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INVITED EDITORIAL
Genetics and Epidemiology, Congenital Anomalies and Cancer

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Many of the basic statistical methods used in epidemiology—regression, analysis of variance, and estimation of relative risk, for example—originally were developed for the genetic analysis of biometric data. The familiarity that many geneticists have with this methodology has helped geneticists to understand and accept genetic epidemiology as a scientific discipline. It worth noting, however, that most of the work in genetic epidemiology during the past decade has been devoted to linkage and other family studies, rather than to population-based investigations of the type that characterize much of mainstream epidemiology (Khoury et al. 1993*b*).

One of the central concepts of epidemiology is the importance of the environment in disease causation (Khoury et al. 1993*a*). The early appreciation by some of the founders of modern medical genetics of the central role of genetic and environmental interactions in the pathogenesis of human disease helped genetic epidemiology to grow (Khoury et al. 1993*a*). It is now clear that almost all disease involves interactions of genetic and nongenetic pathogenic factors in various ways. This is most obvious with respect to common isolated congenital anomalies (Stevenson et al. 1993) and common diseases of adult life, such as arteriosclerotic heart disease, diabetes mellitus, and cancer (King et al. 1992).

One of the most spectacular early successes of epidemiological analysis in medical genetics was Knudson's interpretation of retinoblastoma incidence data in terms of a "two-hit" hypothesis for tumor development (Knudson 1971). Another early success was the recognition, by Robert Miller, of the importance of associations between certain childhood neoplasms and particular patterns of congenital anomalies (Miller 1966, 1967, 1968).

Associations of Malignancy and Congenital Anomalies

Table 1 lists some associations that have been observed between the occurrence of neoplasms and congenital anomalies. Although many other congenital anomaly–neoplasia associations are known (Bolande 1976; Eeles et al. 1996), those included in table 1 illustrate the range of pathogenic mechanisms that are currently recognized as contributing to such associations. In none of these cases is the pathogenesis of the congenital anomalies understood.

Constitutional mutations of both proto-oncogenes and tumor-suppressor genes can cause congenital anomalies. This is not surprising, given the critical roles that many of these gene products play in signaling pathways, control of cellular proliferation, or both. Perhaps it is more surprising that there are so many inherited predispositions to neoplasia that are not associated with congenital anomalies despite the expression of the relevant genes during embryogenesis. Examples of such inherited predispositions to malignancy that occur without apparent association with congenital anomalies include the familial cancer syndromes caused by mutations of *BRCA1*, *TP53*, and *MLM* (Bishop and Hall 1994; van Rensburg and Ponder 1995; Eeles et al. 1996).

Even when the tumor diathesis associated with a particular congenital anomaly or syndrome can be explained in terms of a familiar mechanism such as constitutional loss of a functional tumor-suppressor gene, the oncogenic process may not be straightforward. Neurofibromatosis 1 provides an important example of this principle. Discrete dermal neurofibromas in patients with neurofibromatosis type 1 often exhibit loss of heterozygosity for genetic markers in and near the *NF1* gene (Colman et al. 1995). A somatic mutation of the normal *NF1* homologue has been demonstrated in a discrete neurofibroma from one such patient (Sawada et al. 1996). Despite the apparent involvement of *NF1* as a tumor-suppressor gene in these tumors, they rarely, if ever, progress to malignancy, even though patients with neurofibromatosis type 1 are at greatly increased risk of developing malignant neurofibrosarcomas. However, these malignancies almost always arise from plexiform, not discrete, neurofibromas.

Different mechanisms appear to be involved in some congenital anomaly–neoplasia associations (table 1). Although one can postulate reasonable ways in which abnormalities of DNA repair could lead to neoplasia, the specificity of the neoplasms that develop in condi-

