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Impact of family history of breast cancer on tumour characteristics, treatment, risk of second cancer and survival among men with breast cancer

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Summary

BACKGROUND: Male breast cancer patients have a higher risk of developing a second primary cancer, but whether this risk differs according to the family history of breast or ovarian cancers remains to be elucidated. We aimed to determine the effect of a positive family history among men diagnosed with breast cancer on tumour characteristics, treatment, second cancer occurrence and overall survival.

METHODS: We included 46 patients with known information on the family history of breast or ovarian cancer recorded at the Geneva Cancer Registry between 1970 and 2009. We compared patients with and without a family history with chi-square of heterogeneity, risk of second cancer with standardised incidence ratios (SIRs), and overall survival by Kaplan-Meier methods.

RESULTS: Approximately 20% of men with breast cancer had a positive family history. No differences were observed between men with and without familial risk except that patients with increased risk were more likely to receive radiotherapy and hormone therapy when compared with patients without familial risk. This more complete therapy is likely to be explained by the heightened awareness of cancer treatment among breast cancer patients with affected family members. Six men developed a second cancer. SIRs for second cancer were not significantly increased among patients with or without familial risk (1.93, 95% confidence interval [CI] 0.23–6.97 and 1.04, 95% CI 0.28–2.66, respectively). Overall survival was not significantly different between the two groups.

CONCLUSIONS: Prognosis was similar among patients with or without familial risk. Our results are however based on small numbers and larger registry-based cohorts of males with precise data on familial risk are still warranted.

Key words: *breast neoplasms; male; breast cancer; familial; neoplasms; second primary; survival; epidemiology*

Introduction

Breast cancer is the most common cancer among women in most countries, but it is rare in men, accounting for fewer than 1% of all breast cancer cases [1]. Rare germ-line mutations in *BRCA1* and *BRCA2* are thought to account for between 5% and 10% of all breast cancer cases in unselected populations. Male breast cancer (BC) is more strongly associated with the presence of an inherited *BRCA2* mutation than with the presence of a *BRCA1* mutation, and the lifetime risks of breast cancer for male mutation carriers are about 7% and 1%, respectively [2]. The scarcity of male BC has resulted in comparatively few epidemiological studies assessing the prevalence of a family history of breast and/or ovarian cancer among male BC patients, and its effect on male BC risks. Population-based studies reported that approximately 20% of men with breast cancer have a positive family history of the disease for at least one-degree relative [3–5]. Similar to that of breast cancer in women [6], an increased risk of breast cancer in men has been associated with a family history of breast cancer [5]. Several studies reported that male BC patients had a higher risk of developing a second primary cancer, but none of them assessed whether this risk was modified by a positive family history [7–11].

In this study, we determined the prevalence of a positive family history of breast/ovary cancer among male BC patients. In addition, we evaluated the impact of family history, tumour characteristics and treatment on second cancer occurrence and overall survival.

Materials and methods

Using information from the population-based Geneva Cancer Registry, we identified 71 men (0.7%) out of 10,800 primary invasive breast cancers between 1970 and 2009. The Geneva Cancer Registry collects information from various sources and is considered to be accurate [12]. All hospitals, pathology laboratories and private practitioners in the canton are requested to report all cancer cases to the Registry. Trained tumour registrars systematically abstract data from medical and laboratory records. Physicians regularly receive enquiry forms in order to complete missing clinical and therapeutic data.

Recorded data include sociodemographic information, tumour characteristics (coded according to the International Classification of Diseases for Oncology, ICD-O), treatment given during the first six months after diagnosis, occurrence of other primary cancers, and survival status [13]. No information on *BRCA1*/*BRCA2* status is collected.

Information on complete family history among first- and second-degree relatives (maternal and paternal sides, age at diagnosis, cancer site) has been recorded from medical files since 1990. This information was available for all the 46 males diagnosed for BC in 1990 or later. The validity of family history on breast and/or ovarian cancers is considered high [14]. Depending on the number of family members affected with breast or ovarian cancers, their degree of kinship and the age at onset, we classified breast cancer patients into three familial risk categories as previously described [15]. In brief, the low familial risk category included breast cancer patients without first- or second-degree relatives with breast or ovarian cancer. The high familial risk category included patients who reported one of the following family histories: ≥1 first-degree relative with breast and/or ovarian cancer ≤50 years or ≥2 first-degree relatives with breast and/or ovarian cancer at any age or ≥3 cases of breast and/or ovarian cancer among first- or second-degree relatives. Patients with other types of family history were classified into the moderate familial risk category.

