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Familial risks of breast and prostate cancers: Does the definition of the at risk period matter?

Andreas Brandt [a,*], *Justo Lorenzo Bermejo* [a,b], *Jan Sundquist* [c,d], *Kari Hemminki* [a,c]

[a] *Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120 Heidelberg, Germany*
[b] *Institute of Medical Biometry and Informatics, University Hospital Heidelberg, 69120 Heidelberg, Germany*
[c] *Center for Primary Care Research, Lund University, 205 02 Malmö, Sweden*
[d] *Stanford Prevention Research Center, Stanford University School of Medicine, 5411 Stanford, California, USA*

ARTICLE INFO

Article history:
Received 18 September 2009
Accepted 19 November 2009

Keywords:
Breast neoplasms
Prostate neoplasms
Familial risk
Familial risk period
Clinical counselling

ABSTRACT

Aim: 'Being at familial risk' may have different connotations in studies on familial risk of cancer. The register-based definition of a family history considers individuals with an affected relative at familial risk independently of the family member's diagnostic time. Alternatively, the individuals are classified to be at familial risk only after the diagnosis date of their relative, relevant to clinical counselling and screening situations. The aim of this study was to compare familial breast and prostate cancer risks according to the two definitions.

Patients and methods: The nationwide Swedish Family-Cancer Database with information on cancers from 1958 to 2006 was used to calculate the hazard ratio of breast and prostate cancers according to family history using Cox regression. Family history was defined considering the number and type of affected relatives and the relative's diagnostic age, respectively. Individuals were considered at familial risk from their entry to the study or, alternatively, from the diagnostic time of the relative.

Results: Hazard ratios were equal whether individuals were considered at risk independent of the relative's diagnostic date or only after the relative's diagnostic date.

Conclusion: These results indicate that studies on familial breast or prostate cancer risk which do not take the relative's diagnosis date into account are applicable to screening and clinical counselling situations. The estimates according to the register-based definition are based on larger numbers of patients, which may be crucial for analysis of small groups such as families of multiple cases.

1. Introduction

'Being at familial risk' may have different connotations in studies on familial risk of cancer. The time between diagnosis of cancer and collection of family history information may differ between studies. In interview-based studies on familial risks, the individuals are classified according to the family history at the time of the interview, which usually takes place shortly after cancer diagnosis.[1–3] In this case, the individuals are defined to be at familial risk only after diagnosis of their relatives, this is the so-called 'time-based definition'. This definition is also germane to clinical counselling and screening situations, where increased surveillance is recommended for individuals at familial risk of breast or prostate cancers.[4] If

* *Corresponding author:* Address: Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany. Tel.: +49 6221 421805; fax: +49 6221 421810.
E-mail address: andreas.brandt@dkfz.de (A. Brandt).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.11.016

information on familial relationships and cancer is available from registered sources such as the Swedish Family-Cancer Database, the period of time between diagnosis of cancer and collection of family history may be substantial; the family members of an affected individual might be affected during this period and it is possible to classify as familial cases those where relatives were affected later than probands. Two definitions of family history are possible in this case: the time-based definition considers an individual being at familial risk only after the date of diagnosis of the relative and the 'register-based definition' considers an individual being at familial risk independently of the relative's time of diagnosis.[5–7] Models for the estimation of breast cancer risk have been developed on the basis of studies with both definitions of familial risk. The Gail model and the Claus model rely on the studies with family history collected by interview; the Tyrer–Cuzick model is based on a study using the register-based definition of family history.[1,6,8,9] Therefore, a comparison of familial risks based on the two definitions of 'being at familial risk' is important in order to determine the comparability of the risk estimation models and the adaptability of the register-based definition of family history for clinical counselling and cancer screening situations.

In the present study, we took advantage of the Swedish Family-Cancer Database, with complete information on cancers in siblings and parents between 1958 and 2006, and calculated offspring and sibling risks of breast and prostate cancers according to the register-based and time-based definitions of familial risk considering parental and sibling diagnostic ages. Furthermore, the familial risks were estimated according to the number and type of diseased first degree relatives for the two definitions of familial risk.

