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Do discordant cancers share familial susceptibility?

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ABSTRACT

Aims: Cancer syndromes manifest at many sites albeit with variable penetrance. Genome-wide association (GWA) studies have identified susceptibility loci shared by many types of cancer. Yet, a population level search for shared susceptibility between discordant cancers has been hampered because of lacking population sizes.

Methods: Over 1.1 million patients in the nation-wide Swedish Family-Cancer Database were analysed for discordant familial cancers covering 33 sites. Standardised incidence ratios (SIRs) were calculated for patients whose family members had a defined cancer compared to those whose family members did not have that cancer. Three independent tests for each pair of cancer sites were done using different family relationships.

Results: Lung cancer showed 13 significant discordant associations but most of them were with sites for which smoking is a risk factor. An exception was the clustering of lung cancer and endocrine cancers. Four discordant associations reached a minimal significance level of 5×10^{-6}: colorectum–endometrium, breast–ovary, breast–prostate and melanoma–squamous cell carcinoma of the skin. The association of melanoma and nervous system cancer reached a minimal significance of 10^{-4}. Discarding lung cancer, all other associations were based on a single test whereby they were liable to be chance associations.

Conclusions: This study showed the extraordinary requirements for statistical power in study of multiple cancer sites. In addition to the smoking related sites, associations between breast and prostate cancers, melanoma and nervous system tumours and lung and endocrine tumours found strong statistical support. Within the present sample size limits, we found no evidence of an overall susceptibility to cancer.

1. Introduction

Many, if not most cancer syndromes, present at multiple sites. Hereditary non-polyposis colorectal cancer (HNPCC) causes a high risk of colorectal and endometrial cancers but a lower risk of at least half a dozen other sites.[1] BRCA1 and BRCA2 were identified through breast and ovarian cancer pedigrees but mutation carriers are at an increased risk of at least five other tumours, differing somewhat between BRCA1 and BRCA2 carriers.[2] Questions are thus asked whether there is a general susceptibility to cancer. A direct answer would be to assess discordant clustering of cancers in a population-based family register. Indeed, both the Utah and the Icelandic population databases have published results on discordant sites.[3,4] Similarly, results on discordant familial associations have been reported from the Swedish Family-Cancer Database in several studies focusing on a certain primary site, including for example colorectal cancer.[5]

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Table 1 – Standardised incidence ratios (SIRs) of colorectal cancer for individuals with a family history of any cancer where SIR was significantly increased (α = 5%, two-sided test) or power of SIR 1.2 reached 80%.

Site relative	Parent affected						Sibling affected					
	N	*E*	SIR	95% confidence interval (CI)		Power (%) SIR = 1.2	*N*	*E*	SIR	95% (CI)		Power (%) SIR = 1.2
Upper aerodigestive tract	277	285.0	0.97	0.86	1.09	89	103	95.7	1.08	0.88	1.31	47
Stomach	720	677.6	1.06	0.99	1.14	100	87	75.3	1.16	0.93	1.43	36
Colorectum	2574	1430.9	**1.80**	**1.73**	**1.87**	100	810	366.0	**2.21**	**2.06**	**2.37**	95
Liver	411	408.5	1.01	0.91	1.11	97	56	64.3	0.87	0.66	1.13	31
Pancreas	456	398.1	**1.15**	**1.04**	**1.26**	97	88	76.2	1.16	0.93	1.42	37
Lung	904	875.2	1.03	0.97	1.10	100	319	296.2	1.08	0.96	1.20	91
Breast	1274	1302.1	0.98	0.93	1.03	100	822	814.5	1.01	0.94	1.08	100
Cervix	257	238.3	1.08	0.95	1.22	84	88	85.3	1.03	0.83	1.27	41
Endometrium	417	325.6	**1.28**[a]	**1.16**	**1.41**	93	184	137.4	**1.34**	**1.15**	**1.55**	60
Ovary	309	280.6	1.10	0.98	1.23	89	133	121.9	1.09	0.91	1.29	55
Prostate	1877	1826.0	1.03	0.98	1.08	100	658	634.1	1.04	0.96	1.12	100
Kidney	433	401.7	1.08	0.98	1.18	97	103	106.7	0.97	0.79	1.17	51
Urinary bladder	622	596.3	1.04	0.96	1.13	100	146	169.6	0.86	0.73	1.01	69
Melanoma	257	253.6	1.01	0.89	1.15	86	255	227.4	1.12	0.99	1.27	82
Skin, squamous cell	496	527.3	0.94	0.86	1.03	99	115	107.2	1.07	0.89	1.29	50
Nervous system	338	303.1	1.12	1.00	1.24	91	208	183.2	1.14	0.99	1.30	73
Non-Hodgkin's lymphoma	342	340.4	1.01	0.90	1.12	94	162	151.2	1.07	0.91	1.25	64
Leukaemia	343	355.2	0.97	0.87	1.07	95	132	111.3	1.19	0.99	1.41	53

