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Identification of specific Y-chromosomes associated with increased prostate cancer risk

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Abstract

Background—Evidence supports the possibility of a role of the Y chromosome in prostate cancer, but controversy exists.

Methods—A novel analysis of a computerized population-based resource linking genealogy and cancer data was used to test the hypothesis of a role of the Y chromosome in prostate cancer predisposition. Using a statewide cancer registry from 1966 linked to a computerized genealogy representing over 1.2 million descendants of the Utah pioneers, 1,000 independent sets of males, each set hypothesized to share the same Y chromosome as represented in genealogy data, were tested for a significant excess of prostate cancer.

Results—Multiple Y chromosomes representing thousands of potentially at-risk males were identified to be associated to have a significant excess risk for prostate cancer.

Conclusions—This powerful and efficient *in silico* test of an uncommon mode of inheritance has confirmed evidence for Y chromosome involvement in prostate cancer.

Keywords

Y chromosome; prostate cancer; UPDB

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INTRODUCTION

Evidence suggests that genes present on the Y chromosome may be involved in increased risk for prostate cancer; however, the Y chromosome has received little attention in conventional genetic studies of prostate cancer. Investigation of the Y chromosome is challenging due to lack of recombination and the high content of repetitive and ampliconic sequences; this results in exclusion of the Y chromosome from most genome sequencing projects [1]. The Y chromosome is thought to harbor almost no genes; some rodent groups [2; 3] have lost the Y chromosome and some marsupials have degraded Y chromosomes [4]. There is a sole documented human Mendelian hearing loss disorder exhibiting linkage to the Y chromosome [5].

Y haplogroups are geographically specific, so that males from different ethnic groups have different Y lineages and potentially different predisposition to prostate cancer. It is well recognized that the incidence of prostate cancer is higher in African-American populations than in Caucasians, which is higher than in Japanese men [6; 7]. Further, cytogenetic studies in primary prostate tumors demonstrate that loss of the Y chromosome is the most common chromosomal aberration observed [8].

The Y chromosome is haploid and does not recombine over much of its length. Consequently, classical linkage mapping studies are not possible. Association studies of haplotypes constructed from genetic markers (short tandem repeats i.e., STRs, or single nucleotide polymorphisms i.e., SNPs) have been performed. To date the results of studies of the Y chromosome in prostate cancer cases and controls representing various ethnic groups have been conflicting. Prostate cancer incidence was reported to vary across Y chromosome lineages in a study of Japanese men [9]. No statistically significant differences in haplogroup frequencies were identified in a study of Y chromosomal markers in Korean prostate cancer cases and controls [10]. A rare Y lineage associated with an increased risk of prostate cancer was reported in an analysis of 5 binary Y-chromosome markers in Swedish prostate cancer cases and controls [11]; however, this was not confirmed in an independent data set. Significant risk- and protective effects were identified in a study that analyzed STRs at Yp11.2 in Portuguese cases and controls; testis-specific Y-encoded protein (*TSPY*) was proposed as a candidate gene [12]. In a study of 4 STRs on the Y-chromosome in Malaysian cases and controls significant risk- and protective haplotypes were identified [13]. In a larger study of 34 binary Y chromosome markers in approximately 4,000 cases and 4,000 controls inherited Y-chromosome variation was suggested to play a limited role in prostate cancer in European populations [14].

These previous studies have not clarified the role of the Y chromosome in prostate cancer. One reason for lack of clarity may be insufficiently informative study design. These published analyses of Y chromosomes were performed in unrelated men with prostate cancer, most of whom likely have different Y chromosomes that are associated with differing risks. A more informative design would identify and analyze sets of men who share a specific Y chromosome for association with increased prostate cancer risk. Such a study requires a large population with informative genealogy so that large groups of men sharing

the same Y chromosome can be identified, and so that a statistically reliable and powerful test for an excess of prostate cancer can be made for the specific Y chromosomes.

In this study, a population resource for Utah, the Utah Population Database (UPDB) was analyzed to identify large groups of men sharing the same Y chromosome. Prostate cancer risk in each independent Y-chromosome group was estimated in order to identify those specific Y chromosomes with a significant excess of prostate cancer cases.

