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Clinical-Prostate cancer

Multiple primary cancers in men with sporadic or familial prostate cancer: Its clinical implications

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Abstract

Objective: To evaluate the risk of concordant cancers in patients with prostate cancer (CaP) and examine whether this risk differed according to family history of CaP.

Materials and methods: We examined 1,102 patients with CaP , having prospectively acquired pedigrees, and analyzed information regarding multiple primary cancers. The prevalence of concordant cancers was assessed with respect to the family history of CaP . First-degree familial CaP was defined as a positive history of CaP in first-degree relatives (parents, siblings, and offspring). Odds ratios for each concordant cancer in men with first-degree familial CaP were estimated. Clinical characteristics were compared between men with and without concordant cancers.

Results: The prevalence of multiple primary cancers in sporadic PCa was 12.0%, similar to that of first-degree familial CaP (13.5%, $P = 0.698$). Gastrointestinal cancer was the most common concordant cancer (3.6%), followed by colorectal (2.9%), lung (1.5%), urothelial (1.3%), kidney (1.1%), and other cancers. Colorectal cancer was more frequent in first-degree familial CaP than in sporadic disease (6.8 vs. 2.7%, $P = 0.045$). However, the rates of other concordant cancers were similar between the 2 groups (P range, 0.242−0.963). Compared with sporadic disease, the age-adjusted odds ratio for concordant colorectal cancer in first-degree familial CaP was 2.930 (95% confidence interval, 1.082−7.929). Patients with concordant colorectal cancer had fewer (2.8 vs. 3.9 cores, $P = 0.041$) and a lower percentage of (23.5 vs. 33.1%, $P = 0.030$) positive biopsy cores than CaP only patients.

Conclusions: A family history of CaP was significantly associated with a risk of concordant colorectal cancer. These findings imply that some CaP shares a genetic pathogenesis with colorectal cancer. © 2022 Published by Elsevier Inc.

Keywords: Prostate cancer; Familial; Multiple primary cancer; Clinical characteristics

Abbreviations: CaP, prostate cancer; HBOC, hereditary breast and ovarian cancer; IQR, interquartile range; OR, odds ratio; PSA, prostate-specific antigen; GS, Gleason score; SEER, Surveillance, Epidemiology, and End Results; SNP, single-nucleotide polymorphism

1. Introduction

The American Cancer Society estimates that there will be 180,890 new cases of prostate cancer (CaP) diagnosed in the United States in 2016, and approximately 26,210 men will die of this disease [1]. It has been well documented that CaP is one of the most commonly reported cancers in families along with breast, ovary, lung, and colorectal cancers [2]. According to the pivotal twin study

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comprising 44,788 pairs in European countries, 58% of the variation in CaP was attributed to random environmental effects and 42% to heritable factors, without statistical significance ($P = 0.09$) [3]. Among the heritable causes of PCa, germline mutations in homologous DNA repair genes (e.g., *BRCA2, BRCA1, ATM, PALB2, or CHEK2*) related to hereditary breast and ovarian cancer (HBOC) syndrome [4,5] as well as in some DNA mismatch repair genes (e.g., *MLH1, MSH2, MSH6, or PMS2*) associated with Lynch syndrome [6] are well recognized.

Improvement in CaP survival has resulted in an increase in the proportion of patients with diagnoses of multiple primary cancers, which is defined as the presence of more than one concordant cancer in the same individual. The interest in concordant cancers can be caused by the same environmental or genetic factors that cause PCa [4−6]. Some patients with CaP and their families may be at increased risk for breast and ovarian cancer, melanoma, pancreatic cancer (HBOC syndrome), or colorectal cancer (Lynch syndrome). On these grounds, the recent guideline by the National Comprehensive Cancer Network was extensively revised to include recommendations regarding germline genetic tests for family genetic counseling, cancer risk syndromes, or assessment of personal risk of multiple primary cancers [7].

