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Abstract
The aetiology of testicular cancer is largely unexplained. Research has mainly focused on prenatal exposures, especially to sex hormones, while less attention has been paid to exposures that may act also postnatally. As baldness has been previously associated with testicular cancer risk we focused on baldness and body hairiness, which are both associated with androgen activity . We used data of the EPSAM study, a case-control study on testicular cancer conducted in the Province of Turin, Italy, involving cases diagnosed between 1997 and 2008. Information was collected using mailed questionnaires. Analyses included 255 cases and 459 controls. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate testicular cancer risk among those who developed baldness and among those with body-hairiness. We found an inverse association between testicular cancer and baldness (OR: 0.67, 95% CI: 0.48-0.98) and body hairiness (OR: 0.78, 95% CI: 0.53-1.16), although the latter had wider confidence intervals The inverse association between baldness and testicular cancer is consistent with the results from previous studies. These results suggest that androgens activity may influence testicular cancer risk.

Introduction
Testicular cancer is a relatively infrequent tumor representing less than 2% of all malignancies in men, nevertheless it is the most common tumor among young males in Europe and North America (Forman et al. 2014). More than 90% of testicular tumors are germ-cell cancers, which are histologically classified into seminomas and non-seminomas. The incidence of testicular cancer has been steadily increasing over the last decades in several populations (Bray et al. 2006) for unknown reasons. There are few established risk factors of testicular cancer: age, geographical area, cryptorchidism, contralateral testicular cancer, height, family history and ethnicity (Richiardi et al. 2008). Testicular cancer is considered to originate from an impaired differentiation of germ cells during fetal life (Skakkebaek et al. 1987) and, accordingly, several studies have investigated prenatal and perinatal exposures in association with the risk of testicular cancer (Cook et al. 2010). As differentiation of germ cells is under hormonal control (Rajpert-de Meyts 2007; Sonne et al. 2009), exposures that affect the endocrinological framework during these periods have been deeply studied (Giannandrea et al. 2013). Less attention has been paid to the role of factors that may act also during postnatal life . Among these factors, baldness has been previously associated with a decreased risk of testicular cancer (Petridou et al. 1997; Trabert et al. 2011). Baldness is a well-documented surrogate of cumulative androgen activity and it has been studied in relation to

hormonal dependent neoplasia, such as prostate cancer (Amoretti et al. 2013). More specifically, androgen-dependent alopecia is the most common type of male pattern baldness and is characterized by recession of the frontal hairline. An absence of androgen-dependent alopecia is observed in patients with 5 alpha-reductase deficiency (Randall 2008; Randall et al. 2000), while levels of dihydrotestosterone (DHT), the 5 alpha-reduced metabolite of testosterone, are increased in balding areas (Sawaya & Price 1997). Thus, it is fairly well established that androgen-dependent hair loss results from the effect of DHT on androgen-sensitive hair follicles. Prenatal and postnatal androgens are possibly involved in testicular cancer aetiology. The fact that testicular cancer is hormonal dependent is supported by its rapid increase in incidence starting at pubertal age. In addition late age at puberty has been inversely associated with the risk of testicular cancer (Maule et al. 2012). Therefore puberty has been suggested to be an important window of susceptibility (Richiardi et al. 2007). Androgens are key players in the context of testicular pubertal change, as effector of the hypothalamic-pituitary-gonadal axis, and induce dormant spermatogonia to undergo meiosis and form spermatocytes (Rey et al. 2009). Thus our study focused on baldness, as a surrogate of androgens activity, in relation to testicular cancer. As an additional indicator, we also assessed body hairiness, that is known to be under the control of androgens. Physiologically, testosterone and DHT around puberty stimulate body hair growth, transforming villous follicles, that produce tiny hairs, into terminal ones, that form larger pigmented hairs. An absence of body hair is observed in patients who lack 5 alpha reductase (Randall 2008; Randall et al. 2000) and male hypogonadotropic hypogonadism, a postnatal disorder caused by impaired GnRH and testosterone release, is associated with diminished amount of body hair (Salenave et al. 2012). In addition, hirsutism, an excessive terminal body hair growth in women in a typical male pattern, is related to hyperandrogenemia (Mofid et al. 2012).

