Solid Malignancies in Individuals With Down Syndrome: A Case Presentation and Literature Review

Scott V. Bratman, MD, PhD; Kathleen C. Horst, MD; Robert W. Carlson, MD; and Daniel S. Kapp, MD, PhD

Abstract

Individuals with Down syndrome (DS) are at elevated risk for acute leukemia, whereas solid tumors are uncommon, and most types, including breast cancers, have significantly lower-than-expected age-adjusted incidence rates. This article reports on a man with DS and breast cancer, thought to be the first in the literature, and presents the management of his cancer. The literature on malignancies in patients with DS is reviewed and the major epidemiologic studies that have examined the spectrum of cancer risk in individuals with DS are summarized. Potential environmental and genetic determinants of cancer risk are discussed, and the potential role of chromosomal mosaicism in cancer risk among patients with DS is explored. Trisomy of chromosome 21, which causes DS, provides an extra copy of genes with tumor suppressor or repressor functions. Recent studies have leveraged mouse and human genetics to uncover specific candidate genes on chromosome 21 that mediate these effects. In addition, global perturbations in gene expression programs have been observed, with potential effects on proliferation and self-renewal. (J Natl Compr Canc Netw 2014;12:1537–1545)

Case Report

A middle-aged patient with Down syndrome presented to his physician with a palpable 5-cm mass in the upper-inner quadrant of the left breast. He was a non-smoker and had no known family history of cancer. A diagnostic mammogram showed a left-sided breast mass with microcalcifications and axillary adenopathy. Ultrasound-guided biopsy of the mass revealed carcinoma. On further staging, a bone scan and a CT scan of the chest, abdomen, and pelvis showed no evidence of distant metastasis. The biopsy-proven cancer was clearly seen within the left breast on CT (Figure 1).
The patient underwent a left modified radical mastectomy with axillary lymph node dissection. Pathologic evaluation revealed a 5.6-cm grade 3 infiltrating ductal carcinoma associated with ductal carcinoma in situ with both solid and cribriform types. Immunohistochemistry revealed strong positive staining for estrogen receptor, progesterone receptor, and HER2/neu overexpression. The resection margins were negative. Three of 10 left axillary lymph nodes were found to contain metastatic adenocarcinoma, and extracapsular extension was identified. Pathologic staging was T3N1aM0 (stage IIIA). Results of germline genetic testing for BRCA1 and BRCA2 mutations were negative.

Adjuvant therapy consisted of docetaxel and carboplatin along with trastuzumab for 6 cycles. Trastuzumab monotherapy was continued for a total of 1 year. Doxorubicin was omitted because of concern for cardiotoxicity in patients with Down syndrome. The principal complications of this regimen were severe diarrhea and dehydration, which resolved after the completion of therapy. His ejection fraction remained within normal limits through the duration of treatment with trastuzumab.

The patient was then treated with external-beam radiotherapy to the left chest wall, supraclavicular (SCV) fossa, internal mammary (IM), and left axillary (AX) nodal regions. The doses to the chest wall and SCV/IM/AX regions were 50.4 and 45.0 Gy, respectively, at 180 cGy per fraction, 5 fractions per week. Fields were planned in an attempt to minimize the dose to the lung and heart. A brief treatment break was required to allow for healing after the patient developed moist desquamation on the chest wall.

Tamoxifen was initiated after radiotherapy and continues at the time of writing. At 57 months after surgery, the patient has remained disease-free. He currently has no significant chronic toxicities from his breast cancer therapy.

**Literature Review**

**Male Breast Cancer**

To the authors’ knowledge, this is the first reported case of male breast cancer in a patient with DS. Breast cancer is the leading nonskin cancer in women, accounting for more than 226,000 new diagnoses annually in the United States. The incidence in men is less than 1% of that in women. It is often diagnosed at more advanced stages in men compared with women, likely partly because of poor awareness among men regarding the risk of breast cancer. In addition, the scant breast tissue in many men with the disease may lead to a higher likelihood of skin or muscle invasion by the primary tumor, which portends a worse prognosis. Molecular analyses of breast cancer in men and women have begun to reveal differences in gene expression patterns and genetic drivers. For example, male breast cancer is more frequently associated with germline mutations in BRCA2 rather than BRCA1, in contrast to breast cancer in women. In clinical practice, breast cancer in men is generally treated similar to breast cancer in women, according to stage of disease, tumor hormone receptor expression, and HER2/neu amplification or expression.

