

Ethnic Differences in Cancer Incidence: A Marker for Inherited Susceptibility?

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Cancer incidence varies markedly by ethnicity and geographic location. Ethnic variation in cancer occurrence has traditionally been ascribed to differences in social, cultural, economic, and physical environments. However, this interpretation of the epidemiologic evidence may need to be revised as a result of new biological evidence and theories of carcinogenesis. Carcinogenesis is now recognized to be a multistep process during which mutations or heritable changes in expression occur in genes involved in cellular growth control and genome stability. Inherited cancer susceptibility may be a stronger determinant of ethnic differences in cancer incidence than is currently appreciated. To examine the potential role of inherited susceptibility, the theoretical contribution of inherited susceptibility to ethnic differences in rates is considered using a simple probability model. Germline mutations in tumor suppressor genes *BRCA1* and *p53* are used to illustrate the magnitude of the ethnic differences for breast cancer that might arise from differences in inherited susceptibility. Our simple model suggests that ethnic differences in cancer occurrence can result from differences in genetic susceptibility. However, the magnitude of ethnic relative risk is likely to more strongly reflect differences in the distribution of susceptibility genotypes between groups than the magnitude of the disease risk associated with the genotypes. For many scenarios, the ethnic relative risk arising from differences in susceptibility may be bounded by the ratio of the proportion of susceptible individuals in each group. — *Environ Health Perspect* 105(Suppl 4):897–900 (1997)

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Introduction

It has long been recognized that cancer rates show enormous variation by ethnicity and geographic location (1–4). For example, rates for melanoma in whites living in Queensland, Australia, are 155-fold higher than rates for Japanese residents of northern Japan (Table 1). Blacks in the United States have a 70-fold higher incidence rate for prostate cancer compared with rates for several Asian groups. Large variations of cancer rates by ethnic group

are still apparent when restricted to one geographic location, the United States (Table 2, 3), where blacks have the highest rate for all sites combined and Native Americans have the lowest rate. The variation in the United States is even greater for specific types of cancer, with some types having a 10-fold difference between ethnic groups. Rates for esophageal cancer, for example, vary from 18.9 for blacks to 1.9 for Native Americans. American females show a similar variation by ethnic group. The data indicate that the large differences in cancer rates by ethnic group are not simply a function of geography.

Explanation for Ethnic Differences in Cancer Occurrence

Apparent ethnic variation in cancer incidence may arise from information bias and confounding as well as from true differences in cancer occurrence. The explanations for ethnic differences in cancer rates fall into four categories, which are based in part on lists presented in Polendak (5)

and MacMahon and Pugh (6). The categories are as follows:

Measurement errors:

- Inadequate data—insufficient information, based upon clinical impressions, etc
- Differential access to medical care and diagnostic facilities
- Differences in reporting due to cultural factors or to difference in the severity of disease; differential use of available facilities
- Differing fashions of diagnosis.
- Coding death certification

Differences between groups with respect to more directly associated demographic variables:

- Differences in socioeconomic class and occupation, and secondary factors associated with these differences (see Differences in environment, below)

Differences in environment:

- Climatic differences and their effects
- Geographic variation in disease frequency
- Nutrition or diet
- Differences in personal customs or habits (e.g., reproductive and nursing habits; use of tobacco and alcohol, and differences in sexual practices)
- Differences with respect to social and family structure relationships, role behavior
- Cultural factors
- Differences related to rates of growth and development

Genetic differences:

- HLA class II alleles
- HLA-haplotypes
- Metabolic enzyme polymorphisms
- ABO blood groups

Valid comparison of rates depends upon accurate diagnosis and reporting of cancer cases. Bias from measurement errors can result from differences in access to medical care and utilization of care and to differences in diagnosis and death certificate reporting, all of which probably account for a portion of the ethnic variation in cancer rates (2). The bias from measurement error is likely to be substantial and may also explain some of the international variation in cancer mortality rates. However, international standardization of registration procedures has resulted in improved data on cancer incidence worldwide (2), and it is doubtful that information bias explains much of the ethnic variation in rates calculated from data

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Abbreviations used: SEER, Surveillance, Epidemiology, and End Results Program; SES, socioeconomic status

Table 1. International ethnic variation in cancer incidence.

