Editorial

Loss of Chromosome Y in Leukocytes and Major Cardiovascular Events

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It has been observed for centuries that men have a shorter lifespan than women. The current difference globally is on average 4 years, and the difference is even larger in populations with longer life expectancy, for example, ≈6 years in the European Union and 7 years in Japan.[1] A larger difference in populations with higher longevity suggests that the underlying factors are stronger in populations with a large part of the mortality related to age-associated diseases. Cardiovascular diseases are the leading causes of death globally and are increasing.[2] The share of total mortality that is because of cardiovascular diseases is similar in both sexes, but men fall ill and die from it at a younger age. Cardiovascular disease risk factors are equally important for men and women.[3] Hence, the age differences in incidence and mortality between men and women are because of other reasons than differential environmental risk factor exposures. Recent discoveries on pathological effects from a male-specific genetic risk factor—loss of chromosome Y (LOY) in blood cells—can partly explain the observed sex difference in longevity. Analyses by Haitjema et al[4] in this issue of *Circulation: Cardiovascular Genetics* describe a previously unknown association between LOY in blood cells and major cardiovascular events.

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A high prevalence of LOY in hematopoietic cells of aging men was first described >50 years ago.[5] Currently known risk factor for LOY include age, smoking, and genetic background. For example, the prevalence of LOY increase with age, and up to 20% of normally aging men >80 years of age are affected.[6–8] These results show that LOY is the most common acquired human mutation during life in normal peripheral blood of men, and it is affecting ≈1.6% of the human genome.[9] Current smokers have up to 4-fold risk to carry blood cells without a Y chromosome compared with nonsmokers,[10] and recent genome-wide association studies have identified 19 loci associated with risk for LOY, including genes important for cell proliferation and cell cycle regulation.[7,8]

Although described as a frequent somatic event already in the early days of cytogenetics, LOY was long considered phenotypically neutral and related to normal aging.[11,12] Recent analyses, however, suggest the opposite that LOY in blood cells could be involved with disease processes taking place in various organs. For example, LOY affecting the leukocytes has been found to be associated with increased risk for all-cause mortality, as well as nonhematologic cancer incidence and mortality.[13] Analyses of LOY in blood of men diagnosed with colorectal or prostate cancer[14] or testicular cancer[15] found that patients on average had higher levels of LOY in the blood cells compared with controls. Interestingly, the latter study describes that the level of LOY mosaicism was not different between cases and controls in another testicular cancer cohort and that studied DNA sampled from buccal tissue. This implies that an increased risk for solid tumors in various organs associated with LOY could be related to functions performed by the cells in the peripheral blood (ie, cells of the immune system), as further discussed below. Another important conclusion is that LOY seems to be an important risk factor for cancer also in younger men and not only in elderly because testicular cancer affects younger men.

A critical question is how LOY in leukocytes could be associated with risk for different forms of cancer that develops in various tissues and organs. One hypothesis is that disrupted immune system functions, normally performed by blood cells, might lead to increased risk for neoplastic development in other organs.[1,6,9,10,13] An important function of the immune system is immunosurveillance.[16] If LOY in blood cells leads to impaired immunosurveillance, we would expect that the defense against other types of disease than cancer would also be compromised by LOY in blood cells, and in fact, such associations have been reported. For example, LOY in peripheral blood has been found to be associated with a 6-fold increased risk for incident diagnosis of Alzheimer disease (AD) during follow-up,[6] more than twice as large risk increase than that of the previously known risk factor *apolipoprotein E* genotype. Further analyses showed that the increased risk for AD from LOY was independent from the increased risk for AD associated with age. Interestingly, a deficient immunosurveillance in the central nervous system, which normally eliminates abnormal cells related to an AD phenotype in the brain, has previously also been proposed as a mechanism in AD development.[17–19] Furthermore, LOY in blood cells has been suggested to be involved in autoimmune conditions, such as autoimmune thyroiditis[20] and primary biliary cirrhosis.[21]

The current results presented by Haitjema et al[4] suggest that LOY affecting the immune cells in blood could mediate a 2-fold risk for secondary major cardiovascular events during

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follow-up in men after carotid endarterectomy. This result further strengthens the hypothesis that LOY in leukocytes could cause a reduced ability to fight disease process that takes place in various tissues and organs. Hence, the reduced immune function in leukocytes with LOY could possibly help explain the increased neoplastic proliferation of cells into tumors in the entire body, the increased neurodegenerative processes in the central nervous system leading to AD development, as well as a higher risk of major cardiovascular events. Emerging data now suggest that LOY in blood cells is associated with all major causes of death among men in aging human populations. Hence, as a male-specific genetic risk factor, LOY might help explain why men live shorter lives than women. It is possible that LOY testing of middle-aged men could lead to better risk prediction and greater potential for preventive measures. It is also possible that further research into LOY mechanisms may lead to better understanding of cardiovascular disease in the hope of more effective preventive treatments.

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