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Table 1

Some Examples of Associations between Congenital Anomalies and Malignancy

Congenital Anomaly or Syndrome	Associated Malignancy	Etiology of Syndrome	Putative Mechanism of Predisposition to Neoplasia	Reference(s)
Down syndrome	Acute lymphocytic leukemia	Trisomy 21	Unknown	Miller (1967)
Mixed gonadal dysgenesis	Gonadoblastoma	45,X/46,XY and other chromosomal mosaics with a Y-chromosome	Unknown	Bolande (1976)
Androgen-insensitivity syndrome	Sertoli-cell tumor, tubular adenoma	X-linked recessive (mutation of *AR*)	Unknown	Bolande (1976)
WAGR syndrome	Wilms tumor	Microdeletion involving region of the *WT1* gene	Homozygous loss of *WT1* tumor-supressor-gene activity	Miller (1968)
Gorlin syndrome	Basal cell carcinoma	Autosomal dominant (mutation of *PTC*)	Homozygous loss of *PTC* tumor-supressor-gene activity	Gorlin (1995), Hahn et al. (1996), Johnson et al. (1996)
Neurofibromatosis type 1	Neurofibrosarcoma	Autosomal dominant (mutation of *NF1*)	Homozygous loss of *NF1* tumor-supressor-gene activity; additional steps also involved	Colman et al. (1995), Sawada et al. (1996)
Fanconi pancytopenia syndrome	Acute leukemia	Autosomal recessive (mutations at one of several Fanconi-anemia loci)	Unknown; cells of affected patients frequently acquire cytogenetic abnormalities and are unusually susceptible to DNA cross-linking agents	Auerbach (1995), Joenje et al. (1995)
Multiple endocrine neoplasia type 2B	Medullary thyroid carcinoma, pheochromocytoma	Autosomal dominant (mutation of *RET*)	Constitutional activating mutation of the *RET* proto-oncogene	Holloway and Flowers (1995), Mulligan and Ponder (1995), Eng (1996)
Fetal hydantoin syndrome	Neuroblastoma	Teratogenic effect of maternal phenytoin treatment	Unknown	Hanson and Smith (1975), Allen et al. (1980)

tions such as Fanconi pancytopenia syndrome is difficult to understand. It is equally difficult to understand the specificity of the congenital anomalies that occur in such syndromes.

The increased incidence of tumors in the testes of phenotypic females with androgen insensitivity and in the streak gonads of patients with mixed gonadal dysgenesis seems to be related to the abnormal gonadal development (Bolande 1976), but the molecular mechanisms involved are unknown. Similarly, the molecular basis for the predisposition of children with Down syndrome to transient congenital myeloproliferative disorders and acute leukemia remains unknown.

Population Studies of Associations between Neoplasia and Congenital Anomalies

Most of the known associations between congenital anomalies and neoplasia were first recognized in clinical series. This recognition occurred because a very high incidence of malignancy was observed in patients with a particular congenital anomaly or because a specific congenital anomaly syndrome was found with unusual frequency among patients with a particular malignancy. The associations of neuroblastoma with fetal hydantoin syndrome (Allen et al. 1980) and of Wilms tumor with aniridia (Miller 1968) were discovered in this way.

Other congenital anomaly–neoplasia associations were identified through population-based epidemiological studies. Such studies often deal with only a single type of neoplasm or congenital anomaly but may include a broad range of conditions. Only a few comprehensive population-based investigations of this type have been done. The paper by Narod and his associates in this issue of the *Journal* is one of the largest studies of this type reported to date.

Table 2 summarizes these large comprehensive population-based investigations and shows the difficulties inherent in such studies. The most informative associations are between particular congenital anomaly syn-

Table 2

Some Important Population-Based Studies of Associations between Congenital Anomalies and Malignancy