However, clinical evidences demonstrating the association between primary CaP and concordant cancers are scarce. Except for a few studies [8], almost large-scale epidemiologic studies have reported that patients with CaP have a reduced risk of concordant cancers (15%−42%) [9−13]. Moreover, patterns of increased risk have not been reported consistently, but when noted, they were suggested for urinary bladder, other sites in the urinary tract, or the hemato-lymphoid system [9−13]. On the contrary, the CaP did not increase the risk for concordant breast, ovarian, pancreatic, or colorectal cancer or melanoma [9−13]. These discrepancies between results from genomic studies and epidemiologic studies may be because previous studies did not consider differences in the concordant cancers according to the genetic characteristics ofCaP .

If some concordant cancers share a genetic pathogenesis withCaP , such concordant cancers will be more common in CaP with familial aggregation than in sporadic disease. However, previous studies have rarely investigated this idea. We performed this study to evaluate the risk of concordant cancers in men with primary CaP and examine whether this risk varied depending on family history ofCaP . We hypothesized that risk of some concordant cancers might be higher in patients with CaP with genetic causes (familial CaP) than in those without genetic causes (sporadicCaP).

2. Materials and methods

2.1. Patient selection

The protocol of this study was approved by the institutional review board of Seoul National University Bundang Hospital, Seoul, Republic of Korea (No. B-1511/322-107). All participants agreed to and provided informed consent to participate in this study. All subjects were anonymized before the analysis. After informed consent was obtained, pedigrees including the family history of all types of cancers were prospectively acquired in men who visited our institution for CaP treatment between September 2018 and March 2019. After exclusion of patients who refused to participate and those without pathologically confirmed CaP , with incomplete pedigrees, or with insufficient clinical data, 1,102 participants were included the final analysis.

2.2. Familial history and multiple primary cancers

A family history for all types of cancer, including CaP , was collected on all first-degree relatives (parents, siblings, and offspring) and second-degree relatives (uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings, and double cousins). The effect of family history was not separately considered by the type of relationship, because of the limited number of familial cases among multiple primary cancers. Information regarding each participant's concordant cancer was also prospectively acquired. Multiple primary cancers were defined as the presence of more than one synchronous or metachronous cancer in the same individual [14]. First-degree familial CaP was defined as a positive history of CaP in first-degree relatives. The median (interquartile range, IQR) follow-up period from the initial CaP diagnosis was 26.5 (8.2−57.7) months for the entire cohort.

2.3. Statistical analysis

Descriptive analyses of clinical parameters are presented as the mean with standard deviation or median value with its IQR. The prevalence of a familial history of malignancy in men with CaP was assessed (Appendix 1). The prevalence of multiple primary cancers was evaluated in all men with CaP and separately in those with sporadic and first-degree familial CaP, and its association with familial history of CaP was assessed (Table 1). Using binary logistic analysis, unadjusted and age-adjusted odd ratios (ORs) with their 95% confidence interval (CI) were estimated for the multiple primary cancers and each concordant cancer (Table 2) and family history of other cancers (Appendix 2) in men with first-degree familial CaP . In the cohorts that underwent radical surgery ($n = 751$, 68.1%), clinical characteristics of the CaP only group and multiple primary cancer group were compared (Table 3) to identify other factors that could be correlated with the presence of multiple primary cancers. Continuous parameters were compared using the Student *t*-test, and categorical parameters were compared using the χ^2 test. All tests were 2-tailed with a significance level of 0.05. All statistical analyses were performed using a commercially available program (SPSS® version 21.0; IBM, Chicago, IL, United States).

Table 1
Prevalence of multiple primary cancers in men with sporadic or familial prostate cancer.

	All patients	Sporadic	First-degree familial	
	(n = 1,102)	(n = 1,009)	(n = 74)	P-value[a]
Multiple primary cancers	132 (12.0%)	121 (12.0%)	10 (13.5%)	0.698
Double primary cancers	120 (10.9%)	110 (10.9%)	9 (12.2%)	0.923
Triple primary cancers	12 (1.1%)	11 (1.1%)	1 (1.4%)	−
Types of concordant cancers				
Gastrointestinal	40 (3.6%)	37 (3.7%)	2 (2.7%)	0.667
Colorectal	32 (2.9%)	27 (2.7%)	5 (6.8%)	0.045[b]
Lung	17 (1.5%)	16 (1.6%)	1 (1.4%)	0.876
Urothelial	14 (1.3%)	13 (1.3%)	1 (1.4%)	0.963
Kidney	12 (1.1%)	11 (1.1%)	1 (1.4%)	0.836
Nasopharyngeal	8 (0.7%)	8 (0.8%)	0 (0.0%)	0.442
Hematologic	7 (0.6%)	7 (0.7%)	0 (0.0%)	0.472
Thyroid	5 (0.4%)	4 (0.4%)	1 (1.4%)	0.242
Hepatobiliary	3 (0.3%)	3 (0.3%)	0 (0.0%)	0.639
Soft tissue	3 (0.3%)	3 (0.3%)	0 (0.0%)	0.639
Brain	2 (0.2%)	2 (0.2%)	0 (0.0%)	0.701
Breast	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.786

