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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.

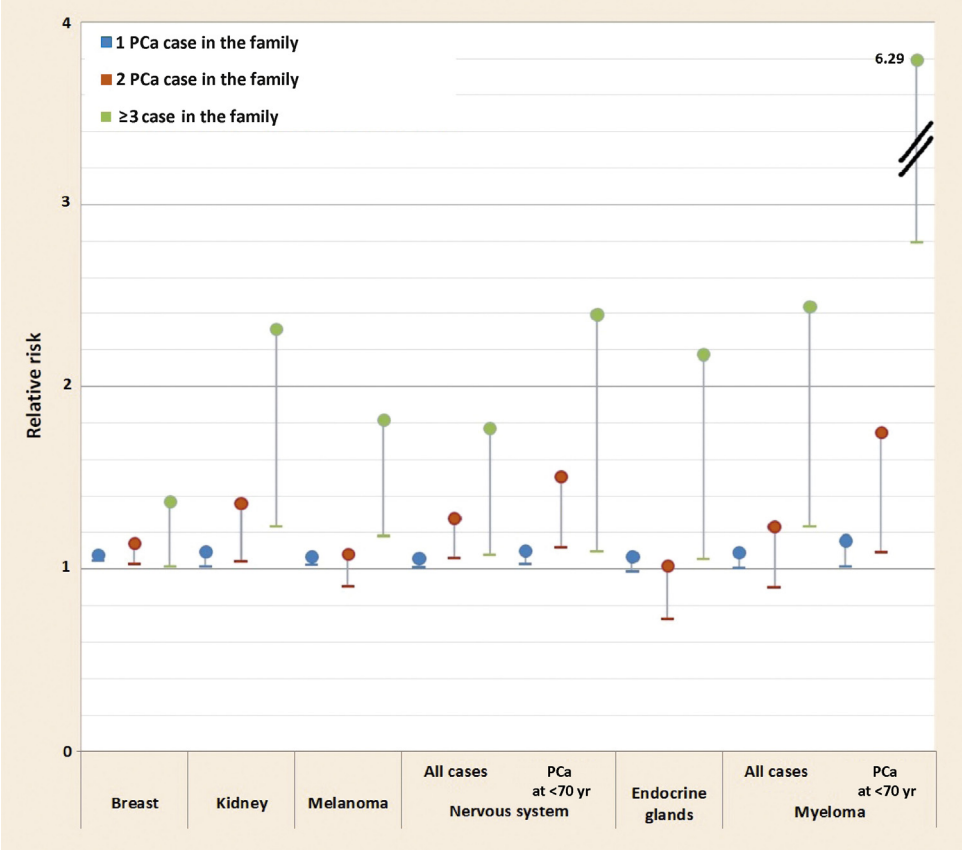

Fig. 1 – Relative risks of six cancers associated with prostate cancer (PCa) in families of increasing numbers of men diagnosed with PCa (one, two, and three members with PCa in one family, shown by different colors). The comparison is to families without PCa. The downward bars show the lower bounds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

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