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Age of onset in familial cancer

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Background: Reliable estimates on the age of onset between familial and sporadic cancers are important for etiological understanding and clinical practice. Specific studies on the age of onset of familial cancer compared with sporadic cancer are less common than studies on familial risks and these are almost lacking for rare cancers.
Materials and methods: The Swedish Family-Cancer Database was used to estimate cumulative risks of all common cancer types according to family history with a stratified Cox model based on Tsiatis' method. We calculated the age at which the cumulative risk of cancer reached 0.1% and 0.5%.
Results: The age to reach a cumulative risk of 0.1% was significantly lower among individuals with a parent or a sibling affected for any of the investigated cancer sites. The age differences ranged from 2.6 years (sons of prostate cancer patients) to 16.3 years (brothers of urinary bladder cancer patients). A cumulative risk of 0.5% was also reached earlier for individuals with a family history, especially for individuals with a parent and a sibling affected.
Conclusions: Cancers in individuals with a family history occur earlier than in sporadic patients. The derived estimates may be useful for clinical counseling and screening recommendations.
Key words: age of onset, cumulative risk, familial cancer, family history, screening

introduction

Hereditary cancer syndromes are associated with an earlier age of onset compared with sporadic cancers [1]. The susceptibility genes for many hereditary cancer syndromes are known and the affected patients are usually mutation carriers of one allele of a tumor suppressor gene [2]. The second allele is lost as a somatic event, which is likely to occur earlier in mutation carriers than in those with two functional alleles. Hence, according to the multistage models of cancer, the early age of onset in syndromatic patients indicates fewer necessary events for tumor formation compared with sporadic patients [3, 4]. Hereditary cancers encompass a small proportion of familial cancers, which are defined through a family history and a lack of a definite genetic basis [5]. Although familial risks have been characterized for most cancers, specific studies on the age of onset of familial cancer compared with sporadic cancer are less common and they are almost lacking for rare cancers [6–9]. Reliable estimates on the age of onset between familial and sporadic cases are important for etiological understanding and clinical practice. If familial cancers show an early age of onset, their similarity to hereditary cancers may suggest a genetic etiology. The definition of the onset difference between familial and sporadic cancers will be useful for clinical counseling and the design and implementation of cancer screening programs, particularly in order to define the starting age for screening [10–12].

The present population-based study uses the nationwide Swedish Family-Cancer Database to explore the difference in age of onset between individuals with and without a family history of cancer. Family history was defined separately for individuals with affected parents, individuals with affected siblings and individuals with both a parent and a sibling affected. All common types of cancer were investigated.

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. 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 the compulsory reports of diagnosed cases, with a coverage of the cancer registration close to 100%. The 2006 update of the Database includes >11.5 million individuals and the cancer cases from 1958 to 2004 [13]. About 1.5 million individuals without identified parents were excluded from the study. The age structure of the Database (children born after 1932) implicates that the maximum age of diagnosis of siblings is 72 years.

Cumulative risks of cancer according to family history were estimated using a stratified Cox model based on Tsiatis' method [14] (PROC PHREG; SAS Version 9.1; SAS Institute, Cary, NC). The strata were defined according to the disease status of parents and siblings. Individuals entered

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the risk period at birth, immigration date or first year of the study (1961). Censoring events were death, emigration, 31 December 2004, absence at census and diagnosis of malignancy at other than the site under consideration. Sex, socioeconomic status, birth period and region were taken into account as covariates. Cumulative risks were estimated separately for men and women. We also calculated the age at which the cumulative risk of cancer reached 1 per 1000 (0.1%) and 5 per 1000 (0.5%) and the age differences for individuals with a family history of cancer [15, 16].

