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Lifetime growth and risk of testicular cancer

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Adult height is associated with testicular cancer risk. We studied to what extent this association is explained by parental height, childhood height and age at puberty. We conducted a case–control study on germ-cell testicular cancer patients diagnosed in 1997–2008 and resident in the Province of Turin. Information was collected using mailed questionnaires in 2008–2011. Specifically, we asked for adult height (in cm), height at age 9 and 13 (compared to peers) and age at puberty (compared to peers). We also asked for paternal and maternal height (in cm) as indicators of genetic components of adult height. The analysis included 255 cases and 459 controls. Odds ratios (ORs) of testicular cancer were estimated for the different anthropometric variables. Adult height was associated with testicular cancer risk [OR: 1.16, 95% confidence interval (CI): 1.03–1.31 per 5-cm increase]. The risk of testicular cancer was only slightly increased for being taller vs. shorter than peers at age 9 (OR: 1.55, 95% CI: 0.91–2.64) or age 13 (OR: 1.26, 95% CI: 0.78–2.01), and parental height was not associated with testicular cancer risk. The OR for adult height was 1.32 (95% CI: 1.12–1.56) after adjustment for parental height. Among participants with small average parental height (<167 cm or less), the OR of testicular cancer for tall (>180 cm) vs. short (<174 cm) subjects was 3.47 (95% CI: 1.60–7.51). These results suggest that the association between height and testicular cancer is likely to be explained by environmental factors affecting growth in early life, childhood and adolescence.

What's new?
Adult height is known to be associated with testicular cancer risk. In this case-control study, the authors examined the extent to which this association is explained by height at various points in life, and also by parental height. They found that adult height is associated with testicular cancer risk, while parental height is not. These findings suggest that the consistently reported association between growth and testicular cancer is likely to be explained by the effect of environmental exposures.

Testicular cancer is the most frequent male tumour among young adults and has been increasing in incidence over the last few decades in many populations.[1] Its aetiology is still largely unknown. Cryptorchidism, family history, history of testicular cancer and ethnicity are established risk factors,[2] and prenatal exposures are likely to play a role.[3,4] Adult height has been repeatedly associated with an increased risk of testicular cancer. A recent meta-analysis estimated a 13% increase in risk with each 5-cm increase in adult height.[5] Indeed, height is at present the strongest potential risk factor for testicular cancer, in terms of the population attributable risk. However, height is considered to be affected by both environmental and genetic factors, and the possible explanations for the association between height and testicular cancer have not been fully investigated.[6,7] Adult height could be a proxy for genetic variants associated with the risk of testicular cancer or it could be a proxy for environmental exposures causing testicular cancer. Furthermore, these environmental exposures could act at different stages of life from the prenatal life to childhood and adolescence and it would be important to identify whether there are specific periods (for example, prenatal life or childhood) in which height-related environmental exposures could affect the risk of testicular cancer. In the attempt to distinguish between these pathways, in the EPSAM study, a case–control study carried out in the North of Italy, we explored the association between adult height and testicular cancer by considering information on parental height, as a proxy of possible genetic influences of growth, as well as on height in childhood and adolescence. Methods Study population Between 2008 and 2010 we conducted a case–control study on testicular cancer in the Province of Turin, Italy. Cases were identified from two sources, which together cover the population of the Province. For the first source we used the records of the regional Hospital Discharge Registry to identify and contact general practitioners (GPs) in the Province of Turin who have had at least one patient who received an orchiectomy (ICD-9 CM surgical procedure codes: 623-624) for testicular cancer (ICD-9 CM diagnostic code: 186) between 1997 and 2008 at ages 15–54 years. Through the 345 GPs who agreed to collaborate (81%), cases were contacted and asked to participate in the study. The second source of cases involved residents in the Province of Turin who were diagnosed with testicular cancer between 1997 and 2008 and were patients at the San Giovanni Battista Hospital, which is the main hospital of the city of Turin. Thus, we contacted case patients through their oncologist if they were patients at the San Giovanni Battista Hospital and through their GPs if they were not. Any identified patient who was not resident in the Province of Turin was excluded