Bold type represents SIRs significantly increased at the two-sided 5% level; underlined SIRs were higher than 1.00 at the two-sided 1% confidence level.

[a] Reverse: *N* = 592, SIR = 1.10, 95% CI = (1.01–1.19).

However, the problems of the previous studies have been limitations of statistical power because the familial risks for discordant sites are usually much lower than those for concordant sites. Additionally, a single study has not had the means of confirming the results in an independent dataset or analysis. A further complication to the interpretation of the results is that not only mutant genes cause cancers at multiple sites but also do environmental exposures and habits shared by family members, with smoking as an example which may account for about 1/3 of familial cluster of lung cancer.[6] A recent interest in across site clustering of cancers stems from genome-wide association (GWA) studies which have identified over 100 genetic variants in some 20 cancers.[7,8] Many cancers show associations with three genomic regions, 5p15.33, 8q24, and 9p21.3, but the individual single-nucleotide polymorphisms (SNPs) do not appear to be shared by the cancer types.

In the present study we assess familial clustering between discordant sites with the most powerful means yet available, the recently updated nation-wide Swedish Family-Cancer Database on over 12 million individuals and 1.1 million first primary cancers. For statistical reasons, we focus on five common cancers, prostate, breast, colorectal and lung cancers and melanoma, and report all their discordant associations among 32 discordant sites fulfilling the inclusion criterion of detecting a relative risk of 1.20 with an 80% probability. For internal validity, we applied three independent tests for each pair of cancer sites, offspring cancer X by parental cancer Y, offspring cancer Y by parental cancer X and sibling cancer X and Y. These data may become useful in guiding therapy and counselling and they may eventually show genetically distinct subtypes of these common cancers.

2. Patients 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.[9] Data on family relationships were obtained from the Multigeneration Register, where children born in 1932 and later are registered with their biological parents as families. Thus, the individuals in the Database can be divided into offspring generation (individuals born in 1932 and later) and parental generation. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases, with coverage of the cancer registration close to 100%.[10] The family history of concordant and any of 32 discordant cancers was defined through parental and sibling probands. The 2010 update of the Database (FCD2008) includes more than 12 million individuals and their 1.1 million cancers from years 1958–2008. The offspring generation of the Database had a maximal age of 76 years while the age of the parental generation was not limited.

Familial relative risk for prostate, breast, colorectal and lung cancers and melanoma were estimated by the standardised

Table 2 – Standardised incidence ratios (SIRs) of lung cancer for individuals with a family history of any cancer where SIR was significantly increased (α = 5%, two-sided test) or power of SIR 1.2 reached 80%.

