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Concordant and discordant familial cancer: Familial risks, proportions and population impact

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Cancer Epidemiology

Relatives of cancer patients are at an increased risk of the same (concordant) cancer but whether they are at a risk for different (discordant) cancers is largely unknown – beyond well characterized hereditary cancer syndromes - but would be of major scientific and clinical interest. We therefore decided to resolve the issue by analyzing familial risks when family members were diagnosed with any discordant cancers. We compared the population impact of concordant to discordant familial cancer. The Swedish Family-Cancer Database (FCD) was used to calculate familial relative risks (RRs) for family members of cancer patients, for the 27 most common cancers. Population attributable fractions (PAFs) were estimated for concordant and discordant family histories. Discordant cancers in the family were detected as significant risk factors for the majority of cancers, although the corresponding RRs were modest compared to RRs for concordant cancers. Risks increased with the number of affected family members with the highest RRs for pancreatic (2.31), lung (1.69), kidney (1.98), nervous system (1.79) and thyroid cancers (3.28), when 5 or more family members were diagnosed with discordant cancers. For most cancers, the PAF for discordant family history exceeded that for concordant family history. Our findings suggest that there is an unspecific genetic predisposition to cancer with clinical consequences. We consider it unlikely that shared environmental risk factors could essentially contribute to the risks for diverse discordant cancers, which are likely driven by genetic predisposition. The identification of genes that moderately increase the risk for many cancers will be a challenge.

Introduction

Familial risks are reasonably well-known for cancer at the same (concordant) sites between family members, but the risks between different (discordant) sites are relatively unknown.[1–4] Based on our current understanding the risks at the same sites could be explained by inherited genetic factors or shared environmental risk factors.[5] For risks between different sites it is known that germline mutations in genes such as TP53 (Li-Fraumeni syndrome), BRCA1/2 (breast-ovarian cancer syndrome) or DNA mismatch repair genes (Lynch syndrome) are predisposed to a set of cancers, but beyond cancer syndromes there is no evidence on overall susceptibility to cancer.[6] However, it is relevant to clinical genetic counseling whether to focus on a family history of a single or a few cancers, or whether to record histories of a multitude of cancers. In particular, as cancer is present in most families when sufficient information is available, it would be prudent to understand which tumor types could be linked on a genetic level and which are likely to be due to pure chance. For example, if there are cases of melanoma, colon cancer and leukemia in a family, is there an increased risk of cancer or is this just a coincidence? For cancer genetics, mechanism of overall predisposition to many cancers would be a fascinating, epochal discovery with implications for cancer prevention and treatment.

Familial risk describes the relative risk of cancer in individuals whose relatives have been diagnosed with a certain cancer, compared to those whose relatives that do not have that cancer. Familial risks are most reliably measured in population based studies where family relationships are known and cancer diagnoses are medically verified, typically in databases from, for example, Utah, Iceland or Sweden.[1–3] The familial proportion shows the proportion of individuals in a given generation or age group with a family member diagnosed with a defined cancer.[7] This is an interesting measure, which is only indirectly related to familial risks. The familial proportion is often cited as 'familial cancer constitutes X% of

Key words: familial cancer, discordant cancer, familial risk, population impact

Abbreviations: PAF: population attributable fraction; RR: relative risk; CI: confidence interval; FDR: first-degree relative; FCD: Swedish Family-Cancer Database; ICD: International Classification of Diseases; CUP: cancer of unknown primary.

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What's new?

Familial cancer risk is well-established, particularly for cancers of the same (concordant) type. By contrast, little is known about possible risks when family members are diagnosed with multiple different (discordant) cancers. Here, using data from the Swedish Family-Cancer Database, familial risks and population impact of concordant and discordant familial cancers were analyzed for the 27 most common malignancies. The occurrence of discordant cancers in families was found to significantly increase cancer risk, though not to the same extent as for concordant cancers. The data suggest that a general genetic susceptibility to cancer exists in some families.

cancer Y' but the figure is often not referenced. Familial proportions are available from population based studies but almost invariably these are lower, often much lower, than the unreferenced figures cited by the authors. The population attributable fraction (PAF) is an estimate of the population impact of a risk factor: how much would cancer risk decrease if the risk factor was not present in the population. In the present context, the PAF depends on the familial risk and the familial proportion, analogous to environmental epidemiology defining PAF through the magnitude of the effect and the size of the exposed population.[8] In a previous study we showed that the overall familial risk of cancer (6%) would rank third after tobacco smoking (19.4%) and unhealthy diet (9.2%).[9,10]

