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Second to fourth digit ratio, handedness and testicular germ cell tumors

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Abstract

Background—Research on early life exposures and testicular germ cell tumors (TGCT) risk has focused on a possible perinatal etiology with a well-known hypothesis suggesting that hormonal involvement during fetal life is associated with risk. Second-to-fourth digit ratio (2D:4D) and left hand dominance have been proposed as markers of prenatal hormone exposure.

Aim—To evaluate associations between 2D:4D digit ratio, right minus left 2D:4D (Δ_{R-L}), and left-hand dominance and TGCT in the U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) Study.

Methods—A total of 246 TGCT cases and 236 non-testicular cancer controls participated in the current study, and completed a self-administered questionnaire. Associations between digit ratio, hand dominance and TGCT were estimated using unconditional logistic regression adjusting for identified covariates.

Results—Right 2D:4D was not associated with TGCT [OR for a one-standard deviation (SD) increase in right hand 2D:4D: 1.12, 95% CI: 0.93–1.34]. The results were consistent when evaluating the association based on the left hand. The difference between right and left hand 2D:4D was also not associated with TGCT risk [OR for a one-SD increase in Δ_{R-L} : 1.03, 95% CI: 0.87–1.23]. Compared to men who reported right-hand dominance, ambidexterity [OR (95% CI) = 0.65 (0.30–1.41)] and left-hand dominance [OR (95% CI) = 0.79 (0.44–1.44)] were not associated with risk.

Conclusions—These results do not support the hypothesis that prenatal hormonal imbalance is associated with TGCT risk. Given the limited sample size, further evaluation of the relationship

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between TGCT and prenatal hormonal factors using digit ratio, Δ_{R-L} , or left-hand dominance and larger sample size are warranted.

Keywords

case-control; testicular cancer; hand pattern; left-handed dominance; digit ratio

INTRODUCTION

Testicular germ cell tumors (TGCT) are the most common malignant neoplasm occurring in young men, ages 15–44, in many countries including the United States [1]. There are few established risk factors for TGCT beyond age, race/ethnicity, adult height, history of cryptorchidism, and family history of TGCT [2]. Research on early life exposures and TGCT risk has focused on a possible perinatal etiology with a well-known hypothesis suggesting that hormonal involvement during fetal life is associated with risk [3;4].

The ratio of second-to-fourth (2D:4D) digit length is established early in life and proposed as an indicator of the hormonal microenvironment of the fetal testis [5–7], and more specifically as an indicator of prenatal androgen stimulation [8]. It was initially proposed [5] and has since been demonstrated that a higher digit ratio is indicative of low androgen and high estrogen *in utero* [6–11]. The difference between the right and left digit ratio (right 2D:4D minus left 2D:4D, abbreviated Δ_{R-L}) has also been suggested as an indicator of prenatal androgen exposure, with lower Δ_{R-L} indicative of higher prenatal testosterone exposure. Reports suggest that digit ratio is not affected by pubertal growth [12] and not related to adult sex hormone levels [13], but may be associated with male infertility, namely low sperm count [5;14]. However, digit ratio was not associated with TGCT in a French case-control study [15].

Hand dominance or handedness has also been suggested to be a marker of *in utero* testosterone exposure; however, the data supporting an association has been less consistent. Studies have reported inverse, null and direct associations between increased prenatal testosterone exposure and left hand dominance [16]. It has also been hypothesized that left hand dominance is associated with high *in utero* estrogen exposure, given a higher prevalence of left-handedness in some diethylstilbestrol (DES) exposed populations [17–19]. Whereas, research from Manning and colleagues linking lower right hand 2D:4D and Δ_{R-L} with left hand writing preference provides evidence supporting an association between high prenatal testosterone and left hand dominance [20]. Using existing data from the U. S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study, we evaluated the association between 2D:4D digit ratio, Δ_{R-L} , left hand dominance and TGCT.

MATERIALS AND METHODS

Study population

Participants in the STEED study were enrolled between 2002 and 2005 [21]. Briefly, men between 18 and 45 years of age who had at least one serum sample stored in the U.S. Department of Defense Serum Repository (DoDSR, Silver Spring, MD) were eligible for the study. Men who developed TGCT while on active duty were eligible to participate as cases while men who did not develop TGCT were eligible to participate as controls. TGCT diagnoses were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, mixed germ cell tumor). Eligible controls (n=928) were matched to cases (n=767) based on age at diagnosis (within one year), ethnicity (white, black, other) and date serum was donated (within 30 days). Participants

with available contact information were mailed an invitation to participate in the current study between May 2008 and April 2009, the invitation to participate included a questionnaire to evaluate quality of life following cancer treatment [22]. The questionnaire also included questions on hand preference and digit length. Specifically men were asked to report their hand preference (right, left or ambidextrous) and to report the length (to the nearest millimeter) of the 2nd and 4th digits from their left and right hands.