Site relative	Parent affected						Sibling affected					
	N	E	SIR	95% confidence interval (CI)		Power (%) SIR = 1.2	N	E	SIR	95% CI		Power (%) SIR = 1.2
Upper aerodigestive tract	230	202.2	1.14	1.00	1.29	76	131	71.3	**1.84**	**1.54**	**2.18**	37
Salivary glands	31	20.2	**1.54**	**1.05**	**2.18**	14	11	9.1	1.21	0.60	2.16	9
Oesophagus	108	74.4	**1.45**	**1.19**	**1.75**	36	41	23.7	**1.73**	**1.24**	**2.35**	13
Stomach	490	480.8	1.02	0.93	1.11	99	75	55.2	**1.36**	**1.07**	**1.70**	30
Colorectum	1054	1073.3	0.98	0.92	1.04	100	320	282.7	**1.13**	**1.01**	**1.26**	89
Liver	340	290.8	**1.17**	**1.05**	**1.30**	90	74	47.3	**1.57**	**1.23**	**1.97**	26
Pancreas	311	281.5	1.11	0.99	1.24	89	60	56.4	1.07	0.81	1.37	27
Lung	1108	595.2	**1.86**	**1.75**	**1.98**	100	540	213.8	**2.53**	**2.32**	**2.75**	79
Breast	871	888.1	0.98	0.92	1.05	100	653	586.0	**1.11**	**1.03**	**1.20**	100
Cervix	265	175.0	**1.52**[a]	**1.34**	**1.71**	72	72	62.5	1.15	0.90	1.45	34
Endometrium	244	229.2	1.07	0.94	1.21	83	85	99.8	0.85	0.68	1.05	47
Prostate	1156	1271.1	0.91	0.86	0.96	100	441	464.4	0.95	0.86	1.04	98
Kidney	332	281.0	**1.18**[b]	**1.06**	**1.32**	89	97	77.7	**1.25**	**1.01**	**1.52**	40
Urinary bladder	478	418.7	**1.14**	**1.04**	**1.25**	97	164	124.6	**1.32**	**1.12**	**1.53**	56
Skin, squamous cell	342	372.4	0.92	0.82	1.02	95	85	78.4	1.08	0.87	1.34	40
Endocrine glands	161	125.9	**1.28**	**1.09**	**1.49**	58	90	71.0	**1.27**	**1.02**	**1.56**	36
Connective tissue	66	53.5	1.23	0.95	1.57	29	33	22.7	**1.45**	**1.00**	**2.04**	16
Non-Hodgkin's lymphoma	248	236.6	1.05	0.92	1.19	84	128	109.7	1.17	0.97	1.39	50
Leukaemia	256	248.9	1.03	0.91	1.16	85	86	78.9	1.09	0.87	1.35	38

Bold type represents SIRs significantly increased at the two-sided 5% level; underlined SIRs were higher than 1.00 at the two-sided 1% confidence level.

[a] Reverse: *N* = 355, SIR = 1.26, 95% CI = (1.13, 1.40).

[b] Reverse: *N* = 277, SIR = 1.18, 95% CI = (1.04, 1.32).

incidence ratio (SIR) using SAS (Version 9.2; SAS Institute, Cary, NC). SIRs were calculated for offspring cancer X when parents or siblings were diagnosed by discordant cancer Y. We carried additionally out analysis by reverse order, i.e. SIR for offspring cancer Y by parental cancer X. This was a completely independent analysis and the significant results are shown in the footnotes if they support a significant association in the Tables. The reverse analysis for siblings was not independent and the results are not reported in the footnotes. The expected case numbers were calculated for the population whose family members had not been diagnosed with the particular cancer. Individuals entered the risk period at birth, immigration date or first year of the study (1961), whatever came last. The follow-up was ended at emigration, 31st December 2008 or at absence at census. Socioeconomic status, calendar period, sex and geographical region were taken into account as covariates. Confidence intervals (CIs), 95% CIs (bolding in the Tables) and 99% CIs (bolding and underlining), were calculated assuming the Poisson distribution. The rounding of the lower CI was based on the third decimal. The results for any of the tested discordant sites were shown when the probability to detect a statistically significant association at the two-sided 5% confidence level for an SIR of 1.20 exceeded 80% either for parental or sibling probands. Results of lower power are additionally shown for any significantly increased SIRs.

