseling uptake than for those without. This result is consistent with the fact that early-onset disease and strong positive family history are both criteria to refer people to genetic evaluation and that they are well-established risk factors for contralateral breast cancer [7, 8, 10, 45]. However, it could also be a consequence of a more intensive surveillance program/self-observation recommended by genetic consultants to moderate- and high-risk patients. Notably, in five out of 10 patients who underwent genetic counseling and developed metachronous breast cancer, contralateral cancer diagnosis occurred after the genetic consultation process and all of these patients followed an enhanced surveillance.

No significant differences in overall survival and in breast cancer-specific survival were observed between patients with and without genetic counseling uptake. Despite a study period of 20 years, the number of deaths from breast cancer was limited among patients who had genetic counseling ($n = 15$) and, accordingly, the statistical power was low to detect differences between the two groups.

The main limitation of the study is the fact that information concerning cancer family history was extracted from medical files or derived by questioning physicians and not directly from the patients. The familial risk of breast cancer was established integrating information available at the time of cancer diagnosis; therefore, patients who developed a positive family history after breast cancer diagnosis could have been missed. Moreover, family structure/size and details of the concerned branch of the family were not taken into account to categorize the familial risk. However, information on family history is accurate as attested by a previous study of our group [46]. Education is not routinely recorded by the Geneva Cancer Registry. We used patient's last occupation, or if unemployed, that of the spouse in order to create a three-level indicator of socioeconomic status. Occupational social class and education measures have been shown to be highly correlated. Despite the fact that the 3 levels of socioeconomic indicators used can only be considered as an approximate indicator of education level, confounding from education is likely to be limited.

In conclusion, we evaluated the actual proportion of breast cancer patients with positive family history of breast cancer that benefit from genetic counseling and assessed the clinical outcome in terms of contralateral breast cancer occurrence and survival in our population. The uptake of genetic counseling among patients with personal and family history of breast cancer is notably increasing overtime. We found a significant proportion of high familial risk patients effectively undergoing genetic consultation process. A better knowledge of demographic and clinical determinants of attending a cancer genetic unit should be helpful to improve the genetic counseling activity and thus, to reach more at-risk breast cancer individuals concerned by effective surveillance and prevention measures.

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References

1. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA (1997) Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 71(5):800–809
2. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209