Of the 482 whom completed the self-administered follow-up questionnaire (response proportion of 47.6%), 479 provided information on handedness and 467 provided information on digit length. The current study population is based on the subset of the original study population that responded to the quality of life questionnaire, thus the matching was no longer retained. Informed consent was obtained from all participants. The study was approved by the institutional review boards of Yale University, the National Cancer Institute, and the Walter Reed Army Institute of Research.

Statistical analysis

Questionnaire data were available for analysis from 246 cases (112 seminoma and 134 nonseminoma) and 236 controls. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression adjusting for age, race, prior cryptorchidism, family history of testicular cancer, and adult height. Right and left hand 2D:4D digit ratios and the difference between the right 2D:4D and left 2D:4D (Δ_{R-L}) were evaluated as continuous variables. These continuous measures were standardized such that the OR reflects the TGCT risk associated with a one-standard deviation (SD) increase in 2D:4D or Δ_{R-L} . Separate models were fit for left and right 2D:4D, Δ_{R-L} , and handedness. Analyses were conducted for all TGCT cases and for seminoma and nonseminoma separately. Due to potential measurement error in self-reported finger length, we conducted a sensitivity analysis restricting to the experimenter-measured range of 2D:4D (between 0.80 and 1.20) [23]. All analyses were conducted using SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA); statistical tests were two sided, with p-value < 0.05 considered statistically significant.

RESULTS

The general characteristics of the study population are shown in Table 1. The median age of cases and controls was similar and the study population was predominantly white (94.1% in controls). Compared to controls, cases were more likely to have a history of cryptorchidism and a family history of testicular cancer among first- or second-degree relatives.

Adjusted ORs for the comparisons of right and left hand 2D:4D, Δ_{R-L} , handedness and TGCT are shown in Table 2. Among male controls the mean right hand 2D:4D (mean 0.988, SD=0.069) and left hand 2D:4D were similar (mean 0.985, SD=0.072). Overall, right 2D:4D was not associated with TGCT [OR for a one-SD increase in right hand 2D:4D: 1.12, 95% CI: 0.93–1.34]. The results were consistent when evaluating the association based on the left hand [OR for a one-SD increase in left hand 2D:4D: 1.08, 95% CI: 0.87–1.23]. The difference between right and left hand 2D:4D was also not associated with TGCT risk [OR for a one-SD increase in Δ_{R-L} : 1.03, 95% CI: 0.87–1.23]. Compared to men who reported right hand dominance, ambidexterity [OR: 0.65, 95% CI: 0.30–1.41] and left-hand dominance [OR: 0.79, 95% CI: 0.44–1.44] were not associated with TGCT risk (Table 2). Analyses by histologic subtype also showed no association (results not shown). Excluding 14 individuals with extreme values for left of right hand 2D:4D did not appreciably change the effect estimates (results not shown).

DISCUSSION

Measures of digit ratio, Δ_{R-L} , and left hand dominance were not associated with TGCT in the STEED study. It is hypothesized that low fetal androgen and/or increased fetal estrogen exposure are important risk factors for TGCT [4], therefore we would have expected a high ratio of 2D:4D to be associated with risk. We did not, however, observe an association between digit ratio and TGCT. Our results are consistent with a French case-control study of 71 TGCT cases and 122 controls that reported no association between digit ratio and TGCT [15]. Our study and the study by Auger and colleagues, however, are limited by small sample size and larger studies of digit ratio and TGCT are warranted. In contrast to direct experimenter-measured digit length in the French case-control study, digit length was self-reported in the current study; however, our mean estimates of right and left 2D:4D in controls were comparable to mean values reported in the literature, albeit with slightly larger standard deviations [9;15].

