Genetic Considerations in Human Cancer Incidence

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DATA THAT ARE CONSISTENT with the inheritance of cancer and that point up promising areas for research in human genetics are reported here. Most previous investigators of the relationship of cancer and genetics (*1–4*) have estimated that the contribution of genetics to cancer incidence is rather slight. None of them, however, have taken into account the genetic phenomena of inbreeding, founder effect, and gene flow (racial admixture). Yet the role of these phenomena in the incidence of diseases that were once thought to be simply "familial" has been amply demonstrated (*5*).

Publication in 1975 of an atlas showing the distribution of U.S. cancer deaths (*6*) provided the first opportunity to view this distribution as a whole. Some of the areas of high cancer incidence in the United States are polluted, stressful, urban places, but others are nonurban and almost pastoral by comparison. Current theories explain well the high incidence in the urban areas, but not in the nonurban. With the exception of some mining districts, none of the nonurban areas have as high a level of carcinogens as the urban areas. The existence of as yet undiscovered carcinogens might explain the cancer incidence. Also, the assortment of local carcinogens could be a factor, as well as variations in the kind and amount of people's exposure. In many ways, though, genetic characteristics offer a more parsimonious explanation. What strikes the genetic demographer is that most of the nonurban areas of high cancer incidence are characterized by inbreeding.

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Study Methods

Study area. A part of southern Louisiana with one of the highest cancer incidence rates in the United States was chosen for study. This area (locally called Acadiana) is primarily rural and agricultural; the chemicals used in farming are similar in type and amount to that in agricultural areas with a lower cancer incidence. There is little industrialization. Retail tobacco sales match those in similar areas of the United States (*7*). No extraordinary carcinogens have been identified in the area. Some characteristics of the two central parishes (counties) of the area are shown in table 1.

The area is noted for the occurrence of rare inherited disorders, especially autosomal recessive traits. Following is a list of the autosomal recessive disorders that have been observed in the study area, along with our pedigree numbers for the disorders.

St. Landry Parish

Admixed group:

1722	Adrenogenital syndrome
0239	Albinism
3591	Congenital cataracts
3676	Hypophosphatasia
1494	Macrocephaly
1125	Polycythemia, child
1818	Tumoral calcinosis

Acadian group:

1487	Agenesis of corpus callosum
.0049	Bloom's syndrome
1577	Cerebellar ataxia
2391	Friedreich's ataxia
2660	Goldenhar's syndrome
1826	Hypoglycemia, leucine induced
.2006	Neuroaxonal dystrophy
1831	Testicular feminization
1331	Weill-Marchesani syndrome

St. Martin Parish

Acadian group:

3868	Enteropathy, protein-losing
.1173	Gangliosidosis, generalized
0011	Hurler's syndrome
0107	Microcephaly
2656	Microcephaly
3441	Microcephaly
.2094	Osteogenesis imperfecta

Because of the relatively large number of founders, no single autosomal recessive disorder is characteristic of the residents, in contrast to the case with inbred groups, such as the Amish, who have a smaller number of founders. Rather, an extensive assortment of all autosomal recessive disorders is seen, and the total number is far greater than in outbred groups of similar size. The population group known as Acadians is the source of most of the inherited diseases in the study area. Constituting a large inbred population isolate, these people have a low rate of illegitimacy and large families (*8*). There are also numerous persons of racially admixed backgrounds (European-African) in the area. Being subject to mating prejudice, they likewise tend to inbreed, so that autosomal recessive diseases are also found in this group. In addition, there is a typical "melting pot" component of the population, exhibiting the usual black and white compartmentalization. Its members do not breed to any great extent with either the Acadians or the admixed group, and little genetic disease is found among them.