In the present study we provide novel estimates for discordant cancers, including familial risks, familial proportion and PAF. For comparison we updated our previous estimates for the same measures in concordant cancers, based on the recent update of the Swedish Family-Cancer Database, the largest family dataset in the world.[2,10]

Materials and Methods

Measures calculated within this study included relative risks, proportions and PAFs for familial cancer. Familial relative risks (RRs) for siblings and offspring of cancer patients were assessed by estimating incidence rate ratios using a Poisson regression model.[11] By this means, incidence rates for people with affected parents or siblings (positive family history) were compared to the corresponding rates for those individuals who had no cancer (negative family history) among their first-degree relatives (FDRs). Incidence rates were obtained by counting cases and person-years according to family history and stratified for sex, age group, calendar period, residential area and socioeconomic status to account for potential confounders. These variables were used as covariates for the model building to get adjusted RRs and corresponding confidence intervals (CIs) as described elsewhere.[2] Familial risk was considered to be significantly increased if the lower bound of the RR's 95% CI was >1.00. A linear trend test was performed. The PAF for familial cancer defines the proportion of cancer burden in the population that is due to an excess familial risk and was calculated as follows[8]:

$$\text{PAF} = \text{proportion of patients with a positive family history} \times \frac{\text{RR}-1}{\text{RR}}.$$

We distinguished between family histories, for concordant and discordant cancers that were defined independently, in order to assure additive PAFs and to derive overall PAFs for familial cancer among FDRs.

The abovementioned measures were calculated for the 27 most common cancers based on the Swedish Family Cancer Database (FCD). The database comprises information from the Multigeneration Register, censuses and death notifications provided by Statistics Sweden, and information from the Swedish Cancer Registry. The latest version of the FCD includes data until 2012 and contains 15,713,897 individuals, whereby all people born in Sweden from 1932 onwards (the offspring generation) were registered with linkage to their biological parents (the parental generation). Complete parental information enabled the identification of full siblings and therefore only individuals with information of both parents were considered to be at risk, totaling in 8,509,071 index individuals. The family sizes among the associated nuclear families varied from a minimum of 3 to a maximum of 20 family members, while the median family comprised of 4 individuals (2 parents and 2 offspring). Among them, 427,196 medically verified cancer cases were recorded and only the first primary cancers were considered. The 7th revision of the International Classification of Diseases (ICD-7) was used to identify the cancer type.

The follow-up for cancer was based on the Swedish Cancer Registry, starting 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 register-based definition of period at risk was used for person-year calculations whereby a person was considered to be at familial risk irrespective of when family members were diagnosed with cancer.[12]

Results

The proportion of cancer patients, who had a concordant cancer in the family along with the corresponding RRs and PAFs, are presented in Table 1. All cancers featured significantly increased familial risks, although the RRs for connective tissue cancer and cancer of unknown primary (CUP) reached a borderline significance only. Risks were increased twofold for most cancers while those of the small intestine (7.27), thyroid gland (6.70), testis (5.68) and Hodgkin lymphoma (5.86) showed the highest RRs. The highest PAFs were obtained for cancers of the prostate (14.71%), breast (7.67%) and colorectum (7.11) which cancers also had the

Table 1. Familial cancer risk and population attributable fraction for concordant cancers.

