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Impact of birth season on second-to-fourth digit ratio, prostate volume, and prostate cancer

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Purpose: The second-to-fourth digit ratio (digit ratio), which is determined *in utero*, is associated with exposure to visible sunlight during early pregnancy and the season of birth. The digit ratio is also associated with benign prostatic hyperplasia (BPH) and prostate cancer. This suggests that BPH and prostate cancer may be related to the birth season. Therefore, this study aimed to determine whether prostate volume and prostate cancer were related to the birth season.

Materials and Methods: A total of 858 male patients with lower urinary tract symptoms were enrolled. The right digit ratio was measured, and the month of birth was surveyed. Serum prostate-specific antigen (PSA) levels were measured, and prostate volumes were measured by transrectal ultrasonography. Patients with suspected prostate cancer underwent prostate biopsy.

Results: The mean age, digit ratio, prostate volume, and serum PSA level of 858 patients were 61.6 years, 0.947, 36.2 mL, and 4.24 ng/mL, respectively. Age, serum PSA levels, prostate biopsy rates, and cancer detection rates did not differ significantly according to the birth season. However, compared with the summer birth group, the winter birth group had lower digit ratios (0.951±0.040 vs. 0.941±0.040; p=0.014), larger prostate volumes (33.4±14.9 mL vs. 38.2±20.7 mL; p=0.008), and more prostate cancer (5.3% vs. 11.3%; p=0.031). Multivariate analysis showed that birth season independently predicted prostate cancer.

Conclusions: The relationships of birth season with prostate volume and prostate cancer may be due to differences in the amount of light exposure during early pregnancy.

Keywords: Birth season; Prostate cancer; Prostate volume; Second-to-fourth digit ratio

INTRODUCTION

An individual's month of birth is known to have a significant impact on the diseases that develop throughout their lifetime [1]. Previous studies revealed relationships between birth month and asthma, attention-deficit/hyperactivity disorder, heart disease, and many other common medical problems [1]. In addition to asthma, considering the finding that male born in winter had lower lung function than male born in other seasons, the birth season may be an early life factor predicting lung function [2]. However, little is known about the relationship between urological diseases and the birth season.

The second-to-fourth digit ratio (digit ratio) on the right hand, which reflects fetal androgen status [3-6], predicts the activity of the androgen receptor (AR) [7]. AR activ-

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ity is well known to increase the risk for benign prostatic hyperplasia (BPH) [8-10] and prostate cancer [11,12]. Also, the digit ratio is associated with BPH [13,14] and prostate cancer [15,16]. One study recently found that the digit ratio, which is determined *in utero*, is associated with exposure to visible sunlight during early pregnancy (first trimester) and the season of birth [17]. Compared with late-spring births, late-autumn births have a lower right-left digit ratio [17]. This means that the digit ratios of participants who were born in late autumn and experienced long days in the second and third prenatal months were low (high prenatal testosterone) [17].

Therefore, there is a relationship between the birth season and the digit ratio related to fetal testosterone [17]. Also, BPH and prostate cancer are associated with the digit ratio. This suggests that BPH and prostate cancer may be related to the birth season. Thus, the present study aimed to explore whether prostate volume and prostate cancer are related to the birth season.

MATERIALS AND METHODS

1. Patients

The present study protocol was reviewed and approved by the Institutional Review Board of Gachon University Gil Medical Center in South Korea (approval number: GDIRB2020-427). We retrospectively analyzed medical records and written informed consent was waived by the board. Among new male patients who presented with lower urinary tract symptoms at a single tertiary academic center from April 2012 to October 2020, a total of 858 patients without previous treatment with 5α-reductase inhibitors for BPH were enrolled. All patients in the present study came from the same ethnic Korean group and were born in South Korea. The right digit ratio was measured, and the month of birth was surveyed. Serum prostate-specific antigen (PSA) levels were measured, and prostate volumes were measured by transrectal ultrasonography without information on the digit ratio. Prostate biopsy was performed in patients with a PSA level of ≥3 ng/mL or suspected prostate cancer on digital rectal examination or ultrasonography. The patients were divided into 4 groups according to birth season. The digit ratio, prostate volume, and proportion of patients diagnosed with prostate cancer were compared according to birth season.