Because the Acadians, in contrast to the racially admixed group, consciously avoid marriage between close relatives, most consangineous marriages occur between

Parishes and boundaries of Louisiana

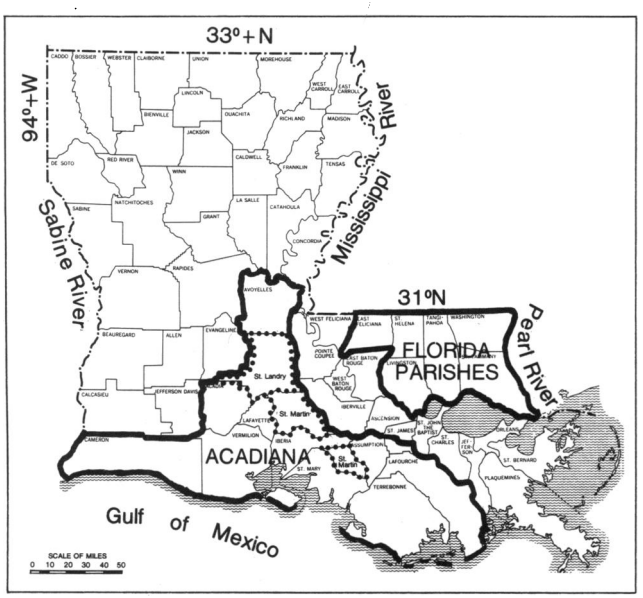

Table 1. Selected characteristics of study area population compared with corresponding characteristics of U.S. population

Characteristics	St. Landry Parish	St. Martin Parish	United States
Population and income			
White population, 1970..number	47,107	21,146	...
Nonwhite population, 1970 ....number	33,257	11,307	...
Population change, 1960–70....percent	−9.9	+13.2	...
Urban population, 1970..percent	39.1	37.3	...
Urban population change, 1960–70	increased	increased	...
Rural population change, 1960–70	decreased	increased	...
White migration, 1960–70.....percent	−10.7	−1.2	...
Nonwhite migration, 1960–70...percent	−22.2	−14.9	...
Population density, 1970.....per square mile	86.2	44.1	57.5
Mean income, 1970	$6,201	$6,204	...
Families below poverty level, 1970 .....percent	38.3	36.1	...
Cancer deaths, 1950–69 [1]			
White males:			
Number of deaths	712	449	...
Rate per 100,000 population	211	221	174
White females:			
Number of deaths	313	197	...
Rate per 100,000 population	109	119	130
Nonwhite males:			
Number of deaths	426	352	...
Rate per 100,000 population	198	226	184
Nonwhite females:			
Number of deaths	226	95	...
Rate per 100,000 population	143	137	139

[1] Cancer deaths for both parishes for period 1950–69 totaled 2,769.

unknowing distant relatives. In both groups, we have found evidence of the founder effect, that is, all cases of a specific genetic disorder can be traced to a single common ancestor. Because of the relative immobility and the large families that characterize both groups, the prevalence of X-linked and autosomal dominant disorders is also elevated.

The Scotch-Irish in the "Florida parishes" (the parishes in southeastern Louisiana bordering Mississippi) constitute another large inbred group. Studies of the coefficient of inbreeding in the Acadians and the Scotch-Irish have revealed remarkably similar scores for random, nonrandom, and total components of inbreeding (*9*). The two groups have similar breeding characteristics, but they are of distinctively different genetic backgrounds. Each group has an array of autosomal recessive disorders that are nearly exclusive of those in the other group. We therefore compared the cancer incidence in the Scotch-Irish group with that in the study area population. Acadiana, in south central Louiana, is centered about 100 air miles from the center of the Florida parishes. The borders of the two areas are within 50 air miles. (See map.)

Sources of data. The study population is known for its high utilization of both public and private medical care facilities. For example, only 0.6 percent of births occur outside hospitals. Regionalized medical care and a public hospital system have existed in the area for nearly 50 years. For nearly 40 years the vital statistics of the area have had a tradition of accuracy. Mason and associates derived the Louisiana data for their studies (*6,10*) from these statistics. In the period of their study, 1950–69, standards of diagnosis and data keeping in the study area were high. With few exceptions, diagnoses of cancer were established through the pathology departments of major hospitals and then were reviewed by tumor boards. We abstracted, collated, and reduced the data that Mason and associates used for their studies—data that were published separately (*10*) from the cancer atlas (*6*)—to obtain an overall representation of the study area. The comparisons of relative incidence in this paper are based on our own analysis.