3. Results

The Database (FCD2008) had information on 1.1 million first cancers, including 159,487 prostate, 156,387 breast, 123,706 colorectal and 80,807 lung cancers and 42,589 melanomas. Table 1 shows SIRs for colorectal cancer in offspring whose parents or siblings were diagnosed with cancer. Concordant colorectal cancer is shown as a reference, showing an SIR of 1.80 when a parent and 2.21 when a sibling was also diagnosed with colorectal cancer; both were significant at a 1% level and had a power to detect an SIR of 1.20 of 100% and 95%, respectively. Parental endometrial cancer showed an association of 1.28 with an even higher association of 1.34 between siblings. The associations with endometrial cancer were significant at the 5% level also in the reverse order, i.e. risk of endometrial cancer in offspring when parents were diagnosed with colorectal cancer (SIR 1.10 in the footnote). The association of 1.15 with parental pancreatic cancer was significant at the 1% level but was not repeated in other

Table 3 – Standardised incidence ratios (SIRs) of breast cancer for individuals with a family history of any cancer where SIR was significantly increased (α = 5%, two-sided test) or power of SIR 1.2 reached 80%.

Site relative	Parent affected						Sibling affected					
	N	E	SIR	95% confidence interval (CI)		Power (%) SIR = 1.2	N	E	SIR	95% CI		Power (%) SIR = 1.2
Upper aerodigestive tract	713	708.8	1.01	0.93	1.08	100	222	215.6	1.03	0.90	1.17	79
Oesophagus	247	254.6	0.97	0.85	1.10	86	75	68.0	1.10	0.87	1.38	33
Stomach	1576	1503.6	1.05	1.00	1.10	100	176	162.7	1.08	0.93	1.25	68
Small Intestine	158	131.8	**1.20**	**1.02**	**1.40**	58	47	45.0	1.05	0.77	1.39	22
Colorectum	3994	3736.4	**1.07**	**1.04**	**1.10**	100	833	838.7	0.99	0.93	1.06	100
Liver	971	963.0	1.01	0.95	1.07	100	141	140.3	1.01	0.85	1.19	61
Pancreas	987	950.0	1.04	0.98	1.11	100	175	164.6	1.06	0.91	1.23	69
Lung	2407	2262.0	**1.06**	**1.02**	**1.11**	100	661	645.5	1.02	0.95	1.11	100
Breast	5533	3082.5	**1.80**	**1.75**	**1.84**	100	3426	1734.0	**1.98**	**1.91**	**2.04**	100
Cervix	596	604.1	0.99	0.91	1.07	100	191	207.0	0.92	0.80	1.06	77
Endometrium	880	842.5	1.05	0.98	1.12	100	319	294.1	1.09	0.97	1.21	90
Ovary	937	695.8	**1.35**[a]	**1.26**	**1.44**	100	331	263.6	**1.26**	**1.12**	**1.40**	87
Prostate	5081	4593.9	**1.11**[b]	**1.08**	**1.14**	100	1481	1337.9	**1.11**	**1.05**	**1.17**	100
Kidney	996	979.2	1.02	0.96	1.08	100	242	230.8	1.05	0.92	1.19	82
Urinary bladder	1609	1522.1	**1.06**	**1.01**	**1.11**	100	374	363.4	1.03	0.93	1.14	95
Melanoma	721	707.0	1.02	0.95	1.10	100	562	552.2	1.02	0.94	1.11	99
Skin, squamous cell	1305	1325.0	0.99	0.93	1.04	100	254	237.6	1.07	0.94	1.21	84
Nervous system	830	772.7	**1.07**	**1.00**	**1.15**	100	440	423.2	1.04	0.95	1.14	97
Thyroid gland	230	217.7	1.06	0.93	1.20	80	138	117.9	1.17	0.98	1.38	53
Endocrine glands	512	471.2	1.09	0.99	1.19	99	246	219.9	1.12	0.98	1.27	81
Non-Hodgkin's lymphoma	886	872.7	1.02	0.95	1.08	100	357	330.0	1.08	0.97	1.20	93
Hodgkin's disease	153	129.1	**1.19**	**1.01**	**1.39**	57	70	66.3	1.06	0.82	1.34	32
Myeloma	484	482.0	1.00	0.92	1.10	99	103	105.7	0.98	0.80	1.18	50
Leukaemia	874	877.1	1.00	0.93	1.07	100	255	253.8	1.01	0.89	1.14	86