results

Table 1 shows the age at which a cumulative risk of a site-specific cancer reaches 0.1% in individuals without affected parents or siblings (sex specific for the sites with a statistical significant difference in onset age between men and women). This age was lowest for cervical cancer [34.4 years, 95% confidence interval (CI) 33.9–35.1 years], and it was highest for stomach cancer in women (60.8 years, 95% CI 60.0–61.6 years). The age to reach a risk of 0.1% for individuals with an affected parent or sibling and the differences in age between individuals with and without a family history of concordant cancer are also shown in Table 1. For example, women with a maternal history of cervical cancer (twenty-two uncensored women) reached this risk with 30.9 years (95% CI 29.6–33.2 years), which was ~3.5 years earlier than women without affected mothers or sisters. The age was lower for women with affected sisters (30.4 years, 95% CI 25.9–33.8 years, difference to women without family history was 4.0 years), but the difference in age according to the type of relative was not statistically significant. Interestingly, the age to reach a cumulative risk of cancer of 0.1% was statistically lower among individuals with a family history for any of the investigated sites. Individuals with a parental history reached a risk of 0.1% between 2.6 years (prostate cancer) and 10.8 years (cancer of nervous system)

Table 1. Age at which the cumulative risk of cancer reaches one per 1000 among individuals without and with affected parents/siblings and difference in diagnosis age compared with individuals with affected parents and siblings

Cancer site	Without family history		With affected parents				With affected siblings			
	Age	95% CI	No.[a]	Age	95% CI	AD[b]	No.[a]	Age	95% CI	AD[b]
Cervix	34.4	33.9, 35.1	22	30.9	29.6, 33.2	−3.5	6	30.4	25.9, 33.8	−4.0
Breast	37.3	37.2, 37.5	168	33.5	33.1, 34.0	−3.8	46	34.0	33.2, 35.1	−3.3
Ovary	41.1	40.2, 42.1	19	33.1	27.2, 36.9	−8.0				
Melanoma	41.8	41.3, 42.3	105	31.5	30.4, 33.3	−10.3	36	32.0	29.8, 34.9	−9.8
Women	40.5	39.9, 41.2	61	30.8	29.3, 32.5	−9.8	23	31.0	28.7, 33.4	−9.5
Men	43.0	42.5, 43.6	44	32.8	31.0, 34.7	−10.3	14	33.0	30.6, 36.6	−10.0
Nervous system	44.1	43.3, 45.0	104	33.3	29.9, 36.8	−10.8	34	29.9	23.4, 34.8	−14.2
Colorectum	47.4	47.0, 47.8	211	41.3	40.3, 42.3	−6.1	23	40.8	39.3, 42.2	−6.9
Endometrium	48.6	48.2, 49.0	15	44.1	39.4, 45.8	−4.5				
NHL	50.8	50.1, 51.3	54	45.3	43.3, 49.1	−5.4	11	47.1	33.7, 50.6	−3.7
Women	52.8	52.2, 53.5	15	48.9	45.4, 50.9	−3.9	10	48.7	36.8, 51.3	−4.8
Men	49.1	48.5, 49.7	39	44.0	42.2, 47.2	−5.1				
Bladder[c]	51.6	51.1, 52.2	63	46.8	44.8, 49.4	−4.8	9	40.4	32.3, 47.2	−11.2
Women	56.9	56.3, 57.5	34	52.8	51.4, 54.0	−4.2				
Men	48.7	48.2, 49.3	25	43.3	41.3, 45.8	−5.3	6	32.3	27.5, 44.8	−16.3
Lung	52.3	51.9, 52.5	129	48.8	48.1, 49.6	−3.5	21	47.2	45.7, 48.7	−5.1
Kidney	52.8	52.3, 53.6	36	47.3	45.5, 50.7	−5.6				
Women	54.8	54.3, 55.5	21	50.0	46.8, 52.0	−4.8				
Men	51.4	50.8, 52.1	16	46.3	42.8, 48.8	−5.1				
Prostate	54.8	54.8, 55.0	200	52.3	51.8, 52.7	−2.6	23	51.1	50.3, 52.0	−3.8
Leukemia	55.4	54.7, 56.4	64	49.4	47.8, 52.3	−6.0	19	41.1	38.7, 50.1	−14.3
Women	56.8	56.0, 57.8	25	50.4	48.8, 53.3	−6.4	14	47.5	40.3, 51.6	−9.3
Men	54.4	53.8, 55.3	38	48.8	46.6, 50.8	−5.6	6	41.0	37.4, 49.3	−13.4
Skin	58.0	57.4, 58.8	62	52.6	51.2, 54.8	−5.4	8	49.8	44.6, 54.9	−8.2
Women	59.6	58.8, 60.4	32	54.4	52.3, 56.9	−5.2				
Men	56.8	56.3, 57.6	31	51.7	50.4, 53.7	−5.1				
Stomach	58.7	58.0, 59.3	57	54.5	52.8, 56.8	−4.2	5	44.6	43.0, 70.9	−14.1
Women	60.8	60.0, 61.6	28	56.8	54.8, 59.4	−3.6	5	54.5	43.5, 70.9	−6.3
Men	57.3	56.5, 58.0	29	53.3	51.3, 55.5	−3.1				
Pancreas	59.7	59.1, 60.3	41	56.3	54.7, 57.4	−3.3	5	52.2	50.8, 56.5	−7.5