Breast cancer staging was based on the pathologic tumour-node-metastasis (TNM) classification or, when absent, the clinical TNM classification [16]. Hormone-receptor status was classified as positive (≥1% of tumour cells expressing receptors) or negative 0% of tumour cells expressing receptors). Treatment received within six months following breast cancer diagnosis was classified as surgery (breast-conservative surgery or mastectomy, yes/no), radiotherapy (yes/no), hormone therapy (yes/no) and chemotherapy (yes/no).

We compared patient and tumour characteristics among males with an increased familial risk (defined by combining moderate and high familial risk categories) versus those with a low familial risk with a chi-squared test of heterogeneity. Patients were followed up for secondary cancer occurrence from six months after the date of breast cancer diagnosis until December 31st 2010. Person-years at risk were calculated to the end of follow-up, date of departure from the Geneva canton, date of second cancer diagnosis or date of death, whichever came first. We compared the incidence of second cancer occurrence among male breast cancer patients with cancer occurrence expected in the male general population with age-period standardised incidence ratios (SIRs) [17]. The expected number of cancers was calculated by multiplying the person-years at risk (stratified by 5-year intervals of age and calendar year) by the strata-specific cancer incidence rates of the male population of the canton of Geneva. The SIR is defined as the ratio of the observed (O) to the expected (E) number of events and represents the relative risk, adjusted for age and calendar year, of developing a second cancer for patients diagnosed with first breast cancer as compared with men without such a diagnosis. To assess statistical significance, exact 95% confidence intervals (CIs) were computed around the SIR assuming that the observed number of second cancers followed a Poisson distribution. We used Kaplan-Meier analysis to calculate breast cancer survival rates for men at increased familial risk and those at low familial risk.

Results

Among the 46 male BC patients with known information on family history, nine (19.6%) were classified as having an increased familial risk of breast and/or ovary cancer, including five at moderate familial risk and four at high familial risk. For all the nine male BC patients, a history of breast cancer, but none of ovarian cancer, was reported in first-degree relatives (four among sisters and five among mothers).

Age at breast cancer diagnosis, stage at diagnosis, histological subtype and hormone receptor status were similar among male BC patients with and without familial risk (table 1). All breast carcinomas were HER2 negative. Male BC patients with a family history of breast cancer were more often treated with radiotherapy than those without a family history (78% vs 35%, $p < 0.03$). This result was not explained by higher tumour size (data not shown) or positive axillary nodes among patients with a positive family history. In addition, all of them received hormone therapy, whereas this treatment was administered to half of those without familial risk ($p < 0.007$).

After a median follow-up of 50 months (mean, 63 months), 6 male BC patients out of 46 (13%) developed a second malignancy (excluding nonmelanoma tumours and *in-situ* carcinomas) at least six months after the diagnosis of breast cancer. Sites of second cancers were as follows: prostate (one case), lung (one case), tongue (two cases), stomach (one case) and contralateral breast (one case). The time interval between breast cancer diagnosis and date of second cancer varied from 24 months to 11.6 years. Compared with the male general population, the risk of developing a second primary cancer among male breast cancer patients was not significantly increased (SIR = 1.23, 95% CI 0.45–2.67; table 2). After stratification by familial risk, the excess risk of second cancer occurrence was not significant either among male BC patients with low familial risk (SIR = 1.04, 95%CI 0.28–2.66) or among those with increased familial risk (SIR = 1.93, 95% CI 0.23–6.97).

At 10 years, the survival rate of male BC patients with increased familial risk was 72% (95% CI 38%–100%) compared with 30% (95% CI 10%–50%) for those with low fa-

milial risk (log-rank test: p = 0.27). No death from breast cancer was observed among patients with familial risk whereas 11 out of 19 deaths were due to breast cancer among those without familial risk.

Discussion

Although family history of breast and/or ovary cancers is one of the strongest risk factors for breast cancer among men, little is known on its prevalence in unselected male BC case series and its impact on disease management and risk of subsequent malignancies. In agreement with previous population-based studies reporting that around 20% of men with breast cancer have a first-degree relative with the disease, we observed an equal proportion among our male BC patients [3–5].