MATERIALS AND METHODS

The Utah Population Database (UPDB)

The UPDB is a population-based resource containing computerized genealogy records for the European-Americans that settled Utah in the mid 1800s and their modern day descendants. The database originated in the early 1970s [15], and has been used extensively for successful gene identification studies (*NF1, BRCA1, BRCA2, p16, APC*). Genealogy data added since the 1970s consists of vital statistics data on trios (e.g. mother, father and child from a birth certificate). The database has been record-linked to the Utah Cancer Registry (UCR), which is part of the national SEER cancer surveillance effort, and contains data on every independent primary tumor occurring in the State of Utah since 1966, when the contribution of cancer data to the UCR became mandated by state law.

The UPDB includes over 6.5 million individuals whose records have been linked to over 400,000 cancer records, birth and death certificates, inpatient hospital data, and more [16; 17]. There are approximately 1.25 million individuals in the UPDB that have genealogy data for parents, all 4 grandparents, and at least 6 of their 8 great grandparents. Restriction to these individuals with high quality and quantity genealogy data (12 of 14 immediate ancestors) is implied for all further discussion. Within this set of over 1.25 million individuals there are a total of 87,037 individuals diagnosed with cancer; 18,291 of them have been diagnosed with prostate cancer. Each male in the UPDB was assigned to a cohort based on 5-year birth year range and birthplace (Utah or not) for estimation of prostate cancer disease rates. Cohort-specific rates of prostate cancer were estimated by dividing the number of UPDB prostate cancer cases by the total number of UPDB males, by cohort.

All males without a father in the genealogy data (founders) were identified; if they had any male descendants the founder was assigned a unique, sequential Y chromosome id (YID); each of their male descendants, and all of his male descendants, and so forth, were assigned this same YID, effectively identifying each independent Y chromosome segregating in the UPDB. This resulted in the identification of 257,252 YIDs for which there were at least 2 males who shared each Y chromosome (a father and son pair constitute the smallest YID group). The largest YID group included 2,264 males. All YIDs were assumed to be distinct based on genealogy data.

Risk for Prostate cancer

Using cohort-specific prostate cancer rates estimated internally from the UPDB, any group of males identified in UPDB can be tested to determine whether there is a significant excess of prostate cancer observed. For any YID founder in the genealogy we can consider 3 sets of

male descendants, the first set includes *all* of the male descendants of the founder, whether descended through male or female lineages; this subset includes the other two subsets. The second subset is those male descendants who share the Y chromosome of the founder, and the third subset is the male descendants who do not share his Y chromosome. The observed number of prostate cancer cases among the male descendants of each founder was counted, and the expected number of prostate cancer cases among the male descendants of each founder was calculated by multiplying the number of descendants in each cohort by the cohort-specific rate of prostate cancer, and summing over all cohorts. This same method was used to calculate the expected number of prostate cancer cases among the two mutually exclusive subsets of male descendants of each founder. RR's were calculated as the ratio of the observed to expected number of cases. A two-tailed significance test for the null hypothesis of relative risk = 1.0 was performed. The number of observed cases was assumed to follow a Poisson distribution with mean and standard deviation equal to the expected number of cases. Confidence intervals for the relative risks were estimated by Agresti's method [18].

Randomization test

An excess of observed prostate cancers among males sharing the same Y chromosome is suggestive of a high-risk Y chromosome; however, it is not sufficient to consider a significant excess among the Y-sharing males in a YID group as conclusive of a Y chromosome effect. Because of the confounding of prostate cancer and maleness, autosomal sharing could be totally, or partially, responsible for what might appear to be Y chromosome sharing. This is obvious when considering, for example, a high-risk prostate pedigree in which most offspring are males. It would not be possible to differentiate between autosomal and Y sharing as being responsible for prostate cancers in such a pedigree.

Since any excess risk for prostate cancer observed in the Y-sharing males may be partly, or entirely, due to autosomal sharing, any excess risk hypothesized to arise from the shared Y chromosome must be assessed against the autosomal risk background of all descendants of each YID founder. A randomization test was used to establish whether each Y-sharing group was significantly different from a cohort-matched, but randomly selected, subset of all of the descendants of the Y-founder. This approach implicitly takes into account the prostate cancer risk in the 'all descendants' and the 'non-Y sharing' group.