Cancer site	Cases negative family history	Any concordant cancer in the family				
		Cases	Proportion in %	RR	95% CI	PAF in %
Upper aerodigestive tract	3508	246	2.83	**1.75**	(1.47-2.08)	**1.22**
Esophagus	1110	45	1.63	**2.62**	(1.77-3.87)	**1.01**
Stomach	2057	341	6.29	**2.17**	(1.87-2.53)	**3.40**
Small intestine	674	39	2.14	**7.27**	(5.11-10.34)	**1.85**
Colorectum	13324	5203	14.71	**1.94**	(1.86-2.01)	**7.11**
Liver	2383	208	3.53	**1.81**	(1.51-2.18)	**1.58**
Pancreas	2494	291	4.42	**2.21**	(1.89-2.59)	**2.42**
Lung	8855	2775	11.38	**2.36**	(2.22-2.51)	**6.56**
Breast	28471	12310	16.13	**1.91**	(1.85-1.97)	**7.67**
Cervix	4103	194	2.17	**1.70**	(1.43-2.02)	**0.89**
Endometrium	4431	534	4.74	**2.26**	(1.98-2.58)	**2.64**
Ovary	3925	448	4.49	**2.95**	(2.65-3.28)	**2.97**
Prostate	20675	15196	24.56	**2.49**	(2.42-2.57)	**14.71**
Testis	3984	132	1.76	**5.68**	(4.48-7.19)	**1.45**
Kidney	3890	364	3.86	**1.97**	(1.72-2.26)	**1.90**
Urinary bladder	5284	886	6.36	**1.93**	(1.77-2.12)	**3.07**
Melanoma	11890	1786	6.27	**2.72**	(2.56-2.90)	**3.97**
Skin, squamous cell	4578	742	6.40	**2.09**	(1.90-2.30)	**3.34**
Nervous system	10947	717	3.22	**1.71**	(1.54-1.89)	**1.33**
Thyroid gland	2452	190	3.40	**6.70**	(5.61-8.01)	**2.90**
Endocrine glands	4171	282	2.92	**2.50**	(2.11-2.95)	**1.75**
Connective tissue	1797	26	0.69	1.79	(0.98-3.28)	0.30
Non-Hodgkin lymphoma	6259	524	3.65	**1.78**	(1.60-1.97)	**1.60**
Hodgkin lymphoma	2353	75	1.69	**5.86**	(4.53-7.59)	**1.40**
Myeloma	1606	100	2.45	**2.23**	(1.79-2.78)	**1.35**
Leukemia	7425	478	3.27	**2.02**	(1.82-2.25)	**1.65**
CUP	3600	268	2.92	1.25	(1.00-1.58)	0.59

largest proportions of cases with a concordant cancer in the family (24.56%, 16.13% and 14.71%, respectively).

Although RRs were only 1.2, or less, regarding a positive family history for discordant cancers in Table 2, all but esophageal and endometrial cancers showed significantly increased familial risks. All estimates were based on >1000 familial patients. For 20 out of 27 investigated cancers, more than half of the patients had at least one discordant cancer in the family. The proportions ranged from 42.02% for prostate cancer to 60.85% for small intestinal cancer. High proportions of familial cancer implied high PAFs with a maximum PAF of 11.78% for small intestinal cancer, followed by 8.54% for CUP and 8.12% for pancreatic cancer.

Summing up concordant and discordant familial cancers to estimate the impact of all familial cancer, the proportions ranged from 46.97% for Hodgkin lymphoma to 66.58% for prostate cancer. A PAF of >10% was then observed for 9 cancers, including stomach (11.33%), small intestinal (13.63%), colorectal (12.16%), pancreatic (10.54%), lung (13.73%), breast (12.18%), ovarian (10.50%), prostate (17.81%) and thyroid (10.53%) cancers.

Considering the number of patients with discordant cancers in the family revealed an increasing trend for RRs (Table 3). For families with 1 or 2 discordant cancers, most significant RRs ranged between 1.02–1.30. For 3 discordant cancers in the family, RRs for stomach, liver, lung, ovarian, kidney and thyroid cancers as well as CUP were 1.40 or higher. CUP even showed an RR of 1.76 for 4 discordant familial cancers, while the RR increased for stomach (1.70) and endocrine glands (1.69) cancers. The highest RRs were obtained in families presenting with 5 or more discordant cancers. Significantly increased RRs were shown for 7 cancers, including pancreatic (2.31), and kidney (1.98), and nervous system (1.79) cancer and myeloma (2.20), for which the RRs were about equal to concordant familial risks from Table 1. Note that trend tests were highly significant for all cancers except for esophageal cancer.

Table 2. Familial cancer risk and population attributable fraction for discordant cancers.