Bold type represents SIRs significantly increased at the two-sided 5% level; underlined SIRs were higher than 1.00 at the two-sided 1% confidence level.

[a] Reverse: N = 1320, SIR = 1.12, 95% CI = (1.06, 1.18).

[b] Reverse: N = 2320, SIR = 1.16, 95% CI = (1.11, 1.21).

comparisons. The SIR for colorectal-connective tissue cancers between siblings was 1.14.

In Table 2, familial associations are shown for offspring lung cancer, with a concordant association of 1.86 through parents and of 2.53 through siblings. Highly significant associations, repeated in at least two comparisons were observed with oesophageal, liver, cervical, kidney, bladder and endocrine gland tumours. Notably, the SIRs for associations with parental oesophageal and cervical cancers, of 1.45 and 1.52, and those of sibling oesophageal and liver cancers of 1.73 and 1.57 were high, as was the sibling association with upper aerodigestive tract cancer of 1.84. A total of 13 proband sites showed significant associations, some with a modest power to find an association of 1.20. Sites not commonly associated with smoking included the colorectum and connective tissue, each with a single borderline association, salivary glands and the endocrine glands, mentioned above with two independent associations.

The concordant associations for breast cancer were 1.80 through mothers and 1.98 through sisters (Table 3). Highly significant associations, replicated in all three comparisons were found with ovarian and prostate cancers. Daughters' breast cancer was also increased when parents were diagnosed with small intestinal, colorectal, lung, bladder and nervous system cancers and with Hodgkin's lymphoma, however, these increases were noted in one comparison only.

The concordant prostate cancer associated with SIRs of 2.28 and 3.25 with paternal and fraternal prostate cancer (Table 4). The association with breast cancer, also noted in Table 3 was replicated in all comparisons done. Among other sites, only parental anal and ovarian cancers associated with prostate cancer.

The concordant associations of melanoma were 2.62 and 2.94 through parental and sibling probands (Table 5). Strong familial association was found for skin squamous cell carcinoma in all comparisons done. Other associations were

Table 4 – Standardised incidence ratios (SIRs) of prostate cancer for individuals with a family history of any cancer where SIR was significantly increased (α = 5%, two-sided test) or power of SIR 1.2 reached 80%.

