Survey of Excess Familiality in Prostate Cancer

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Background

Prostate cancer (PCa) is the most commonly diagnosed cancer among men, and has long been recognized to occur in familial clusters. However, identification of genes predisposing individuals to prostate cancer has been difficult. Putative PCa predisposition loci identified by genetic linkage have been reported on almost all chromosomes, but successful confirmation reports have been rare. PCa is a complex disease likely involving multiple genes and variable phenotypic expression. As a step toward understanding PCa heterogeneity, we used the resources of the Utah Population Database to review several PCa-related phenotypes for excess familiality. PCa subgroups that can be shown to have a strong familial component become candidates for linkage analysis and other genetic testing to determine the genetic basis for the observed phenotype.

Data Resource

- Utah Population Database (UPDB)
  - Records for approximately 2.2 million individuals
  - Up to 9 generations of genealogical data linking individuals into pedigrees
  - Linked to death certificates from Utah vital records, providing cause of death data since 1904
- Utah Cancer Registry (UCR)
  - Part of Surveillance, Epidemiology and End Results (SEER) program since 1973
  - All cancer events except basal and squamous cell carcinomas are required to be reported
  - Fully linked to UPDB
- At the time of this study 17,379 PCa cases from UCR were linked to UPDB genealogies
- The following tables summarize the primary variables from UCR and UPDB used in this study

Table 1: Age at PCa diagnosis

Age (years)	N
40-49	143
50-59	1283
60-69	5436
70-79	7184
80-89	3051
≥90	273

Table 2: Age at PCa-related death

Age (years)	N
40-49	15
50-59	166
60-69	801
70-79	2028
80-89	1943
≥90	420

Table 3: ICD cause-of-death codes for PCa

ICD Revision	Code	N
6	177	35
7	177	487
8	185	650
9	185	2719
10	C61	1487

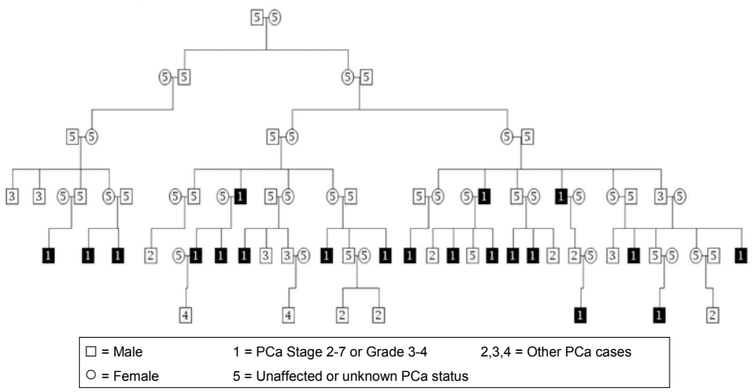
Table 4: PCa Stage at diagnosis

Stage Code	Description	N
1	Localized	6973
2,3,4,5	Regional	6840
7	Distant metastases/ Systemic disease	5206

Table 5: PCa Grade at diagnosis

Grade Code	Description	N
1	Well differentiated	7205
2	Moderately differentiated	6930
3	Poorly differentiated	3035
4	Undifferentiated, anaplastic	209

Sample PCa pedigree ascertained from Utah Population Database



Genealogical Index of Familiality (GIF)

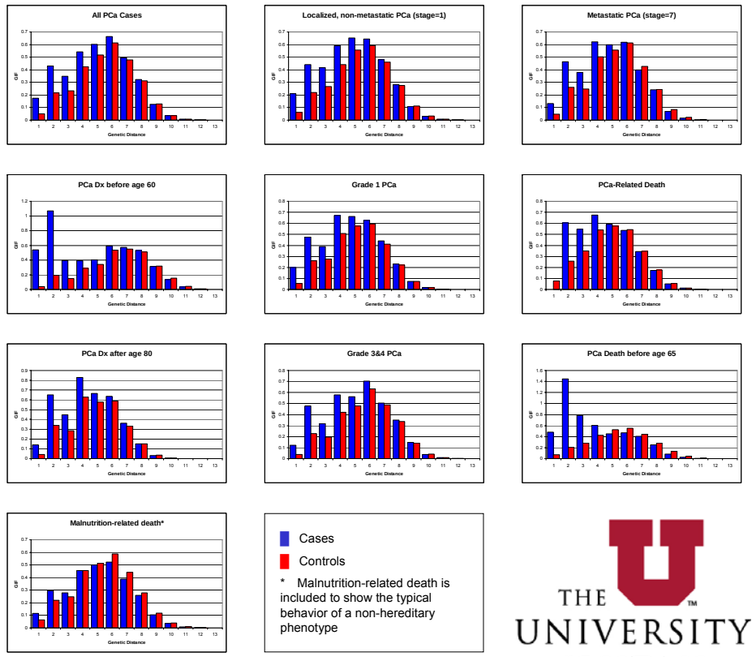
The GIF statistic tests the hypothesis that a set of individuals is more closely related than would be expected by chance. The statistic is computed for the cases and for 1000 sets of controls that are carefully matched to each subject in the case group based on sex, year of birth and place of birth. An empirical p-value determines the significance of the relatedness of the cases in comparison to the repeated controls.