**Neoplasia Risk in Patients With DS**

DS is associated with a distinct spectrum of risk for neoplasia. Conflicting data exist on the overall incidence and types of malignancies seen in individuals with DS. This is possibly related to the small numbers of patients reported, the variation and completeness of the available data and risk factors reported, changes in competing risks as the average lifespan increases, and the uncertain impact of varying rates of Robertson translocations and mosaic trisomy 21. However, the preponderance of evidence shows that the incidence of acute leukemia among individuals with DS is elevated, whereas most solid tumors are strikingly rare. Interestingly, in addition to acute leukemia, germ cell tumors occur at an increased frequency in individuals with DS, a finding that cannot be completely attributed to high rates of cryptorchidism in men with...
The incidence of and mortality from cancer reported in individuals with DS are summarized in Tables 1 and 2, respectively.

Several studies have examined the incidence of breast cancer in patients with DS. Satge et al reported less than 10% of expected breast cancer deaths among women with DS in France. Two Scandinavian population-based studies determined standardized incidence ratios (SIRs) of breast cancer in patients with DS compared with age-matched euploid cohorts, and reported SIRs of 0 and 0.4, respectively. Furthermore, 2 additional studies from the United States reported age-matched standardized mortality ratios of 0.09 and 0.04 for breast cancer in patients with DS. An autopsy study from Japan identified 17 solid malignancies but no breast cancers.

Several factors have been proposed to contribute

| Table 1 Summary of Epidemiologic Studies on Cancer SIRs in Patients With DS |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Year            | Hasle et al     | Boker et al     | Hill et al      | Goldacre et al  | Patja et al     | Sullivan et al  |
| Nation          | Denmark         | Israel          | Sweden/Denmark  | England         | Finland         | Australia       |
| Total Individuals With DS | 2814           | 1846           | 4872           | 1453           | 3581           | 1298           |
| Leukemia Cases (N) | 36             | 7              | 37             | 15             | 22             | 13             |
| Leukemia, SIR   | 17.63           | 25.18          | 19.5           | 18.90          | 10.50          | 8.42           |
| All Solid Tumors Cases (N) | 24             | 28             | 32             | 8              |                |                |
| All Solid Tumors, SIR | 0.50           | 0.8            | 1.20           | 0.57           | 0.44           |
| Solid Tumor Types, SIR |
| Testis          | 1.86            | 3.7            | 12.00          | 4.80           | 1.94           |
| Other male genital | 45.5          | 0.50           |
| Ovary           | 1.97            |                |                |                |                |
| Colon           | 0.89            | 2.1            | 3.10           | 1.50           |
| Stomach         | 1.10            | 3.5            | 1.50           |
| Small intestine (ileum) | 8.3           | 0              | 21.11          |
| Peritoneum      | 67.77           |                |                |                |                |
| Liver           | 6.0             | 2.40           |
| Gallbladder     | 6.00            | 13.56          |
| Pancreas        | 0.90            |                |
| Lung            | 0.24            |                |                |
| Breast          | 0               | 0.5            | 0.40           |
| Endometrial     | 0.83            | 2.2            | 0.70           |
| Prostate        | 0               |                |
| Kidney          | 0.84            | 0.6            | 0.50           |
| Bladder         | 1.69            | 0.30           | 0.29           |
| Skin (melanoma) | 0.25            | 0.30           | 1.60           |
| Brain (nervous system) | 0.30         | 0.7            | 0.40           |
| Eye             | 3.68            |                |                |
| Bone            | 2.10            |                |
| Endocrine       | 1.4             |                |
| Unspecified     | 3.27            | 0.6            |

Abbreviations: DS, Down syndrome; SIR, standardized incidence ratio.
to the reduced risk of solid tumors in patients with DS. These factors seem to outweigh biologic features of DS that promote tumorigenesis in other contexts, including increased chromosomal instability, higher intracellular levels of reactive oxygen species, deficient DNA repair mechanisms, immunodeficiency, and the presence of known oncogenes on chromosome 21.20

**Environmental Contributions to Cancer Risk in Individuals With DS:** Differences in environmental exposures may directly impact carcinogenesis in patients with DS. Patients with DS have been reported to have a lower likelihood of tobacco and alcohol use and occupational exposures to carcinogens, although this has not, in general, been well documented.15 In some cases, insufficient awareness among patients and caregivers could contribute to reduced or delayed diagnosis of many cancer types in this population. This may be confounded by the lack of symptoms or atypical presentation of cancer in individuals with intellectual disabilities.28,29 In addition, routine examinations and certain specific cancer screening may be neglected in patients with DS, contributing to delayed or missed diagnoses. For example, a Canadian study reported that compliance with guidelines for physical examination and medi-

