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Editorial

Why Y? Downregulation of Chromosome Y Genes Potentially Contributes to Elevated Cancer Risk

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On average, men die earlier than women (1). Although differences in environmental, lifestyle, and exposure factors certainly explain some of the earlier mortality of men, recent population-based genomic investigations suggest somatic mutations could also influence this reduced overall life expectancy of men. In particular, an expanding body of evidence suggests somatic loss of the sex-determining Y chromosome, referred to as mosaic loss of Y (LOY), might be an important biomarker for elevated mortality rates among men, perhaps indirectly or through events on the Y chromosome itself (2,3). LOY is the most common copy number alteration in male leukocytes and is characterized by a mosaic mixture of normal cells with one copy of the Y chromosome and mutant cells with loss of the entire Y chromosome (4). LOY detected in peripheral leukocytes has been associated in early studies with hematologic malignancies (5,6) as well as nonhematologic disorders, including solid tumors, Alzheimer's disease, and cardiovascular disease (2,7–11). However, further larger studies are needed to confirm these reports.

Although many observational studies suggest a connection between LOY and cancer as well as other chronic diseases, little is known concerning the biological mechanisms in which loss of the Y chromosome in leukocytes or other tissues might confer elevated risk of disease. The Y chromosome has been characterized as a genetic wasteland with many highly repetitive elements that are slowly eroded over evolutionary time (12). Relative to the X chromosome and other autosomes, the Y chromosome has a low gene census, and most genes have been directly related to sex development or spermatogenesis. Determining exactly which chromosome Y genes, when deleted, might be of importance for cancer risk has emerged as an active area of scientific investigation. In this issue of the Journal, Cáceres et al. (13) seek to shed light on this gap in knowledge by investigating downregulation of chromosome Y gene expression as a potential predictor of cancer risk and as a possible mediator of the relationship between LOY and cancer risk.

Cáceres et al. (13) conducted an integrated investigation including 371 men across 47 tissues from Genotype-Tissue Expression gene-expression data, 12 cancer studies with tumor and normal tissue expression from The Cancer Genome Atlas (TCGA), and additional independent studies in an effort to explain the biological effects of reduced chromosome Y gene expression in a variety of tumor and normal tissues. They constructed a novel approach for defining and detecting what they have termed "extreme" downregulation of chromosome Y (EDY) gene expression using transcriptomic data from RNA-sequencing or expression microarrays. Specifically, the authors defined EDY as substantial overall downregulation of chromosome Y gene transcripts relative to autosomal genes. They identified a cross-tissue effect in which men with EDY in a single tissue were more likely to have EDY in another. An analysis in tumor and normal tissues from 12 TCGA cancer sites identified an association between EDY and cancer both overall and across age strata. Additional analyses suggest a stronger association between EDY and cancer than between LOY and cancer, with EDY mediating an estimated 49% of the age-adjusted association between LOY and cancer status. There was high agreement between EDY and LOY in both normal and tumor tissue across all cancer studies (mean = 87%); however, the imperfect correlation suggests that biological correlates independent of LOY such as *EGFR* copy number and methylation across Y might influence EDY. EDY was found to be more common than LOY in nondiseased Genotype-Tissue Expression tissue, suggesting measuring EDY could have utility in disease association analyses independent of LOY. Likewise, in TCGA, EDY displayed stronger associations with cancer than LOY in three different approaches, namely, cross-cancer meta-analyses, Bayesian network analyses, and mediation analyses. Because EDY explains more of the variability in cancer than LOY, a functional relationship could exist in which LOY precedes EDY, and therefore EDY could potentially serve as a functional and measurable intermediate of the relationship between LOY and cancer. While an association was observed between LOY and age, no association was observed between EDY and age.

Transcription analyses of TCGA tumor samples identified genes, such as *DDX3Y*, *EIF1AY*, *KDM5D*, *RPS4Y1*, *UTY*, and *ZFY*,

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that were statistically significantly downregulated across cancer sites and explained 89% of the variability of EDY. These genes are interesting from a cancer perspective because they have functional roles in cell cycle regulation and have chromosome X homologues that escape X-inactivation. These X homologues have been implicated in male-based loss of function in several cancers, suggesting a potential tumor suppressor role of these genes when transcription levels are depleted.

Cáceres et al. (13) provide preliminary insights into EDY as a possible mediator for the relationship between LOY and cancer risk and highlights relevant chromosome Y genes that could be of key importance for cancer risk. Future in vitro and in vivo functional investigation of these genes will be instrumental in better understanding potential etiologic roles in cancer initiation. In addition, carefully designed follow-up studies are needed to ensure a direct functional relationship between EDY and cancer, rather than the observed association possibly being driven by confounding effects of environmental exposures (eg, smoking) or germline susceptibility variants that are risk factors for both EDY and cancer.

EDY is one of many potential biologic mechanisms that could functionally explain observed associations between mosaic LOY and cancer. Evidence from genome-wide association studies suggests mosaic LOY serves as a correlated proxy for poor inherited DNA damage repair capacity and reduced cell cycle checkpoint control that could result in elevated cancer risk (7,14). Additionally, LOY could be a marker of immune dysfunction such that individuals with poor immune surveillance might be at increased cancer risk (4). In light of these possibilities, Cáceres et al. (13) present strong evidence for EDY as an exciting new avenue of investigation for cancer research and suggest measuring EDY could have added utility in determining cancer risk over DNA-based measures of mosaic LOY.

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