Type of cancer	Ratio, high/low	High incidence area	Low incidence area
Melanoma	155	Australia (Queensland)	Japan (Osaka)
Lip	151	Canada (Newfoundland)	Japan (Osaka)
Nasopharynx	100	Hong Kong	United States (Southwest)
Prostate	70	United States (Atlanta, black)	China (Tianjin)
Liver	49	China (Shanghai)	Canada (Nova Scotia)
Penis	42	Brazil (Recife)	Israel (Born in Europe, America)
Oral cavity	34	France (Bas-Rhin)	India (Poona)
<i>Cervix uteri</i> (female)	28	Brazil (Recife)	Israel (non-Jews)
Esophagus	27	France (Calvados)	Romania (urban Cluj)
Stomach	22	Japan (Nagasaki)	Kuwait (Kuwaitis)
Thyroid	22	Hawaii (Chinese)	Poland (Warsaw City)
Multiple myeloma	22	United States (Alameda, CA, black)	Philippines (rural)
Kidney	21	Canada (Northwest Territory, Yukon)	India (Poona)
<i>Corpus uteri</i> (female)	21	United States (San Francisco Bay area, white)	India (Nagpur)
Lung	19	United States (New Orleans, black)	India (Madras)
Colon	19	United States (CT, white)	India (Madras)
Testis	17	Switzerland (urban Vaud)	China (Tianjin)
Bladder	16	Switzerland (Basel)	India (Nagpur)
Lymphosarcoma	12	Switzerland (Basel)	Japan (rural Miyagi)
Pancreas	11	United States (Los Angeles, Korean)	India (Poona)
Hodgkin's disease	10	Canada (Quebec)	Japan (Miyagi)
Brain	9	New Zealand (Polynesian Islanders)	India (Nagpur)
Larynx	8	Brazil (São Paulo)	Japan (rural Miyagi)
Ovary (female)	8	New Zealand (Polynesian Islanders)	Kuwait (Kuwaitis)
Rectum	8	Israel (Born in Europe, America)	Kuwait (Kuwaitis)
Breast (female)	7	Hawaii (Hawaiian)	Israel (non-Jews)
Leukemia	5	Canada (Ontario)	India (Nagpur)

Data from Fraumeni et al. (1), adapted from Parkin et al. (2).

Table 2. United States variation in cancer incidence for males by site: average annual age-adjusted incidence rates in males.

Type of cancer	White	Black	Hispanic	Native American	Chinese	Japanese	Filipino	Hawaiian
All sites	404.1	490.2	265.5	184.5	292.7	303.6	242.0	398.9
Esophagus	4.9	18.4	2.9	1.9	6.1	5.6	4.9	15.1
Stomach	11.5	20.5	20.8	26.1	14.5	38.6	9.6	40.4
Colon	40.3	40.7	17.9	8.4	33.6	42.1	24.0	25.8
Rectum	20.0	14.9	11.5	5.0	19.3	23.4	16.9	18.7
Liver	2.7	5.2	4.5	19.5	7.1	10.2	9.8	2.7
Gall bladder	0.8	0.8	1.5	8.9	1.2	1.5	1.2	1.4
Lung/bronchus	82.1	119.6	32.2	14.2	60.2	48.4	39.9	108.2
Skin melanoma	9.8	0.8	1.6	2.2	0.4	1.5	1.2	1.6
Prostate	77.3	122.8	71.5	45.5	32.5	45.7	47.4	59.6
Testis	4.2	0.8	3.0	1.8	1.9	1.3	0.5	2.6
Bladder	30.2	15.1	10.9	3.6	13.9	12.5	6.0	10.6
Brain/nervous system	7.3	4.3	4.9	3.1	3.0	3.1	3.4	3.1

Based on data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, adapted from Parker et al. (2).

Table 3. United States variation in cancer incidence for females by site: average annual age-adjusted incidence rates in females.