Cancer site	Cases negative family history	Any discordant (but no concordant) cancer in the family					All familial cancer		
		Cases	Proportion in %	RR	95% CI	PAF in %	Cases	Proportion in %	PAF in %
Upper aerodigestive tract	3508	4943	56.84	**1.10**	(1.04-1.17)	**5.20**	5189	59.66	6.41
Esophagus	1110	1598	58.05	1.05	(0.95-1.16)	2.84	1643	59.68	3.85
Stomach	2057	3021	55.75	**1.17**	(1.08-1.26)	**7.93**	3362	62.04	11.33
Small intestine	674	1108	60.85	**1.24**	(1.12-1.38)	**11.78**	1147	62.99	13.63
Colorectum	13324	16833	47.60	**1.12**	(1.09-1.15)	**5.05**	22036	62.32	12.16
Liver	2383	3302	56.03	**1.12**	(1.05-1.20)	**6.10**	3510	59.56	7.69
Pancreas	2494	3806	57.75	**1.16**	(1.09-1.24)	**8.12**	4097	62.16	10.54
Lung	8855	12747	52.29	**1.16**	(1.12-1.20)	**7.17**	15522	63.67	13.73
Breast	28471	35551	46.57	**1.11**	(1.08-1.13)	**4.52**	47861	62.70	12.18
Cervix	4103	4653	51.99	**1.06**	(1.01-1.12)	**3.00**	4847	54.16	3.89
Endometrium	4431	6289	55.88	1.05	(0.99-1.11)	2.56	6823	60.63	5.20
Ovary	3925	5597	56.14	**1.16**	(1.10-1.21)	**7.53**	6045	60.63	10.50
Prostate	20675	25993	42.02	**1.08**	(1.05-1.11)	**3.10**	41189	66.58	17.81
Testis	3984	3397	45.21	**1.08**	(1.01-1.15)	**3.38**	3529	46.97	4.83
Kidney	3890	5186	54.94	**1.16**	(1.10-1.23)	**7.78**	5550	58.79	9.68
Urinary bladder	5284	7755	55.69	**1.14**	(1.09-1.19)	**6.88**	8641	62.05	9.95
Melanoma	11890	14820	52.01	**1.10**	(1.07-1.14)	**4.84**	16606	58.27	8.81
Skin, squamous cell	4578	6265	54.08	**1.08**	(1.03-1.13)	**3.90**	7007	60.48	7.24
Nervous system	10947	10606	47.62	**1.10**	(1.05-1.14)	**4.17**	11323	50.84	5.51
Thyroid gland	2452	2940	52.67	**1.17**	(1.09-1.25)	**7.63**	3130	56.07	10.53
Endocrine glands	4171	5216	53.95	**1.10**	(1.04-1.16)	**4.73**	5498	56.86	6.48
Connective tissue	1797	1947	51.64	**1.17**	(1.05-1.30)	**7.43**	1973	52.33	7.73
Non-Hodgkin lymphoma	6259	7558	52.70	**1.09**	(1.05-1.13)	**4.30**	8082	56.36	5.90
Hodgkin lymphoma	2353	2009	45.28	**1.10**	(1.02-1.18)	**4.09**	2084	46.97	5.50
Myeloma	1606	2381	58.26	**1.09**	(1.02-1.17)	**4.95**	2481	60.70	6.30
Leukemia	7425	6731	46.00	**1.11**	(1.06-1.15)	**4.47**	7209	49.26	6.12
CUP	3600	5303	57.82	**1.17**	(1.08-1.27)	**8.54**	5571	60.75	9.13

Discussion

The present nationwide study covered all 2-generation families in Sweden, with a median number of 4 individuals per family with a maximum of 20 family members. These data demonstrate 5 novel features of familial cancer. First, of the 27 cancers considered all but esophageal and endometrial cancers (probably because these are relatively late onset cancers) showed a significant familial risk for a discordant family history. Second, the proportion of families with discordant cancers ranged from 42.02% for prostate cancer to 60.85% for small intestinal cancer. Combining concordant and discordant family histories, 66.58% of families with a prostate cancer had a family history of any cancer, which was the highest percentage. By contrast, Hodgkin lymphoma showed the lowest percentage of 46.97%. Third, the above proportions indicate that from 33% to 55% of all families have none or a single member diagnosed with cancer. The rest have at least 2 cancer patients. Fourth, even though RRs for any discordant cancer were considerably smaller than those of concordant cases, because of their higher proportions, discordant cancers resulted in PAFs which exceeded those for concordant cancer for all but prostate, breast and colorectal cancers. Fifth, familial risk increased uniformly by the number of family members with discordant cancer. For pancreatic, kidney and nervous system cancers, myeloma and CUP the RRs were equal or higher than RRs for concordant cancer when 4 or more family members were diagnosed with discordant cancer. None of the clusters of discordant cancers could be explained by known cancer syndromes, and for myeloma and CUP no such syndromes have even been described.