women with breast cancer and 101,986 women without the disease. Lancet 358(9291):1389–1399
3. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 62(3):676–689
4. Lalloo F, Evans DG (2012) Familial breast cancer. Clin Genet 82(2):105–114
5. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K, American Society of Clinical Oncology (2010) American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol 28(5):893–901
6. Dawson LA, Chow E, Goss PE (1998) Evolving perspectives in contralateral breast cancer. Eur J Cancer 34(13):2000–2009
7. Chen Y, Thompson W, Semenciw R, Mao Y (1999) Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev 8(10):855–861
8. Kollias J, Ellis IO, Elston CW, Blamey RW (1999) Clinical and histological predictors of contralateral breast cancer. Eur J Surg Oncol 25(6):584–589
9. Hartman M, Czene K, Reilly M, Bergh J, Lagiou P, Trichopoulos D, Adami HO, Hall P (2005) Genetic implications of bilateral breast cancer: a population based cohort study. Lancet Oncol 6(6):377–382
10. Beckmann KR, Buckingham J, Craft P, Dahlstrom JE, Zhang Y, Roder D, Stuart-Harris R (2011) Clinical characteristics and outcomes of bilateral breast cancer in an Australian cohort. Breast 20(2):158–164
11. Graeser MK, Engel C, Rhiem K, Gadzicki D, Bick U, Kast K, Froster UG, Schlehe B, Bechtold A, Arnold N, Preisler-Adams S, Nestle-Kraemling C, Zaino M, Loeffler M, Kiechle M, Meindl A, Varga D, Schmutzler RK (2009) Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 27(35):5887–5892
12. Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, Xue S, Teraoka S, Bernstein L, Capanu M, Reiner AS, Riedel ER, Thomas DC, Mellemkjaer L, Lynch CF, Boice JD Jr, Anton-Culver H, Bernstein JL (2010) Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol 28(14):2404–2410
13. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, Olopade OI, Domchek S, McLennan J, Eisen A, Foulkes WD, Rosen B, Sun P, Narod SA (2011) Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 104(9):1384–1392
14. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC, Easton DF, On behalf of EMBRACE (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 105(11):812–8225
15. Julian-Reynier C, Sobol H, Sevilla C, Nogues C, Bourret P, French Cancer Genetic N (2000) Uptake of hereditary breast/ovarian cancer genetic testing in a French national sample of BRCA1 families. The French Cancer Genetic Network. Psychooncology 9(6):504–510
16. Hagoel L, Dishon S, Almog R, Silman Z, Bisland-Becktell S, Rennert G (2000) Proband family uptake of familial-genetic counselling. Psychooncology 9(6):522–527
17. Brooks L, Lennard F, Shenton A, Lalloo F, Ambus I, Ardern-Jones A, Belk R, Kerr B, Craufurd D, Eeles R, Evans DG (2004) BRCA1/2 predictive testing: a study of uptake in two centres. Eur J Hum Genet 12(8):654–662
18. Landsbergen K, Verhaak C, Kraaimaat F, Hoogerbrugge N (2005) Genetic uptake in BRCA-mutation families is related to emotional and behavioral communication characteristics of index patients. Fam Cancer 4(2):115–119
19. Evans DG, Binchy A, Shenton A, Hopwood P, Craufurd D (2009) Comparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. Clin Genet 75(2):124–132
20. Sanz J, Ramon y Cajal T, Torres A, Darder E, Gadea N, Velasco A, Fortuny D, Lopez C, Fisas D, Brunet J, Alonso MC, Balmana J (2010) Uptake of predictive testing among relatives of BRCA1 and BRCA2 families: a multicenter study in northeastern Spain. Fam Cancer 9(3):297–304
21. Ropka ME, Wenzel J, Phillips EK, Siadaty M, Philbrick JT (2006) Uptake rates for breast cancer genetic testing: a systematic review. Cancer Epidemiol Biomarkers Prev 15(5):840–855
22. Schwartz MD, Hughes C, Roth J, Main D, Peshkin BN, Isaacs C, Kavanagh C, Lerman C (2000) Spiritual faith and genetic testing decisions among high-risk breast cancer probands. Cancer Epidemiol Biomarkers Prev 9(4):381–385
23. Clark SB, Bluman LG, Borstelmann N, Regan K, Winer EP, Rimer BK, Skinner CS (2000) Patient motivation, satisfaction, and coping in genetic counseling and testing for BRCA1 and BRCA2. J Genet Couns 9(3):219–235
24. Wood ME, Mullineaux L, Rahm AK, Fairclough D, Wenzel L (2000) Impact of BRCA1 testing on women with cancer: a pilot study. Genet Test 4(3):265–272
25. Bouchardy C, Benhamou S, Schaffar R, Verkooijen HM, Fioretta G, Schubert H, Vinh-Hung V, Soria JC, Vlastos G, Rapiti E (2011) Lung cancer mortality risk among breast cancer patients treated with anti-estrogens. Cancer 117(6):1288–1295
26. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P (2007) Cancer incidence in five continents, vol IX. IARC Scientific Publications No 160, Lyon
27. Percy C, Fritz A, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (2000) International classification of diseases for oncology, 3rd edn. World Health Organization, Geneva
28. Sobin LH, Wittekind Ch (2002) TNM classification of malignant tumours, UICC, 6th edn. Wiley, New York
29. Verkooijen HM, Chappuis PO, Rapiti E, Vlastos G, Fioretta G, Sarp S, Sappino AP, Schubert H, Bouchardy C (2006) Impact of familial risk factors on management and survival of early-onset breast cancer: a population-based study. Br J Cancer 94(2):231–238
30. Bosompra K, Flynn BS, Ashikaga T, Rairikar CJ, Worden JK, Solomon LJ (2000) Likelihood of undergoing genetic testing for cancer risk: a population-based study. Prev Med 30(2):155–166
31. Bottorff JL, Ratner PA, Balneaves LG, Richardson CG, McCullum M, Hack T, Chalmers K, Buxton J (2002) Women's interest in genetic testing for breast cancer risk: the influence of sociodemographics and knowledge. Cancer Epidemiol Biomarkers Prev 11(1):89–95
32. Pujol P, Lyonnet DS, Frebourg T, Blin J, Picot MC, Lasset C, Dugast C, Berthet P, de Paillerets BB, Sobol H, Grandjouan S, Soubrier F, Buecher B, Guimbaud R, Lidereau R, Jonveaux P, Houdayer C, Giraud S, Olschwang S, Nogue E, Galibert V, Bara C, Nowak F, Khayat D, Nogues C (2013) Lack of referral for genetic counseling and testing in BRCA1/2 and Lynch

syndromes: a nationwide study based on 240,134 consultations and 134,652 genetic tests. Breast Cancer Res Treat 141(1):135–144
33. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE (1994) Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 343(8899):692–695
34. Claus EB, Schildkraut JM, Thompson WD, Risch NJ (1996) The genetic attributable risk of breast and ovarian cancer. Cancer 77(11):2318–2324
35. Whittemore AS, Gong G, Itnyre J (1997) Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 60(3):496–504
36. Anglian Breast Cancer Study Group (2000) Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 83(10):1301–1308
37. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72(5):1117–1130
38. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25(11):1329–1333
39. Rebbeck TR, Kauff ND, Domchek SM (2009) Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 101(2):80–87
40. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304(9):967–975
41. NCCN Clinical Practice Guidelines in Oncology (2010) Genetic/familial high-risk assessment: breast and ovarian, version 4.2013. www.nccn.org
42. ACOG Committee on Pratice Bulletins (2009) Hereditary breast and ovarian cancer syndrome. Gynecol Oncol 113(1):6–11
43. Gadzicki D, Evans DG, Harris H, Julian-Reynier C, Nippert I, Schmidtke J, Tibben A, van Asperen CJ, Schlegelberger B (2011) Genetic testing for familial/hereditary breast cancer-comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. J Community Genet 2(2):53–69
44. Zon RT, Goss E, Vogel VG, Chlebowski RT, Jatoi I, Robson ME, Wollins DS, Garber JE, Brown P, Kramer BS, American Society of Clinical Oncology (2009) American Society of Clinical Oncology policy statement: the role of the oncologist in cancer prevention and risk assessment. J Clin Oncol 27(6):986–9931
45. Bouchardy C, Benhamou S, Fioretta G, Verkooijen HM, Chappuis PO, Neyroud-Caspar I, Castiglione M, Vinh-Hung V, Vlastos G, Rapiti E (2011) Risk of second breast cancer according to estrogen receptor status and family history. Breast Cancer Res Treat 127(1):233–241
46. Verkooijen HM, Fioretta G, Chappuis PO, Vlastos G, Sappino AP, Benhamou S, Bouchardy C (2004) Set-up of a population-based familial breast cancer registry in Geneva, Switzerland: validation of first results. Ann Oncol 15(2):350–353