2. Materials and methods

The Swedish Family-Cancer Database was created in the 1990s by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry and death notifications.[5] Data on family relationships were obtained from the Multigeneration Register, where children born in Sweden in 1932 and later are registered with their biological parents as families. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases, with coverage of the cancer registration close to 100%.[10] The 2008 update of the Database includes more than 11.8 million individuals and their cancers from years 1958 to 2006. This study was based on the individuals from the offspring generation (children born after 1932) with linkage to both parents in the Database, in total 3.9 million men and 3.7 million women. Family history information was obtained from the complete Database. The age structure of the Database implicates that the maximum age of diagnosis in the offspring generation was 74 years. The age of the individuals in the first generation was not limited.

We calculated the hazard ratio of breast and prostate cancers for the individuals with an affected first degree relative compared to those without an affected first degree relative using Cox regression according to the type of affected relative (parent or sibling) considering the diagnostic age of the relative (PROC PHREG; SAS Version 9.1; SAS Institute, Cary, NC). According to the register-based definition, the individuals with a diseased relative entered the group with a family history from their entry to the study. According to the time-based definition, the family history information was included as a time-dependent covariate: the individuals were considered as lacking a family history before the parents' or siblings' diagnostic date and to be at familial risk afterwards. In addition, hazard ratios were estimated according to the number and type of diseased first degree relatives. Thereby, for the time-based definition, the individuals with multiple affected relatives were considered to have one affected relative between the diagnosis of the first and the second relatives, two affected relatives after the diagnosis of the second relative and so on. Individuals entered the risk period at birth, immigration, or first year of the study (1961). Censoring events were death, emigration, December 31, 2006, absence at census and diagnosis of malignancy at sites other than the site under consideration. Socioeconomic status, calendar period, age at first birth, number of children and region were taken into account as covariates. Unfortunately, we were not aware of a statistical test for the difference between the hazard ratios according to the two definitions: the hazard ratios are neither independent nor can be estimated within the same model as the familial risk time for the time-based definition is a subset of the familial risk time for the register-based definition.

3. Results

Table 1 shows, for the register-based and for the time-based definitions of family history, the mean age at entry to the familial risk period and the mean time at familial risk according to the parental diagnostic age. Furthermore, the number of individuals affected during the familial risk periods and the hazard ratios for offspring of breast and prostate cancers are presented. The mean familial risk time was substantially smaller for the time-based definition. However, the individuals entered on average the familial risk period before the risk ages for breast and prostate cancers, except for the individuals with a parent diagnosed at late age. Consequently, except for women with a mother diagnosed at a late age ($\geqslant$85 years), the majority of breast cancer cases in daughters occurred after the maternal diagnostic date, i.e. the majority of cases defined as familial cases according to the register-based definition were also defined as familial according to the time-based definition. The hazard ratios of breast cancer for women with an affected mother compared to those without a family history according to the two definitions were similar. Also, almost all prostate cancers in affected father–son pairs were first diagnosed in the father. Therefore, the hazard ratios according to the register-based definition of family history and according to the time-based definition of family history were nearly equal.

Table 2 shows the corresponding data for the individuals with an affected sibling. For the time-based definition of familial risk, the individuals entered the familial risk period on average during the risk ages of breast and prostate cancers and the mean time at familial risk was small, especially for men with a brother affected by prostate cancer. Nevertheless,

Table 1 – Hazard ratio of breast cancer (top) and prostate cancer (bottom) according to parental diagnostic age for register-based definition of family history and for time-based definition of family history.