[a] compared to sporadic group using χ^2 test;
[b] P <0.05;

3. RESULTS

3.1. Prevalence of family history of cancers in men with PCa

Among the 1,102 analyzed probands, a family history of cancer was observed in 50.5% of all relatives (n = 557) and 45.6% of first-degree relatives (n = 503; Appendix 1). In all relatives, a family history of gastrointestinal cancer was the most common (16.1%), followed by hepatobiliary, (11.0%), lung (8.9%), prostate (8.4%), colorectal (6.4%), nasopharyngeal (3.8%), breast (3.4%), gynecological (2.4%), thyroid (1.6%), hematologic (1.4%), and other cancers (Appendix 1). Familial and first-degree familial CaP was observed in 8.4% (n = 93) and 6.7% (n = 74), respectively, and it was the fourth most common in the participants' family histories of cancer (Appendix 1).

3.2. Prevalence of multiple primary cancers in men with CaP

Among the 1,102 analyzed patients, multiple primary cancers were observed in 132 patients (12.0%): double primary cancers in 120 patients (10.9%), and triple primary cancers in 12 patients (1.1%; Table 1). The rates in first-degree familial CaP were not significantly different from those in sporadic CaP (13.5 vs. 11.8%, P = 0.698; Table 1). In the entire cohort, gastrointestinal cancer was the most common concordant cancer (3.6%), followed by colorectal (2.9%), lung (1.5%), urothelial (1.3%), kidney (1.1%), and other cancers (Table 1). Among the concordant cancers, colorectal cancer was more frequent in first-degree familial CaP than in sporadic disease (6.8 vs. 2.7%, P = 0.045; Table 1). However, rates of other concordant cancers were similar in the 2 groups (P range, 0.242−0.963; Table 1).

3.3. Risks for concordant second cancers according to family history of PCa

Binary logistic regression analyses were performed to estimate the risks for multiple primary cancers and each type of concordant tumor (Table 2) and for family history of other cancers (Appendix 2) in men with first-degree familial CaP. Unadjusted and age-adjusted ORs for multiple primary cancers in first-degree familial CaP were not significantly increased (OR=1.160 and 1.557, respectively), compared to sporadic disease (Table 2). Among the concordant cancers, unadjusted OR for colorectal cancer in first-degree familial CaP was significantly increased (OR=2.687; 95% CI, 1.003−7.193) compared with that in sporadic disease (Table 2). After adjustment for age, these trends became more prominent (OR=2.930; 95% CI, 1.082−7.929; Table 2). However, other concordant cancers showed no significant difference in risk of occurrence in first-degree familial PCa (unadjusted OR; P range, 0.509−0.949; Table 2). Similar analyses were applied to assess the ORs for family history of other cancers (Appendix 2).

Table 2
Odds ratios (ORs) for the multiple primary cancers in men with first-degree familial prostate cancer.

	Unadjusted risks[†]			Age-adjusted risks[a]		
	OR	95% CI	p-value	OR	95% CI	P-value
Multiple primary cancers	1.160	0.580−2.320	0.674	1.557	0.669−3.621	0.304
Types of concordant cancers						
Gastrointestinal	0.724	0.171−3.060	0.660	0.757	0.178−3.209	0.705
Colorectal	2.687	1.003−7.193	0.049[b]	2.930	1.082−7.929	0.034[b]
Lung	0.866	0.113−6.625	0.890	0.924	0.120−7.098	0.910
Urothelial	1.070	0.138−8.290	0.949	1.168	0.150−9.115	0.882
Kidney	1.267	0.161−9.945	0.822	1.260	0.160−9.901	0.826
Other cancers	0.508	0.068−3.790	0.509	0.534	0.071−3.994	0.541

OR, odds ratio; CI, confidence interval;
[a] by the binary logistic regression analysis;
[b] P < 0.05;

Table 3
Comparisons of clinical characteristics of prostate cancer (CaP) between CaP only group and multiple primary cancers group ($n = 751$).