Material and Methods

Study design The EPSAM study is a population-based case-control on germ-cell testicular cancer diagnosed between 1997 and 2008 among residents of the Province of Turin, Italy. Full details of the study design have been described elsewhere (Richiardi et al. 2014). The study was approved by the local Ethical Committee and informed consent was obtained from each subject. To cover the population of the Province of Turin we identified cases from two sources. For the first source we used the records of the Regional Discharge Registry to identify and contact general practitioners (GPs) in the Province of Turin who have had at least one patients who received an orchiectomy (ICD-9 CM surgical procedures codes: 623-624) for testicular cancer (ICD-9 CM diagnostic code: 186) between 1997 and 2008 at ages 15-54 years.. In total, 345 (81%) of the identified GPs agreed to collaborate inviting the cases to participate in the study. Second source of cases included residents in the Province of Turin who were followed at the San Giovanni Battista Hospital (the main hospital in the city of Turin) for testicular cancer diagnosed between 1997 and 2008. Thus all subjects, irrespectively of the source, were resident in the Province of Turin at the time of diagnosis. Cases were contacted through their oncologist if they were patients at the San Giovanni Battista Hospital, or through their GPs if they were not. Information from the histological reports was used to confirm the diagnosis and restrict the study to germ-cell testicular cancers: 14 cases were excluded as they had a tumor of non-germ cell origin, a spermatocytic seminoma or a cancer in-situ. One case with missing histological information was included in the study assuming that the tumor was most likely of germ-cell origin. Controls were selected from the same two sources used to identify the cases, and according to a population-based principle. Specifically, for each case selected through his GP, we contacted up to two men randomly chosen from the list of the same GP, matching on year of birth and residence. For each case selected from the San Giovanni Battista Hospital, we contacted up to two patients admitted at the same hospital between 2008 and 2009 for non-neoplastic diseases unrelated to hormonal factors and infertility, frequency matched to cases on year of birth and residence. These controls were recruited from different wards: 47% from the ENT (Ear Nose Throat) ward, 24% from the urology ward, 11% from the lithotripsy unit, 8% from the

blood bank outpatients ward and 10% from other wards of the hospital. Between 2008 and 2010, cases and controls were asked to complete a postal questionnaire and to donate a saliva sample. Response rate was higher among the subjects identified through the hospital (82% for cases and 84% for control) than among the patients contacted through their GPs (49% for cases and 40% for controls).

Exposure assessment

The questionnaire focused mainly on lifestyles, hobbies, occupations and other exposures occurring specifically during puberty (i.e. at 13 years of age), as well as the main established or suggested risk factors for testicular cancer. The current study focuses on baldness and hairiness as surrogates of exposure to androgen levels. Participants were asked to report whether they had ever observed any natural hair-loss and, if so, to report the age at first hair loss. They were also asked about the level of hairiness on the chest and the back at age 18, using four categories, from none to very abundant hair.

Statistical methods

We used unconditional logistic regression to estimate odd ratios (ORs) and 95% confidence intervals (CIs) of testicular cancer, adjusting for the matching variables, namely year of birth (in 5-year groups), area of residence (City of Turin or the rest of Province of Turin) and method of contact/identification of the study subject (GPs or hospital). We broke the individual matching on GPs, as using conditional logistic regression would have resulted in a large number of incomplete strata and a consequent severe loss of study power. Individuals not born in Italy were excluded (5 cases and 6 controls). Analyses were also adjusted for age at diagnosis for cases and a comparable reference age for controls (randomly assigned on the basis of the cases' age-distribution) as well as educational level (junior high school or less, high school, university degree) and cryptorchidism (self-reported as having been confirmed by a physician). Two controls with missing information on educational level were excluded from the analyses. In additional analyses, we further adjusted for adult height and age at voice change (earlier, at same age or later than peers), which is an indicator of age at puberty. Age at voice change was preferred to age at start shaving, as measure of age at puberty, because the latter depends also on body hairiness. However, since height and age at puberty may be also indicators of postnatal hormonal exposure, to avoid over-adjustment we reported in the main analyses only results unadjusted for these two variables. We considered a lag time of 5 years for baldness, thus subjects who reported starting losing hair less than 5 years before the diagnosis for cases and the reference date for controls were considered as unexposed. This was introduced to avoid reverse causation from the disease and its treatment (Randall et al. 2000; Trüeb 2010) . In addition, since we interviewed cases up to 10 years after the diagnosis, their recall of the age at starting loosing hair could have been affected, in either direction, by the diagnosis of the disease if the two events were relatively close in time. The introduction of the lag time resulted in the reclassification of 12.5% of cases (n=33) and 13.5% of controls (n=13.5%) from exposed to unexposed status. In sensitivity analyses we excluded reclassified individuals as well as halved the lag time from 5 to 2.5 years In addition to ever baldness, we also assessed age at baldness (before diagnosis or reference date for the controls) using tertiles defined on the distribution of age at baldness among controls. For the analyses on body hairiness we generated a dichotomous variable combining chest hairs with back hairs (no reported hair on the chest and on the back vs at least sparse hair either on the chest or on the back). We finally analyzed the two variables jointly, mainly to compare subjects with both baldness and body hairiness with subject with none of them. Furthermore, in a sensitivity analysis we checked for possible biases introduced by the use of two sources of participants by comparing results in key variables (baldness and body hairiness) in cases and controls identified and contacted through the hospital and cases and controls identified and contacted through the GPs. All analyses were also conducted among seminomas and non-seminomas separately. In these analyses, mixed germ-cell tumors were categorized with non-seminomas. Analyses were performed using the software STATA 11.

