Unusual Features of Thyroid Carcinomas in Japanese Patients with Werner Syndrome and Possible Genotype–Phenotype Relations to Cell Type and Race

Werner syndrome (WS) (MIM#277700) is an uncommon autosomal recessive disease whose phenotype includes progeroid features, constitutional genetic instability, and an elevated risk of selected neoplasms including thyroid carcinoma.1,2 In their recent article3 Ishikawa et al. suggested that the different spectrum of mutations in the WS gene (WRN) in Japanese WS patients may confer a higher risk of thyroid carcinoma, and that N- and C-terminal WRN mutations may favor papillary or follicular thyroid carcinoma histology, respectively. These suggestions are intriguing but recent results suggest they are unlikely to be correct.

Both of these suggestions assume that different mutant WRN alleles encode truncated mutant proteins that retain different amounts or combinations of WRN nuclease and RecQ helicase consensus domains although lack a C-terminal nuclear localization signal.4 However, recent results from our laboratory in Seattle and the laboratory of Dr. Ishikawa’s colleagues at the AGENE Research Institute in Kanagawa5 indicate that WS patient cell lines lack detectable mutant protein by two different criteria. These analyses included Japanese mutations 4 and 6, which together represent 80% of the WRN mutations identified in Japanese WS patients (unpublished data).5 Thus many (and perhaps all) WS-associated WRN mutations are likely to be functionally equivalent null alleles. These results make it unlikely that a different spectrum of WRN mutations alone explains the elevated risk of thyroid carcinoma in Japanese WS patients. However, the consistent absence of WRN protein from WS patient cells could both favor and partially explain the development of thyroid carcinomas with follicular or anaplastic, as opposed to the more common papillary, histology. These issues should be clarified further when more is known regarding WRN function and genetic modifiers of WRN functional pathways in human somatic cells and in animal models of WS.

A second issue, related to Table 4 in the article by Ishikawa et al.3, is that a Web-accessible, locus specific mutational database for WS-associated WRN mutations currently is available. This database, established as part of the HUGO Locus-Specific Mutational Database Initiative, updates and corrects some of the data presented in Table 4 and includes additional WRN mutation and polymorphism data. The database uses a systematic nomenclature to describe WRN mutations and polymorphisms and is cross-referenced and linked to Web sites for the Human Gene Mutation Database and Online Mendelian Inheritance in Man. There also is a link to the International Registry of Werner Syndrome at the University of Washington, where WS diagnostic and pathology consulting assistance can be obtained. The URL for the WRN Mutational Database is http://www.pathology.washington.edu/werner/.
REFERENCES


Author Reply

Our report concerned peculiarities in the epidemiologic distribution of thyroid carcinoma, which occurs excessively among Japanese but not white patients with Werner syndrome (WS). In addition to the difference by race, there are differences by age (younger patients), gender (fewer females), and cell type (much more follicular) in WS patients compared with a registry for thyroid carcinoma in the general population of Japan. All four follicular thyroid tumors studied had germline mutations in the C-terminal region, and the single papillary tumor studied was in the N-terminal region, possibly a genotype-phenotype relation.

Based on three studies that were unavailable to us at the time of our study because the reports were not yet published, Dr. Monnat states that “...many (and perhaps all) WS-associated WRN mutations are likely to be functionally equivalent null alleles.” Therefore, it is “unlikely that a different spectrum of WRN mutations alone explains the elevated risk of thyroid carcinoma in Japanese WS patients.”

The speed of progress in molecular genetics rapidly can change the interpretation of durable clinical data, a foundation of our study. Until the functions of wild and mutant WRN proteins are understood fully, we keep open the possibility that different mutations may cause different phenotypes. The recently announced website for WRN mutations cited by Monnat should speed the resolution of these and other questions from clinical data regarding WS.

Yuichi Ishikawa, M.D.
Haruo Sugano, M.D.
Department of Pathology
The Cancer Institute
Tokyo, Japan
Robert W. Miller, M.D.
Genetic Epidemiology Branch
National Cancer Institute
Bethesda, Maryland
Makoto Goto, M.D.
Tokyo Metropolitan Otsuka Hospital
Tokyo, Japan

A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides

In a recent study, Hardell and Eriksson\(^1\) found a nonsignificant association between their study subjects’ reported use of glyphosate and non-Hodgkin lymphoma. The authors interpreted this result conservatively due to the low prevalence of reported glyphosate use among study subjects (4 cases and 3 controls) and other methodologic limitations of their study. However, they considered the association worthy of concern, citing the following toxicologic findings for glyphosate: excess mutations and chromosome aberrations in studies of mouse lymphoma cells,\(^2–5\) excess sister-chromatid exchanges (SCEs) in cultures of human lymphocytes,\(^6\) and a somewhat increased incidence of various cancers in one carcinogenicity study of mice.\(^7\)

Hardell and Eriksson’s summary of the relevant toxicology data included six studies, five of which did not use glyphosate as the test material.\(^2–5,7\) In these studies the test material was sulfosate, the trimesium salt of glyphosate. Sulfosate has a somewhat different toxicology profile than glyphosate. Nonetheless, it is worth pointing out that the U.S. Environmental Protection Agency (EPA) considered the mouse lymphoma findings\(^2–5\) to be false-positives due to sulfosate’s acidity; sulfosate was not mutagenic in this assay when the pH was adjusted to a physiologic level.\(^6\) Also, the EPA characterized the sulfosate mouse carcinogenicity study\(^7\) as showing “...no evidence of carcinogenicity...at the doses tested” and classified sulfosate...
as category E (no evidence of carcinogenicity in humans). 8

Hardell and Eriksson did not address the weight of evidence for glyphosate that is contrary to their view. The one glyphosate toxicology study cited 6 showed a weak positive SCE finding in human lymphocytes in vitro. This study had many limitations, and numerous, more specific mutagenicity assays have not shown positive results for glyphosate. 9 Extensive reviews of the available toxicologic data have been completed recently by the EPA 10,11 and the World Health Organization. 12 These agencies concluded that glyphosate is not mutagenic or carcinogenic. The EPA classified glyphosate as category E. 10,11

Finally, we note that the exposure classification methodology used by Hardell and Eriksson, based on study subjects’ reported glyphosate use, is not likely to be meaningful. Agricultural or residential uses do not result in appreciable inhalation exposure due to glyphosate’s extremely low vapor pressure. Exposure opportunity is almost exclusively through dermal contact. Glyphosate, however, has been shown to have very low skin penetrability in experimental studies. 13 A study of forestry sprayers by Lavy et al. found indications of significant dermal exposure but no indication, based on biomonitoring, of an absorbed dose of glyphosate. 14 This raises the question of whether reports of glyphosate use, even if accurate, indicate any meaningful exposure.

REFERENCES
7. Pavkov KL, Turnier JC. Two-year chronic toxicity and ongo-
an odds ratio of 3.04 and a 95% confidence interval of 1.08–8.52 (there were 8 exposed cases and 8 exposed controls) (Hardell et al., unpublished data). In a multivariate analysis of exposure to different herbicides, we still found an increased risk for glyphosate.

The fact that regulatory agencies do not classify glyphosate as a human carcinogen is expected because of the obvious lack of published epidemiologic studies of humans so far. Certainly interpretation of epidemiologic results needs to be discussed, and obviously there is a need for further studies of glyphosate and the development of lymphoma.

REFERENCES