2. Birth season

In our study, the birth season was set according to the definition of the solar season based on insolation (the quantity of solar radiation), in which the solstices and equinoxes are located in the middle of the seasons. In the northern hemisphere, the summer solstice, the longest day of the year, is in June, and the winter solstice, the shortest day of the year, is in December. Therefore, in the present study, May, June, and July were defined as summer; November, December, and January as winter; February, March, and April as spring; and August, September, and October as autumn.

3. Statistical analysis

The basic data are expressed by a descriptive method. Statistical analyses were performed by use of Student's t-test and the chi-squared test. Multivariate logistic regression analysis was performed to find independent predictors for prostate cancer risk. Analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA), and differences with p-values of less than 0.05 were considered statistically significant.

RESULTS

1. Patient clinical characteristics

The mean age, digit ratio, prostate volume, serum PSA level, and PSA density (PSAD) of the 858 patients were 61.6 years, 0.947, 36.2 mL, 4.24 ng/mL, and 0.107 ng/mL/mL, respectively (Table 1). Of the total patients, 177 were suspected of having prostate cancer and underwent prostate biopsy. Sixty-seven of these patients were diagnosed with prostate cancer (Table 1). There were no significant differences in age, serum PSA level, PSAD, prostate biopsy rates, or cancer detection rates according to birth season (Table 1, Table 2). However, digit ratio, prostate volume, and the proportion of prostate cancer differed according to the birth season (Table 1, Table 2).

2. Digit ratio, birth month, and birth season

Fig. 1 shows the digit ratio according to the birth month and birth season. There was a significant curvilinear association (inverted U-shape) between the digit ratio and the birth month (Fig. 1A). Fig. 1A shows the June and November birth patterns, where male born in the summer tended to have an increased digit ratio. Compared with the summer birth group, the winter birth group had a lower digit ratio (0.951±0.040 vs. 0.941±0.040, p=0.014; Table 2, Fig. 1B).

3. Prostate volume, birth month, and birth season

Fig. 2 shows the prostate volume according to the birth month and birth season. There was a significant curvilinear association (U-shape) between prostate volume and birth

Table 1. Characteristics of the study population

Variable	Total	Birth season			
		Spring	Summer	Autumn	Winter
Number of patients	858	257	189	208	204
Age (y)	61.6±10.6	61.6±10.4	60.5±10.0	62.2±11.0	62.2±11.1
Digit ratio	0.947±0.039	0.950±0.038[a]	0.951±0.040[c]	0.947±0.038	0.941±0.040[a,c]
PV (mL)	36.2±19.2	36.1±19.6	33.4±14.9[b,c]	36.9±20.4[b]	38.2±20.7[c]
PSA (ng/mL)	4.24±11.69	4.53±12.53	4.59±15.54	3.87±8.01	3.94±9.44
PSAD (ng/mL/mL)	0.107±0.305	0.110±0.283	0.129±0.473	0.093±0.172	0.096±0.234
Biopsy (%)	20.6 (177/858)	21.0 (54/257)	17.5 (33/189)	19.7 (41/208)	24.0 (49/204)
Cancer (%)	7.8 (67/858)	6.2 (16/257)	5.3[c] (10/189)	8.7 (18/208)	11.3[c] (23/204)
Detection (%)	37.9 (67/177)	29.6 (16/54)	30.3 (10/33)	43.9 (18/41)	46.9 (23/49)

Values are presented as number only or mean±standard deviation.
PV, prostate volume; PSA, prostate-specific antigen; PSAD, PSA density.
[a]:p-value <0.05 for spring vs. winter. [b]:p-value <0.05 for summer vs. autumn. [c]:p-value <0.05 for summer vs. winter.
According to the definition of the solar season, the birth seasons were set as follows. Spring: February, March, and April; summer: May, June, and July; autumn: August, September, and October; and winter: November, December, and January.
Student's t-test was used.