Results

The elevation in overall cancer incidence in the study area was primarily in males (table 1). Some 15 varieties of cancer were of significantly elevated incidence in the two parishes comprising the study area as compared with that for the United States (table 2). These parishes are among the 30 counties in the United States with the highest incidence of lung cancer. The total cancer incidence was also significantly elevated compared with similar areas in the United States. However, elevated cancer incidence was not an across-the-board phenomenon. In fact, there were some interesting paradoxes. Some cancer varieties that would be expected to be of high incidence turned out to be of low incidence and vice versa (table 3). Significantly low incidence as

Table 2. Types of cancer of high incidence in study area, by race and sex of patient

ICD 8 No.	Cancer site	St. Landry Parish				St. Martin Parish			
		White male	Nonwhite male	White female	Nonwhite female	White male	Nonwhite male	White female	Nonwhite female
141–148	Other mouth, tongue	*					*	*	*
151	Stomach					*			
155	Biliary passages and liver	**	*						
157	Pancreas	**				**			
161	Larynx						*		
162, 163	Trachea, bronchus, lung	***			*	***		**	
172–174	Uterus								*
177	Prostate					**	*		
180	Kidney				*				*
181	Bladder	**	*					**	*
190	Melanoma					*			
191	Other skin	*				*			
193	Central nervous system	***						*	
196	Bone		*		*				*
201	Hodgkin's disease					*			*
147–199	Other	***				***		**	
	Total	***				***			

* Among State economic areas (S.E.A.s) in the United States with incidence in highest decile and significant.
** Incidence in highest decile among U.S. counties.
*** Incidence in highest decile among U.S. counties and significant.
SOURCE: Reference 6.

compared with similar areas was found for colon and rectal cancer among white males and females, as well as for breast, ovarian, and cervical cancer among white females. The expected nonwhite to white incidence ratio was reversed for total cancer incidence in males, as well as for at least 14 cancer varieties (table 4).

The spectrum of cancer incidence in the study area differed markedly from that in the Florida parishes of Louisiana (table 5). Table 5 includes only the varieties of cancer with statistically reliable numbers, although rarer varieties also showed differing spectrums.

Table 3. Comparison of cancer incidence in study area with expected incidence in the South

ICD 8 No. and cancer site		Incidence In St. Martin Parish	Incidence In St. Landry Parish	Expected Incidence In the South
141–148	Other mouth, tongue (male)	High	High	Low
161	Larynx (male)	High	....	Low
181	Bladder (male)	....	High	Low
181	Bladder (female)	High	....	Low
140	Lip (female)	Low	....	High
171	Cervix (female)	....	Low	High

SOURCE: Reference 10.

Discussion

There is a known sexual difference in cancer incidence (male greater than female), and this difference held in the study area. The female incidence rates were similar to those for the remainder of the United States. The meaning of these observations is difficult to interpret, but when considered along with the incidence figures for individual varieties of cancer, they may indicate that no single carcinogen accounts for the elevated incidence in the study area. As already shown, there were significant increases in certain varieties of cancer in

Table 4. Cancer incidence ratios for study area that were the reverse of those for the United States