	CaP only	Multiple primary cancers[a]		Concordant colorectal cancer[a]	
	($n = 671$)	($n = 80$)	*P*-value	($n = 14$)	*P*-value
Preoperative parameters					
Age at diagnosis (yrs)	65.2 (±7.2)	67.4 (±6.4)	0.005[b]	65.4 (±7.5)	0.911
PSA (ng/mL)	14.9 (±32.1)	11.7 (±12.0)	0.081	10.9 (±8.1)	0.124
Palpable nodule on DRE	126 (18.8%)	17 (21.3%)	0.303	1 (7.1%)	0.114
Prostate biopsy					
Biopsy Gleason score	7.0 (±0.8)	7.1 (±0.8)	0.896	6.9 (±0.6)	0.365
Number of biopsied cores	12.3 (±1.4)	12.5 (±1.0)	0.138	12.4 (±0.8)	0.606
Number of positive cores	3.9 (±2.8)	3.5 (±2.7)	0.159	2.8 (±1.8)	0.041[b]
Percentage of positive cores (%)	33.1 (±23.0)	28.8 (±21.6)	0.110	23.5 (±13.2)	0.030[b]
Tumor characteristics					
Pathologic Gleason score	7.2 (±0.6)	7.2 (±0.7)	0.896	7.1 (±0.3)	0.400
Gleason score upgrading	184 (27.4%)	22 (27.5%)	0.988	3 (21.4%)	0.618
Extracapsular extension (ECE)	218 (32.5%)	26 (32.5%)	0.589	4 (28.6%)	0.910
Seminal vesicle invasion (SVI)	88 (13.1%)	8 (10.0%)	0.406	2 (14.3%)	0.929
Bladder neck invasion (BNI)	32 (4.8%)	2 (2.5%)	0.354	0 (0.0%)	0.678
Positive surgical margin (PSM)	142 (21.2%)	16 (20.0%)	0.559	2 (14.3%)	0.792
Lymph node involvement (LNI)	35 (5.2%)	4 (5.0%)	0.868	0 (0.0%)	0.489
Percentage of tumor volume (%)	16.4 (±16.6)	14.7 (±15.6)	0.360	14.5 (±20.7)	0.740

PCa, prostate cancer; PSA, prostate specific antigen; DRE, digit rectal examination
[a] by the student *t*-test (continuous variables), and χ^2 test (categorical variables)
[b] $P < 0.05$

First-degree familial CaP did not affect the odds of having a first-degree family history of other cancers (unadjusted OR; *P* range, 0.240−0.995; Appendix 2).

3.4. Comparison of clinical features between PCa only and multiple primary cancers groups

In the cohort that underwent radical surgery ($n = 751$, 68.1%), we compared clinical characteristics between the CaP only and multiple primary cancers groups (Table 3). Patients with concordant cancers were significantly older (67.4 vs. 65.2 years, $P = 0.005$) and tended to have lower prostate-specific antigen (PSA) but without statistical significance (11.7 vs. 14.9 ng/mL, P=0.081) than patients with CaP only (Table 3). However, other preoperative variables including clinical stage, biopsy Gleason score (GS), number, and percentage of positive biopsy cores between 2groups were not significantly different (*P* range, 0.110 −0.896; Table 3). Moreover, postoperative variables including surgical GS, rates of GS upgrading, pathologic staging, surgical margin status, and percentage of tumor volume did not differ between 2 groups (*P* range, 0.354 −0.988; Table 3).