Table 2. Comparison of participant characteristics by birth season (summer vs. winter)

Variable	Birth season		OR	95% CI	p-value
	Summer	Winter			
Number of patients	189	204			
Age (y)	60.5±10.0	62.2±11.1			0.100
Digit ratio	0.951±0.040	0.941±0.040			0.014
PV (mL)	33.4±14.9	38.2±20.7			0.008
PSA (ng/mL)	4.59±15.54	3.94±9.44			0.617
PSAD (ng/mL/mL)	0.129±0.473	0.096±0.234			0.375
Biopsy (%)	17.5 (33/189)	24.0 (49/204)			0.109
Cancer (%)	5.3 (10/189)	11.3 (23/204)			0.031
Detection (%)	30.3 (10/33)	46.9 (23/49)			0.130
Biopsy					
No	156	155	1.494	0.912–2.450	0.110
Yes	33	49			
Cancer					
No	179	181	2.275	1.053–4.916	0.033
Yes	10	23			
Detection					
No	23	26	2.035	0.802–5.160	0.132
Yes	10	23			

Values are presented as number only or mean±standard deviation.
PV, prostate volume; PSA, prostate-specific antigen; PSAD, PSA density; OR, odds ratio; CI, confidence interval.
According to the definition of the solar season, the birth seasons were set as follows. Summer: May, June, and July and winter: November, December, and January.
Student's t-test and chi-squared test were used.

month (Fig. 2A). Fig. 2A shows the July and November birth patterns, in which male born in the summer tended to have a lower prostate volume. Compared with the summer birth group, the winter birth group had a larger prostate (33.4±14.9 mL vs. 38.2±20.7 mL, p=0.008; Table 2, Fig. 2B).

4. Prostate cancer, birth month, and birth season

Fig. 3 shows the proportion of prostate cancer according to the birth month and birth season. There was a significant curvilinear association (U-shape) between the proportion of prostate cancer and the birth month (Fig. 3A). Fig. 3A shows the July and November birth patterns, where male born in

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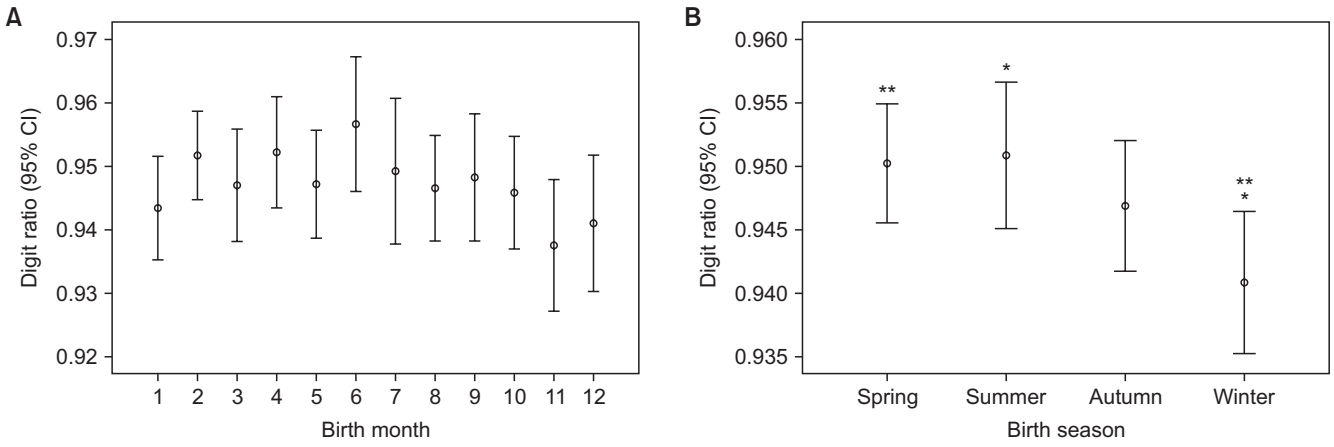

