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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