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Platinum Priority – Brief Correspondence

Editorial by William B. Isaacs on pp. 166–167 of this issue

Familial Associations Between Prostate Cancer and Other Cancers

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Abstract

Prostate cancer (PCa) has a large familial component, but understanding of its genetic basis is fragmentary. Breast cancers may be associated with PCa, but whether this is true for other tumor types is poorly established. We used a novel approach to study familial associations of any type of cancer with PCa. We assessed the relative risk (RR) for all types of tumors as a function of the number of first-degree relatives diagnosed with PCa. We hypothesized that for a familial association to be real, the RR for a given type of cancer should increase with the number of PCa diagnoses. In families with multiple PCa patients, significantly increased risks were observed for female breast cancer (RR 1.37 for families with three men with PCa), kidney cancer (RR 2.32), nervous system tumors (RR 1.77; RR 2.40 when PCa was diagnosed before age 70 yr), and myeloma (RR 2.44; RR 6.29 when PCa was diagnosed before age 70 yr). Some evidence of association was also found for melanoma (RR 1.82) and endocrine tumors (RR 2.18). The consistency and magnitude of the effects suggest that familial PCa is genetically associated with breast, kidney, and nervous system tumors and myeloma. This suggestion has implications for clinical counseling and design of genetic studies.

Patient summary: It is known that prostate cancer runs in families, but it is not known whether other cancers are common in such families. We showed that at least breast, kidney, and nervous system tumors and myeloma occur more often than by chance.

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Prostate cancer (PCa) has the largest familial component of all common cancers: 22% of diagnosed men have a first-degree relative—a father, a brother, or both—diagnosed with the same cancer, and high-risk families with at least three affected first-degree relatives account for 15% of familial PCa and 3% of all PCa [1]. Nevertheless, the search for high-risk predisposing genes has not been successful. Although *BRCA2* and *HOXB13* mutations confer an increased individual risk of PCa, their population impact is modest [2]. In addition, numerous low-penetrance loci have been described for PCa, and the known loci and the above mutations

combined are estimated to account for about one-third of familial risk of PCa [2]. Families with *BRCA2* mutations would be expected to manifest other *BRCA2*-related cancers, but at the population level, only breast cancer shows familial associations with PCa [3,4]. In the present study, we applied a novel approach to search for familial associations between of PCa and other cancers by assessing clustering of all types of cancers in families with increasing numbers of PCa. The large population size of the Swedish Family-Cancer Database allows a powerful search of discordant cancers, even in families with three or more patients with PCa. The

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data have implications for familial genetic counseling and for identifying novel predisposing genes for PCa.

In the Swedish Family-Cancer Database, 15.7 million persons are organized in families with cancer data from the Swedish Cancer Registry. The offspring generation (8.5 million persons with 427 196 cancers) comprised people born from 1932 onward. The latest follow-up of the database includes data through 2012; therefore, the maximum age of offspring was 80 yr, whereas the ages of their biological parents (the parental generation) were not limited. Using the seventh revision of the International Classification of Diseases, 36 different cancers were analyzed, but data on only 23 were reported because familial cases were few among 13 cancers. The follow-up for cancer in the offspring generation started 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. Analysis by TNM category was hampered because the classification was introduced in 2002.

Methods of calculating familial relative risks (RRs) for offspring cancer when first-degree relatives (parents and/or siblings) were diagnosed with cancer are described elsewhere [1]. Briefly, incidence rates for persons with affected relatives were compared with rates for those

whose relatives had no cancer. Incidence rates were obtained by counting cases and person-years according to family history, stratified for sex, age group, calendar period, residential area, and socioeconomic status to account for potential confounders. These variables were used as covariates for model building for adjusted RRs, corresponding 95% and 99% confidence intervals (CIs), and a trend test.