ICD 8 No. and cancer type		Ratio, St. Landry	Ratio, St. Martin	Ratio, United States
141–148	Other mouth, tongue	Nonwhite male < white male *	.....	Nonwhite male > white male
150	Esophagus	Nonwhite male < white male	.....	Nonwhite male > white male
153	Colon	.....	White male ‡ < nonwhite male	White male > nonwhite male
154	Rectum	White female ‡ < nonwhite female	.....	White female > nonwhite female
155	Liver, biliary	White female < nonwhite female	.....	White female > nonwhite female
157	Pancreas	Nonwhite male < white male **	Nonwhite male < white male **	Nonwhite male > white male
157	Pancreas	.....	Nonwhite female < white female	Nonwhite female > white female
161	Larynx	.....	Nonwhite male < white male *	Nonwhite male > white male
170	Breast	White female ‡ < nonwhite female	White female ‡ < nonwhite female	White female > nonwhite female
180	Kidney	White female < nonwhite female †	.....	White female > nonwhite female
181	Bladder	White male ** < nonwhite male *	.....	White male > nonwhite male
196	Bone	White male < nonwhite male †	.....	White male > nonwhite male
201	Hodgkin's disease	.....	White female < nonwhite female †	White female > nonwhite female
147–199	Other	Nonwhite male < white male ***	Nonwhite male < white male ***	Nonwhite male > white male
	Total	Nonwhite male < white male ***	Nonwhite male < white male ***	Nonwhite male > white male

* Among State economic areas in United States with incidence in highest decile and significant.
** Incidence in highest decile among U.S. counties.
*** Incidence in highest decile among U.S. counties and significant.
† Distribution not available, but incidence significantly high assuming normal curve.
‡ Incidence significantly low among U.S. counties.
SOURCE: References 6 and 10.

females. These increases do not correspond to increases in males in a manner that could be interpreted as the effect of the same carcinogen on different sexes.

As noted, inbreeding, founder effect, and racial admixture are prominent genetic characteristics of the study area. If autosomal recessive genes were a factor in the etiology of cancer, inbreeding would elevate cancer incidence and could be the major contributor to the elevated cancer incidence in the study area. The effect of inbreeding would be fairly specific for individual cancers and could be sex limited overall. Prior studies of inbreeding and familial cancer incidence, which have relied primarily upon verbal information from the affected person, have not demonstrated any particular effects of inbreeding on incidence. On the other hand, the few prospective studies that have been based on direct study of family members have uniformly demonstrated an elevated incidence of cancer in the families of cancer patients (*11,12*). Our own studies demonstrate that parents of children with autosomal recessive disorders seldom acknowledge consanguinity, but upon a discreet pedigree study, it is frequently found.

A more specific effect of inbreeding could be an elevated incidence of the autosomal recessive disorders that Harnden (*4*) and Swift (*13*) found to be associated with elevated cancer incidence:

ammaglobulinemia, Swiss type	De Sanctis-Cacchione syndrome
albinism	Franconi's pancytopenia
ataxia-telangectasia	tyrosinemia
Bloom's syndrome	Werner's syndrome
Chédiak-Higashi syndrome	xeroderma pigmentosum

Albinism, Franconi's pancytopenia, and tyrosinemia are known to exist among Acadians but have not yet been ascertained in the study area. Bloom's syndrome is known to exist in the study area. Cancer incidence in homozygotes with autosomal recessive disorders is about 100 times that in the general population, and in heterozygotes it is about 50 times that in the general population. Since an average of 50 percent of the descendants of the original heterozygote in such families will be heterozygous for the disorder, it is possible that in a relatively closed population a large number of heterozygotes will exist. Yet the types of cancer thought to be most frequent among heterozygotes are leukemia and lymphoma, and neither of these was significantly elevated in the study area. Thus, this theory may not offer an adequate explanation of the high cancer incidence.