Site relative	Parent affected						Sibling affected					
	N	E	SIR	95% confidence interval (CI)		Power (%) SIR = 1.2	N	E	SIR	95% CI		Power (%) SIR = 1.2
Upper aerodigestive tract	439	442.1	0.99	0.90	1.09	98	144	154.4	0.93	0.79	1.10	66
Stomach	1121	1130.9	0.99	0.93	1.05	100	119	121.4	0.98	0.81	1.17	57
Colorectum	2462	2458.1	1.00	0.96	1.04	100	675	652.3	1.04	0.96	1.12	100
Anus	47	31.9	**1.47**	**1.08**	**1.96**	20	19	20.6	0.92	0.56	1.44	13
Liver	697	663.2	1.05	0.97	1.13	100	103	103.3	1.00	0.81	1.21	48
Pancreas	623	646.6	0.96	0.89	1.04	100	136	125.0	1.09	0.91	1.29	58
Lung	1295	1364.3	0.95	0.90	1.00	100	461	489.2	0.94	0.86	1.03	99
Breast	2320	2002.5	**1.16**[a]	**1.11**	**1.21**	100	1492	1343.4	**1.11**	**1.06**	**1.17**	100
Cervix	357	362.7	0.98	0.89	1.09	95	124	132.4	0.94	0.78	1.12	60
Endometrium	533	506.5	1.05	0.97	1.15	99	238	232.9	1.02	0.90	1.16	83
Ovary	497	445.9	**1.12**	**1.02**	**1.22**	98	224	205.8	1.09	0.95	1.24	79
Prostate	5571	2444.6	**2.28**	**2.22**	**2.34**	100	3112	958.6	**3.25**	**3.13**	**3.36**	100
Kidney	660	643.9	1.03	0.95	1.11	100	202	174.4	**1.16**	**1.00**	**1.33**	70
Urinary bladder	912	946.6	0.96	0.90	1.03	100	324	282.6	**1.15**	**1.03**	**1.28**	89
Melanoma	363	368.6	0.99	0.89	1.09	95	420	371.8	**1.13**	**1.02**	**1.24**	96
Skin, squamous cell	801	869.2	0.92	0.86	0.99	100	169	183.0	0.92	0.79	1.07	73
Nervous system	475	466.9	1.02	0.93	1.11	98	328	296.4	1.11	0.99	1.23	90
Endocrine glands	293	272.5	1.08	0.96	1.21	88	181	160.7	1.13	0.97	1.30	67
Non-Hodgkin's lymphoma	491	523.5	0.94	0.86	1.03	99	280	252.0	1.11	0.99	1.25	85
Myeloma	346	317.7	1.09	0.98	1.21	92	77	80.4	0.96	0.76	1.20	41
Leukaemia	601	562.6	1.07	0.99	1.16	99	193	178.3	1.08	0.94	1.25	72

Bold type represents SIRs significantly increased at the two-sided 5% level; underlined SIRs were higher than 1.00 at the two-sided 1% confidence level.

[a] Reverse: N = 5081, SIR = 1.11, 95% CI = (1.08, 1.14).

found through parental colorectal, breast, nervous system, endocrine gland and connective tissue tumours, and through sibling kidney cancer; however only the association with the nervous system was replicated in reverse comparisons.

4. Discussion

The present study is the first systematic approach in the Swedish Family-Cancer Database to assess familial risks for discordant cancers. The base population of 12 million is more than one order of magnitude larger than those of Utah and Iceland previously used for across site analyses.[3,4] Three foreseen problems have been the reason for our previous hesitation. First, based on discordant analyses in studies focusing on individual sites we have noted that for discordant sites both the familial case numbers and risks tend to be very small. Second, multiple comparisons between 32 discordant sites yield 1024 associations. The conservative Bonferroni correction would call for using a p-value 0.05 divided by the number of comparison, i.e. an adjusted p-value of 0.05×10^{-3}.[11] Third, lacking of large reference databases, comparisons to the existing literature are not possible and comparisons to known cancer syndromes are often not productive because the syndromes are rare compared to familial aggregation.

We felt that it is now important to answer questions about familial clustering of cancer between discordant sites because the GWA studies are showing that close genomic loci are shared between cancer sites.[7,8] The Family-Cancer Database (FCD2008) was updated in 2010, extending the offspring population to age 76 years, well past the median age of about 71 years in the Swedish Cancer Registry. As the sibling population can only be defined in the second generation, we were convinced the 76 year old sibling population would serve as an independent study group, in addition to parents and offspring. Thus at the onset of the present study we defined three independent comparisons, risk in offspring cancer X by parental cancer Y, risk in offspring cancer Y by parental cancer X and risks between siblings with cancer X and Y. This implied that the present study involved $3 \times 1024 = 3072$ comparisons. Instead of using the formal Bonferroni correction (which would define the limit of significance at 0.00002 $= 2 \times 10^{-5}$), we thought that internal consistency should define validity. We used the common 5% CIs and additionally 1% CIs. Moreover, rather than attempting to report all 3072 comparisons, we focused on the discordant sites where the study had

Table 5 – Standardised incidence ratios (SIRs) of melanoma for individuals with a family history of any cancer where SIR was significantly increased (α = 5%, two-sided test) or power of SIR 1.2 reached 80%.