from the study. Controls were also selected from these two sources, namely from residents in the Province of Turin admitted for other diseases at the San Giovanni Battista Hospital in the city of Turin (as controls for the cases identified through the hospital) and from the GP lists (as controls for the cases identified through GPs). We used this mixed design to increase the participation rates. In particular, we chose hospital controls for the hospital-identified cases to increase the response rate for this group of controls, and to make it similar to the corresponding group of cases. For each of the cases identified through their GP, we randomly extracted two controls from the GP lists, matching for year of birth and GP. Controls were invited via their GP to participate in the study. For each of the cases identified through the hospital we identified up to two controls frequency matched by year of birth and residence among patients admitted, on an inpatient or outpatient basis, at the San Giovanni Battista Hospital between 2008 and 2009. To reach relatively young patients and to include a mixture of diseases, we recruited these controls in several wards. In particular, patients were recruited at the ENT (ear nose throat) wards (47%), urology wards (24%), mainly including patients who underwent circumcision, lithotripsy unit (11%), blood bank outpatient ward (8%), gastroenterology outpatient ward (6%) and other wards of the hospital (4%). The study, therefore, is population-based (in that it aimed to recruit all cases occurring in the population of the Province of Turin during 1997–2008) and recruited cases and controls through two sources, namely through the main hospital of the Province and through GPs for cases who were not patients at the main hospital. As further described below, we conducted sensitivity analyses to explore the impact of this study design on possible bias. The response rates among subjects contacted through their GPs were 49% for cases and 40% for controls, whereas response rates among subjects contacted through the hospital were 82% among cases and 84% among controls. Thus, the overall response rate was 57% among cases and 48% among controls resulting in 274 cases and 467 controls who completed the study questionnaire. Among subjects contacted through their GP, respondents were born earlier than nonrespondents (2.0 years among cases, p50.03; 2.2 years among controls, p50.002), while had a similar proportion of residence in the city of Turin or the rest of the Province. Based on information from the histological reports, we restricted the study to germ-cell testicular cancers (14 cases of non germ-cell origin or spermatocytic seminomas excluded); we did not exclude 11 cases for whom we could not retrieve a copy of the histology report, as the majority of testicular cancer cases are of germ-cell origin. Finally, we excluded five cases and six controls who were not born in Italy. Exposure information Cases and controls completed a postal questionnaire focussing in particular on the pubertal period (namely 13 years of age), including hobbies, physical exercise and lifestyle. Questions included height and weight at different ages and age at puberty. Participants also donated a saliva sample using the Oragene™ kit for measuring genetic variants. The current analyses focused on height and growth. The questionnaire recorded information on height at age 13 compared to peers and height in adulthood in cm. Information was also available on age at puberty (age at starting shaving, age at voice change and age at reaching adult height—all compared to peers). It also included self-reported information on low birth weight (<2,500 g). At the end of the data collection, we decided to ask further questions to the study participants about their parents' height as well as their own height when they were attending elementary school (hereafter referred to as height at age 9). The rationale for these additional questions was as follows: (i) to use parental height as a proxy for genetic components of adult height and (ii) to have information on childhood height that was not affected by age at puberty onset (i.e., at age 9 instead of 13 years). Therefore, we recontacted all cases and controls between April 2011 and November 2011 by telephone, mail or email to obtain information on maternal and paternal height as well as height at age 9 years compared to peers. Those controls who had been initially identified through the hospital were recontacted only by mail because for these subjects we did not have information on their telephone number or email address from the first questionnaire. In total, 88% of cases and 75% of controls answered this second questionnaire. Statistical analyses We estimated odds ratios (ORs) for testicular cancer with corresponding 95% confidence intervals (CIs) using unconditional logistic regression. We broke the individual matching on GP, as using conditional logistic regression with a stratum for each GP would have resulted in severe loss of study power owing to incomplete strata in which either the case or the two controls did not participate. However, we did adjust in all models for the other matching variables, including year of birth (in 5-year periods), residence (city of Turin, rest of the Province of Turin) as well as for method of contact/identification of the study subjects (GPs or hospital). All models were also adjusted for cryptorchidism (self-reported as having been confirmed by a physician) and educational level (primary or secondary school, college and university degree). Two participants were excluded from the analyses because of missing educational level. It should be noted that matching on GP means matching mainly on residence and socioeconomic status. These two variables were adjusted for in our analyses. We analysed separately each of the three height variables (height at age 9, height at age 13 and adult height) as well as maternal and paternal height. We also estimated the effect of adult height after adjustment for maternal and paternal height, height at age 9 or age at puberty. Adult height was categorized into tertiles. Measures at ages 9 and 13 years were grouped into three categories (taller, same height and shorter than peers). The indicators of age at puberty were grouped into three categories (earlier, same and later than peers). For age at starting shaving, we included in the category of same age as peers three cases and six controls who reported that they did not need shaving. Maternal and paternal height were categorized into tertiles. As mentioned above, we checked for possible biases introduced by the use of two sources of controls by comparing results in key variables (adult height and cryptorchidism) in cases and controls identified and contacted through the hospital and cases and controls identified and contacted through the GPs. These sensitivity