Table 6: Summary of GIF analysis for prostate cancer subgroups

		Overall GIF			GIF without 1° and 2° relatives		
Phenotype Group	N	Cases	Controls	Empirical P	Cases	Controls	Empirical P
All PC Cases	17,379	3.75	3.02	<0.001	2.80	2.52	<0.001
Localized PCa (Stage=1)	6973	3.87	3.03	<0.001	2.80	2.48	<0.001
Metastatic PCa (Stage=7)	1506	3.54	3.01	<0.001	2.57	2.45	0.174
PCa Dx before age 60	1426	4.99	3.14	<0.001	2.98	2.76	0.034
PCa Dx after age 80	3324	3.92	2.99	<0.001	3.13	2.61	<0.001
Grade 1 PCa	7205	3.80	2.99	<0.001	2.73	2.41	<0.001
Grade 3/4 PCa	3244	3.81	3.02	<0.001	2.89	2.55	<0.001
PCa-related death	5378	3.83	2.94	<0.001	2.39	2.25	0.008
PCa death before age 65	456	5.01	2.98	<0.001	2.30	2.42	0.661
Malnutrition Death*	1481	2.97	2.98	0.528	2.28	2.45	0.918

- All PCa subgroups analyzed show greater than expected familiality
- Cases with metastatic disease show reduced significance when the contribution of close relatives is removed
- Relatedness of group who died from PCa before age 65 also loses significance beyond close relatives

The graphs below show the contribution made to the GIF statistic by individuals with varying degrees of relatedness. Each step on the horizontal axis represents increasingly distant relatives. In familial diseases, we expect the case group to be consistently higher than the controls for several steps. In each frame the blue bars represent the case group and the red bars represent the average results of 1000 matched control sets.



Familial Relative Risk (FRR)

The resources of the UPDB allow us to make population-based estimates of relative risk for family members of individuals with specific phenotypes. The table below shows the relative risk to first, second and third degree relatives of cases for developing the same PCa phenotype.

Table 7: Summary of Familial Relative Risks for prostate cancer subgroups

Phenotype / Relationship	Subjects	Observed Cases	Expected Cases	FRR	95% CI
All PCa Cases	17,379				
1°		5330	2762.8	1.93	1.88—1.98
2°		5256	4071.4	1.26	1.26—1.33
3°		9312	8402.1	1.11	1.09—1.13
Localized PCa (Stage=1)	6973				
1°		1061	521.4	2.04	1.91—2.16
2°		1293	898.4	1.44	1.36—1.52
3°		2332	1979.1	1.18	1.13—1.23
Metastatic PCa (Stage=7)	1506				
1°		51	27.3	1.87	1.39—2.46
2°		62	40.8	1.52	1.16—1.95
3°		161	137.3	1.17	0.99—1.37
PCa Dx before age 60	1426				
1°		119	18.6	6.4	5.30—7.65
2°		58	24	2.42	1.84—3.13
3°		114	80	1.42	1.18—1.71
PCa Dx after age 80	3324				
1°		322	157.5	2.04	1.83—2.28
2°		288	203.8	1.41	1.25—1.59
3°		809	700.1	1.16	1.08—1.24
Grade 1 PCa	7205				
1°		1159	596.6	1.94	1.83—2.06
2°		1193	922.7	1.29	1.22—1.37
3°		2688	2271.5	1.18	1.14—1.23
Grade 3/4 PCa	3244				
1°		238	110.4	2.16	1.89—2.45
2°		224	154.7	1.45	1.26—1.65
3°		655	519.7	1.26	1.17—1.36
PCa-related death	5378				
1°		786	406.4	1.93	1.80—2.07
2°		985	700.4	1.41	1.32—1.50
3°		1534	1334.7	1.15	1.09—1.21
PCa death before age 65	456				
1°		9	2.3	3.91	1.79—7.4
2°		16	5.3	3.02	1.72—4.90
3°		15	9.8	1.53	0.85—2.52
Malnutrition-related death*	1481				
1°		31	25.5	1.21	0.83—1.73
2°		49	44	1.11	0.82—1.47
3°		125	115.8	1.08	0.90—1.29

Non-significant result Result significantly greater than general PCa
* Included to show behavior of non-hereditary phenotype

Conclusions

- All of the PCa subgroups examined show a significant familial component
- Best result was for early diagnosis group (age at Dx less than 60 years)
  - GIF = 4.99 was the second largest observed
  - FRR = 6.4 for first degree relatives was largest observed
  - FRR values for all relative groups were significantly higher than the values for general PCa
- Strong familiality for PCa-related death prior to age 65 is not observed in distant relatives.
  - May be the result of a small sample size
- Localized vs. Metastatic PCa cases
  - Metastatic PCa loses familial significance beyond first and second degree relatives
    - Result may be affected by relatively small sample size.
  - FRR values for localized cases were significantly higher than the values for general PCa in both second and third degree relatives

•Our results show that early-onset PCa cases and those cases with localized disease have the strongest familial relationships. These two phenotypes may therefore be strong candidates for linkage analysis or other genetic testing to identify genes that are associated with prostate cancer.

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