The results are surprising considering the lack of evidence on general susceptibility to cancer. This view is embedded in

Table 3. Familial cancer risk for multiple discordant cancers in the family.

Cancer site	Cases negative family history	1 discordant cancer			2 discordant cancers			3 discordant cancers			4 discordant cancers			≥5 discordant cancers			Trend test p values
		Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI	
Upper aerodigestive tract	3508	3378	**1.08**	(1.02-1.14)	1259	**1.14**	(1.06-1.22)	259	**1.25**	(1.09-1.45)	43	1.27	(0.91-1.79)	4	0.51	(0.17-1.54)	**<.0001**
Esophagus	1110	1082	1.04	(0.93-1.16)	407	1.06	(0.91-1.23)	86	1.12	(0.83-1.50)	15	1.14	(0.58-2.26)	8	2.45	(0.97-6.21)	0.1979
Stomach	2057	2009	**1.11**	(1.02-1.20)	791	**1.25**	(1.12-1.39)	176	**1.44**	(1.18-1.75)	35	**1.70**	(1.10-2.61)	10	2.00	(0.90-4.47)	**<.0001**
Small intestine	674	770	**1.24**	(1.12-1.37)	275	**1.24**	(1.08-1.42)	49	1.16	(0.87-1.54)	11	1.56	(0.87-2.80)	3	1.85	(0.61-5.65)	**0.0002**
Colorectum	13324	11844	**1.10**	(1.06-1.13)	4048	**1.15**	(1.10-1.21)	774	**1.24**	(1.13-1.36)	137	**1.36**	(1.10-1.67)	30	1.51	(0.97-2.36)	**<.0001**
Liver	2383	2239	**1.10**	(1.02-1.18)	816	**1.13**	(1.02-1.24)	201	**1.42**	(1.19-1.69)	38	**1.56**	(1.06-2.31)	8	1.35	(0.58-3.14)	**<.0001**
Pancreas	2494	2561	**1.13**	(1.06-1.20)	972	**1.20**	(1.10-1.30)	216	**1.35**	(1.15-1.58)	42	**1.54**	(1.09-2.19)	15	**2.31**	(1.29-4.12)	**<.0001**
Lung	8855	8604	**1.11**	(1.07-1.16)	3290	**1.23**	(1.17-1.30)	710	**1.40**	(1.26-1.56)	110	**1.31**	(1.01-1.70)	33	**1.69**	(1.06-2.71)	**<.0001**
Breast	28471	25686	**1.09**	(1.06-1.11)	8214	**1.14**	(1.11-1.17)	1389	**1.24**	(1.16-1.32)	216	**1.28**	(1.09-1.51)	46	1.38	(0.97-1.97)	**<.0001**
Cervix	4103	3338	1.05	(0.99-1.10)	1089	**1.09**	(1.01-1.18)	187	1.15	(0.97-1.37)	34	1.29	(0.87-1.92)	5	0.89	(0.32-2.48)	**0.0047**
Endometrium	4431	4228	1.02	(0.96-1.09)	1633	1.09	(1.00-1.19)	346	**1.19**	(1.01-1.41)	66	1.26	(0.87-1.83)	16	1.38	(0.65-2.91)	**0.0075**
Ovary	3925	3777	**1.11**	(1.05-1.17)	1448	**1.23**	(1.15-1.32)	302	**1.41**	(1.23-1.63)	53	**1.43**	(1.04-1.98)	17	**2.11**	(1.20-3.70)	**<.0001**