Fig. 1. Digit ratio, birth month, and birth season. (A) Digit ratio and birth month. There was a significant curvilinear association (inverted U-shape) between digit ratio and birth month (June and November birth patterns). The digit ratio was highest in June births and lowest in November births; that is, male born in summer tended to have an increased digit ratio. (B) Digit ratio and birth season. Compared with the summer birth group, the winter birth group had lower digit ratios (0.951±0.040 vs. 0.941±0.040; p=0.014). According to the definition of the solar season, the birth seasons were set as follows. Spring: February, March, and April; summer: May, June, and July; autumn: August, September, and October; and winter: November, December, and January. CI, confidence interval. Student's t-test was used. *p-value <0.05 for summer vs. winter. **p-value <0.05 for spring vs. winter.

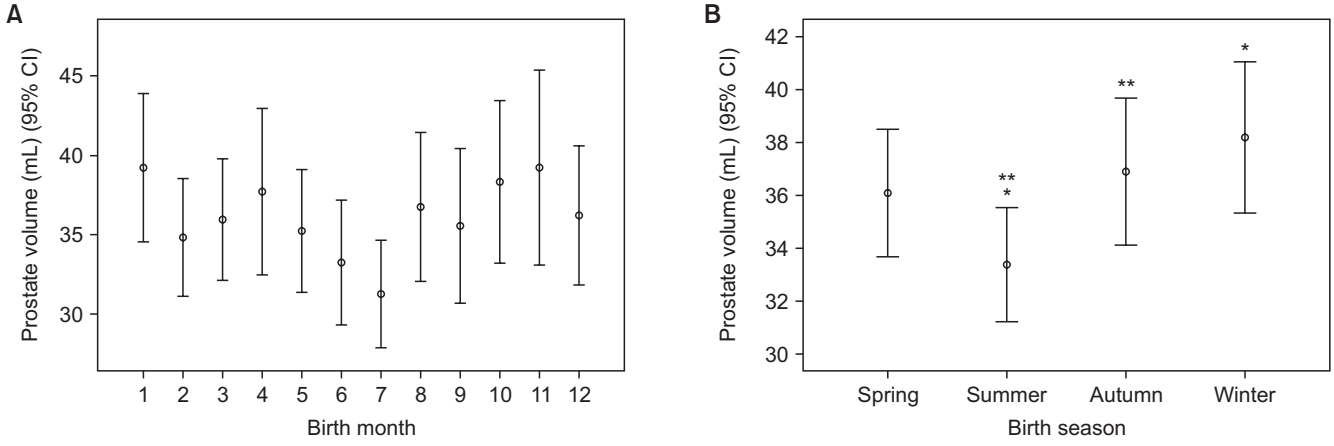

Fig. 2. Prostate volume, birth month, and birth season. (A) Prostate volume and birth month. There was a significant curvilinear association (U-shape) between prostate volume and birth month (July and November birth patterns). Prostate volume was smallest in July births and largest in November births; that is, male born in the summer tended to have a lower prostate volume. (B) Prostate volume and birth season. Compared with the summer birth group, the winter birth group had larger prostates (33.4±14.9 mL vs. 38.2±20.7 mL; p=0.008). According to the definition of the solar season, the birth seasons were set as follows. Spring: February, March, and April; summer: May, June, and July; autumn: August, September, and October; and winter: November, December, and January. CI, confidence interval. Student's t-test was used. *p-value <0.05 for summer vs. winter. **p-value <0.05 for summer vs. autumn.

the summer tended to have a lower proportion of prostate cancer. Compared with the summer birth group, the winter birth group had more prostate cancer (5.3% vs. 11.3%, p=0.031; odds ratio [OR]=2.275, p=0.033; Table 2, Fig. 3B).

