Breast Cancer Res Treat (2017) 166:897–902
DOI 10.1007/s10549-017-4468-1

EPIDEMIOLOGY

Familial associations of male breast cancer with other cancers

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Received: 16 May 2017 / Accepted: 16 August 2017 / Published online: 23 August 2017

Abstract
Purpose Male breast cancer is associated with female breast cancer in families but whether male breast cancer clusters with other discordant cancers has not been studied. As concordant male breast cancers are utterly rare, discordant associations of male breast cancer with other cancers may reveal genetic and possible environmental risk factors contributing to male breast cancer susceptibility.
Methods We calculated relative risks (RRs) for male breast cancer in families with discordant cancers, and conversely, for discordant cancers in families of male breast cancer patients, based on 15.7 million individuals in the Swedish Family-Cancer Database.
Results Among 1428 male breast cancer patients, 16.2% had a female relative diagnosed with breast cancer. Ovarian and female anal cancers showed the strongest associations with male breast cancer (p value < 0.0005). The other significant associations included colorectal, small intestinal, and thyroid cancers, cancer of unknown primary and non-Hodgkin lymphoma but these were each based on a single positive association with male breast cancer. The RRs for male breast cancer were increased in families in which multiple patients were diagnosed with diverse cancers, reaching an RR of 2.58 when three or more family members were affected.
Conclusions The results suggest that male breast cancer shares susceptibility with a number of other cancers but confirmation is needed in other datasets.

Keywords Familial cancer · Discordant cancer · Familial risk · Genetic association

Introduction

The incidence of male breast cancer is only 1/200 of the incidence of female breast cancer in Sweden and elsewhere in the Western countries. The rareness of male breast cancer has been a limitation for studying the role of family history. Familial relative risks (RRs) have been approximately equal between male breast cancer with a female family history as among females but data on male–male risks are lacking [1–3]. Also are lacking data on possible familial clustering of male breast cancer with other male or female cancers. A study from 1991 reported an excess of uterine cancers in relatives of male breast cancer patients [1]. A very high risk (RR 93) of second male breast cancer was noted by us and we also reported an increase in second prostate cancers after male breast cancer [4, 5]. In an international consortium on second cancers after male breast cancer increases were observed for cancers at several sites: the small intestine (RR 4.95), rectum (1.78), pancreas (1.93), nonmelanoma skin (1.65), prostate (1.61), and lymphohematopoietic system (1.63) [6]. It has been shown that the frequency of deleterious *BRCA1/2* mutations is considerably higher in male breast cancer than in female breast cancer, with *BRCA2* being the most

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commonly mutated gene [7, 8]. The Swedish frequency estimates for *BRCA2* mutations were about 20% of male breast cancer, as reviewed [8]. Several pathological features were reported to distinguish breast cancer in male and female carriers of *BRCA1* and *BRCA2* mutations, including estrogen and progesterone receptor positivity [9]. *BRCA2* mutations are known to increase risks for other cancers, including ovarian, prostate and pancreatic cancers, and uveal melanoma, and possible also esophageal and stomach cancers [10]. Other predisposing genes for male breast cancer may be *PALB2,CHEK2*1100delC, and *RAD50B* [9, 11]. Yet a review concluded that for most cases of male breast cancer the causes remain unknown [12].

We investigated here familial associations of 1428 male breast cancer with any cancer using the most recent update of the Swedish Family-Cancer Database. The analyses for other (discordant) cancers were based on a two-way assessment of familial RRs for male breast cancer in families with patients with another cancer X, and conversely in a reverse order, familial RRs for cancer X in families with increasing numbers of patients with male breast cancer. As the study included many comparisons, we gave statistical significance of the results at three levels (5, 1, and 0.1%) and provided summary trend tests.

Methods

Swedish Family-Cancer Database (FCD) includes all Swedish people born since 1932 (offspring generation) with their biological parents (parental generation) [13]. The latest version of this database contains 15.7 million individuals among which 1.8 million were cancer patients recorded to the end of 2012. The three digital codes of seventh revision of the International Classification of Diseases (ICD-7) were used to identify 35 most common primary cancers and cancer of unknown primary. However, as many cancers were rare in male breast cancer families we displayed data on discordant cancers based on a minimum number of ten cases or a significant association ($p < 0.05$). The follow-up for cancer in offspring generation (8.5 million individuals) was started from the beginning of 1958, the birth year, or the immigration year, whichever came latest. The follow-up was terminated when a person was diagnosed with cancer, emigrated, or died, or at the end of 2012, whichever came first. The number of first-degree relatives (including parents and/or siblings) who were affected with cancer was considered as family history.