<table>
<thead>
<tr>
<th>Year</th>
<th>Holland et al24</th>
<th>Scholl et al26</th>
<th>Hermon et al5</th>
<th>Yang et al1</th>
<th>Hill et al19</th>
<th>Day et al22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nation</td>
<td>United Kingdom</td>
<td>United States</td>
<td>United Kingdom</td>
<td>United States</td>
<td>Sweden/Denmark</td>
<td>United States</td>
</tr>
<tr>
<td>Total DS Deaths (Total DS Individuals)</td>
<td>352 (2033)</td>
<td>793</td>
<td>346 (1425)</td>
<td>17,897</td>
<td>742 (4872)</td>
<td>600 (14,781)</td>
</tr>
<tr>
<td>Leukemia Cases (N)</td>
<td>7</td>
<td>25</td>
<td>11</td>
<td>345</td>
<td>35</td>
<td>26</td>
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<tr>
<td>Leukemia, SMR</td>
<td>17.9</td>
<td>1.70</td>
<td>13.04</td>
<td>1.57</td>
<td>33.2</td>
<td>17.0</td>
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<tr>
<td>All Solid Tumors Cases (N)</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>344</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>All Solid Tumors, SMR</td>
<td>2.63</td>
<td>0.07</td>
<td>0.07</td>
<td>22</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2 Summary of Epidemiologic Studies on Cancer SMRs in Patients With DS**

<table>
<thead>
<tr>
<th>Solid Tumor Types, SMR</th>
<th>Testis</th>
<th>Ovary</th>
<th>Colon</th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Liver</th>
<th>Gallbladder</th>
<th>Pancreas</th>
<th>Lung</th>
<th>Breast</th>
<th>Endometrial</th>
<th>Prostate</th>
<th>Kidney</th>
<th>Bladder</th>
<th>Skin (melanoma)</th>
<th>Brain</th>
<th>Oral</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia, SMR</td>
<td>8.40</td>
<td>3.23</td>
<td>25.2</td>
<td>0.07</td>
<td>7.2</td>
<td>0.13</td>
<td>3.3</td>
<td>8.2</td>
<td>0.14</td>
<td>0.02</td>
<td>0.09</td>
<td>0.62</td>
<td>0.04</td>
<td>0</td>
<td>0.13</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Solid Tumors, SMR</td>
<td>2.63</td>
<td>0.07</td>
<td>0.07</td>
<td>22</td>
<td>18</td>
<td></td>
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<td></td>
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</table>

Abbreviations: DS, Down syndrome; SMR, standardized mortality ratio.
Down Syndrome and Cancer

Primary referrals by family physicians was less than 50% in patients with DS aged 19 years or older. As additional information accumulates on the types of malignancy developing in patients with DS, with perhaps patient-specific risk factors being identified, a change in the screening recommendations and other surveillance measures may need to be considered.

Tobacco smoke is known to drive the development of many types of solid cancer. It has been postulated that the lower incidence of lung cancer in patients with DS is related to the decreased smoking rates. However, reports vary regarding the smoking rates among individuals with intellectual disabilities. The relative success of a pilot program providing smoking education in these patients suggests that further efforts should be directed toward eliminating or decreasing tobacco use in patients with DS. Better documentation of the effects of direct and second-hand smoke exposure in these patients is also needed.

Exposure to ultraviolet radiation is the predominant environmental risk factor for skin cancers, including cutaneous melanoma. However, excessive sun exposure was not noted for the 3 patients with DS with cutaneous melanoma reported in the literature. It may be assumed that patients with DS, if appropriately supervised, would be at lower risk of developing blistering sunburns or excessive indoor tanning, but studies detailing ultraviolet exposure in patients with DS are lacking. Similarly, no studies noted the incidence of other potentially hazardous environmental exposures (eg, pesticides, metals, combustion by-products, coal) in patients with DS that have been associated with increased risk of melanoma and other cancers in the general population.

Many cancers of the breast and prostate are driven partly by estrogens and androgens, respectively. Hormonal changes among patients with DS could influence the low incidence of these cancers. For example, some degree of hypogonadism has been reported in young men with DS. However, normal ages have been reported for the onset and completion of puberty in individuals with DS. Additional studies are needed on the potential association of hormonal exposure and cancer incidence among individuals with DS.

With regard to the risk of acute leukemia in individuals with DS, it has been hypothesized that the tendency toward social isolation among these individuals could lead to a reduction in early-life infections, which are thought to provide a protective effect against childhood acute leukemias. A case-control study within the Children's Oncology Group (COG) demonstrated that infections within the first 2 years of life are associated with lower risk for acute leukemias in children with DS. Asthma, which may be more common in patients with DS, has been linked to a reduced incidence of early-life infections and an increased rate of acute leukemias. However, another case-control study came to the opposite conclusion, and instead demonstrated an association between breastfeeding and lower rates of acute leukemias.