Studies evaluating digit ratio and cancer risk using larger sample sizes have reported that osteoarthritis and prostate cancer were inversely associated with right hand 2D:4D [24;25] and breast cancer was positively associated with left hand 2D:4D and inversely associated with Δ_{R-L} [26]. The study of prostate cancer is consistent with the current understanding of the hypothesized role of prenatal hormonal patterns and cancer risk. Specifically, men with a low ratio of 2D:4D, indicating higher fetal testosterone, were at a greater risk of prostate cancer, whereas an additional study reported no association between digit ratio and prostate cancer [27]. The study of breast cancer demonstrates the importance of evaluating Δ_{R-L} ; the inverse relationship between breast cancer and Δ_{R-L} suggests that higher prenatal testosterone may be consistent with an increased risk of breast cancer [26].

The association between *in utero* hormone exposure and hand preference is less clear. Given studies showing increased prevalence of left-hand dominance with *in utero* DES exposure, we hypothesized that left-hand dominance would be inversely associated with TGCT risk. We did not, however, observe an association between handedness and TGCT. Our results are consistent with a report by Swerdlow and colleagues (259 cases and 251 controls) that also reported no association between hand dominance and TGCT [28].

Studies evaluating hand dominance and cancer risk have reported increased risk of breast cancer among left-handed women compared with right-handed women [29–31] as well as associations between handedness and laterality of breast cancer [32;33]. The studies of breast cancer and handedness are consistent with the current hypothesized role of prenatal estrogen exposure and breast cancer risk.

There are several limitations to keep in mind when interpreting these results. The response proportion for the follow-up questionnaire on which this analysis is based was low; however, the sampled group was representative of the STEED population as demonstrated by the similar distribution of demographic variables [22;34]. Further, the study is limited by small sample size. Finally, as discussed by Caswell and Manning [23] self-reported finger length raises the possibility of measurement error. Self-reported finger length measured directly from the finger resulted in more extreme values when compared with photo assessment of digit ratio [23]. The authors suggested that the use of self-reported finger length was still a valuable tool if used in large samples and outliers of digit-ratio are removed. Fewer than 2% of our sample had digit ratio values less than 0.80 or greater than 1.20; exclusion of these extreme values did not change the effect estimates or alter the overall study conclusions. To the extent that there is exposure misclassification in the assessment of digit ratio, the bias would likely be non-differential with-respect-to case-control status and would likely lead to attenuation of the effect estimates.

The data presented here does not support the hypothesis that prenatal androgen stimulation, as measured by digit ratio, is associated with TGCT. The data also do not support an association between left-hand dominance and TGCT. However, given the limited sample size and participant-reported measure of digit length, further evaluation of the relationship between TGCT and prenatal hormonal factors using digit ratio, Δ_{R-L} , or left hand dominance and larger sample size are warranted.

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Table 1

Characteristics of study participants stratified by case-control status, STEED Study, 2002–2005

	Cases (n=246)		Controls (n=236)	
	Median (IQR)		Median (IQR)	
Age	28 (24–35)		28 (24–34)	
Height	180 (175–185)		178 (175–183)	
Race	n	%	n	%
White	220	89.4	222	94.1
Black	1	0.4	3	1.3
Other	25	10.2	11	4.7
Cryptorchidism				
Yes	23	9.4	3	1.3
No	223	90.6	233	98.7
First- or second-degree family history of testicular cancer				
Yes	10	4.1	3	1.3
No	236	95.9	233	98.7

Table 2

Second-to-fourth (2D:4D) digit ratio, handedness and testicular germ cell tumors (TGCT), STEED Study, 2002–2005.

	Cases	Controls	OR ^I	95% CI
<i>Digit ratio</i>	Mean (SD)	Mean (SD)		
Right hand 2D:4D	0.995 (0.072)	0.988 (0.069)	1.12	(0.93, 1.34)
Left hand 2D:4D	0.988 (0.073)	0.985 (0.072)	1.08	(0.89, 1.29)
Δ_{R-L}	0.006 (0.053)	0.004 (0.048)	1.03	(0.87, 1.23)
<i>Handedness</i>	n (%)	n (%)		
Right-handed	206 (84.8)	188 (79.7)	1.00	reference
Left-handed	24 (9.9)	30 (12.7)	0.79	(0.44, 1.44)
Ambidextrous	13 (5.3)	18 (7.6)	0.65	(0.30, 1.41)

OR = odds ratio, CI = confidence interval, SD = standard deviation, 2D = second digit (index finger), 4D = fourth digit (ring finger), Δ_{R-L} = difference between right and left 2D:4D

^I ORs adjusted for age, race, adult height, history of cryptorchidism and first- or second-degree family history of TGCT; 2D:4D and Δ_{R-L} measures were standardized such that the OR reflects a 1 SD increase.