For each YID group, the total number of Y-sharing descendants in each cohort was counted. Then, descendants were chosen at random, without replacement, from the set of *all* male descendants of the founder, with the restriction that the cohort counts and total counts matched the configuration of the YID group. This was repeated for a total of 10,000 replicates. For each replicate, the number of prostate cancer cases among the replicate sampled set of descendants was counted. These 10,000 counts of cases determined the null distribution. The number of replicates for which the case count exceeded the actual case count in the YID group was used to estimate the empirical statistical significance of an excess of prostate cancer for each YID group. A significance threshold of $p < 0.05$ was used; each dataset represents an independent experiment.

Institutional Review Board approval was in place for this study. Analysis was performed without use of personal identifiers.

RESULTS

To ensure power to assess prostate cancer risk we considered the 1,000 YIDs (groups of Y-chromosome-sharing males) with the largest total male membership in the UPDB. These YID groups ranged in size from 168 to 2,379 males who share a Y chromosome. Each of these 1,000 YID groups had at least two prostate cancer cases observed among all Y-sharing male descendants; the maximum number of prostate cancer cases observed in any YID group was 59.

Table I shows summary data for the 100 YID groups with the most significant excess of prostate cancer (ranked by p value for the randomization test for excess prostate cancer cases) selected from the largest 1,000 YID groups. Table I includes summary data for each YID, including the number of male descendants of the founder male counted 3 ways: total male descendants (# males), number of male descendants who do not share the Y chromosome of the founder (# non-YID males), and number of male descendants sharing the Y chromosome of the founder (# YID males). Table I also shows the number of prostate cancer cases observed in each of the 3 groups of males, followed by the empirical p-value observed in the randomization test.

The randomization test considers whether the excess of prostate cancers observed in Y-sharing males is significantly greater than that observed in non Y-sharing males, thus a YID with excess prostate cancers among the Y sharing males, even if not a significant excess, would have a significant result if there were many fewer prostate cancers observed in the entire pedigree. An example of this is YID 28 in Table I where 12 overall prostate cancer cases were observed among male descendants of the founder (p=0.19); 7 among Y chromosome sharers (6.35 expected; p = 0.84), and 5 were observed in non Y chromosome sharers (11.3 expected; p =0.07). The randomization test empirical p value for the RR ratio was 0.03. Prioritization of Y chromosomes for study will rank such Y chromosomes lower than those with a significant excess of prostate cancer among Y chromosome sharers.

With a nominal cutoff of $p<0.05$ one would expect to see 50 false positives out of 1000 independent experiments; 73 of the YID groups summarized in Table I showed a significant excess of prostate cancer cases observed among the YID sharing descendants of the founder compared to all descendants (empirical $p < 0.05$). This suggests that there are Y chromosomes associated with increased risk for prostate cancer that is independent of risk is conferred by the autosomes. Figure 1 shows an example high-risk prostate pedigree with significant evidence for an excess of cases among Y chromosome sharing males. This example pedigree is the pedigree with rank 32 in Table I.

Characteristics of Y chromosome associated prostate cancer

It is of interest whether prostate cancer cases that appear to be due to Y chromosome variants differ in characteristics of the prostate cancer. The available cancer characteristics for all of the Y sharing prostate cancer cases who were descendants in the 73 YID Y-

chromosomes with a significant excess of prostate cancer (n=951 cases) were compared to those characteristics measured for all prostate cancer cases in UPDB (n=18,291). The results for age at diagnosis, BMI, survival months, percent of cases with high grade at diagnosis, and percent of cases with distant stage at diagnosis are shown in Table II.

DISCUSSION

A role of the Y chromosome in prostate cancer risk seems likely given published evidence. In light of the confounding of prostate cancer with male sex and the difficulty of sequencing the Y chromosome, it is understandable that Y chromosome predisposition genes would rarely have been searched for, or identified. Considering the evidence supporting the existence of multiple prostate cancer predisposition genes on autosomal chromosomes (from both linkage and association studies), as well as the likely existence of environmental risk factors, and the potential over-diagnosis of prostate cancer based on PSA screening, it is no surprise that it has been difficult to appropriately test the Y chromosome hypothesis.

Here analysis of a unique population-based genealogical resource linked to 50 years of statewide cancer data has identified specific Y chromosomes shared by multiple males with known cancer status. This resource has allowed a test of whether some Y chromosomes are associated with an excess risk of prostate cancer. Many Y chromosomes are well represented in the UPDB, with from hundreds, and up to thousands, of males sharing the same Y chromosome. This analysis has provided strong evidence of Y chromosome involvement in prostate cancer, and has identified a powerful resource of individuals and pedigrees for efficiently examining these high-risk Y chromosomes to identify and characterize the predisposing genes or variants.