		Register-based definition of family history						Time-based definition of family history					
	Parental diagnostic age	Mean age at entry to familial risk period[a] (sd) (years)	Mean time at familial risk (sd) (years)	N[b]	HR	95% CI (confidential interval)		Mean age at entry to familial risk period[c] (sd) (years)	Mean time at familial risk (sd) (years)	N[b]	HR	95% CI	
Breast cancer	0–39	1.3 (5.4)	26.4 (13.0)	84	3.37	2.72	4.17	8.0 (5.4)	19.9 (12.7)	84	3.32	2.68	4.11
	40–49	3.3 (6.2)	32.3 (11.5)	467	2.16	1.97	2.36	16.8 (6.2)	19.2 (13.2)	467	2.13	1.94	2.33
	50–59	4.9 (6.4)	36.7 (9.4)	847	1.89	1.77	2.02	25.8 (6.4)	16.6 (12.6)	829	1.86	1.74	1.99
	60–74	9.2 (7.0)	41.0 (7.8)	1793	1.67	1.59	1.75	36.8 (7.0)	14.9 (10.5)	1589	1.67	1.59	1.75
	75–84	15.1 (6.5)	42.0 (7.9)	872	1.59	1.49	1.70	47.6 (6.5)	11.5 (8.0)	583	1.59	1.46	1.72
	85-	18.3 (6.1)	41.6 (8.4)	276	1.55	1.38	1.74	55.0 (6.1)	7.6 (5.9)	114	1.47	1.22	1.77
Prostate cancer	0–59	3.1 (7.1)	33.2 (10.2)	128	3.45	2.90	4.10	24.8 (7.1)	12.3 (12.2)	128	3.36	2.83	4.00
	60–67	5.4 (6.7)	38.9 (8.2)	552	2.82	2.59	3.07	32.3 (6.7)	13.0 (11.4)	552	2.76	2.53	3.00
	68–74	8.9 (6.9)	41.7 (7.1)	1031	2.29	2.15	2.44	38.1 (6.9)	13.7 (10.2)	1024	2.23	2.10	2.38
	74–82	12.4 (7.1)	42.5 (6.8)	1328	1.97	1.87	2.08	43.8 (7.1)	12.5 (8.9)	1299	1.93	1.83	2.04
	82-	15.9 (7.1)	42.6 (7.0)	597	1.67	1.54	1.81	49.8 (7.1)	10.1 (7.5)	548	1.66	1.53	1.81

a Age at entry to familial risk period: age at entry to the study.
b Number of individuals affected during familial risk period.
c Age at entry to familial risk period: maximum of age at parental diagnostic time and age at entry to the study.

Table 2 – Hazard ratio of breast cancer (top) and prostate cancer (bottom) according to siblings' diagnostic age for register-based definition of family history and for time-based definition of family history.

		Register-based definition of family history						Time-based definition of family history					
	Sibling diagnostic age	Mean age at entry to familial risk period[a] (sd) (years)	Mean time at familial risk (sd) (years)	N[b]	HR	95% CI		Mean age at entry to familial risk period[c] (sd) (years)	Mean time at familial risk (sd) (years)	N[b]	HR	95% CI	
Breast cancer	0–39	8.2 (7.9)	40.3 (7.9)	180	2.42	2.09	2.80	34.5 (7.9)	15.2 (9.8)	154	2.28	1.95	2.67
	40–49	12.0 (7.2)	41.8 (7.7)	678	2.05	1.90	2.21	44.2 (7.2)	11.3 (7.2)	465	1.97	1.79	2.15
	50–59	15.7 (7.0)	42.1 (7.7)	955	1.85	1.73	1.97	52.2 (7.0)	7.7 (5.1)	450	1.83	1.66	2.01
	60–74	19.2 (6.3)	41.9 (8.1)	544	1.64	1.51	1.79	59.5 (6.3)	4.1 (3.1)	138	1.77	1.49	2.09
Prostate cancer	0–59	15.0 (7.1)	42.4 (6.9)	453	4.47	4.08	4.90	53.8 (7.1)	5.2 (4.3)	299	4.42	3.95	4.94
	60–67	18.7 (6.1)	42.6 (6.6)	831	2.99	2.79	3.21	59.3 (6.1)	3.6 (2.7)	439	3.21	2.92	3.53
	68–74	20.7 (5.2)	42.6 (6.3)	265	2.42	2.14	2.73	63.2 (5.2)	2.0 (1.5)	81	2.58	2.06	3.21

a Age at entry to familial risk period: age at entry to the study.
b Number of individuals affected during familial risk period.
c Age at entry to familial risk period: maximum of age at sibling diagnostic time and age at entry to the study.

the hazard ratios of breast and prostate cancers for siblings of breast and prostate cancer patients compared to those without a family history according to the two definitions were similar.