Study	Design	Study Population	Major Associations Found	Comments
Miller (1969)	Rates of congenital anomalies among children with various neoplasms compared with published rates for normal populations; secondary analysis of distribution of deaths from malignancy among children with various classes of congenital anomalies	Death certificates of 29,457 children who died of malignant neoplasms in the United States, 1960–66	1. Down syndrome and acute lymphocytic leukemia 2. Wilms tumor and anirida 3. Wilms tumor and renal anomalies	1. Study included a total of 156 children with congenital anomalies and neoplasms 2. Considerable underreporting of congenital anomalies on death certificates is likely 3. Both neoplasms and congenital anomalies were considered in large, heterogeneous categories
Windham et al. (1985)	Record linkage of Norwegian Medical Birth Registry and Cancer Registry; comparisons with overall rates of various malignancies obtained from the Cancer Registry, with appropriate adjustments for age and gender	22,856 infants with congenital anomalies, born in Norway, 1967–79	1. Overall rate of malignancy was higher than expected 2. Down syndrome and leukemia 3. CNS anomalies and brain tumors	1. Study included a total of 42 children with congenital anomalies and malignancy 2. Congenital anomalies were reported on birth certificates; underascertainment is likely 3. Both congenital anomalies and neoplasms were considered in large, heterogeneous groups
Mann et al. (1993)	Case-control study of newly diagnosed children with malignancy; congenital anomalies determined by interview with parents and review of medical records	555 children with malignant neoplasms, residing in three health-authority regions of England	1. Overall rate of congenital anomalies among cases was higher than expected 2. Associations within individual diagnostic groups were not statistically significant	1. Study included 60 children with both congenital anomalies and malignancy 2. Congenital anomalies were classified in large, heterogeneous groups
Mili et al. (1993*a*)	Record linkage of Metropolitan Atlanta Congenital Defects Program with Georgia Center for Cancer statistics; comparisons with overall rates of various malignancies obtained from the cancer registry, with appropriate adjustments for age and gender	19,373 children <1 year of age, with congenital anomalies, born in Metropolitan Atlanta, 1968–87	1. Overall rate of malignant neoplasia at <15 years of age was higher than expected 2. Down syndrome and acute leukemia 3. Pyloric stenosis and cancer (various kinds)	1. Study included 31 children with both congenital anomalies and malignancy 2. Congenital anomalies were well ascertained and classified in detail 3. Malignancy probably was underascertained, because of mobility of population and because cancer registry was initiated 7 years after birth-defects registry
Mili et al. (1993*b*)	Record linkage of State Health Registry of Iowa birth defects and cancer registries; comparisons with overall rates of various malignancies, obtained from the cancer registry, with appropriate adjustments for age and gender	10,891 children <1 year of age, with congenital anomalies, born in Iowa, 1983–89	1. Overall rate of malignant neoplasia at <7 years of age was higher than expected 2. Down syndrome and acute leukemia	1. Study included 16 children with both congenital anomalies and malignancy 2. Congenital anomalies were well ascertained and classified in detail
Narod et al. (1997)	Rates of congenital anomalies among children with various neoplasms compared with rates found in the entire study group or reported by the British Columbia Health Surveillance Registry	20,029 cases of malignancy diagnosed in children under age 15 years and reported to the British National Registry of Childhood Tumors, 1971–86	1. Overall frequency of congenital anomalies was higher among children with solid tumors than among those with leukemia or lymphoma 2. Rates of congenital anomalies among children with Wilms tumor, Ewing sarcoma, hepatoblastoma, or gonadal and germ-cell tumors were higher than expected 3. Spina bifida, eye abnormalities, rib malformations, and spine abnormalities were more common than expected, among children with malignancy	1. Study included a total of 720 children with congenital anomalies and neoplasms 2. Cases with an established genetic cause were eliminated, to focus study on identification of new associations 3. Congenital anomalies were reported at time of cancer diagnosis and by postal questionnaire to patients' family physicians; classification was into large, heterogeneous groups

dromes and specific kinds of childhood malignancy, both of which are rare occurrences in the general population. This means that no more than a few hundred patients with malignancy are likely to be found among every million children in the population and that only a small proportion of these will also have congenital anomalies, even if a relatively strong association exists. Consequently, associations of a particular malignant neoplasm with a specific congenital anomaly usually are based on only a handful of concurrences and, because of limited statistical power, may not be seen in population-based studies, even if they are large. Spurious associations resulting from multiple comparisons also may be a problem if the analysis is extended to include associations between many specific congenital anomalies and neoplasms.

Table 2 also reveals a more subtle problem with these studies. There are only a few ways to obtain large sets of population-based data on the occurrence of both congenital anomalies and malignancies. Most studies use birth-defects registries, cancer registries, birth certificates, or death certificates, alone or in some combination. Each of these data sources has important limitations. Registries that are designed to keep track of information of one sort (e.g., cancer cases) tend to be much less efficient when used for other purposes (e.g., to identify children with congenital anomalies). Moreover, there often is a trade-off between the size of the database and the quality and detail of the data that it contains.

This means that population-based studies are most useful to investigate unrecognized associations between large groups of congenital anomalies and malignancy or to confirm associations suggested in clinical series or case reports. Population-based studies are less useful for fine-grained analysis of such associations or for determination of their etiologic significance.

The study by Narod and his associates illustrates these points well. Congenital anomalies in general were more frequent among children with solid tumors than among those with leukemia or lymphoma, but this relationship does not seem to be the result of an association between any specific malignancy or congenital anomaly. Some expected associations were apparent—for example, those of Wilms tumor with renal malformations and of Rubinstein-Taybi syndrome with brain tumors. Other associations observed by Narod et al. cannot be interpreted without analyzing the data with greater diagnostic specificity. The association of Wilms tumor with "chondrodystrophy," for example, is more likely to be biologically important if all of the children with chondrodystrophy prove to have one particular condition, such as Jeune syndrome, than if the patients with chondrodystrophy actually have a variety of different entities.

Following up the leads provided by this study will require the combined efforts of clinical geneticists, epidemiologists, oncologists, and molecular geneticists. Additional population-based genetic-epidemiology studies and carefully documented clinical series are necessary to define the associations more clearly and to differentiate those that are spurious from those that are biologically important. Individual patients with both congenital anomalies and malignancy should be studied intensively to look for pathogenic clues such as unusual prenatal exposures, chromosomal microdeletions, or characteristic mutations of genes involved in embryogenesis, oncogenesis, or both.

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