Relative risks (RRs), calculated for the offspring generation, were used as a measure of assessing familial risks by comparing incidence rates for persons with affected relatives to incidence rates for those whose relatives had no cancer. In the two-way comparison, firstly, RR for male breast cancer was calculated when family history was cancer X, and then in the reverse order RR for cancer X was calculated when family history was male breast cancer. For parents and offspring (large majority of familial cases) these comparisons are independent but for siblings the pairs of cases are the same. Significant results in two-way analyses provide support for a true association but a lacking two-way association is no strong evidence against an association because age distributions and case numbers may differ between two-way analyses.

Poisson regression model was employed to estimate RRs and corresponding confidence intervals (CIs) for 5, 1, and 0.1% significance levels. These can be combined to calculate a joint significance for associations [14]. Trend tests were performed by modeling the number of familial cancers as a continuous covariate. Potential confounders, including age group, sex, calendar period, residential area, and socioeconomic status, were added to the model as covariates. SAS version 9.4 was used to perform the statistical analysis.

The study was approved by the Ethical Committee of Lund University.

Results

The total number of male breast cancers was 1428 and of these 272 were diagnosed in the 0–80 year offspring generation for which RRs were calculated. No concordant male–male breast cancers were found (expected number 0.11) but 16.2% of the offspring with male breast cancer had at least one first-degree relative with female breast cancer. The RR for male breast cancer was 1.76 when one first-degree relative was diagnosed with female breast cancer and in the reverse order RR for female breast cancer was 1.90 when a first-degree relative was diagnosed with male breast cancer (Table 1, also listing 95% CIs for all RRs). Both of these RRs were significant at a 0.1% level (joint significance $0.001 \times 0.001 < 10^{-6}$). The reference was families with no male breast cancers in first-degree relatives with RR 1.00 (not shown). A total of 8 discordant cancers are included in Table 1 (at least ten cases or a significant positive association; no significant negative associations were noted). Significant association for male breast cancer were found with colorectal (1.47), anal (4.64), and ovarian (2.20, 0.01% significance) cancers and with cancer of unknown primary (1.94). The RR for male breast cancer was 19.09 in a single family of two women diagnosed with ovarian cancer (joint p value for male breast cancer–ovarian cancer associations <0.0005). RRs for all cancers (i.e., RR for male breast cancer when first-degree relatives had any cancers) were highly significant

Table 1 Familial associations between male breast cancer and other cancers

Cancer site	Patients with no family history	Cases with 1 affected first-degree relative			Cases with 2 affected first-degree relatives			Cases with ≥3 affected first-degree relatives			*P* trend
		N	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI	
Colorectum											
Risk of male breast cancer	239	33	**1.47**	1.02–2.12	–	–	–	–	–	–	**0.0478**
Risk of colorectal cancer	35,334	26	1.32	0.90–1.93	–	–	–	–	–	–	0.1801
Anus											
Risk of male breast cancer	270	2	**4.64**	1.15–18.63	–	–	–	–	–	–	0.0838
Risk of anal cancer	1086	2	3.22	0.80–12.88	–	–	–	–	–	–	0.1664
Lung											
Risk of male breast cancer	255	16	1.12	0.67–1.85	1	1.95	0.27–13.89	–	–	–	0.5371
Risk of lung cancer	24,364	13	0.94	0.55–1.62	–	–	–	–	–	–	0.8233
Breast											
Risk of male breast cancer	228	41	***1.76***	1.26–2.46	3	2.28	0.73–7.11	–	–	–	**0.0010**
Risk of breast cancer	76,250	82	***1.90***	1.53–2.36	–	–	–	–	–	–	**<0.0001**
Ovary											
Risk of male breast cancer	265	6	1.23	0.55–2.77	1	**19.09**	2.68–136.06	–	–	–	0.2198
Risk of ovarian cancer	9958	12	**2.20**	1.25–3.88	–	–	–	–	–	–	**0.0157**
Prostate											
Risk of male breast cancer	233	36	1.32	0.93–1.88	2	1.27	0.32–5.12	1	6.38	0.89–45.53	0.0669
Risk of prostate cancer	61,825	39	1.11	0.81–1.52	–	–	–	–	–	–	0.5117
Melanoma											
Risk of male breast cancer	268	4	0.61	0.23–1.64	–	–	–	–	–	–	0.2878
Risk of melanoma	28,481	15	1.01	0.61–1.67							0.9797
Non-Hodgkin lymphoma											
Risk of male breast cancer	263	9	1.43	0.74–2.78	–	–	–	–	–	–	0.3160
Risk of non-Hodgkin lymphoma	14,331	10	1.35	0.72–2.50	–	–	–	–	–	–	0.3708
Cancer of unknown primary											
Risk of male breast cancer	259	13	1.94	1.11–3.38	–	–	–	–	–	–	**0.0346**
Risk of cancer of unknown primary	9165	6	1.18	0.53–2.63	–	–	–	–	–	–	0.6919
All cancers[a]											
Risk of male breast cancer	81	131	***1.75***	1.32–2.31	44	**1.63**	1.13–2.36	16	***2.58***	1.50–4.42	<0.0001
Risk of all cancers	428,558	290	***1.24***	1.10–1.39	–	–	–	–	–	–	**0.0004**
All cancers[b]											
Risk of male breast cancer	105	124	**1.48**	1.14–1.92	33	1.31	0.88–1.94	10	**2.03**	1.06–3.89	0.0074
Risk of all cancers	352,308	208	1.09	0.95–1.25							0.2040