We calculated also the hazard ratios of breast and prostate cancers according to parental and sibling diagnostic ages considering the individuals at risk only until the parental and sibling diagnostic time. The findings were in line with the above results: the differences between the hazard ratios before and after the relative's diagnosis were not statistically significant (data not shown).

Table 3 shows the numbers of breast cancers according to the family history for the register-based and the time-based definition of family history. For example, 289 women with breast cancer from the study population had a mother and a sister affected by breast cancer. Amongst these women, 29 were affected before their mother and sister; therefore, these women were considered as lacking a family history according to the time-based definition. Another 116 of these women were affected after their mother and before their sister and 13 after their mother but before their sister. Consequently, these cases were included in the groups 'mother affected only' and 'sister affected only' for the time-based definition. A total of 131 women were affected after their mother and sister and the family history was defined as 'mother and sister affected' for the time-based definition.

Table 4 shows the corresponding data for prostate cancer. Interestingly, the number of men considered to have an only affected father was higher for the time-based definition than for the register-based definition.

Table 3 – Numbers of breast cancer cases according to family history for register-based and time-based definition of family history.

Affected relatives according to register-based definition of family history	Affected relatives according to time-based definition of family history					
	None	Mother only	Sister only	Mother + 1 sister	2 Sisters	Total
None	42,530	–	–	–	–	42,530
Mother only	673	3666	–	–	–	4339
Sister only	1115	–	1136	–	–	2251
Mother + 1 sister	29	116	13	131	–	289
2 Sisters	34	–	33	–	35	102
Total	44,381	3782	1182	131	35	

Table 4 – Numbers of prostate cancer cases according to family history for register-based and time-based definition of family history.

Affected relatives according to register-based definition of family history	Affected relatives according to time-based definition of family history							
	None	Father only	Brother only	Father + 1 brother	2 brothers	Father + 2 brothers	3 Brothers	Total
None	21,028	–	–	–	–	–	–	21,028
Father only	85	3551	–	–	–	–	–	3636
Brother only	676	–	701	–	–	–	–	1377
Father + 1 brother	4	193	1	204	–	–	–	402
2 brothers	48	–	47	–	49	–	–	144
Father + 2 brothers	–	13	–	12	–	15	–	40
3 Brothers	6	–	6	–	6	–	10	28
Total	21,847	3757	755	216	55	15	10	

Table 5 – Hazard ratio of breast cancer (top) and prostate cancer (bottom) according to family history for register-based definition of family history and for time-based definition of family history.

		Register-based definition of family history				Time-based definition of family history			
	Affected relatives	N[a]	HR	95% CI		N[a]	HR	95% CI	
Breast cancer	Mother only	4339	1.74	1.69	1.80	3784	1.78	1.72	1.84
	Sister only	2251	1.86	1.79	1.94	1183	1.92	1.81	2.04
	Mother + 1 sister	289	2.81	2.50	3.15	133	2.73	2.30	3.23
	2 Sisters	102	2.43	2.00	2.95	36	2.42	1.75	3.36
Prostate cancer	Father only	3636	2.12	2.05	2.20	3757	2.16	2.09	2.24
	Brother only	1377	2.96	2.80	3.13	755	3.32	3.08	3.57
	Father + 1 brother	402	5.51	5.00	6.09	216	5.96	5.21	6.81
	2 Brothers	144	7.71	6.54	9.08	55	9.15	7.03	11.93
	Father + 2 brothers	40	8.82	6.46	12.02	15	10.30	6.21	17.10
	3 Brothers	28	17.74	12.26	25.67	10	22.19	11.94	41.26

a Number of individuals affected during familial risk period.

In Table 5, the hazard ratios of breast and prostate cancers for individuals with affected first degree relatives compared to individuals without affected first degree relatives is shown for the register-based and the time-based definitions of family history according to the numbers and types of affected relatives. Considering breast cancer, the hazard ratios were equal for the two definitions. For prostate cancer, the hazard ratios were higher for the time-based definition than for the register-based definition except for men with an affected father only. However, the numbers of cases were small for men with more than one affected relative, especially for the time-based definition. Thus, the confidence intervals for the hazard ratios of men with multiple affected relatives were relatively wide and overlapping for the two definitions.