analyses gave similar results in the two groups; the p value for interaction between method of contact and height was 0.75 and the corresponding p value for cryptorchidism was 0.93. Furthermore, analyses on the association of height with testicular cancer after one by one exclusion of each disease group from the pool of controls identified through the hospital did not reveal bias introduced by the choice of the diagnostic categories (data not shown). Thus, the two sources of study subjects were combined in all analyses, although, as just described, a variable for the method of identification/contact was always included in multivariable models. Further analyses were conducted to assess whether parental height modified risk estimates for adult height. For this analysis, we combined parental and maternal height into average parental height and created two categories using the observed median of average parental height (167 cm) as the cut-point. We then analysed the interaction between this variable and adult height categorized into tertiles. Results Some 255 cases and 459 controls were included in the analyses, of which 224 cases and 343 controls participated in the second round of questions on parental height and anthropometric measures at age 9 years. Table 1 summarizes the characteristics of the study participants. Cases and controls were similar in all reported characteristics except for prevalence of cryptorchidism, which was much higher among cases. As reported in Table 2, each increase in 5 cm in adult height was associated with a 16% (95% CI: 3–31%) increase in testicular cancer risk. We did not find evidence of association of height at age 9 and 13 years with testicular cancer risk, although the OR estimates were slightly increased for taller vs. shorter subjects. Notably, maternal and paternal height were not found to be risk factors for testicular cancer. We also found a positive association between low birth weight and risk of testicular cancer, although this was based on a small number of exposed cases and wide CIs. Table 3 reports the results for the different indicators of age at puberty. None of the indicators revealed a clear association with testicular cancer. In all further analyses we controlled confounding by age at puberty using age at starting shaving as the indicator of age at puberty, as this variable had the largest heterogeneity. Among controls, adult height increased by 3.7 cm for every 5-cm increase in average parental height ($p<0.001$; data not shown in tables). We also found that, among controls, an increase in 5 cm in average parental height was associated with height at age 9 (OR of being taller than peers compared with shorter than peers: 2.48, 95% CI: 1.67–23.68) and height at age 13 (after adjustment for age at puberty, the OR of being taller compared to shorter than peers was 2.71, 95% CI: 1.84–3.99). The results of the multivariable analyses on adult height adjusted by the different aspects of growth are summarized in Table 4. Adjustment for age at puberty and height at age 9 years had a marginal impact on OR estimates, whereas the positive association between adult height and testicular cancer risk changed after adjustment for parental height (OR of testicular cancer per 5-cm increase in adult height: 1.32, 95% CI: 1.12–1.56). There were only trivial changes in the estimates reported in Table 4 when low birth weight was also taken into account (data not shown in tables). Table 5 reports the results of the analysis on the effect modification of adult height introduced by parental height. The effect of having an adult height in the third tertile (>180 cm) compared to the first tertile (<174 cm) was larger for subjects with a parental height below the median (OR: 3.47, 95% CI: 1.60–7.51) than those with a parental height above the median (OR: 1.50, 95% CI: 0.88–2.55). Consistently we found an OR of testicular cancer of 1.31 (95% 1.12–1.54) for each 5-cm increase in the difference between adult height and average parental height (data not shown in tables). When analyses were stratified on median maternal height or median paternal height instead of median average parental height, results were similar to those reported in Table 5. Discussion In this study, we found that adult height, but not parental height, is associated with the risk of testicular cancer. Adult height has been associated with testicular cancer risk in a number of previous studies. In a recent metaanalysis of 13 studies, Lerro et al.[5] estimated a 13% increased risk of testicular cancer per each 5-cm increase in height. After the publication of the meta-analysis one further study from the United States found a similar effect of height on the risk of testicular cancer.[8] Our unadjusted estimate is very close to the results of the meta-analysis, but, in our study, the risk estimate increased to 32% after adjustment for parental height. Two Swedish studies investigated the effect of adjustment for birth weight on the association between adult height and risk of testicular cancer, finding no evidence of confounding. [7,9] We found similar results in our study, although it should be noted that we used retrospectively self-reported information on birth weight, which is likely to be inaccurate. However, the lack of confounding effect by birth weight is not unexpected as low birth weight is associated with only a weak increase in risk of testicular cancer.[4] In our study, we also considered age at puberty in the analyses. Age at puberty has been previously associated with the risk of testicular cancer, as reviewed in a recent metaanalysis, [10] and it is a determinant of growth and timing at growth. We did not find strong evidence of an association between the specific indicators of age at puberty and the risk of testicular cancer: the results on age at starting shaving are consistent with those reported in the recent meta-analysis, whereas the results on age at voice change are less consistent. However, if our results are added to those of the metaanalysis, the pooled estimates remain virtually unchanged: the relative risk for late age at starting shaving vs. same age as peers remains 0.84,[10] and the relative risk for late age at voice change increases from 0.87[10] to 0.88. Our study has two main limitations. First, some of the measures of height, especially those at ages 9 and 13 years, are likely affected by a large degree of nondifferential misclassification that might have contributed to the underestimate of the main effects as well as to residual confounding when the variables were treated as confounders. For example, we found that the effect of adult height was only marginally changed by adjustment for height in childhood; however, this could be explained by residual confounding owing to adjustment for a misclassified variable. In addition, there might be correlations among the sources of misclassification of the different variables (e.g., a person always over-reporting height), which can introduce