[a]Number of cases that occurred before the age at which the cumulative risk of cancer reaches one per 1000; data are only shown for cancer sites with more than four cases.

[b]AD: Age difference to individuals without affected parents/siblings

[c]Urinary bladder.

Cancer sites are ordered according to the age at which the cumulative risk of cancer among individuals without a family history reaches one per 1000. CI, confidence interval; NHL, non-Hodgkin's lymphoma.

earlier than those without a family history. The earlier onset was particularly large for nervous system malignancies (−10.8 years in individuals with a parental history) and melanoma (−9.8 years in women and −10.3 years in men). For individuals with a sibling history, the age difference compared with individuals without a family history ranged from 3.3 years (breast cancer) to 16.3 years (urinary bladder cancer in men). There were no statistically significant differences between the ages of onset for individuals with a parental history and individuals with a sibling history.

Table 2 shows the corresponding data for a cumulative risk of 0.5%. For melanoma and breast, colorectal, prostate and lung cancers, the number of cases permitted to examine the age at which individuals with both an affected parent and an affected sibling reached a cumulative risk of 0.5%. Data are only presented for cancer sites where individuals without a family history reached a cumulative risk of 0.5%. Among individuals without a family history of concordant cancer, the age to reach a cumulative risk of 0.5% was lowest for breast cancer (45.5 years) and highest for pancreatic cancer (72.0 years). Again, family history was associated with a younger age to reach the cumulative risk of 0.5%, the difference being particularly large for cervical cancer (−20 years) and melanoma (∼13 years for individuals with parents affected by melanoma). For individuals with a sibling history, the age difference compared with individuals without a family history ranged from 4.3 years (breast cancer) to 19.6 years (cervical cancer). Interestingly, individuals with a sibling history reached a cumulative risk of 0.5% statistically earlier than individuals with a parental history for prostate (−4.3 versus −2.9 years) and kidney cancers (women −13.8 versus −4.9 years, men −13.8 versus −7.1 years). Individuals with both a parent and a sibling affected reached a cumulative risk of 0.5% between 35.8 years (melanoma) and 7.2 years (breast and prostate cancers) before individuals without a family history.

discussion

Data on the age of onset of familial cancer have previously been addressed by age group specific reporting of relative risks and population attributable proportions [6–9]. However, to our

Table 2. Age at which the cumulative risk of cancer reaches five per 1000 among individuals with and without affected parents/siblings and difference in diagnosis age of individuals with affected parents and siblings compared with individuals without family history