4. Discussion

The present study compared offspring and sibling risks of breast and prostate cancers considering individuals at familial risk independently of the diagnostic time of the relative ('register-based definition of family history') and only after the diagnostic time of the relative ('time-based definition of family history'). Familial relationships and cancer data originated from reliable and practically complete registered

sources covering the whole Swedish population up to age 74 years and their parents. Therefore, an accurate definition of the periods in which individuals were considered at familial risk according to the two definitions was possible. However, a small number of parents and siblings will be diagnosed with breast or prostate cancer in the future (right truncation), which means that the family history of these individuals was incorrectly classified for the register-based definition. By contrast, these were correctly classified for the time-based definition of family history.

We found that the familial risks according to the diagnostic age of the affected relative were similar for the two definitions. This result was expected for offspring of breast and prostate cancer patients because the majority of the parents were affected before their offspring reached the risk ages for these cancers. However, also the sibling risks were almost equal, and this was true even for the groups with the highest sibling diagnostic ages, in which the familial follow-up started at an advanced age and the mean time at familial risk was low.

Clinical guidelines emphasise the increased risk of individuals with multiple relatives affected by breast and prostate cancers.[11,12] Therefore, we calculated the familial risks for the two definitions also according to the type and number of affected first degree relatives. For the time-based definition, the individuals with multiple affected relatives until the end of the study contributed familial risk time and cases to types of family histories with fewer affected relatives. Thus, individuals with different levels of familial risk were considered to have the same family history. For the register-based definition, the individuals contributed familial risk time and cases based on the affected relatives at the end of the study only. This might explain in part the higher familial risks for prostate cancer according to the time-based definition compared to familial risks according to the register-based definition. Considering breast cancer, the risks for the two definitions were similar although the number of breast cancers in women with more than one affected relative was more than 2-fold smaller for the time-based definition.

In clinical counselling and screening situations, the aim is to predict the risk of an individual based on the information about the currently known cases in the family. The results of this study demonstrate that studies on familial breast or prostate cancer utilising the register-based definition are applicable for these situations although they do not take the relative's diagnostic date into account. Furthermore, breast cancer risk estimation models are comparable, irrespective of the two definitions of 'being at familial risk' in the underlying studies. An advantage of the register-based definition of family history is that the individuals are at familial risk for a longer period, translating to more accurate estimates of familial risks. The advantage of large case numbers will become useful in the analysis of any rare events such as multiplex familial cases of breast and prostate cancers and early onset cases.

Familial breast and prostate cancers are associated with an earlier age of onset compared to sporadic cancers.[3,13,14] Consequently, the familial risk might be higher before than after the relative's diagnosis because the individuals are younger before their relative's diagnostic date. However, we did not find evidence that this caused differences between the familial risks according to the register-based or the time-based definitions of the family history. By contrast, the individuals with a close relative affected by cancer may participate in cancer screening more often, more frequently or earlier, in particular individuals with several affected relatives.[15,16] Therefore, the risk of cancer after the diagnosis in a relative might be influenced by overdiagnosis due to increased surveillance of familial cases. In the previous studies, we have assessed the effect of screening on familial risk by comparing the familial relative risks shortly after the diagnosis of the relative with the risks after five or more years after diagnosis. The results suggested that screening might influence the risk shortly after the relative's diagnosis but that the effect on the overall familial risk is small.[17,18] In general, the present results support these findings as we found similar familial risks according to the register-based and the time-based definitions of family history. However, increased surveillance may play a role for the higher familial risks of prostate cancer according to the time-based definition for the individuals with multiple affected relatives.

In conclusion, this study provides evidence that familial risks of breast and prostate cancers are similar whether individuals are considered at familial risk independent of the diagnostic time of the relative or only after the relative's diagnostic date. The register-based approach will offer a methodological advantage in the analysis of small groups such as families of multiple cases.

5. Sources of support

This work was funded by Deutsche Krebshilfe; the Swedish Cancer Society; The Swedish Council for Working Life and Social Research.

The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

Conflict of interest statement

None declared.

Acknowledgements

This work was funded by Deutsche Krebshilfe; the Swedish Cancer Society; The Swedish Council for Working Life and Social Research. The funding sources were not involved in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

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