Exposure to vitamin supplementation in utero and early in life has been proposed to impact leukemogenesis in patients with DS. Analysis of the COG cohort has also suggested that regular multivitamin use during the first year of life may predispose patients with DS to developing acute leukemias. Another study suggested mixed effects of vitamin supplementation, depending on the timing of exposure during pregnancy.

The associations detected in these case-control studies tend to be of marginal statistical significance, and the findings warrant independent confirmation. By nature of the epidemiologic study designs, causative relationships cannot be proven. Thus, although unique patterns of exposure may influence tumorigenesis in patients with DS, environmental factors may not fully explain differences in cancer incidence. Because most prior work has focused on acute leukemia, additional studies will be required to examine the effect of environmental exposures on the risk of solid cancers in individuals with DS.

**Mosaicism of Trisomy 21 and Cancer Risk:** Genetic mosaicism is the phenomenon whereby an individual harbors cells with 2 or more distinct genotypes as a result of mitotic errors during the course of development. Mosaicism can affect any chromosome, and nondisjunction leading to trisomy of chromosome 21 can occur during early development or even within adult tissues. In principle, any combination of tissues could be specifically affected by mosaicism of trisomy 21, depending on the stage of development during which the causative nondisjunction event occurred. In other manifestations of mosaic trisomy 21, a proportion of the cells within a certain organ are afflicted. In general, the phenotypic manifestations associated with DS with mosaic trisomy 21 depends on the proportion of trisomy 21 cells in a particular organ.
Studies of patients with DS with mosaic trisomy 21 have supported the hypothesis that a dosage effect from genes encoded by chromosome 21 contributes to the low incidence of many solid tumors. Patients with DS with a higher dosage of genes encoded on chromosome 21 (eg, those without mosaic trisomy 21) should be expected to have a lower incidence of solid tumors than those with mosaic trisomy 21 or individuals without trisomy 21. A recent population-based study of 3530 persons with DS in Denmark reported that the percentage of patients dying of neoplasms was 13.3% among patients with mosaic DS compared with 5.8% for those with standard trisomy 21,16 consistent with a possible gene dosage effect of trisomy 21. Similarly, the incidence of congenital heart defects was higher in patients with standard trisomy 21 than in patients with mosaic DS. These results are in agreement with previous studies showing higher intellectual potential, verbal facility, and visual perceptual abilities among individuals with mosaic DS compared with those with standard trisomy 21 DS.47

Interestingly, tissue-specific mosaicism has been linked with particular manifestations of DS, including reduced IQ and congenital heart defects.48 In a similar manner, tissue-specific rates of mosaicism could potentially influence the site-specific rates of malignancy and help partly explain the variation in rates of malignancy seen among reported series of patients with DS. Additional studies to determine the influence of dosage-sensitive repressor or suppressor genes located on chromosome 21 are warranted.49

Chromosome 21, Oncogenes, and Tumor Repressors: Constitutional aneuploidies generally cause whole chromosome instability, which may contribute to tumorigenesis and cancer progression.50,51 This phenomenon could influence the increased risk of many solid malignancies among individuals with Klinefelter syndrome (XXY), Turner syndrome (XO), and Edwards syndrome (trisomy 18). Thus, the reduced incidence of most solid malignancies among individuals with DS is unlike that seen in individuals with other constitutional aneuploidies. This distinction has led to the suspicion that specific genes encoded on the extra copy of chromosome 21 might directly affect cancer risk. Hundreds of genes are encoded on chromosome 21.52 A subset of these genes may promote the development of acute leukemia and germ cell tumors, whereas others may repress tumorigenesis or tumor growth.

Acquired trisomy 21 is a common feature of germ cell tumors and acute leukemia in euploid individuals without DS, often occurring in isolation from other major cytogenetic events.19,53–55 This indicates the oncogenic potential of chromosome 21 gain and is consistent with the suspected oncogenic function of genes encoded by chromosome 21. Comparisons of gene expression differences between acute leukemias in individuals with and without DS have not been fruitful in identifying potent oncogenes on chromosome 21.56 Rather, studies using mouse models of DS57–59 have led the way, resulting in the identification of Dyrk1a as a candidate DS-specific oncogene.60 Dyrk1a gain-of-function may cooperate with somatic Gata1 mutations to potentiate leukemogenesis. The proposed mechanism of leukemogenesis relates to the inhibitory effect of Dyrk1a on the calcineurin/nuclear factor of activated T cells (NFAT) pathway, leading to megakaryoblastic expansion.50