Cancer site	Without family history		With affected parents				With affected siblings				With affected parent and sibling			
	Age	95% CI	No.[a]	Age	95% CI	AD[b]	No.[a]	Age	95% CI	AD[b]	No.[a]	Age	95% CI	AD[b]
Breast	45.5	45.3, 45.7	715	41.6	41.2, 42.0	−3.9	225	41.3	40.5, 41.9	−4.3	20	38.3	36.7, 41.0	−7.2
Endometrium	57.8	57.3, 58.3	61	51.8	51.0, 53.3	−6.0	17	49.6	48.5, 53.4	−8.3				
Ovary	58.3	57.5, 59.2	82	47.6	45.2, 49.4	−10.7	23	44.3	42.1, 47.1	−14.0				
Colorectum	59.0	58.8, 59.3	749	53.8	53.2, 54.5	−5.3	104	52.7	51.3, 53.8	−6.5	14	39.8	37.2, 44.8	−19.3
Prostate	59.8	59.6, 59.8	641	56.8	56.6, 57.0	−2.9	99	55.4	54.9, 55.8	−4.3	21	52.6	51.1, 53.3	−7.2
Lung	61.6	61.3, 61.9	397	57.8	57.2, 58.5	−3.8	86	56.5	54.8, 57.5	−5.1	6	53.3	49.7, 56.3	−8.3
Women	62.0	61.7, 62.3	220	58.1	57.4, 59.0	−3.9	50	56.6	55.3, 58.3	−5.4				
Men	61.3	60.9, 61.6	179	57.4	56.9, 58, 3	−3.8	35	56.1	54.3, 57.3	−5.2				
Melanoma	62.5	61.9, 63.2	317	50.1	47.8, 51.9	−12.4	144	48.2	46.3, 49.4	−14.3	6	26.7	25.3, 41.8	−35.8
Women	60.8	60.1, 61.5	175	47.8	46.3, 50.3	−13.0	77	46.4	44.5, 48.6	−14.4				
Men	64.4	63.7, 65.0	146	51.8	50.3, 53.0	−12.6	73	48.9	48.1, 50.7	−15.5				
Bladder[c]	64.4	64.0, 64.9	195	59.7	58.6, 61.0	−4.8	37	59.8	57.3, 63.4	−4.7				
Women	71.6	71.0, 72.0	69	65.3	64.6, 67.1	−6.3	7	66.6	63.6, 67.8	−5.0				
Men	61.1	60.7, 61.6	107	56.3	54.9, 57.8	−4.8	25	55.5	52.1, 59.8	−5.6				
Nervous system	66.3	65.5, 67.1	234	59.7	58.4, 62.0	−6.6	109	56.9	54.4, 71.8	−9.3				
NHL	66.7	65.9, 67.2	140	60.5	59.3, 62.5	−6.2	43	59.4	57.0, 66.0	−7.3				
Women	69.7	68.9, 70.6	55	62.6	61.8, 66.0	−7.1	26	63.0	59.0, 69.9	−6.7				
Men	64.4	63.8, 65.2	84	59.3	56.8, 60.8	−5.2	16	57.1	54.8, 61.3	−7.3				
Kidney	69.0	68.4, 70.0	112	63.3	59.9, 66.4	−5.7	24	55.7	50.3, 58.6	−13.3				
Women	71.4	70.9, 71.9	46	66.5	63.8, 69.2	−4.9	12	57.6	53.3, 62.7	−13.8				
Men	66.7	65.8, 67.6	61	59.6	57.8, 63.8	−7.1	11	52.9	47.7, 57.8	−13.8				
Cervix	69.9	66.8, 70.3	92	48.9	45.2, 69.9	−21.0	28	50.3	39.6, 63.7	−19.6				
Skin	71.3	70.7, 71.8	147	64.4	63.3, 66.7	−6.8	22	65.2	61.7, 66.3	−6.1				
Leukemia	71.9	71.2, 71.9	132	63.9	62.9, 66.4	−8.0	40	59.3	59.1, 64.3	−12.6				
Pancreas	72.0	71.8, 72.0	85	66.9	65.7, 66.9	−5.1	16	62.6	59.5, 67.1	−9.4				

Cancer sites are ordered according to the age at which the cumulative risk of cancer among individuals without a family history reaches five per 1000.
[a]Number of cases that occurred before the age at which the cumulative risk of cancer reaches one per 1000; data are only shown for cancer sites with more than four cases.
[b]AD: Age difference to individuals without affected parents/siblings.
[c]Urinary bladder.
CI, confidence interval; NHL, non-Hodgkin's lymphoma.

knowledge, the present study is the first one to consider differences in age at which a defined cumulative incidence is reached for any familial and sporadic cancers. This type of analysis is particularly practical for clinical consideration because it gives the age by which a constant risk is attained in familial and sporadic cases. An important advantage was the accuracy and completeness of the analyzed data, which minimized biases related to selection and recall. Although this study is the largest one published to date, the numbers of familial cases to estimate cumulative risks were small for some cancer sites. Another, albeit minor limitation is the possible incorrect definition of some family histories due to the fact that some parents and siblings were affected by cancer before cancer registration started in 1958 and some parents and siblings will be diagnosed with cancer in the future.