5. Multivariate logistic regression analysis for prostate cancer risk

The results of multivariate logistic regression analysis indicated that birth season (summer [reference] vs. winter: adjusted OR=3.250, p=0.034), age (adjusted OR=1.097, p<0.001), and PSA level (adjusted OR=1.199, p<0.001) independently predicted prostate cancer (Table 3).

6. Comparison of patients diagnosed with prostate cancer by birth season (summer vs. winter)

The prostate biopsy findings of prostate cancer patients did not differ significantly between birth seasons (summer vs. winter) (Table 4). Although number of positive cores, core cancer volume, and Gleason score appeared to be slightly

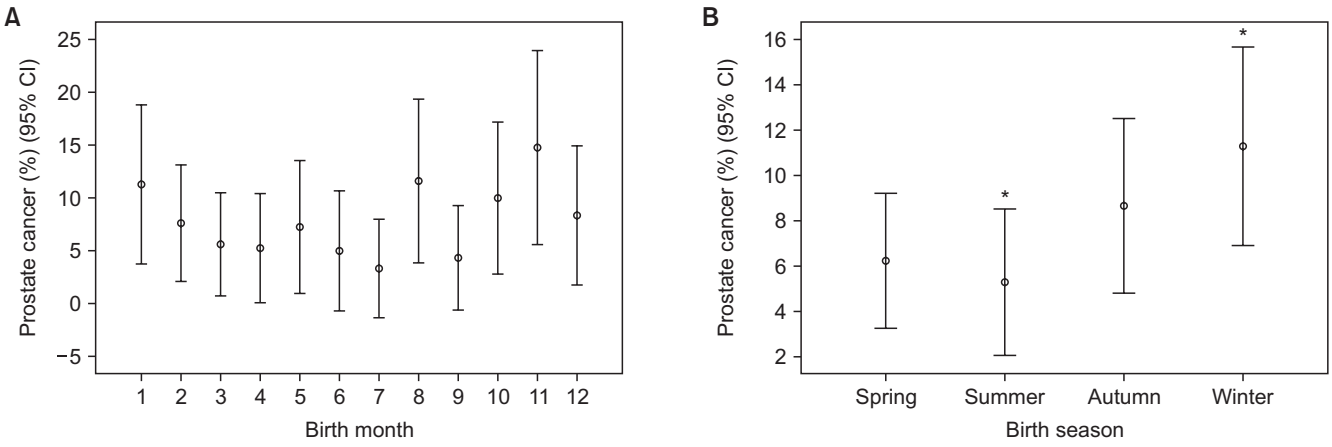

Fig. 3. Prostate cancer, birth month, and birth season. (A) Prostate cancer and birth month. There was a significant curvilinear association (U-shape) between prostate cancer and birth month (July and November birth patterns). The incidence of prostate cancer was lowest in July births and highest in November births; that is, male born in the summer tended to have a lower proportion of prostate cancer. (B) Prostate cancer and birth season. Compared with the summer birth group, the winter birth group had more prostate cancer (5.3% vs. 11.3%, p=0.031; OR=2.275, p=0.033). According to the definition of the solar season, the birth seasons were set as follows. Spring: February, March, and April; summer: May, June, and July; autumn: August, September, and October; and winter: November, December, and January. OR, odds ratio; CI, confidence interval. Student's t-test was used. *p-value <0.05 for summer vs. winter.