Prostate	20675	18524	**1.07**	(1.04-1.09)	6208	**1.11**	(1.08-1.15)	1100	**1.14**	(1.07-1.22)	139	1.09	(0.91-1.30)	22	0.77	(0.49-1.20)	**<.0001**
Testis	3984	2558	1.07	(0.99-1.15)	709	1.10	(0.98-1.24)	113	1.26	(0.96-1.66)	17	1.39	(0.69-2.80)				**0.0117**
Kidney	3890	3565	**1.14**	(1.08-1.20)	1261	**1.17**	(1.08-1.26)	290	**1.42**	(1.23-1.64)	54	**1.59**	(1.16-2.19)	16	**1.98**	(1.11-3.54)	**<.0001**
Urinary bladder	5284	5243	**1.11**	(1.05-1.16)	2010	**1.21**	(1.13-1.28)	407	**1.27**	(1.12-1.44)	80	**1.52**	(1.16-2.00)	15	1.25	(0.67-2.35)	**<.0001**
Melanoma	11890	10470	**1.08**	(1.04-1.12)	3622	**1.15**	(1.10-1.21)	621	**1.19**	(1.08-1.33)	91	1.14	(0.87-1.49)	16	0.93	(0.50-1.76)	**<.0001**
Skin, squamous cell	4578	4284	1.05	(1.00-1.11)	1596	**1.12**	(1.04-1.21)	320	**1.19**	(1.02-1.38)	51	1.15	(0.80-1.66)	14	1.41	(0.70-2.82)	**0.0003**
Nervous system	10947	7565	**1.07**	(1.04-1.11)	2507	**1.15**	(1.09-1.20)	430	**1.19**	(1.07-1.32)	82	**1.44**	(1.14-1.82)	22	**1.79**	(1.15-2.79)	**<.0001**
Thyroid gland	2452	2016	**1.10**	(1.03-1.17)	750	**1.29**	(1.18-1.41)	138	**1.43**	(1.19-1.73)	25	**1.63**	(1.07-2.51)	11	**3.28**	(1.73-6.24)	**<.0001**
Endocrine glands	4171	3624	**1.07**	(1.01-1.13)	1277	**1.13**	(1.03-1.22)	252	**1.26**	(1.07-1.50)	55	**1.69**	(1.19-2.41)	8	1.15	(0.46-2.89)	**<.0001**
Connective tissue	1797	1372	**1.14**	(1.05-1.23)	467	**1.22**	(1.09-1.37)	87	**1.33**	(1.05-1.68)	16	1.54	(0.90-2.63)	5	2.14	(0.83-5.53)	**<.0001**
Non-Hodgkin lymphoma	6259	5199	**1.06**	(1.01-1.10)	1886	**1.14**	(1.07-1.21)	386	**1.28**	(1.14-1.45)	69	**1.41**	(1.06-1.87)	18	1.64	(0.95-2.86)	**<.0001**
Hodgkin lymphoma	2353	1479	**1.08**	(1.00-1.15)	445	**1.15**	(1.03-1.28)	72	1.23	(0.96-1.57)	11	1.26	(0.68-2.35)	2	1.03	(0.24-4.40)	**0.0020**
Myeloma	1606	1602	1.06	(0.99-1.14)	618	**1.13**	(1.03-1.24)	130	**1.23**	(1.03-1.48)	22	1.23	(0.80-1.88)	9	**2.20**	(1.14-4.28)	**0.0003**
Leukemia	7425	4771	**1.08**	(1.04-1.13)	1597	**1.16**	(1.09-1.24)	300	**1.26**	(1.10-1.43)	54	**1.42**	(1.05-1.92)	9	1.04	(0.50-2.16)	**<.0001**
CUP	3600	3481	1.10	(0.99-1.23)	1441	**1.30**	(1.14-1.50)	298	**1.40**	(1.07-1.82)	63	**1.76**	(1.00-3.08)	20	2.34	(0.87-6.30)	**<.0001**