bias in an unpredictable direction. For adult and parental height, which were reported in centimetres instead of in comparison to peers, the level of misclassification is likely to be lower. Accordingly, we found a strong association between parental height and adult height, which magnitude is in line with studies with prospectively collected information.[11] The second main limitation of our study is connected with the relatively low participation proportion among cases and controls. A response rate of about 50% is not unusual in testicular cancer studies, which target young adults; nevertheless, it may be a potent source of bias. However, our study focussed on exposures that occurred in childhood and adolescence and these are unlikely to be directly associated with participation. As noted in the Methods section, although the study was population-based targeting the population of the Province of Turin, we recruited cases and controls from two sources, namely the San Giovanni Battista Hospital of the city of Turin and the GP lists for those cases who were not patients at San Giovanni Battista Hospital. We used this approach to increase the response rates, which, consistently, in our study was higher among cases and controls contacted through the hospital. We checked whether the use of the two sources could have had introduced bias in our results by comparing the OR estimates of testicular cancer for adult height and for cryptorchidism in the two subgroups (i.e., cases and controls chosen from the two sources). We found similar findings and, thus, always kept the two sources combined. Taken these limitations into account, this is, to our knowledge, the first study that has attempted to distinguish between the effect of parental height and the effect of adult height on the risk of testicular cancer. The former is likely to be primarily (but not exclusively) determined by genetic factors, whereas the latter is likely to be primarily (but once again not exclusively) determined by environmental factors. A recent study evaluated 15 height-related genetic variants in association with testicular cancer risk.[6] Two of them were associated with a 50% increased risk, and adjustment for these variants had little impact on the association between adult height and the risk of testicular cancer. Our study is consistent with these results, as it suggests that environmental components of growth acting throughout childhood are more important than genetic factors. Nutrition, infections, socioeconomic status, overcrowding and chronic diseases have all been suggested to affect growth,[11,12] but little is known about their effects on testicular cancer.[13–15] Our data suggest, however, that some of these factors could be important determinants of the lifetime risk of testicular cancer. On the basis of our results, we cannot conclude on whether these factors start acting already in early postnatal life, as results on height in childhood and the subsequent risk of testicular cancer, maybe due to misclassification, were not strong and CIs were quite large. In conclusion, these findings support previous evidence of a positive association between adult height and testicular cancer risk, and suggest that this association can be already seen in childhood. The association between growth and testicular cancer is likely to be explained by environmental factors affecting growth in the life course.