Bold and bold italic values indicate that the 99% CI and 99.9% CI did not overlap with 1.00 respectively

[a] All cancers include breast cancer and all other cancers

[b] All cancers include all other cancers except breast cancer

and reached 2.58 ($p < 0.001$) when at least three first-degree relatives were diagnosed with any cancer, including male breast cancer and female breast cancer. However, the excess risk remained high when only discordant cancers were included in first-degree relatives (no male or female breast cancer included).

Table 2 shows results when only female first-degree relatives were considered and only sites with significant associations were shown. RRs were increased for female small intestinal cancer (4.72) in families of male breast cancer, and for male breast cancer in families of female thyroid cancer (3.40) and non-Hodgkin lymphoma (2.46). Anal cancer was increased in both of two-way analyses (joint $p < 0.0005$). RRs for all cancers were also increased.

Analysis of male breast cancer risks in families of male cancer patients showed no significant associations. The

Table 2 Familial associations between male breast cancer and female cancers

Cancer site	Patients with no family history	Cases with 1 affected first-degree relative			Cases with 2 affected first-degree relatives			Cases with ≥3 affected first-degree relatives			*P* trend
		N	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI	
Small intestine											
Risk of male breast cancer	271	1	2.25	0.32–16.02	–	–	–	–	–	–	0.4756
Risk of small intestinal cancer	745	2	4.72	1.18–18.91	–	–	–	–	–	–	0.0807
Colorectum											
Risk of male breast cancer	254	18	1.59	0.97–2.57	–	–	–	–	–	–	0.0748
Risk of colorectal cancer	16,119	14	1.52	0.90–2.57	–	–	–	–	–	–	0.1409
Anus											
Risk of male breast cancer	270	2	**6.90**	1.72–27.76	–	–	–	–	–	–	**0.0382**
Risk of anal cancer	727	2	4.80	1.20–19.21	–	–	–	–	–	–	0.0782
Lung											
Risk of male breast cancer	263	9	1.68	0.87–3.28	–	–	–	–	–	–	0.1549
Risk of lung cancer	12,061	9	1.28	0.67–2.41	–	–	–	–	–	–	0.4740
Thyroid gland											
Risk of male breast cancer	268	4	3.40	1.27–9.14	–	–	–	–	–	–	**0.0424**
Risk of thyroid cancer	4105	2	1.02	0.25–4.07	–	–	–	–	–	–	0.9809
Non-Hodgkin lymphoma											
Risk of male breast cancer	265	7	2.46	1.16–5.21	–	–	–	–	–	–	**0.0399**
Risk of non-Hodgkin lymphoma	5641	3	1.01	0.323.12	–	–	–	–	–	–	0.9901
All cancers[a]											
Risk of male breast cancer	148	107	***1.58***	1.23–2.02	16	**2.07**	1.23–3.47	1	1.26	0.18–8.98	**0.0001**
Risk of all cancers	222,859	166	***1.35***	1.16–1.57	–	–	–	–	–	–	**0.0002**
All cancers[b]											
Risk of male breast cancer	185	79	1.32	1.01–1.72	8	1.73	0.85–3.51	–	–	–	**0.0186**
Risk of all cancers	146,881	84	1.05	0.85–1.30	–	–	–	–	–	–	0.6488

Bold and bold italic values indicate that the 99% CI, and 99.9% CI did not overlap with 1.00 respectively

[a] all cancers include breast cancer and all other cancers

[b] all cancers include all other cancers except breast cancer

case numbers were so small that they provided null support for the results in Table 2.

We identified multiple primary or in situ cancers when male breast cancer patients were first-degree relatives based on Table 1. The first of multiple cancers was always male breast cancer (Table 3). Among breast cancer–male breast cancer familial pairs 19 men had any multiple primary or in situ cancers, RR 2.20 ($p < 0.001$). When the multiple primary was prostate cancer the RR was 3.08 ($p < 0.001$) and when it was squamous cell skin cancer the RR was 4.58 ($p < 0.01$). Among prostate–male breast cancer familial pairs six men had both male breast cancer and multiple prostate cancer, RR 2.65.