When the characteristics of patients with concordant colorectal cancer were compared with those of men with CaP only, patients with concordant colorectal cancer had a significantly lower number of positive core (2.8 vs. 3.9 cores, $P = 0.041$) and a lower percentage of positive cores (23.5 vs. 33.1%, $P = 0.030$) than men with CaP only (Table 3). However, other preoperative variables (age, PSA, clinical stage, biopsy GS, and number of biopsied cores) and postoperative variables (surgical GS, GS upgrading rate, pathologic stage, surgical margin status, and percentage of tumor volume) did not correlate with concordant colorectal cancer (*P* range, 0.114−0.929; Table 3).

4. Discussion

The primary objective of this study was to evaluate the risk of concordant cancers, overall and by organ site, in a cohort of patients diagnosed with CaP. A second objective was to examine whether the risks for concordant cancers differed according to family history of CaP. Determining the specific patterns of concordant cancers for which a cancer patient may be at increased risk has implications for surveillance and screening as well as for elucidating etiology [15].

4.1. Prevalence of multiple primary cancers in men with CaP

The current study investigated the 1,102 patients who visited our institution for CaP treatment and agreed to compile their pedigree between September 2018 and March 2019. Because patients with repeated visits were included, median follow-up from the initial CaP diagnosis was 26.5 (8.2−57.7) months. Furthermore, all independent synchronous or metachronous cancers were considered concordant

cancers, including those that were diagnosed before the initial diagnosis of the index CaP. In total, 132 (12.0%) men with multiple primary cancers were observed (Table 1). Previous studies utilizing similar definition for multiple primary cancers demonstrated a prevalence similar to that of the current study, ranging from 11.5% to 11.8% [10,15].

In previous studies in Detroit [15] and New York [10], lung (285 of 1,511 concordant sites) [15] and colon (27 of 115 sites) [10] were the most common concordant tumor sites. On the contrary, in our study of an Asian population, concordant gastrointestinal cancer was the most common (40 of 144 sites), followed by colorectal (32 of 144 sites), lung (17 of 144 sites), urothelial (14 of 144 sites), kidney (12 of 144 sites), and other cancers (Table 1). This difference occurs because the patterns of concordant cancers are fundamentally dependent on the cancer epidemiology of the population to which the study cohorts belongs. Therefore, most previous studies compared the incidence of concordance cancers to epidemiological data obtained from the Surveillance, Epidemiology, and End Results (SEER) database or national cancer registry of the target populations [8−13]. According to contemporary cancer statistics of Korea, gastric cancer had the highest incidence in men (20,509 cases/year), followed by lung (17,790 cases/y), colorectal (16,672 cases/y), prostate (11,800/y), liver (11,774 cases/y), and thyroid cancer (5,538 cases/y) in 2016 [16]. Our pattern of concordant second cancers in men with CaP was similar to the primary cancer incidence of the contemporary Korean population (Table 1).

However, prevalence of concordant urothelial (Fourth; 14 of 144 sites) and kidney cancer (Fifth; 12 of 144 sites; Table 1) in our study population was lower than the incidence of primary urothelial (Eighth; 3,488/ y) and kidney cancer (Ninth; 3,410/y) in the general population [16]. This may suggest detection bias due to some diagnostic tests including urinalysis, cystoscopy, or imaging studies being performed in our series. Some studies suggested that increased risk of concordant urothelial cancer was associated with radiation treatment for the index CaP [15,17]. On the contrary, others insisted that the higher prevalence of concordant urothelial cancer is only due to the detection bias, because a significant excess of concordant cancer was observed during the early periods (12−48 months) after diagnosis of CaP, but not during the subsequent follow-up [9,13]. In our cohort, who were manly treated with radical surgery (68.1%), the excess of concordant urothelial cancer along with concordant kidney cancer suggests that these findings are due to detection bias rather than the radiation treatment.

4.2. Difference in concordant cancers according to family history of CaP

The causes of concordant cancers can be the same environmental and heritable factors that contribute to primary cancers. CaP is a highly heritable disease [18,19]. A complex polygenic model is the currently most accepted in explaining the risk for CaP pathogenesis and can also apply for concordant second cancers. A complex polygenic model involves common low-penetrance susceptibility alleles causing individually small but cumulatively significant risk and rarer genetic variants causing greater risk [20]. Through genome-wide association studies, more than 100 single-nucleotide polymorphisms (SNPs) associated with CaP risk have been identified [21,22]. Consistent reports have identified germline mutations in the genes *BRCA1, BRCA2, MMR, HOXB13, CHEK2, or NBS1* as conferring greater risks for CaP, with some leading to a more aggressive disease behavior [21−23].