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Table 1. Characteristics of cases and controls

Characteristic	Cases, $N = 255$		Controls, $N = 459$	
	N	%	*N*	%
Year of birth				
1955–1959	47	18.4	101	22.0
1960–1964	35	13.7	67	14.6
1965–1959	45	17.6	73	15.9
1970–1974	55	21.6	92	20.0
1975–1979	48	18.8	78	17.0
1980+	25	9.8	48	10.5
Method of identification and contact				
General practitioners	170	66.7	308	67.1
Hospital	85	33.3	151	32.9
Residence				
City of Turin	100	39.2	201	43.8
Rest of the Province	155	60.8	258	56.2
Histology				
Seminomas	129	52.9		
Nonseminomas[1]	115	47.1	–	–
Missing	11	–	–	–
Educational level[2]				
Primary school or less	93	36.5	161	35.1
Secondary school	105	41.2	202	44.0
University degree	57	22.3	96	20.9
Cryptorchidism[3]				
No	226	88.6	445	97.0
Yes	29	11.4	14	3.0

[1] Including mixed germ-cell cancers.
[2] Primary school implies in total 8 years at school, secondary school implies in total 13 years at school (8 years of primary plus 5 years of secondary school).
[3] Cryptorchidism confirmed by a physician.

Table 2. Anthropometric variables and risk of testicular cancer

Characteristic	Cases *N* (%)	Controls *N* (%)	OR[1]	95% CI
Adult height (cm)	(253)	(456)		
<174	63 (24.9)	150 (32.9)	1.00	Ref
174–179	86 (34.0)	158 (34.6)	1.31	0.87–1.96
180+	104 (41.1)	148 (32.5)	1.62	1.08–2.44
Each 5-cm increase			1.16	1.03–1.31
Height age 13 compared to peers	(253)	(452)		
Shorter	40 (15.8)	86 (19.0)	1.00	Ref
Same	131 (51.2)	227 (50.2)	1.21	0.78–1.88
Taller	82 (32.4)	139 (30.8)	1.26	0.78–2.01
Height age 9 compared to peers	(224)	(343)		
Shorter	31 (13.8)	69 (20.1)	1.00	Ref
Same	118 (52.7)	169 (49.3)	1.58	0.96–2.62
Taller	75 (33.5)	105 (30.6)	1.55	0.91–2.64
Maternal height (cm)	(221)	(341)		
<160	54 (24.4)	72 (21.1)	1.00	Ref
160–165	119 (53.8)	184 (54.0)	0.90	0.58–1.39
166+	48 (21.7)	85 (24.9)	0.80	0.48–1.34
Per 5-cm increase	–	–	0.92	0.80–1.06
Paternal height (cm)	(221)	(337)		
<170	69 (31.2)	101 (30.0)	1.00	Ref
170–175	91 (41.2)	164 (48.7)	0.80	0.52–1.21
176+	61 (27.6)	72 (21.4)	1.25	0.76–2.04
Per 5-cm increase	–	–	1.03	0.90–1.18
Low birth weight (<2,500 g)	(236)	(412)		
No	219 (92.8%)	391 (94.9%)	1.00	Ref
Yes	17 (7.2%)	21 (5.1%)	1.37	0.69–2.71