Systematic review

Finally, to synthesize the evidence on the association between baldness and testicular cancer risk we made a systematic review looking for previous studies on baldness and testicular cancer through a PubMed search carried out on December 31, 2014. We used different combinations of the following terms: “testicular cancer”, “baldness”, “hair-loss”, “alopecia”. The PubMed search identified 104 articles, of which only two included information on association between baldness and testicular cancer. The references of a review on hormonal exposure and testicular cancer (Gianandrea et al, 2013) and references of the identified papers were scrutinized, but we did not find additional relevant articles.

Results

Overall, 255 testicular cancer cases (54% seminomas and 46% non-seminomas) and 459 controls were included in the analysis. Non-seminoma cases were on average 5 years younger at diagnosis (median age: 31 years) than seminoma cases (36 years). Selected characteristics of the study subjects are summarized in Table 1. Cases and controls had a similar educational level, while, as expected, the prevalence of cryptorchidism was higher in cases (11.4%) than controls (3.0%). As shown in Table 2, baldness up to 5 years before diagnosis/reference date was reported by 23.5% of cases and 31.8% of controls, corresponding to an adjusted OR of 0.67 (95% CI: 0.46- 0.98). Analysis on age at baldness and risk of testicular cancer showed an inverse association (p for trend: 0.01). Results were qualitatively similar for seminomas and non-seminomas although the association for ever baldness was stronger among seminomas (Table 2). Analysis on body hairiness and testicular cancer showed a lower risk of testicular cancer for having at least sparse body hair when compared to having no hair (OR 0.78; 95% CI: 0.53-1.16); (Table 3). Joint analysis of the two variables revealed that subjects who reported both baldness and body hairiness had a lower testicular cancer risk compared to subjects with not reported baldness and body hairiness (OR: 0.54, 95% CI: 0.31-0.92); (Table 4). Furthermore, the strength on inverse association with testicular cancer risk was similar between subjects who reported only baldness and subjects who reported only body hairiness. When we adjusted for height and age at puberty the OR estimates were only slightly changed: the OR for baldness was 0.71 (95% CI: 0.48-1.04), while the OR for lack of body hair was 0.79 (95% CI: 0.52-1.19). Both provisional exclusion of subjects reclassified after the introduction of a 5-year lag time between baldness and diagnosis of testicular cancer (or reference date for controls) and halving of this lag time from 5 to 2.5 years did not change the results more than marginally. Results for baldness and body hairiness were similar in subjects identified and contacted through their GP and those identified and contacted through the hospital (the p value for interaction with method of contact was 0.43 for baldness and 0.74 for body hairiness) The two studies identified in our systematic Pubmed search were conducted in Greece (Petridou et al. 1997) and in the USA (Trabert et al. 2011). The Greek study included 97 cases and 198 controls, while the US study had 187 cases and 148 controls. Both studies analysed self-reported baldness, using the HamiltonNorwood scale to assess the pattern and the amount of hair loss. They both found an inverse association between baldness and testicular cancer risk. The Greek study reported results for the different grades of the Hamilton-Norwood scale compared with non-bald men. To enhance comparability, we used the data reported in the Table of the manuscript to calculate an OR for baldness vs no baldness: OR= 0.45 (95% CI:0.25-0.79). The US study, instead, calculated an overall OR for baldness and testicular cancer finding an OR of 0.60 (95% CI: 0.40-1.00) .When these two results were combined with our estimate we obtained a fixed-effect pooled OR of 0.59 (95% CI: 0.45-0.78). We used the same approach to estimate pool ORs stratified by histological subtypes, obtaining a pooled OR of 0.66 (95% CI: 0.46-0.93) for seminoma and a pooled OR of 0.54 (95% CI: 0.37-0.77) for non seminoma.