As already mentioned, some patients with CaP and their families may be at increased risks for breast and ovarian cancer, melanoma, and pancreatic cancer in association with germline mutations in homologous DNA repair genes [4,5] or colorectal cancer in association with DNA mismatch repair genes [6]. This hypothesis is evident by recent genetic studies which demonstrated that 10.8% of men with CaP and one or more additional cancers harbored cancer-predisposing germline mutations such as *BRCA2, ATM, MLH1, BRIP1, PALB2, FGFR3, CHEK2, or HOXB13* [24] or showed that male carriers of *BRCA1/2* mutations have the increased risk for breast cancer and CaP in men [20].

However, previous epidemiologic studies have failed to clearly demonstrate these associations [9−13]. In previous studies, CaP did not increase the risk of concordant breast, ovarian, pancreatic, or colorectal cancer or melanoma [9−13]. This might be because the previous studies did not consider differences in the concordant cancers according to the genetic characteristics of CaP. An increased risk of concordant cancers in specific organs of the familial CaP group compared with the CaP only group in our study may be attributable to genetic effects in a susceptible population.

In the present study, the prevalence of concordant colorectal cancer were clearly higher in the first-degree familial CaP group than in the sporadic CaP group (6.8 vs. 2.7%, P=0.045; Table 1). We demonstrated a 2.7−2.9 fold increase in the unadjusted and age-adjusted risk of concordant colorectal cancer in men with first-degree familial CaP compared with men with sporadic disease ($P = 0.049$ and 0.034; Table 2). Our findings suggest that some men with genetic susceptibility to primary CaP share some genetic factors with the pathogenesis of colorectal cancer. To our best knowledge, our study is the first demonstrating a difference in concordant cancers according to the family history of index CaP.

4.3. Clinical implications of the current study

However, except for the number ($P = 0.041$) and percentage ($P = 0.030$) of positive cores, no other preoperative variable (age, PSA, clinical stage, biopsy GS, and number of biopsied cores) or postoperative variable (surgical GS, GS upgrading rate, pathologic stage, surgical margin status,

and percentage of tumor volume) presented a correlation with concordant colorectal cancer (P range, 0.114−0.929; Table 3). The lower number and percentage of positive cores in the concordant colorectal cancer group might be a result of overfitting due to the small number of patients included in this group ($n = 14$). These findings suggest that other than a family history CaP, there are few clinical parameters for predicting the concordant colorectal cancer. On these grounds, we believe that the recently revised guideline for germline genetic tests for family genetic counseling, cancer risk syndromes, or assessment of personal risk for second cancers is timely, and genetic tests in patients with CaP will be more essential in the future. Counseling in accord with genetic tests results can provide more accurate information about various risks than a family history of CaP only. A recent large-scaled genetic study demonstrate that a polygenic hazard score established using 54 SNPs could predict the onset age of aggressive CaP ($z = 11.2$, $P < 0.0001$, hazard ratio [HR] = 2.9) that could not be predicted by a family history of CaP alone ($z = 0.9$, $P = 0.37$, HR = 1.1) [25] supports that.

4.4. Limitations of the current study

Our study has several limitations. First, our study has innate limitations of a retrospective study. To lessen these limitations, all pedigrees and information on concordant cancers were obtained prospectively. Second, because of the absence of data regarding the onset of second tumors, a crude incidence rate could not be calculated, and therefore, the relative risks in a reference cohort also could not be estimated. Third, due to the small number of events, risk of other well-known susceptible concordant cancers such as breast and pancreatic cancers could not be compared according to the family history of CaP, and our positive association between familial prostate cancer and concordant colorectal cancer could not be confirmed, solidly. Fourth, genetic tests could not be performed in our cohorts. Fifth, to establish the casual relationships between heredity and concordant cancer, all other risk factors (e.g., environmental factor, life styles, diet, etc.) should be adjusted. However, due to limited information for these, these analyses could not be performed in this study. Lastly, our subjects consisted of patients of Korean ancestry only. Therefore, further well-designed studies including genetic analysis are needed to confirm our current results.