[1]Odds ratio adjusted for residence, year of birth, cryptorchidism, method of identification/contact and educational level.
Abbreviations: OR: odds ratio; CI: confidence interval; Ref: reference.

Table 3. Indicators of puberty and risk of testicular cancer

Indicator compared to peers	Cases *N* (%)	Controls *N* (%)	OR[1]	95% CI
Age at start shaving	(252)	(456)		
Earlier	30 (11.9)	59 (12.9)	0.89	0.54–1.46
Same	152 (60.3)	262 (57.5)	1.00	Ref
Later	70 (27.8)	135 (29.6)	0.89	0.63–1.28
Age at voice change	(250)	(450)		
Earlier	21 (8.4)	38 (8,4)	0.99	0.56–1.75
Same	211 (84.4)	384 (85.3)	1.00	Ref
Later	18 (7.2)	28 (6.2)	1.13	0.60–2.12
Age at reaching adult height	(247)	(445)		
Earlier	32 (13.0)	50 (11.2)	1.22	(0.75–2.00)
Same	185 (74.9)	341 (76.6)	1.00	Ref
Later	30 (12.1)	54 (12.1)	1.05	(0.64–1.72)

[1]Odds ratio adjusted for residence, year of birth, cryptorchidism, method of identification/contact and educational level.
Abbreviations: OR: odds ratio; CI: confidence interval; Ref: reference.

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) of testicular cancer for adult height: multiple regression models[1]

Characteristic	OR (95% CI) unadjusted for growth variables	OR (95% CI) adjusted for a age at puberty indicators	OR (95% CI) adjusted for height at age 9 years	OR (95% CI) adjusted for parental height
Adult height (cm)				
<174	1.00	1.00	1.00	1.00
174–179	1.21 (0.77–1.91)	1.16 (0.73–1.84)	1.15 (0.72–1.83)	1.33 (0.82–2.13)
180+	1.79 (1.13–2.85)	1.77 (1.11–2.81)	1.84 (1.09–3.10)	2.26 (1.32–3.88)
Each 5-cm increase	1.21 (1.05–1.39)	1.20 (1.05–1.38)	1.23 (1.05–1.45)	1.32 (1.12–1.56)

[1]219 cases and 336 controls with complete information on adult height, height at age 9, age at start shaving and parental height. All ORs are adjusted for residence, year of birth, cryptorchidism, method of identification/contact and educational level.

Table 5. Odds ratios (ORs) and 95% confidence intervals (CIs) of testicular cancer for combinations of parental and adult height[1]

	Average parental height	
Adult height (cm)	Below median (167 cm or less)	Above median (>167 cm)
<174	1.00 (Ref) (cases: 40, controls:77)	0.97 (0.44–2.14) (cases: 12, controls: 30)
174–179	1.22 (0.68–2.17) (cases: 38, controls: 61)	1.20 (0.67–2.16) (cases: 34, controls: 61)
180+	3.47 (1.60–7.51) (cases: 27, controls: 16)	1.50 (0.88–2.55) (cases: 68, controls: 91)

[1]ORs are adjusted for residence, year of birth, cryptorchidism, method of identification/contact and educational level.