Table 5. Proportions of Louisiana parishes in two inbred areas, each with genetically different founders, that ranked above the 90th percentile for U.S. counties in incidence of common varieties of cancer

Cancer variety and patients' sex and color	*Florida parishes*	*Acadiana parishes*
All cancers combined, all sex-color groups combined	.29	.94
Liver, white male	0	.50
Pancreas, white male	.29	.56
Pancreas, white female	0	.31
Lung, white male	.57	.94
Lung, white female	.29	.31
Bladder, white male	0	.31
Uterus, white female	.43	0

No association is presently known between recessive inheritance and most of the varieties of cancer of elevated incidence in the study area. Clues from many of them point toward dominant or incomplete dominant inheritance. The difficulties in differentiating dominant and recessive inheritance in inbred populations are well known (*14*). Consanguineous marriages over several successive generations can result in a quasi-dominant pedigree pattern of disorders that have recessive inheritance. Indeed, few instances of the inheritance of cancer reliably show transmission from the affected to the affected over several generations. Often generations are skipped and no cancer occurs—a situation likely to exist when recessive transmission occurs in inbred populations. Consequently, recessive inheritance could well explain the elevated cancer incidence in the study area.

The importance of carcinogens in the study area is not lessened by these observations; in fact, their importance may be increased. Inbred strains of animals with a high spontaneous cancer rate are frequently used in studies of carcinogens. In human beings, inbreeding may produce "strains" that have an elevated cancer rate and may also make these strains more susceptible to carcinogens.

Founder effect would influence the incidence of inherited cancer in two ways. It would elevate the incidence only of those varieties of cancer for which the founders had genes, and it would result in a cancer incidence spectrum different from that for the surrounding populations. Regarding the first effect, we can only hypothesize that the varieties of currently elevated incidence are those for which the group's founders had genes. This hypothesis would be strengthened if the persons with given varieties of cancer could be traced to common ancestors. The instances of paradoxial cancer incidence in the study area support the hypothesis, because only certain cancer varieties show a reverse trend in incidence to that for the South in general. If the founders had genes for the elevated

varieties and not for the others, a lower than expected incidence would be found for the others. Also, indirect support for this hypothesis is provided by the difference in the cancer incidence spectrum for the study area from that for the Florida parishes. Both share a similar environment and have similar degrees of inbreeding, but they had different founders. The founder effect, outside of overt dominant inheritance, substantiates recessive inheritance.

Racial admixture leads to several interesting social phenomena in the study area. A person of admixed background is generally classified as black, but may exhibit marked aspirations toward classification as white. Historically, and even currently, such aspirations have been documented in court cases. Once attained, the white classification is usually jealously, often fanatically, guarded. Such guarding was a factor in the assassination of a well-known State Governor. People of admixed background often shun marriage with blacks, preferring to marry other admixed persons or whites.

Classification of admixed persons in the study area as black would elevate the recorded incidence in blacks of a disease initially of equal incidence in both blacks and whites. The racially admixed, however, tend to opt for a classifiation of white as they reach an age when they can express their aspirations or when, as with time, marriage preferences lead them to wish to become "more white." Ultimately, then, given this tendency, the racial admixture in the study area would elevate the disease incidence recorded for whites. Since racial admixture was more common in the 19th century in the study area than it is now, the current excess of cancer recorded for whites might be well explained by this hypothesis. Of note, however, is that racial admixture is a very fluid phenomenon, so that in the course of establishing an equilibrium, it could result in an excess cancer incidence being recorded for blacks.

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SYNOPSIS

THURMON, THEODORE F. (Louisiana State University School of Medicine in New Orleans), and ROBERTSON, KATHLEEN P.: *Genetic considerations in human cancer incidence. Public Health Reports, Vol. 94, September–October 1979, pp. 471-476.*

Analysis by the methods of genetic demography can offer plausible explanations for the unusual distribution of cancer in an area of high incidence. The important demographic characteristics include inbreeding, founder effect, and racial admixture. Inbreeding would elevate cancer incidence if autosomal recessive genes played a role in cancer etiology. Founder effect would limit this phenomenon to those recessive genes observed in the founding group and result in a cancer spectrum different from that of the surrounding populations. The preference of a racially admixed group for classification as white could result in an excess of cancer patients being classified as white. The population groups in southern Louisiana typify the kind of "human genetics laboratory" that inbred groups offer to investigators of the genetic aspects of cancer.