Discussion

The expected number of male–male breast cancer pairs was 0.11, indicating that this nation-wide study was underpowered to find concordant cases of male breast cancer. However, the present analyses provided novel results on familial risk on male breast cancer. The RR between male and female breast cancer equals the RR for concordant female breast cancer which has been previously shown [1–3]. Not only are familial risks matching between male and female breast cancer but so are familial proportions: 16.2% of male breast cancer patients had a first-degree relative with female breast cancer, while the percentage is

Table 3 Familial associations of male breast cancer with breast and prostate cancer in individuals with first-degree relatives diagnosed with multiple primary or in situ cancer

Familial cancers (Offspring-First degree relatives)	Cancer type in first-degree relatives diagnosed with multiple cancers	*N* of cases given by first-degree relatives diagnosed with multiple cancers	RR[b]	*95%* CI[b]
Breast cancer–male breast cancer	All	19[a]	***2.20***	1.40–3.45
	Breast–breast	2	2.19	0.55–8.76
	Breast–prostate	9	***3.08***	1.60–5.92
	Breast–skin	3	**4.58**	1.48–14.20
Prostate cancer–male breast cancer	All	8[a]	1.38	0.68–2.73
	Breast–prostate	6	2.65	1.19–5.90

Bold and bold italic values indicate that the 99% CI, and 99.9% CI did not overlap with 1.00, respectively

[a] Number of cases whose first-degree relatives diagnosed with multiple cancers and with breast cancer as the first primary cancer

[b] RR estimation and CI calculation are based on the same reference groups as in Table 1

16.1 for female breast cancer pairs from this Database (unpublished result).

The association of male breast cancer with ovarian cancer ($p < 0.0005$) could be related to *BRCA2* mutations which have been estimated to account for 20% of Swedish male breast cancers [7, 12]. Prostate cancer risk is also increased in *BRCA2* mutation carriers but no significant familial excess was found in the present study although the trend test was close to being significant (0.0669) for male breast cancer in prostate cancer families. However, many male breast cancer patients were diagnosed with second prostate cancer, and it could be speculated that such double primary cancers may signal involvement of *BRCA2* [7].

The other association with this high level of statistical support was with female anal cancer. The main risk factor for anal cancer is infection by human papilloma virus and genetic predisposition is unknown [15, 16]. Anal cancer is of squamous cell histology, and curiously squamous cell skin cancer was a common second cancer diagnosed after first male breast cancer. Papilloma virus types in skin and anus are likely to be different and the common denominator, if any, may be compromised immune function in some male breast cancer patients [16].

The associations with colorectal, small intestinal and thyroid cancer, cancer of unknown primary, and non-Hodgkin lymphoma were based on a single significant association and need to be confirmed in other settings. Cancer of unknown primary is a fatal metastatic cancer for which clinicians and pathologists could not find a primary site [17]. Familial associations of cancer of unknown primary with many primary cancers, including female breast cancer, have been described [18]. None of the cancers (colorectal, small intestinal and thyroid cancer, cancer of unknown primary, and non-Hodgkin lymphoma) associated with male breast cancer are typically manifested in the *BRCA2* syndrome or belong to *CHEK2**1100delC associated cancers which include, in addition to female breast cancer, stomach, kidney, and prostate cancers and sarcoma [19]. Small intestinal cancer showed the highest risk for second cancers after first male breast cancer in the international consortium study which also reported an increased risk for rectal cancer [6].

The results for 'All cancers' were remarkably high, RR reaching 2.58 in Table 1 for families of three or more cancer patients, including female breast cancer. We have recently characterize familial risks for families presenting with various cancers, and the present results provide further evidence for shared familial risks between many cancers [20–23].

In summary, we provide here novel data for the rare field of male breast cancer which showed that 16.2% of male breast cancer patient had a family member with female breast cancer. All discordant associations were with cancers which are not typically associated with genes predisposing to male breast cancer, with the exception of ovarian cancer, suggesting contribution by *BRCA2*. The results support the notion that much of male breast cancer predisposition is yet unknown [12]. In the same token, the risks in families with multiple patients with diverse cancers suggest that high or moderate penetrant genes or environmental factors such as inflammation or smoking could be involved causing predisposition to many cancers. As families with two male breast cancers could not be found in the population of 15.7 million individuals, a pedigree-based gene identification approach for male breast cancer could include families with single male breast cancers with other male breast cancer associated cancers.

Acknowledgements A.H. is Jane and Aatos Erkko Professor of Oncology at the University of Helsinki. This work was funded by the German Cancer Aid, the EU Transcan funding by the German Federal Ministry of Education and Research, Jane and Aatos Erkko Foundation, University of Helsinki and Helsinki University Central Hospital, and the Swedish Research Council for Health, Working Life and Welfare (in Swedish: FORTE; Reg. No. 2013-1836), and FORTE

(Reg. No. 2014-0804) and the Swedish Research Council (2012-2378 and 2014-10134) as well as ALF funding from Region Skåne.

Compliance with ethical standards

Conflicts of interest AH. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

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