Table 3. Multivariate logistic regression analysis for prostate cancer risk

Variable	B	S.E.	Wald	df	p-value	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	0.092	0.020	21.495	1	<0.001	1.097	1.055	1.140
Digit ratio	-4.268	4.338	0.968	1	0.325	0.014	0.000	68.950
PV	-0.015	0.008	3.384	1	0.066	0.985	0.969	1.001
PSA	0.181	0.025	53.171	1	<0.001	1.199	1.142	1.259
Birth season			9.114	3	0.028			
Summer	(Reference)							
Autumn	0.586	0.576	1.035	1	0.309	1.797	0.581	5.560
Winter	1.179	0.555	4.509	1	0.034	3.250	1.095	9.649
Spring	-0.151	0.627	0.058	1	0.810	0.860	0.252	2.940
Contant	-5.693	4.250	1.794	1	0.180	0.003		

PV, prostate volume; PSA, prostate-specific antigen; B, estimated logit coefficient; S.E., standard error; df, degree of freedom; CI, confidence interval.
According to the definition of the solar season, the birth seasons were set as follows. Spring: February, March, and April; summer: May, June, and July; autumn: August, September, and October; and winter: November, December, and January.

higher in the summer birth group than in the winter birth group, these differences were not significant (Table 4). Also, there were no significant differences in age, digit ratio, prostate volume, serum PSA level, or PSAD between the birth seasons (Table 4).

DISCUSSION

In this study, we observed that the digit ratio, prostate volume, and risk for prostate cancer were related to the birth season and month of birth. Our data showed that the winter birth group had a lower digit ratio, larger prostate, and more prostate cancer than did the summer birth group. Furthermore, birth season independently predicted prostate cancer. Among the several articles identifying associations between the birth season and month of birth and several diseases, no studies of the relationship to prostate volume have been conducted. A recent retrospective population study in the United States found 55 diseases that were significantly dependent on the birth month. Among the diseases mentioned, prostate cancer was related to the month of birth (n=20,353, p=0.002), but the mechanism was not explained [1].

The present study showed June–July and November birth patterns; that is, the digit ratio was highest in June births and lowest in November births, the prostate volume

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Table 4. Comparison of the patients diagnosed with prostate cancer according to birth season (summer vs. winter)

Variable	Birth season		p-value
	Summer	Winter	
Number of patients	10	23	
Age (y)	67.5±7.5	71.7±8.2	0.181
Digit ratio	0.934±0.023	0.935±0.037	0.988
PV (mL)	40.6±17.1	50.2±21.4	0.218
PSA (ng/mL)	50.59±48.61	19.22±22.49	0.078
PSAD (ng/mL/mL)	1.442±1.594	0.438±0.585	0.081
Number of positive cores	8.70±3.34	6.35±3.95	0.111
Max core cancer volume (%)	53.69±24.47	39.27±28.42	0.174
Max sum of GS	7.30±1.06	6.83±0.98	0.223
5	0	1	0.362
6	2	9	
7	5	7	
8	1	5	
9	2	1	
Max primary GS	3.70±0.67	3.48±0.51	0.307
3	4	12	0.284
4	5	11	
5	1	0	
Max secondary GS	3.60±0.70	3.35±0.65	0.323
2	0	1	0.768
3	5	14	
4	4	7	
5	1	1	

Values are presented as number only or mean±standard deviation.
PV, prostate volume; PSA, prostate-specific antigen; PSAD, PSA density; GS, Gleason score.
According to the definition of the solar season, the birth seasons were set as follows. Summer: May, June, and July and winter: November, December, and January.
Student's t-test and chi-squared test were used.

was smallest in July births and largest in November births, and the risk for prostate cancer was lowest in July births and highest in November births. As shown in Fig. 1A, the birth pattern of the digit ratio of our study is similar to the results of Szwed et al. [17]. A low right digit ratio (winter births) was significantly associated with the long days (summer) at the end of the first trimester of pregnancy [17].