Site relative	Parent affected						Sibling affected					
	N	*E*	SIR	95% confidence interval (CI)		Power (%) SIR = 1.2	*N*	*E*	SIR	95% CI		Power (%) SIR = 1.2
Upper aerodigestive tract	231	233.9	0.99	0.86	1.12	83	49	63.7	0.77	0.57	1.02	32
Stomach	461	465.2	0.99	0.90	1.09	98	43	46.5	0.92	0.67	1.25	26
Colorectum	1386	1229.0	**1.13**	**1.07**	**1.19**	100	255	246.2	1.04	0.91	1.17	85
Liver	297	305.1	0.97	0.87	1.09	91	46	40.1	1.15	0.84	1.53	22
Pancreas	312	304.0	1.03	0.92	1.15	91	39	47.6	0.82	0.58	1.12	24
Lung	784	774.7	1.01	0.94	1.09	100	156	186.4	0.84	0.71	0.98	73
Breast	1320	1176.3	**1.12**	**1.06**	**1.18**	100	554	561.4	0.99	0.91	1.07	100
Endometrium	276	286.5	0.96	0.85	1.08	90	76	85.2	0.89	0.70	1.12	40
Ovary	257	236.2	1.09	0.96	1.23	83	93	81.0	1.15	0.93	1.41	40
Prostate	1685	1582.5	**1.07**	**1.02**	**1.12**	100	404	393.9	1.03	0.93	1.13	97
Kidney	340	322.0	1.06	0.95	1.17	92	89	67.6	**1.32**	**1.06**	**1.62**	35
Urinary bladder	539	510.3	1.06	0.97	1.15	99	94	105.7	0.89	0.72	1.09	51
Melanoma	683	260.7	**2.62**	**2.43**	**2.82**	86	500	170.1	**2.94**	**2.69**	**3.21**	70
Skin, squamous cell	594	432.3	**1.37**[a]	**1.27**	**1.49**	98	94	70.8	**1.33**	**1.07**	**1.63**	35
Nervous system	326	274.6	**1.19**[b]	**1.06**	**1.32**	88	144	137.5	1.05	0.88	1.23	60
Endocrine glands	198	164.7	**1.20**	**1.04**	**1.38**	69	66	68.9	0.96	0.74	1.22	33
Connective tissue	84	64.8	**1.30**	**1.04**	**1.61**	33	24	23.2	1.03	0.66	1.54	15
Non-Hodgkin's lymphoma	300	298.6	1.01	0.89	1.13	91	100	100.1	1.00	0.81	1.22	48
Leukaemia	319	291.2	1.10	0.98	1.22	90	90	79.2	1.14	0.91	1.40	39

Bold type represents SIRs significantly increased at the two-sided 5% level; underlined SIRs were higher than 1.00 at the two-sided 1% confidence level.

[a] Reverse: *N* = 110, SIR = 1.44, 95% CI = (1.18, 1.73).

[b] Reverse: *N* = 273, SIR = 1.28, 95% CI = (1.13, 1.44).

a reasonable power (80% to detect an SIR of 1.20). Noting the problem of multiple comparisons we discuss no single associations, irrespective of the significance level.