pathological diversity of cancer as a disease of many organ systems (sites) and histological types. In accordance, previous family studies have provided no support to the hypothesis of an overall susceptibility to cancer. Importantly, their limitation has been pairwise analysis of cancers rather than allowing any combination of cancers in family members.[1,3,4,13] The present data in Table 3 testify to this point; when only one family member was diagnosed with a discordant cancer most RRs were below 1.10.

Twin and other type of family data have described a heritable component for all cancer but this has been smaller than that for common individual cancers, and twin studies typically consider cancer in two individuals.[14–16] A recent joint analysis of genome-wide association studies on 13 different sporadic cancers provided evidence against genetic sharing between pairs of cancers.[17]

Thus the most likely explanation as to why our study might have been more sensitive than previous negative studies was that we considered family history of any and many discordant cancers. Another important factor was the unsurpassed statistical power of the present study, covering 44,000 concordant and 207,555 discordant familial cancers. The proportions and kinds of familial cancers depend on the age structure of the generations under study. In the present study the second generation was born after 1931; thus the oldest individuals reached age 80 in the last follow-up year of 2012. This is well past the median age of cancer diagnosis in the Swedish Cancer Registry, which is 70 years.[18] However, as the median birth year of the second generation was 1947, this age cohort only reached their 65th birthday year in 2012. Thus cancers in the second generation have a modest overrepresentation of early onset cancers. Early age of onset features many but not all familial cancers[19]; however we did not carry out age-specific analysis because considering ages of onset of all family members with different cancers would be utterly complex. In a recent study on discordant cancers in prostate cancer families, the differences by age of onset were modest.[20] Another variable with possible influence on the results is the family size. We assume however that familial risks would not be influenced because a 3-generation analysis from this Database showed that the proportions of cancers were relatively uniform and without systematic trends, even when the family sizes varied from <5 to >60 individuals.[21] The present results were internally credible because a clear 'dose-response' relationship was observed in risk increase by the number of affected relatives with discordant cancer.

It is unlikely that shared environmental risk factors could essentially contribute to the risks for diverse discordant cancers. Even the risk factors that are known to influence cancers at several sites and which have a genetic component, including tobacco smoking and obesity, would not have a major influence on cancers, such as prostate and breast cancers.[22] In the same vein, environmental risk factors shared by family members are difficult to demonstrate even in the spousal setting, with the exception of smoking related cancers.[10,23] Thus the most likely explanation to the observed clustering of discordant cancers in families is genetic predisposition, possibly with interacting environmental factors.

Second and multiple primary cancers account for over 20% of the notifications to the Swedish Cancer Registry.[18] There is a large body of literature on second primary cancers which generally shows that the patients are at an increased risk of any cancer, including discordant cancer.[24–26] The risks are known to interact with the family history for discordant cancer, which would be in line with the current findings.[27,28] Although multiple primary cancers can have many etiologies the presentation of discordant cancers may in part be an expression of an overall cancer risk at the individual level, which may be enforced by a family history of cancer.

The best examples of predisposing genes with pleotropic effects on multiple cancer are found in the domain of cancer syndromes caused by tumor suppressor genes, all of which were initially linked to one or a few cancers but in the course of time more involved sites of lower risk were identified.[6] For example, hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome), caused by mutations in mismatch repair genes, was initially identified in colorectal cancer families, but it was later associated with a high risk of endometrial cancer and with a somewhat lower risk of many other cancers.[29] BRCA1 and BRCA2, also caused by mutations in DNA repair, were identified in breast and ovarian cancer families but now several other cancers are linked to these mutations.[30]

Pathways including tumor suppressor genes are involved in essential cellular processes shared by many tissues, which is the biological rationale why damage in such genes would have pleiotropic effects. Such critical cancer promoting cellular processes have been coined as 'hallmarks of cancer'.[31–34] It is conceivable that many key genes in such pathways could be polymorphic or under control of distal regulators which would influence the general risk of cancer, resulting in an unspecific increase in cancer risk perhaps through impaired immune surveillance or chronic inflammation. Examples of such pleiotropic polymorphisms are emerging in various cancers.[35–37] Most tumor suppressor genes support a single or a few cellular processes but recently detected 'super enhancers' are key regulatory elements of gene pathways, potentially promoting oncogenic processes in many cancers.[38,39] While the importance of super enhancers remains to be established we could speculate that they cause, at most, modest pleotropic risks because high-risk genes would have been identified in high-risk cancer families.

In conclusion, the present data have major clinical and mechanistic implications. Although the existence of several cancer predisposition syndromes is now well established and appreciated also by practicing oncologists, our findings shed light on an enigmatic but very common group of patients. Such patients have families with a collection of different tumors without seeming to fit any of the well-known syndromes. Our findings indicate that there is indeed a more unspecific type of genetic predisposition to cancer. This has

immediate clinical consequences. In the general practice, a patient with a strong history of "various tumors" should be taken seriously if there are signs and symptoms suggestive of cancer. In the oncology practice, these patients should be monitored not only for the relapse of the presenting tumor but tumors elsewhere. This is easily achieved with modern imaging techniques such as computer tomography and positron emission tomography. For genetic counseling, it will be useful to realize that there is such a thing as unspecific cancer predisposition which may increase the susceptibility for many tumor types. However, our findings would have further practical relevance if the molecular reasons for the observed cancer risk could be defined. In medicine, it remains as true as ever that establishing causality on a molecular level remains key for designing interventions.

Disclosure of Potential Conflicts of Interest

A.H. 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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