The hypothesis of a Y chromosome contribution to prostate cancer risk has support from many studies. Identification of specific Y chromosomes associated with increased risk is difficult, and was only possible here because the UPDB has decades of linked genealogy and cancer data. Nevertheless, even with genealogy and cancer data in extended pedigrees it is not always possible to discriminate between the possibilities of autosomal versus Y chromosome contribution. In the simple example of a family with a preponderance of sons, autosomal and Y chromosome inheritance could lead to the same pedigree pattern. For this reason we performed a randomization test for Y chromosome status; this test provided significant evidence for the independent role of the Y chromosome for the observed effects.

This analysis of 1,000 Y chromosomes suggests that approximately 73/100 or 7.3% of Y chromosomes are associated with high risk for prostate cancer. Analysis of a subset of the prostate cancer cases from the largest YID groups with the most significant excess of prostate cancer suggests few clinically significant differences in the prostate cancer characteristics compared with all prostate cancer cases in the UPDB, although most of the differences are likely statistically significant given the overall sample size for Utah prostate cancer cases (Table II). We did not precisely estimate penetrance of the hypothesized Y chromosome variant given the censoring of prostate cancer diagnosis data prior to 1966 and the presence of multiple males in each YID group who are still too young to have been diagnosed. A rough estimate of 11% penetrance is obtained when only considering those

male descendants born after 1866 and before 1940 in the 73 high risk YID groups considered here.

Since the Utah genealogy data only extends to the mid 1700s, some of the YID groups could potentially represent the same Y chromosome; lack of genealogy data would prevent such identification. In addition some genealogy may not be correctly represented in the UPDB. In future studies, the coalescence of YIDs that appear to be independent, but are not, could be determined by sufficiently informative genotyping or sequencing.

Most of the males identified as sharing the same Y chromosome by their representation in genealogy data are expected to share. In decades of study of Utah high-risk pedigrees, the genealogy data in the UPDB has been used for the ascertainment and study of pedigrees. Pedigree analysis with genetic markers (which allow identification of non-paternity or other incompatibilities) has almost universally confirmed the validity of the genealogy data with very few misrepresentations. This may be due in part to the fact that non-paternity rates in Utah have been reported to be low compared to US figures of 1.5% [19], as well as to the significant attention given to the correct construction of Latter-Day Saint (LDS or Mormon) genealogies.

While prostate cancer is an obvious phenotype to begin investigation of Y-chromosome-associated risk, this innovative study design can be applied to many different phenotypes represented in the Utah resources. Initial focus on those other cancers that also show evidence of Y chromosome losses in tumors is warranted. Loss of the Y chromosome has been noted for many cancers in addition to prostate cancer, including: male breast cancer (63% loss) [20], head and neck tumors (69% loss) [21], urothelial bladder cancer (23% loss) [22], hepatocellular cancer (90% loss) [23], pancreatic cancer (67% loss) [24–26], esophageal squamous cell carcinoma (100% loss) [27], and hematological disorders (10% loss) [28]. The analysis of informative Y chromosome groups in the UPDB can increase understanding of a role for the Y chromosome for these cancers, as well as for many other phenotypes of interest. Initial disease association studies for Y chromosome association with risk can be performed efficiently, without data collection and with no subject recruitment.

This analysis has also identified Y chromosomes that appear to be associated with a significant *deficit* of prostate cancer; data not shown. It is possible that study of these “low-risk” Y chromosomes might allow identification of protective genes or variants for resistance to prostate cancer. Identification of such resistance (or protective) genes for disease could be as valuable as the identification of high-risk genes in terms of advancing our knowledge of prostate cancer genetics. However, the UPDB data are much more powerful for identifying a significant excess, than a significant deficit, for cancer. Data for cancers diagnosed before 1966, or outside Utah, are censored in the UPDB, and incorrect genealogy data typically leads to record linking failure. Thus data quality issues might more easily contribute to the conclusion of a significant deficit of observed cancers in the absence of such an effect. The hypothesis of inherited resistance to prostate cancer is provocative and will be pursued, but is likely not possible as a purely insilico study such as this one.