Figure 1 shows familial risks for cancers other than PCa as a function of the number of men diagnosed with PCa; the comparison was to families with no PCa (RR 1.00). Data are shown for six cancers with significantly increased RRs in families with at least three PCa patients. Data on all 23 cancers, including PCa, are shown in Supplementary Table 1. For all six cancers in Figure 1, RRs increased systematically by the number of affected family members with PCa. In families with at least three PCa cases, increased risks of myeloma (RR 2.44; 95% CI, 1.24–4.82), kidney cancer (RR 2.32; 95% CI, 1.23–4.36), and nonthyroid endocrine tumors (RR 2.18; 95% CI, 1.06–4.49) were noted. Increased risks were also observed for melanoma (RR 1.82; 95% CI, 1.18–2.80), nervous system tumors (RR 1.77; 95% CI, 1.08–2.91), and female breast cancer (RR 1.37; 95% CI, 1.02–1.86). RRs for male breast cancer were not significant. For comparison, Supplementary Table 1 shows that the risk of PCa was increased almost eightfold in families in which three members already had PCa.

Fig. 1 – Relative risks of six cancers associated with prostate cancer (PCa) in families of increasing numbers of men diagnosed with PCa (one, two, and three members with PCa in one family, shown by different colors). The comparison is to families without PCa. The downward bars show the lower bounds of the 95% confidence intervals. The full data can be found in Supplementary Table 1. PCa = prostate cancer.

Table 1 – Risks of prostate cancer when family members were diagnosed with discordant cancers

Cancer site in the family	Cases with negative family history	1 cancer case in the family			≥2 cancer cases in the family		
		Cases	RR	95% CI	Cases	RR	95% CI
Upper aerodigestive tract	60 798	1061	0.98	0.91–1.05	5	0.50	0.18–1.41
Stomach	59 793	2041	0.97	0.93–1.02	30	0.97	0.65–1.45
Colorectum	56 147	5451	1.02	0.98–1.05	266	0.99	0.85–1.15
Liver	60 471	1379	1.01	0.95–1.08	14	0.95	0.50–1.82
Pancreas	60 494	1352	0.98	0.92–1.04	18	1.01	0.59–1.71
Lung	58 584	3188	0.95	0.91–0.99	92	0.76	0.59–0.96
Breast	54 966	6523	1.12	1.08–1.16	375	1.08	0.95–1.24
Cervix	61 036	824	0.93	0.86–1.02	4	0.90	0.26–3.14
Endometrium	60 361	1489	1.08	1.01–1.14	14	0.70	0.38–1.30
Ovary	60 606	1240	1.06	0.99–1.13	18	1.28	0.75–2.19
Prostate	46 668	12 985	2.20	2.14–2.27	2211	4.81	4.51–5.14
Testis	61 721	141	1.09	0.90–1.33	2	2.59	0.50–13.48
Kidney	60 294	1544	1.05	0.99–1.12	26	1.44	0.92–2.26
Urinary bladder	59 562	2262	1.00	0.95–1.04	40	0.82	0.58–1.16
Melanoma	60 300	1527	1.06	1.00–1.12	37	1.03	0.72–1.47
Skin, squamous cell	59 908	1913	0.93	0.88–0.99	43	1.06	0.73–1.53
Nervous system	60 323	1507	1.08	1.01–1.14	34	1.66	1.11–2.48
Thyroid gland	61 431	428	1.13	1.00–1.27	5	2.08	0.67–6.41
Endocrine glands	60 939	918	1.11	1.04–1.20	7	0.86	0.38–1.95
Non-Hodgkin lymphoma	60 380	1464	1.00	0.94–1.06	20	0.91	0.55–1.52
Myeloma	61 073	784	1.06	0.98–1.15	7	1.07	0.45–2.59
Leukemia	60 366	1476	1.07	1.00–1.15	22	1.20	0.68–2.11
CUP	60 145	1700	1.05	0.98–1.11	19	1.12	0.63–1.97

CI = confidence interval; CUP = cancer of unknown primary; RR = relative risk.