Male BC patients were reported to present a more advanced stage of disease than women mainly because they are less likely to report symptoms that would lead to an earlier diagnosis [2, 18]. However, breast carcinoma in men is not

Table 1: Characteristics of men with breast cancer according to family history of breast cancer.

	Familial risk of breast/ovarian cancer		
	Low (n = 37)	**Moderate/high (n = 9)**	**p-value**
Age at diagnosis, mean years (SD)	69 (12)	68 (13)	0.72
Stage, n (%)			
I	4 (13%)	3 (33%)	0.58
II	14 (45%)	3 (33%)	
III	9 (29%)	2 (22%)	
IV	4 (13%)	1 (11%)	
Histological subtype			
Ductal	32 (86%)	7 (78%)	0.61
Others	5 (14%)	2 (22%)	
Axillary nodes			0.35
Negative	11 (38%)	5 (56%)	
Positive	18 (62%)	4 (44%)	
Unknown	8 (–)		
Oestrogen receptor status[a]			
Negative	2 (8%)	0 (0%)	1.00
Positive	22 (92%)	8 (100%)	
Unknown	13 (–)	1 (–)	
Progesterone receptor status[a]			
Negative	4 (17%)	1 (12%)	1.00
Positive	20 (83%)	7 (88%)	
Unknown	13 (–)	1 (–)	
HER2 status[b]			1.00
Negative	12 (100)	7 (100)	
Positive	0 (0%)	0 (0%)	
Unknown	25 (–)	2 (–)	
Surgery			
No	6 (16%)	1 (11%)	1.000
Yes[c]	31 (84%)	8 (89%)	
Radiotherapy			
No	24 (65%)	2 (22%)	0.0288
Yes	13 (35%)	7 (78%)	
Hormone therapy			
No	19 (51%)	0 (0%)	0.0062
Yes	18 (49%)	9 (100%)	
Chemotherapy			
No	25 (68%)	6 (67%)	0.624
Yes	12 (32%)	3 (33%)	

[a] Information collected from 1995
[b] Information collected from 2001
[c] For the “low” category: 24 mastectomies and 7 breast conservatory surgeries (BCS)
For the “high” category: 8 mastectomies

Table 2: Standardised incidence rates (SIRs) of secondary cancer among men with breast cancer according to familial risk of breast cancer.

Familial risk	**Person-years**	**Observed cases (O)**	**Expected cases (E)**	**SIR (O/E)**	**95% CI**
Low	173.60	4	3.85	1.04	0.28–2.66
Moderate/high	48.17	2	1.04	1.93	0.23–6.97
All	221.78	6	4.88	1.23	0.45–2.67

CI = Confidence interval

biologically more aggressive than in women, and five-year survival rates did not differ from those observed for female breast cancer patients nor were they significantly better [18–21]. In our study, mean age at diagnosis of breast cancer and presentation with stages III/IV disease were comparable in men with and without a family history of breast cancer, confirming previous observations reported by Hill and colleagues [22].

Breast cancer patients with affected family members will have heightened awareness regarding cancer treatment and, as a result, receive more adequate or more complete therapy [15]. The current study confirms that, as for women with breast cancer, male BC patients at increased familial risk were more likely to receive radiotherapy and hormone therapy when compared with male BC patients without a family history.

The incidence of second primary cancer occurrence in male BC patients with a positive familial history of breast cancer has been poorly examined. We found no elevation of the overall risk of subsequent malignancies after breast cancer for men with a family history of breast cancer or for those without a family history; however, the SIRs are based on only four and two patients, respectively, and had wide confidence intervals. We found a better survival rate among patients with increased family history of breast/ovarian cancer than for those wothout a family history. This difference, not statistically significant, could not be explained by age or stage at diagnosis nor by length of follow-up which was very similar in the two groups. The more complete cancer treatment among patients with family history is the most likely explanation for the better survival rate observed in this group.

The strength of this study is its population-based design with detailed collection of patient and tumour characteristics. Moreover, information on family history is accurate as attested by its high sensitivity and specificity (98% and 97%, respectively) [14], although we cannot rule out a possible misclassification of some patients, which could alter the results substantially.