5. Conclusions

The prevalence of multiple primary cancers in men with CaP was 12.0% was unaffected by a family history of index CaP. Concordant colorectal cancer was more frequent in first-degree familial CaP than in sporadic disease, and the age-adjusted risk for concordant colorectal cancer is increased 2.9 fold in men with first-degree familial CaP. These results suggest that some men with genetic susceptibility to primary CaP share some genetic factors with pathogenesis of colorectal cancer.

Research involving human participants or animals

The protocol of this study was approved by the IRB of our institution (Seoul National University Bundang Hospital, Seoul, Republic of Korea, No. B-1511/322-107).

Informed consent

All participants agreed to and provided informed consent to participate in this study. All subjects were anonymized before the analysis.

Author contribution

Myong Kim: Conceptualization, methodology, formal analysis, data curation, and writing−original draft. **Joohon Sung**: Methodology, formal analysis, and data curation. **Jung Kwon Kim**: Methodology, formal analysis, and data curation. **Hakmin Lee**: Methodology and data curation. **Jong Jin Oh**: Methodology, investigation, and writing −review and editing. **Sangchul Lee**: Methodology, investigation, and writing−review and editing. **Sung Kyu Hong**: Data curation and writing−review and editing. **Seok-Soo Byun**: Conceptualization, methodology, investigation, data curation, writing−original draft, writing−review and editing, and supervision. All authors have read and approved the manuscript.

Ethics statement

The protocol of this study was approved by the institutional review board of Seoul National University Bundang Hospital, Seoul, Republic of Korea (No. B-1511/322-107). All participants agreed to and provided informed consent to participate in this study. All subjects were anonymized before the analysis. The manuscript or portions thereof are not under consideration by another journal or electronic publication and have not been previously published. Relevant data used in this study are available upon request due to ethical restrictions and privacy protections. Requests to access data should be directed to the corresponding author (ssbyun@snubh.org). All authors have no direct or indirect commercial financial incentive associated with publishing the article.

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Appendix 1: Prevalence of familial history of malignancy in men with prostate cancer (*n*=1,202)

Family history of cancer	Family history 557 (50.5%)	First-degree family history 503 (45.6%)
Types of cancer		
Gastrointestinal	177 (16.1%)	156 (14.2%)
Hepatobiliary	121 (11.0%)	104 (9.4%)
Lung	98 (8.9%)	84 (7.6%)
Prostate	93 (8.4%)	74 (6.7%)
Colorectal	70 (6.4%)	62 (5.6%)
Nasopharyngeal	42 (3.8%)	34 (3.1%)
Breast	38 (3.4%)	35 (3.2%)
Gynecological	26 (2.4%)	23 (2.1%)
Thyroid	18 (1.6%)	17 (1.5%)
Hematologic	15 (1.4%)	12 (1.1%)
Urothelial	9 (0.8%)	9 (0.8%)
Soft tissue	8 (0.7%)	8 (0.7%)
Kidney	5 (0.5%)	5 (0.5%)
Brain	2 (0.2%)	1 (0.1%)

Appendix 2: Odds ratios (ORs) for the family history of other cancers in men with first-degree familial prostate cancer

	Unadjusted risks[a]			Age-adjusted risks[a]		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Gastrointestinal	0.830	0.404−1.702	0.611	0.816	0.398−1.677	0.581
Hepatobiliary	1.003	0.448−2.245	0.995	1.003	0.448−2.247	0.994
Lung	0.494	0.152−1.603	0.240	0.494	0.152−1.605	0.241
Colorectal	1.234	0.479−3.180	0.663	1.228	0.475−3.170	0.672
Nasopharyngeal	0.413	0.056−3.063	0.387	0.413	0.056−3.067	0.388
Breast	0.400	0.054−2.967	0.370	0.403	0.054−2.987	0.374
Gynecological	0.626	0.083−4.713	0.650	0.612	0.081−4.610	0.634
Thyroid	1.876	0.421−8.362	0.409	1.799	0.402−8.052	0.443
Other cancers	0.413	0.056−3.063	0.387	0.401	0.054−2.975	0.371

OR, odds ratio; CI, confidence interval;
[a] by the binary logistic regression analysis.

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