Discussion

In our study we found that self-reported baldness is inversely associated with testicular cancer. This result is consistent with a US and a Greek study previously conducted on this topic. Indeed all three studies found an inverse association between baldness and testicular cancer, even though they were

conducted in three different countries Also our finding of an inverse association between age at baldness and risk of testicular cancer is consistent with the results of the US study (Trabert et al. 2011), while the Greek study did not analyze age at baldness(Petridou et al. 1997). Finally, the inverse association that we found between body hairiness and testicular cancer is consistent with the results on baldness. This is further supported by the results of the analysis considering baldness and body hairiness jointly. In analysis stratified by histological subtype we found that inverse association between baldness and testicular cancer was stronger among seminomas, while previous studies showed an inverse association stronger among non seminomas. These differences are likely due to a limited power for stratified analysis. However in our study and in the previous two studies results on seminoma and non seminoma were qualitatively similar. This is also strengthened by consistency of pooled estimates stratified by histological subtypes. Our study has two main limitations. First, exposure information was self-reported. In particular, the questionnaire used to collect data did not include in the questionnaire the pictorial Hamilton-Norwood Scale to assess the stage and the pattern of baldness. The lack of information about pattern and the amount of baldness narrowed our analytic capability, allowing us to detect only an effect of overall baldness. Bald patterns might be of importance; for example a recent metaanalysis of seven case-controls studies totaling 8,994 patients with prostate cancer suggested that only vertex pattern baldness is associated with prostate cancer risk (Amoretti et al. 2013). However, the previously conducted US study on baldness and risk of testicular cancer, which obtained information using the Hamilton-Norwood Scale, did not find heterogeneities among bald patterns and relied on ever baldness (all patterns combined) for the main analyses. The second main limitation of our study is related to the low participation proportion among cases and controls. Low response rate (about 50%) is not unusual in testicular cancer studies, which target a young population; nevertheless it could be a source of bias. However our study focuses on exposure variables that are unlikely to directly affect participation and/or acted several years before interview. As noted above , to increase the response rate, we have contacted the cases and controls through two approaches, the hospital and the GPs. We checked whether the use of the two approaches could have had introduced bias by comparing OR estimates of testicular cancer for baldness and body hairiness in the two subgroups and we found no evidence of heterogeneity. Taken these limitations into account, our results suggest an effect of androgen activity on the risk of testicular cancer. We cannot determine if the major role is played by exogenous hormones, endogenous hormonal levels, hormonal metabolism or individual sensitivity to hormones. All four components could play a role and , more broadly, baldness may represent a proxy of the overall androgen status considered as the result of all these components. For example a meta-analysis (Zhuo et al. 2012) found an association between androgenic alopecia and a polymorphism of the androgen receptor gene (locus Xq11-q12), suggesting that baldness is also related to individual sensitivity to androgens. Indeed there are important ethnic differences both in the androgen status and in the incidence of testicular cancer further suggesting that there is a complex interplay between the different components. For what concerns the genetic factors, it should be considered that our study was carried out in a Caucasian population and men born outside Italy were excluded from the analyses The suggested inverse direction of the association between postnatal androgen status and risk of testicular cancer complements what has been proposed for prenatal anti-androgen exposures.(Rajpert-de Meyts & Hoei-Hansen 2007). It has been postulated that testicular cancer development is associated with endocrine abnormalities during prenatal life; in particular to conditions and exposures that affect gonocytes differentiation, which is considered to be under control of sex hormones, especially androgens (Skakkebaek et al. 1987). Parallely, during puberty, androgen activity induces dormant spermatogonia to undergo meiosis and form spermatocytes. Thus even exposures that influence the sex hormonal status during puberty could affect testicular cancer risk. This qualitative consistency between androgen status in fetal life and in postnatal life in relation to testicular cancer is of interest and would suggest that there are different windows of susceptibility during lifetime (Richiardi et al. 2007). Consistently the degree of androgen-status (low or high) during windows of susceptibility could affect testicular cancer risk.

Nevertheless, we cannot exclude that our indicators are simply proxies for androgen exposure during the prenatal period. Indeed, sensitivity to androgens is an inherited trait that modulates response to androgens throughout life, even prenatally, and androgens circulating in maternal blood during pregnancy are produced by the fetus, and it is likely that there is a positive correlation between production of endogenous androgens in fetal and postnatal life. In conclusion, our results support previous evidence of inverse association between baldness and testicular cancer and suggest a link between surrogates of postnatal androgen status and risk of testicular cancer. Additional studies of endogenous hormone activity are warranted in order to evaluate any causal role of androgen sensitivity, androgen levels and androgen metabolism in testicular cancer aetiology.

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