On the other hand, and despite a study period of forty years, the limitations of this study are the small number of male BC patients and its low statistical power to detect differences in cancer risks, due to further subclassifications into low and moderate/high familial risk of breast cancer.

Larger registry-based cohorts of affected males with precise data on familial risks are still warranted to provide more precise results.

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References

1 Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006;367(9510):595–604.

2 Johansen Taber KA, Morisy LR, Osbahr AJ, III, Dickinson BD. Male breast cancer: risk factors, diagnosis, and management (Review). Oncol Rep. 2010;24(5):1115–20.

3 Friedman LS, Gayther SA, Kurosaki T, Gordon D, Noble B, Casey G, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet. 1997;60(2):313–9.

4 Ewertz M, Holmberg L, Tretli S, Pedersen BV, Kristensen A. Risk factors for male breast cancer – a case-control study from Scandinavia. Acta Oncol. 2001;40(4):467–71.

5 Rosenblatt KA, Thomas DB, McTiernan A, Austin MA, Stalsberg H, Stemhagen A, et al. Breast cancer in men: aspects of familial aggregation. J Natl Cancer Inst. 1991;83(12):849–54.

6 Hartman M, Hall P, Edgren G, Reilly M, Lindstrom L, Lichtenstein P, et al. Breast cancer onset in twins and women with bilateral disease. J Clin Oncol. 2008;26(25):4086–91.

7 Auvinen A, Curtis RE, Ron E. Risk of subsequent cancer following breast cancer in men. J Natl Cancer Inst. 2002;94(17):1330–2.

8 Bagchi S. Men with breast cancer have high risk of second cancer. LancetOncol. 2007;8(3):198.

9 Grenader T, Goldberg A, Shavit L. Second cancers in patients with male breast cancer: a literature review. J Cancer Surviv. 2008;2(2):73–8.

10 Hemminki K, Granstrom C. Re: Risk of subsequent cancer following breast cancer in men. J Natl Cancer Inst. 2002;94(24):1892.

11 Wernberg JA, Yap J, Murekeyisoni C, Mashtare T, Wilding GE, Kulkarni SA. Multiple primary tumors in men with breast cancer diagnoses: a SEER database review. J Surg Oncol. 2009;99(1):16–9.

12 Bouchardy C. Switzerland, Geneva. In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M et al., editors. *Cancer Incidence in Five Continents Vol. IX.* Lyon: International Agency for Research on Cancer; 2007. p. 369–70.

13 *ICD-O International classification of diseases for oncology.* 3 ed. Geneva: World Health Organization (WHO); 2000.

14 Verkooijen HM, Fioretta G, Chappuis PO, Vlastos G, Sappino AP, Benhamou S, et al. Set-up of a population-based familial breast cancer registry in Geneva, Switzerland: validation of first results. Ann Oncol. 2004;15(2):350–3.

15 Verkooijen HM, Chappuis PO, Rapiti E, Vlastos G, Fioretta G, Sarp S, et al. Impact of familial risk factors on management and survival of early-onset breast cancer: a population-based study. Br J Cancer. 2006;94(2):231–8.

16 *TNM Classification of Malignant Tumours.* 6 ed. New York: John Wiley & Sons; International Union Against Cancer (UICC); 2002.

17 Statistical Methods in Cancer Research – Volume II – The Design and Analysis of Cohort Studies. Breslow NE & Day NE, eds. IARC Scientific Publications No. 82, 1987.

18 Miao H, Verkooijen HM, Chia KS, Bouchardy C, Pukkala E, Laronningen S, et al. Incidence and outcome of male breast cancer: an international population-based study. J Clin Oncol. 2011;29(33):4381–6.

19 Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer. 2004;101(1):51–7.

20 Kiluk JV, Lee MC, Park CK, Meade T, Minton S, Harris E, et al. Male breast cancer: management and follow-up recommendations. BreastJ. 2011;17(5):503–9.

21 Cutuli B, Le Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, et al. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. Crit Rev Oncol Hematol. 2010;73(3):246–54.

22 Hill A, Yagmur Y, Tran KN, Bolton JS, Robson M, Borgen PI. Localized male breast carcinoma and family history. An analysis of 142 patients. Cancer. 1999;86(5):821–5.