A study by Boland et al. [1] showed a peak risk for prostate cancer in the birth month of March and a dip in October. It is difficult to know the exact reason for the difference in birth patterns between our study and the study of Boland et al. [1]. The differences may have been caused by racial and geographic (latitude) differences. Compared with South Korea, the United States is more ethnically diverse and geographically wider (South Korea: 33.1–38.6 degrees north latitude; United States: 24–48 degrees north latitude). However, according to the monthly distribution graph in the study by Boland et al. [1], the risk for prostate cancer peaked in the birth month of March but was quite high in January. This is similar to our study, which showed that the risk for prostate cancer was high not only in the birth month of November but also in January (Fig. 3A). In addition, the risk for prostate cancer appeared to be considerably lower not only in October but also in July [1], which is similar to our study showing the lowest risk for prostate cancer in the birth month of July (Fig. 3A).

Several diseases demonstrate birth month dependencies with known mechanisms [1]. However, most of the mechanisms driving these seasonal birth month effects remain inconclusive or unknown. On the basis of previous studies showing that BPH and prostate cancer are related to the digit ratio and one study reporting that the digit ratio is formed in early pregnancy and has a relationship with the month of birth, we studied the relationship between BPH and prostate cancer with the month of birth and birth season. A closer look at the background for our hypothesis and reasoning is as follows.

The digit ratio is formed *in utero* and depends on the balance of testosterone and estrogen [3-5]. In humans, digit ratios tend to be lower in males, and fetal studies have shown that sexual dimorphism of the digit ratio is determined at the end of the first trimester of pregnancy [18,19]. Recently, the digit ratio was reported to be associated with exposure to visible sunlight in early pregnancy [17]. The digit ratios of participants who were born in late autumn (corresponding to winter in terms of solar season) and experienced long days (summer) in the second and third prenatal months were low (high prenatal testosterone) [17]. This means that a low right digit ratio and a low right-left digit ratio (winter births) were significantly associated with the long days (summer) at the end of the first trimester of pregnancy [17]. Moreover, in this regard, a study of birth seasonality and digit ratio can be explained by the solstitial-melatonin-testosterone (SMT) hypothesis [20]. Sunlight inhibits melatonin production by the pineal gland and reduces glutathione levels in the skin. Melatonin inhibits the formation of fetal testosterone, and glutathione may act against testosterone [17]. Thus, sunlight is thought to increase the amount and effect of fetal testosterone [17].

Sunlight stimulates the action of testosterone through melatonin. Melatonin plays an important role in a variety of essential physiologic functions, including circadian rhythm regulation and visual, cerebrovascular, reproductive, neuroendocrine, and neuroimmune functions [21]. Melatonin is produced primarily in the pineal gland and is released in a circadian fashion, with high levels occurring

at night in all species [22]. In addition, Adamsson et al. [23] observed a higher peak level of melatonin during the dark winter period. Maternal melatonin levels dip at the summer solstice and peak at the winter solstice [24]. The period of melatonin secretion is proportional to the dark period, and thus melatonin acts as a neuroendocrine transducer of photoperiodic information [22]. Melatonin easily crosses the placenta untransformed and enters the circulation of the fetus [25]. Information about day length and circadian cycle is transferred to the fetus through the maternal melatonin rhythm [26]. Thus, photoperiodic information perceived by the mother serves to synchronize the physiology of the fetus [26]. Furthermore, photoperiodic information received *in utero* from the mother affects the gonadal growth of fetuses and newborns [27,28].

In the fetus, the sex differences of digit ratio extend into the first trimester [18,19]. Fetal testosterone is released from week 8 and peaks at week 14 of pregnancy. During this period, testosterone is involved in significant organizations in the brain and other organ systems. This suggests that the time window for the determination of the digit ratio may be sometime between 8 and 14 weeks. The developmental window of determination of the digit ratio may be related to the timing of SMT effects. In other words, when a mother receives a lot of visible sunlight during the first trimester of pregnancy, it is thought that the maternal melatonin level decreases, the fetal testosterone level increases, and the right digit ratio is lowered. Thus, the prostate volume and risk for prostate cancer increase after middle age. Therefore, in this study, we observed that compared with the summer birth group, the winter birth group had lower digit ratios, larger prostates, and more prostate cancer.