Interestingly, inhibition of the calcineurin/NFAT pathway has also been implicated as a mechanism underlying reduced solid cancer incidence in individuals with DS. Modest overexpression of Dscr1 and Dyrk1a induced by trisomy 21 is sufficient to inhibit this pathway.61 In mouse models, Dscr1 gain inhibits tumor neoangiogenesis, which is critical for tumor growth and progression.52,63 Other chromosome 21 genes that are expressed in endothelial cells and inhibit angiogenic responses to vascular endothelial growth factor include endostatin/Col18a1, ADAMT1, ERG, Pttg1, and JAM-B/JAM2.64,65 High serum endostatin levels have been reported in patients with DS and may help explain the relative decrease in certain solid tumors. This may also have therapeutic implications.66

The concept of a tumor repressor has been used when reduced tumorigenesis is caused by an extra copy and/or mild overexpression of a wild-type gene product. In addition to Dscr1 and Dyrk1a, other chromosome 21 genes demonstrating tumor repressor activity in mouse models include the transcription factors Ets2 and Sim2,66,67 Ets2, which is a proto-oncogene in other contexts,68 provides a dose-dependent reduction of intestinal tumor accumulation in cancer-prone ApcMin mice.69 Sim2 expression in breast cancer cells had multiple inhibitory effects on malignant phenotypes, including proliferation, anchorage-independent growth, and invasive behavior.67 Future studies should examine the effect of copy number gain and expression of these putative...
tumor repressor genes on tumorigenesis and cancer progression in individuals without DS.

**Effect of Trisomy 21 on Epigenetic Regulation of Gene Expression:** Phenotypes in individuals with DS have been attributed to 2 competing models: (1) gene dosage effects from the extra chromosome 21, and (2) genetic instability as a result of the extra DNA material. In support of the first model, complete transcriptional silencing of the extra chromosome 21 ameliorates the defects in proliferation and neurogenesis that are hallmarks of trisomy 21 cells. Recently an entirely different model has been proposed based on the results of comparative whole transcriptome sequencing of cells from a pair of monozygotic twins, one of whom has constitutional trisomy 21. Surprisingly, gene expression changes were observed across all chromosomes and not just in chromosome 21. These changes were not randomly distributed, but rather were organized into large contiguous domains that corresponded to known epigenetic regulatory events. Two specific genes on chromosome 21 were recently implicated in changes to global histone methylation patterns affecting transformation. In addition, it is also possible that the extra genetic material in trisomy 21 cells has epigenetic effects on gene expression. Future studies are needed to evaluate how such global epigenetic changes may impact tumorigenesis and cancer progression in different tissues.

**Cancer Stem Cells and Trisomy 21:** Cancer stem cells (CSCs) are malignant cells that maintain the capacities for self-renewal and for giving rise to more differentiated progeny within tumors. Among solid tumor types, CSCs were first isolated in human breast adenocarcinoma and have since been identified in many other cancer types. Because unlimited self-renewal is an essential attribute of both stem cells and cancer, a reduction in solid malignancies among individuals with DS could reflect pervasive defects in stem cell function. In this vein, recent work implicates increased expression of the chromosome 21 gene USP16 in deficient self-renewal of somatic stem cells. USP16 opposes the function of the polycomb repressive complex (PRC), relieving epigenetic suppression of the tumor suppressor gene CDKN2A. Thus, trisomy 21 may result in stronger cell cycle checkpoint controls and reduced self-renewal of potential cancer cell progenitors in certain tissues. In leukemia precursor cells, however, trisomy 21 may provide the opposite effect, also as a result of PRC inhibition.

**Conclusions**
This article presents a patient diagnosed with breast cancer despite 2 strong protective genetic factors: male gender and DS. This is possibly the first case reported of male breast cancer associated with DS. Many factors likely contribute to the scarcity of breast cancer and most other solid tumors in patients with DS. Several genes on chromosome 21 with potential tumor suppressor or repressor functions have been uncovered recently. Further research is needed to provide a deeper understanding of the relationship between DS and organ-specific cancers.

Without doubt, much progress has been made in the conceptual framework of cancer risk in patients with DS. Yet for any individual patient with DS, precise tools for predicting the development of cancer or for optimizing early detection and treatment of cancer are still far off. Future efforts will need to delve deeper into the molecular drivers of cancer in patients with DS, with the ultimate goal of providing practical approaches that have the potential for immediate clinical impact. The consequences of these studies could reach far beyond patients with DS, because it is likely that similar determinants for cancer risk affect individuals with other chronic medical conditions.

**Acknowledgments**
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**References**

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