Bolding indicates that the 95% CI did not overlap with 1.00. The 99% CI did not overlap with 1.00.

We carried out a separate analysis in families in which all PCa cases in any relatives were diagnosed before age 70 yr. The risk of nervous system cancer and myeloma were further increased in these families, reaching RRs of 2.40 (95% CI, 1.10–5.23) and 6.26 (95% CI, 2.79–14.17), respectively, in families with at least three members with PCa (Fig. 1 and Supplementary Table 1).

We studied with some detail the associated endocrine organs and histology of the associated breast, kidney, and nervous system tumors but found no obvious differences in the background distributions.

In the reverse analysis, the risk of PCa was assessed in families of discordant cancers (Table 1). Because familial clustering for other cancers is rarer than for PCa, only families with one or at least two non-PCa cancers could be considered. The risk of PCa was increased systematically only in families with nervous system tumors, reaching an RR of 1.66 (95% CI, 1.11–2.48) in families presenting with at least two nervous system cancers. PCa was increased in families with a single member diagnosed with breast cancer (RR 1.12; 95% CI, 1.08–1.16) and endometrial cancer (RR 1.08; 95% CI, 1.01–1.14), melanoma (RR 1.06; 95% CI, 1.00–1.12), and endocrine gland tumors (RR 1.11; 95% CI, 1.04–1.20).

Familial clustering may be due to shared genes, shared environment, their interactions, or increased screening [5]. Strong environmental risk factors linking PCa with endocrine and nervous system tumors, myeloma, or melanoma are not apparent, and thus a genetic contribution is likely [2]. For the association with breast cancer, *BRCA2* mutations may contribute; however, because the PCa association was stronger in families with a single breast

cancer in comparison to those with multiple breast cancers, shared hormonal pathways may be the main common mechanism [6,7]. The RR of PCa in Swedish *BRCA2* mutation carriers was reported to be only 2.3 [8]. In previous studies investigating familial risks between pairs of cancers, weak associations of PCa with breast cancer and myeloma were reported [3,9]. Family studies from Iceland detected associations of kidney cancer and melanoma with PCa [10]. In the Utah population database, PCa risk was found in melanoma families [11]. The kind of genes that could explain the observed associations is open to speculation. Individual low-risk genes contribute minimally to familial risk, and it is not known whether a polygenic set of low-risk PCa-related alleles would cause risk for another cancer [1,2,12]. Similarly, high-risk genes shared by PCa and other cancers are not known. By exclusion, the remaining options are as yet unidentified moderate-risk genes and/or gene–environment interactions.

Multiple testing may be an issue in exploratory studies such as the present one; however, the results are unlikely to be due to chance when they are supported by “dose response,” namely, significant and increasing RRs for a defined cancer in families with increasing numbers of patients with PCa [3]. If two RRs are significant at a minimal probability of 0.05 (ie, melanoma in Supplementary Table 1), the combined probability is $0.05 \times 0.05 = 0.0025$. Incidentally, this is the adjusted significance using the Bonferroni correction with 22 cancers tested [3]. For breast cancer, three RRs were significant at $p < 0.01$, yielding a combined probability of $< 10^{-6}$.

In summary, the convincing dose-response data showing increased risks of kidney and nervous system tumors and

myeloma provide strong familial evidence that they share as yet unknown predisposing genes with PCa. The evidence for melanoma and endocrine tumors is less compelling, and for breast cancer, the role of *BRCA2* may not be sufficient to explain the associations.

Author contributions: Kari Hemminki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: K. Hemminki.

Acquisition of data: Sundquist.

Analysis and interpretation of data: Frank, K. Hemminki, A. Hemminki.

Drafting of the manuscript: K. Hemminki, A. Hemminki.

Critical revision of the manuscript for important intellectual content: A. Hemminki, Sundquist, Frank.

Statistical analysis: Frank.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2016.07.031>.

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