According to the SMT hypothesis, we hypothesized that the amount of light in early pregnancy was important. The solar season is based on insolation (the amount of light), in which the solstices and equinoxes are located in the middle of the seasons. However, the meteorologic season, which is commonly used in our daily life, is based on temperature, and not the amount of light. Therefore, in the present study, we used the solar season instead of meteorologic or astronomical seasons. Late-spring and late-autumn in the study of Szwed et al. [17] probably correspond to summer and winter in terms of solar season.

In the present study, unlike the prevalence of prostate cancer, the prostate biopsy findings of prostate cancer patients did not differ between birth seasons (summer vs. winter) (Table 4). Although number of positive cores, core cancer volume, and Gleason score appeared to be slightly higher in the summer birth group than in the winter birth group, the difference was not statistically significant (Table 4). Actually, the total number of patients in the summer and winter birth groups who had prostate cancer was 33 (10 in the summer and 23 in the winter birth group). So, we think that the number of prostate cancer patients was not sufficient to reveal differences in prostate biopsy findings. Also, in our data, although there was no statistical difference in PSA levels, the proportion of patients with very high PSA levels (≥50 ng/mL) was relatively higher in the summer birth group than in the winter birth group (summer: 4/10 [40.0%] vs. winter: 3/23 [13.0%]). For this reason, we think that the summer birth group seemed to have a slightly higher number of positive cores, core cancer volume, and Gleason score than did the winter birth group. But there was no statistically significant difference (Table 4).

Our study had several limitations. First, we did not measure actual serum testosterone levels. It is important to measure the mother's testosterone level at the time of pregnancy as well as the patient's testosterone level at the time of the hospital visit to determine the effect of birth season on the development of BPH and prostate cancer. A study that measures the mother's testosterone level at the time of pregnancy and investigates the incidence of prostate cancer after about 60 years is methodologically perfect but impossible to carry out in practice. However, the digit ratio is known to be a potential indicator of fetal sex steroid exposure [3-6]. There are many reports that the sex difference in digit ratio is greater in the right hand than in the left, and there are suggestions that the right hand may be more sensitive to the effects of testosterone [3,29-33]. In addition, in 1988, Henderson et al. [34] suggested a possible relationship between prenatal androgen exposure and later development of prostate cancer. Therefore, instead of a direct measurement of testosterone levels, we measured right digit ratios. Second, we could not measure the actual exposure to visible sunlight at the time of pregnancy. Also, we could not measure the patients' circadian rhythms or melatonin levels at the time of pregnancy. Instead, these measures were replaced with the month of birth and the season of birth based on the results of Adamsson et al. [23]. Third, we enrolled patients from a very specific demographic group, thus limiting the generalizability of our observations to other populations. Hence, larger-scale and multicenter studies are required to validate the present findings.

CONCLUSIONS

Our results demonstrated that the digit ratio, prostate volume, and risk for prostate cancer varied depending upon

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the season of birth. Compared with the summer birth group, the winter birth group had lower digit ratios, larger prostates, and more prostate cancer. Furthermore, birth season independently predicted prostate cancer. This may be due to the difference in the amount of light exposure in early pregnancy.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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None.

AUTHORS' CONTRIBUTIONS

Research conception and design: I-Nae Park and Tae Beom Kim. Data acquisition: Tae Beom Kim. Statistical analysis: I-Nae Park. Data analysis and interpretation: I-Nae Park and Tae Beom Kim. Drafting of the manuscript: I-Nae Park and Tae Beom Kim. Critical revision of the manuscript: I-Nae Park and Tae Beom Kim. Approval of the final manuscript: I-Nae Park and Tae Beom Kim.

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