Association analysis of Y chromosome haplotypes, followed with sequence analysis of regions of interest, could allow identification of the genes or variants on the Y chromosome responsible for the increased risk for prostate cancer observed for some Y chromosomes. Identification of Y chromosome haplotypes or variants associated with increased risk for prostate cancer would expand understanding of the genetics of prostate cancer and potentially permit meaningful counseling and personalized screening for men identified to be at risk. Identification of specific Y-haplotypes associated with increased risk would support a very different sort of risk prediction scenario than individual genetic testing. One high-risk Y chromosome can represent many men. For example, in the Utah database there is a single Y chromosome shared by over 2,000 men born since the 1700's. Y-haplotype data is relatively inexpensive and straightforward to generate, and risk estimates from a single test could be useful to many individuals.

CONCLUSIONS

Insilico analysis of an existing population-based genealogy linked to cancer records has shown significant evidence for specific Y chromosomes that are associated with increased risk for prostate cancer. This efficient approach using an existing genealogical resource can be extended to consider Y chromosome involvement for other phenotypes, and can be extended to consideration of other modes of inheritance.

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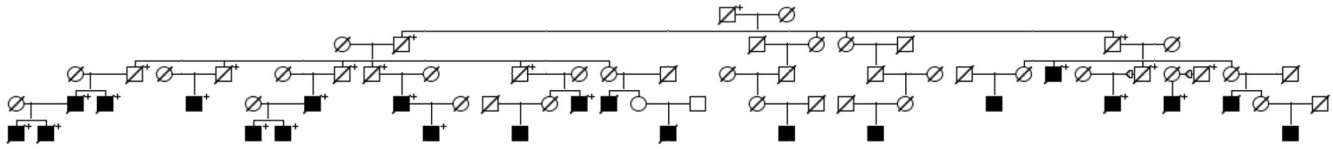

Figure 1.

Example pedigree with significant excess of prostate cancer among Y chromosome-sharing males.

High-risk prostate cancer Y chromosome pedigree 32 (from Table I) showing only descendants leading to prostate cancer cases. Those male descendants who share the founder's Y chromosome are marked with "+". Only prostate cancer cases diagnosed since the Utah Cancer Registry began in 1966 are known; males in upper generations remain unknown for prostate cancer status.

Table I

Test for excess risk for prostate cancer by YID for the 100 YIDs with the most significant randomization test results.

Rank	# Males	# Non-YID males	# YID males	All PRCA Obs	Non-YID Obs	YID Obs	Emp p-value	Rank	# Males	# Non-YID males	# YID males	All PRCA Obs	Non-YID Obs	YID Obs	Emp p-value
1	2515	2295	220	34	15	19	0.0000	51	6216	5871	345	57	44	13	0.0336
2	1460	1289	171	20	7	13	0.0001	52	3229	3049	180	42	32	10	0.0340
3	2829	2519	310	32	16	16	0.0002	53	2254	2001	253	25	15	10	0.0347
4	3418	3061	357	27	12	15	0.0003	54	2457	2197	260	22	13	9	0.0353
5	3694	3404	290	34	23	11	0.0006	55	10595	9790	805	127	94	33	0.0359
6	4403	3966	437	39	23	16	0.0010	56	3689	3468	221	30	24	6	0.0359
7	1165	992	173	13	4	9	0.0011	57	6632	6397	235	49	42	7	0.0368
8	4981	4633	348	74	50	24	0.0017	58	7875	7678	197	70	62	8	0.0372
9	1107	861	246	16	3	13	0.0020	59	1669	1431	238	24	12	12	0.0380
10	2695	2519	176	22	13	9	0.0021	60	1647	1470	177	18	10	8	0.0394
11	7349	7138	211	65	52	13	0.0025	61	4822	4151	671	31	17	14	0.0395
12	2941	2569	372	27	10	17	0.0026	62	2183	1996	187	23	16	7	0.0398
13	2496	2305	191	37	25	12	0.0035	63	606	391	215	7	0	7	0.0401
14	7720	7299	421	61	47	14	0.0037	64	15927	15459	468	135	118	17	0.0408
15	5240	4716	524	71	45	26	0.0048	65	14093	13035	1058	201	157	44	0.0417
16	2403	2145	258	26	12	14	0.0053	66	2224	1869	355	27	10	17	0.0437
17	5329	4967	362	82	60	22	0.0058	67	2989	2767	222	30	17	13	0.0438
18	3452	3023	429	38	21	17	0.0062	68	5745	5506	239	43	36	7	0.0446
19	3308	3138	170	34	25	9	0.0086	69	1117	865	252	12	3	9	0.0453
20	1968	1653	315	17	7	10	0.0097	70	3427	3108	319	38	25	13	0.0454
21	4006	3633	373	42	26	16	0.0098	71	2891	2614	277	33	22	11	0.0463
22	1547	1319	228	20	8	12	0.0103	72	942	754	188	3	0	3	0.0488
23	3670	3471	199	30	21	9	0.0103	73	10154	9953	201	103	96	7	0.0499
24	5230	4589	641	47	25	22	0.0115	74	2464	2266	198	21	14	7	0.0507
25	751	555	196	13	2	11	0.0115	75	6898	6549	349	49	37	12	0.0515
26	1487	1277	210	27	14	13	0.0123	76	2104	1883	221	12	5	7	0.0529
27	1548	1338	210	13	6	7	0.0155	77	995	790	205	7	0	7	0.0538

