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DISEASE & ILLNESS

Are Persons with Down Syndrome Protected Against Some Forms of Cancer?

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Down syndrome (DS), or Trisomy 21, is defined by an extra copy of chromosome 21 in all cells. In humans there are normally 2 copies of each of 23 chromosomes for a total of 46 in each cell; in DS there are 47.

An extensive review of literature available in 1998 showed that the distribution of cancer in DS is quite different than in the general population (GP). A number of epidemiological studies identified then, or published since, have confirmed that DS is associated with a marked increased risk of leukemia. Increased risks of incidence of or mortality from lymphomas and a few solid tumors have also been reported. On the other hand, a number of studies have suggested that other solid tumors are less common in persons with DS than in the general population. A potential DS-related protective effect against some cancers has been suggested, and this has encouraged a number of studies of a possible genetic mechanism of tumor suppression related to DS.

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Evidence on which tumors may be over- or under-represented in DS is mixed. Ten studies reviewed in Sasco et al. (*International Journal Disabil Hum Dev.* 2008;7[4]:415-422) reported risks of incidence or mortality for various cancers among persons with DS. Compared to the general population, risk of mortality or incidence of leukemia was 10 to 30 times higher in DS. Solid tumors over-represented in DS included testicular (2 to 13 times more common) and liver (2 to 7 times more common) cancers. Lung (0.2 to 0.5 times as common) and breast (0.4 to 0.6 times as common, and in one study no cases were observed) cancers were under-represented. No cases of oral cancer in DS were observed in any of the studies reviewed. For most solid tumor sites, however, the results were not statistically significant.

Lower numbers of lung or oral cancer deaths are not surprising and are probably due in part to a lower incidence of smoking among persons with DS. A similar pattern has been observed in other populations of developmentally disabled persons, including cerebral palsy. Breast cancer may be underrepresented partly due to lower levels of estrogen in persons with DS.

In a study of death certificates in the US, Yang et al. (*Lancet.* Mar 23 2002; 359 [9311]:1019-1025) found that persons with DS were underrepresented when solid tumors were listed as the cause of death. They compared DS deaths due to solid tumors with deaths in the general population by way of an epidemiological measure called the standardized mortality odds ratio (SMOR), reporting SMORs ranging from 0.0 to 3.2 depending on the specific tumor. Most solid tumor SMORs fell in the neighborhood of 10 percent. However, the authors rightly cautioned against interpreting this as an indication that these tumors are actually less common in DS, noting that "[SMORs] for cancer in people with Down's syndrome could be falsely reduced if the rate of cancer mortality is unchanged but the death rate for other medical conditions—eg, dementia—is greatly increased." And it is well known that death rates for a number of other medical conditions, including dementia, are indeed greatly increased in DS. Another potential source of bias in the analyses of Yang et al. is that for persons with DS who died of cancer, DS may not be noted on the death certificate. This would presumably occur if DS were not considered to have contributed to the underlying cause of death. Though this would be unlikely in the case of deaths due to leukemia (which has long been known to be more common in DS), it might be quite likely in the case of deaths due to solid tumors not considered to be related at all to DS. Thus the number of cases of deaths due to solid tumors in DS may be substantially underrepresented in this study.

A number of studies have investigated the possible tumor suppressing effects of some of the genes located on chromosome 21, the idea being that because persons with DS have extra copies of these genes in their cells, this may explain their reduced risk of development of or death from certain solid tumors. One of these genes in particular, Down syndrome candidate region 1 (DSCR1, also called RCAN1), has been shown to modulate the development of vascular endothelial growth factor (VEGF), which is critical for the development of new blood vasculature in

normal cells as well as in tumor cells. The results of studies of the effect of this gene, and its various isoforms, have been mixed.

In a study published last month in *Nature*, Baek and colleagues reported on the potential protective effect of one isoform of DSCR1 based on experiments with mice (*Nature*. 25 June 2009 2009;459:1126-1131). Of note is that Baek et al. cite Yang et al. as evidence that in DS, "the mortality from cancers was 10 percent of expected." As noted above, however, this 10 percent figure for overall solid tumor mortality in DS is not supported by any study of cancer mortality in DS, not even the study of Yang et al.

Conclusion: The pattern of cancer incidence and mortality in DS is certainly very different than in the general population. Leukemia is far more common in DS than in the general population, and lymphomas appear to be more common as well. Among solid tumors, testicular cancer and liver cancer occur somewhat more frequently in DS, while breast cancer, lung cancer, and possibly oral cancer and urological tumors occur somewhat less frequently (though not by as much as Yang et al.'s study might seem to suggest). With respect to other solid tumors, the question remains open, probably because rates of incidence and of mortality are not much different from those of the GP. Researchers continue to explore the possible DS genetic connection with the growth of certain solid tumors and many are confident that this will lead to improvements in the prevention and treatment of cancer in DS and in the general population. To facilitate this work, precise analyses of epidemiological evidence will be very important.

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