THREE AUTHORS REPLY

Patterns of occurrence, clinical behavior, tumor histology, and chromosomal complement distinguish 3 groups of germ cell tumors that occur in the testis: teratomas and yolk sac tumors in the very young, spermatocytic seminomas in the elderly, and seminomas and nonseminomas in adolescent boys and young men, which are referred to as testicular germ cell tumors (TGCTs) (1). We investigated whether seminoma and nonseminoma subtypes of TGCTs that occur in adolescents and young men are likely to have distinct etiologies (2). We used a case-only method that utilized etiologic information from patients with 2 primary tumors and was first described by Colin Begg (3). Inference was based on odds ratio estimates of concordance of candidate subtypes among paired tumors, with values exceeding 1.0 expected in the presence of etiologic heterogeneity. After we accounted for age at first diagnosis, we found no association between seminoma and nonseminoma subtypes in 488 men with 2 primary TGCTs (odds ratio = 1.09, 95% confidence interval: 0.71, 1.70). Dr. Begg cautions that interpretation depends upon the period in which the two cancers occur. This requires confidence that the 2 tumors are biologically independent: Second tumors should be true primaries rather than unrecognized metastases and should not have been caused by treatment of first tumors. Anatomic patterns of TGCT metastasis and TGCT treatment practices suggest that most paired primary TGCTs are likely to be biologically independent. We therefore interpreted the null association between histology of first and second TGCTs as being consistent with seminoma and nonseminoma subtypes that share major risk factors.

We appreciate the interest of Drs. Stang and Rusner in the interpretation of this result. We concur that the reported standardized incidence ratio estimates of 10–20 indicate that the risk of a second TGCT among men with a first TGCT is far greater than risk of a first TGCT among men in the general population. However, the standardized incidence ratio compares risk between 2 types of populations (men with a TGCT and men in the general population). We do not regard the differing risk between such populations as contradicting the passage from Dr. Begg’s 2010 report that was cited (“the probability of occurrence of a first cancer in an individual [is] the same as the probability of a second cancer, given the occurrence of the first cancer” (3, p. 937)), because the passage refers to risks of first and second tumors in an individual. This point is emphasized in the sentence that immediately follows in Dr. Begg’s original report: “The idea here is that the cancer risk of any individual is approximately constant over the period in which the two cancers occur” (3, p. 937).

Stang and Kuss previously addressed the etiologic heterogeneity of TGCTs (4) in a systematic review followed by quantitative analysis of epidemiologic studies wherein risk factor associations were estimated separately for seminoma and nonseminoma subtypes. These authors concluded that the results, based on 1,148 estimates, do “not support the hypothesis that risk ratio estimates for seminoma and nonseminoma differ” (4, p. 477). Therefore, the most comprehensive study addressing measured risk factors in relation to etiologic heterogeneity of TGCTs (4) accords with our study addressing the same question based on men with 2 primary TGCTs (2). Although the tendency for nonseminoma to be diagnosed approximately 10 years earlier than seminoma remains to be explained, we postulate that subtypes may progress at different rates or that the histological fate of TGCTs may be influenced by age-related processes.

Because TGCTs in adolescents and young men are regarded as a tumor group distinct from teratomas and yolk sac tumors in the very young (1), tumors in the very young were not included in our case-only analysis (2). We agree with Drs. Stang and Rusner that differences between these tumor groups may indicate distinct etiologies, but such differences do not influence our inferences regarding the etiology of seminoma and nonseminoma of adolescents and young men.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCES


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DOI: 10.1093/aje/kwu042; Advance Access publication: March 19, 2014