Rank	# Males	# Non-YID males	# YID males	All PRCA Obs	Non-YID Obs	YID Obs	Emp p-value	Rank	# Males	# Non-YID males	# YID males	All PRCA Obs	Non-YID Obs	YID Obs	Emp p-value
28	1986	1742	244	12	5	7	0.0156	78	4226	4012	214	43	32	11	0.0543
29	2447	2205	242	18	11	7	0.0160	79	2363	2139	224	25	15	10	0.0558
30	13511	12848	663	128	106	22	0.0169	80	10971	10652	319	101	88	13	0.0564
31	4344	4050	294	35	24	11	0.0179	81	6260	6071	189	67	59	8	0.0570
32	984	812	172	22	8	14	0.0196	82	1422	1217	205	8	4	4	0.0584
33	3613	3287	326	48	32	16	0.0196	83	6826	6555	271	84	71	13	0.0585
34	1387	1199	188	12	4	8	0.0206	84	1062	886	176	11	4	7	0.0604
35	2398	2150	248	32	17	15	0.0207	85	4069	3528	541	39	21	18	0.0619
36	1180	969	211	7	1	6	0.0208	86	8608	8274	334	66	54	12	0.0642
37	1043	872	171	12	4	8	0.0210	87	4623	4122	501	69	48	21	0.0644
38	4808	4490	318	60	44	16	0.0218	88	4363	3967	396	42	29	13	0.0654
39	2552	2259	293	32	20	12	0.0218	89	3671	3446	225	36	29	7	0.0657
40	3500	3262	238	46	32	14	0.0266	90	4005	3727	278	43	30	13	0.0658
41	2516	2321	195	16	12	4	0.0270	91	1979	1805	174	22	15	7	0.0675
42	1371	1194	177	19	11	8	0.0273	92	2644	2338	306	16	9	7	0.0682
43	2080	1783	297	24	9	15	0.0279	93	8010	7782	228	76	69	7	0.0683
44	6094	5824	270	58	48	10	0.0288	94	2014	1789	225	21	11	10	0.0702
45	1975	1781	194	22	12	10	0.0297	95	1989	1689	300	29	14	15	0.0703
46	10389	9192	1197	94	63	31	0.0316	96	2318	2098	220	31	18	13	0.0706
47	2879	2687	192	28	19	9	0.0328	97	8226	7332	894	100	65	35	0.0708
48	5831	5498	333	59	48	11	0.0328	98	5819	5535	284	31	24	7	0.0729
49	2165	1895	270	17	6	11	0.0330	99	4484	4228	256	48	37	11	0.0741
50	6652	6310	342	55	43	12	0.0331	100	2747	2567	180	22	16	6	0.0748

Table II

Clinical characteristics of the prostate cancer cases in all Y chromosome-sharing prostate cancer cases belonging to the 73 YID groups with a significant excess of prostate cancer.

Group	n	mean age	mean BMI	survival months	% high grade	% distant stage
High-risk Y cases	951	69.3	26.8	101.6	26	4.8
All prostate cases	18,291	70.5	26.9	94.6	27	5.1