Lung cancer served as a proof of principle. The spouse correlation of lung cancer, with a relative risk of about 1.40 is likely to be largely due to shared smoking habits, with a small contribution by passive smoking.[12] With the exception of endocrine glands, all discordant associations of lung cancer at the 1% significance were known smoking related sites.[13] The data correlated also with the known relative risks of smoking related cancers. The SIR for pancreatic cancer was 1.11, of borderline significance. According to an IARC working group, the relative risk of pancreatic cancer in smokers is about three, compared to a risk of 20 for lung cancer. Thus, for the smoking related sites it is not possible to draw any conclusions about the possible contributing genetic causes. However, genetic causes may explain the clustering of lung cancer and endocrine cancers. Associations with lung cancer are not discussed further.

Using 1% significance levels and showing an effect in all the three comparisons, defines a minimal significance level of $(0.01)^3 = 0.000001 = 10^{-6}$. The following discordant associations reached this significance level: colorectum–endometrium (minimal significance 5×10^{-6}), breast–ovary, breast–prostate and melanoma–squamous cell carcinoma of the skin. The two first associations are manifested in known cancer syndromes and for the last one ultraviolet irradiation is a known risk factor.[1,2,14] We have previously shown in detailed analyses that a large proportion of the clustering of colorectal and endometrial cancers can be traced to HNPCC.[15,16] Only the breast–prostate association remains as a yet unexplained familial clustering but many shared hormonal mechanisms have recently been presented for the two cancers.[17,18] When relaxing the significance level and disregarding lung cancer, the association of melanoma with nervous system cancer reached a minimal significance level of 10^{-4}. The CDKN2A gene mutations predispose to familial melanoma[19]; recent GWA studies have shown that the p16 locus encoding CDKN2A and CDKN2B at chromosome 9p.21.3 influences glioma and melanoma risk and naevus density on the skin.[20–22]

The minimal requirement for a discordant site to be considered was a power 80% to detect a risk of 1.20. Because the number of offspring–parent pairs exceeded those of siblings, the power was accordingly higher for the former pairs. The size of the present study can be appreciated by noting that

approximately one half of the offspring–parents associations had a 100% power to detect a SIR of 1.20. Effect size of the validated discordant associations (at least 1% significance) between offspring and parents ranged from 1.52 to 1.14 in lung cancer for which the concordant risk was 1.86. For colorectal cancer the range was from 1.28 to 1.15 (concordant SIR 1.80), for breast cancer it was 1.35 to 1.07 (1.80), for prostate cancer the only discordant SIR was 1.16 (2.28) and for melanoma from 1.37 to 1.12 (2.62). The relatively high discordant risks for lung cancer may imply that in addition to a strong environmental factor (smoking), other shared behavioural and genetic factors may contribute. For colorectal and breast cancers, even the highest discordant excess risks (SIR-1.00) accounted only for 40% of the excess concordant familial risks; for prostate cancer and melanoma these were only about 10%. For colorectal cancer the highest discordant association was found for endometrial cancer, most likely because of HNPCC. For breast cancer the highest discordant association was with ovarian cancer, probably related to shared response to oestrogens and, to a small extent, to known genetic causes (BRCA).[23] Thus for cancers for which no *a priori* sharing was known the discordant familial risks were very low compared to the concordant risks.

In conclusion, the present study illustrated the challenges posed by the exploration of shared susceptibility to several cancers. While it has been possible to show significant familial risk for all common cancers, the present study could point out only six discordant associations in cancer not related to smoking.[24] The main issues are statistical power and multiple comparisons, which we have been able to deal with for common but not for rare cancers. Other issues are the possible causes of shared susceptibility. The example on lung cancer showed that the shared smoking habit is apparently increasing the familial risk of a number of cancers. The possible role of UV irradiation as a shared risk factor of melanoma and skin cancer was another example. Other unknown environmental and life-style factors may be difficult to exclude. However, the role of genetic factors was the most plausible explanation for the aggregation of colorectal and endometrial cancers. As an overall conclusion, the presented data argue against any major shared susceptibility to common cancers. Any future search should assume at the onset that the discordant risks, if any, will be small compared to the concordant risks.

Conflict of interest statement

None declared.

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