Our data indicate that individuals with parents or siblings affected by cancer are diagnosed at earlier ages than individuals without a family history. This outcome could be deduced from the increased familial relative risks at the investigated cancer sites [6, 9]. The familial risks tend to decrease with the age of diagnosis of the probands for some cancer sites [6, 17–22]. Thus, the decreased age at which individuals with a family history reached a given cumulative risk was not only due to a higher prevalence of cancer at any age but also to a higher prevalence of early onset cancer. The even lower age of onset for individuals with both a parent and a sibling affected is in concordance with the higher familial relative risks for these individuals. Inherited cancer syndromes are likely to contribute to the early age of onset, particularly among individuals with two affected first-degree relatives.

Hereditary nonpolyposis colorectal cancer (HNPCC) is characterized by a strong predisposition to colorectal and endometrial cancers [5]. The syndrome has been associated with germline mutations in five mismatch repair genes (*MSH2, MLH1, MSH6, PMS1, PMS2*) [23]. The commonly cited mean age of diagnosis of colorectal cancer within HNPCC is 45 years, which is by far younger than the 63 years in the general population [23]. However, a recent study has reported a mean onset age of 55 years in male and 60 years in female members of the HNPCC families [24]. Despite this variation, HNPCC is likely to contribute to the lower age at which individuals with a family history reach a given cumulative risk. The contribution may be particularly important to the difference of 19.3 years among individuals with both a parent and a sibling affected to reach the cumulative risk of 0.5%. Similarly, *BRCA1* and *BRCA2* mutations are likely to account for some early onset patients for breast and ovarian cancers; however, these mutations are thought to account for no more than 20% of familial breast cancer [5, 25–28]. The difference in the age of onset could also be influenced by overdiagnosis due to increased surveillance of familial cases: individuals with a close relative affected by cancer may participate in cancer screening more often, more frequently or earlier [29].

The present results provide scientific bases for the conduct of screening and surveillance programs. The American Cancer Society recommends average-risk women to start with mammography screening at the age of 40 years. Women with more than one relative affected by breast cancer should undergo screening 10 years earlier [12]. The present data are largely in agreement with these recommendations. Women without a family history reached a cumulative risk of 0.5% at the age of 45.5 years. The corresponding ages for sisters and daughters of affected women were 41.6 and 41.3 years, respectively. For women with a mother and a sister with breast cancer, the age to reach this risk was 38.3 years. Despite their practical relevance, the present data should be interpreted with care because they are on the basis of risk estimations rather than on an assessment of the mortality reduction by mammography screening, which is the basis of the guidelines for average-risk women [12]. Regarding colorectal cancer, the starting age for screening recommended by the American Gastroenterological Associtaion is 50 years for average-risk individuals, 10 years earlier for individuals with an affected first degree relative or 10 years in advance of the earliest diagnosis in the family, whichever comes first (excluding individuals in familial adenomatous polyposis and HNPCC families, who are given special recommendations) [11]. Our study supports the recommendation to start colorectal cancer screening earlier, although we cannot readily exclude syndromatic patients [30, 31]. The age at which individuals with both a parent and a sibling affected reached the cumulative risk of 0.5% for colorectal cancer was 20 years lower than for individuals without a family history, most likely encompassing many HNPCC families. The known colorectal cancer syndromes account for 1%–5% of colorectal cancer, while their proportion of familial colorectal cancer is around 15%–20% [23, 32].

We conclude that, for most common types of cancer, individuals with affected parents or siblings are diagnosed at earlier ages than individuals without a family history. The difference in age of onset depends on the number of affected relatives, while the affected proband, parent and sibling caused no large difference. With the discussed limitations, the present data may help to evaluate and improve current screening strategies. They offer scientific bases for the design of clinical counseling and screening activities for the familial cancers currently lacking established management options.

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