Type of cancer	White	Black	Hispanic	Native American	Chinese	Japanese	Filipino	Hawaiian
All sites	316.1	296.6	220.4	168.8	242.2	214.0	202.6	344.1
Esophagus	1.6	5.0	0.8	0.3	1.2	0.8	1.9	2.2
Stomach	5.1	8.5	10.0	12.3	8.7	19.0	7.2	17.9
Colon	32.3	35.0	16.7	8.1	23.7	25.7	14.9	16.3
Rectum	12.8	10.8	7.6	3.2	10.9	10.9	8.1	8.1
Liver	1.1	1.7	1.9	2.6	4.7	2.4	3.2	2.7
Gall bladder	0.6	1.1	7.1	17.1	1.0	1.7	1.8	1.3
Lung/bronchus	29.7	31.2	15.6	4.6	27.6	13.2	17.9	45.8
Skin melanoma	8.2	0.7	2.2	0.7	0.7	1.0	0.9	1.0
Breast	91.5	76.4	50.9	25.6	58.7	57.1	45.6	104.6
<i>Cervix uteri</i>	8.8	19.7	17.1	20.0	10.5	5.8	10.8	14.5
Bladder	7.7	5.5	3.3	0.4	4.0	4.4	3.1	6.0
Brain/nervous system	5.1	2.9	2.4	1.8	2.7	2.2	1.3	4.2

Based on data from the SEER Program, adapted from Parker et al. (2).

collected by the Surveillance, Epidemiology, and End Results Program (SEER) in the United States.

There are marked differences in the United States and worldwide in the ethnic distribution of age, socioeconomic status (SES), and occupation (3,7-11). Because these factors are strong determinants of cancer risk, differences in their distribution among ethnic groups could explain a portion of the ethnic variation in cancer rates. However, variation in age is accounted for in the data by age adjustment and does not contribute to ethnic differences in rates; while critical review of the literature is beyond the scope of this discussion, SES and occupation do not appear to fully explain the ethnic variation in cancer risk for most cancer sites (3,7,9-11).

Environmental factors, including lifestyle and dietary factors, have traditionally been thought to be the main contributors to ethnic differences in cancer rates (3,9,11). In a now classic analysis, Doll and Peto (11) examined international differences in cancer rates and concluded that 80% of cancers had environmental causes. However, new biological evidence and theories of carcinogenesis suggest this interpretation of ethnic variation in cancer rates may need to be revised.

Carcinogenesis is now recognized to be a multistep process with crucial steps involving mutations or heritable changes in expression of key genes involved in cellular growth control and genome stability (12-14). Cancer risk is determined by the probability of mutations in key genes (13). In this model, individual genetic susceptibility can arise by two pathways; first, from mutations in key genes on the pathway to cancer, such as oncogenes and tumor suppressor genes; and second, from genotypes that increase the probability of mutations in key genes in conjunction with specific environmental exposures.

The role of genetic susceptibility as an explanation for ethnic variation in cancer risk has not been extensively studied. Overall measures of genetic differences in populations indicate that genetic variation is as least as great within ethnic groups as between groups. However, ethnic variation in the distribution of specific susceptibility genotypes does occur. The distribution of a number of mutations in tumor suppressor genes and metabolic polymorphisms has been reported to vary by ethnic group (15-17).

Incidence rates for breast cancer show marked contrasts among ethnic groups

(16,18–20). Mutations in the *BRCA1* gene are associated with increased risk for breast and ovarian cancer. This gene is composed of 5592 nucleotides spread over 100,000 bases of genomic DNA. It contains 22 coding exons that produce an 1863 amino acid protein, which shows no homology to any known protein except for a RING finger motif near the *N*-terminus. It is thought to act as a tumor suppressor gene (21).

Carriers of *BRCA1* mutations are heterozygotes and have been shown to have a greater than 85% lifetime risk of developing breast cancer and 45% risk of ovarian cancer compared to a 12% risk for women in the general population (22,23). The risk of breast cancer for carriers of *BRCA1* mutations varies by age; women 50 years of age have a 50% risk for breast cancer. The frequency of *BRCA1* mutations within a population varies between ethnic groups, from 1 in >1000 for Japanese to 1 in 100 for Ashkenazi Jews (16,19,24). Studies have also indicated that some mutations are specific for a given ethnic group, such as the 185 *delAG* mutation found in the Ashkenazis (25). Differences in genotype distribution may result from differences in consanguinity, mutation rate, natural selection, and random effects such as founder effects and isolation (4).

To consider the potential contribution of genetic susceptibility to ethnic variation in cancer incidence, we used simple probability models to estimate the magnitude of cancer risk differences that might stem from ethnic differences in genetic susceptibility arising from one of the two pathways to increased risk and inheritance of mutations in a tumor suppressor gene. We assumed the simple case where risk is independent of exposure.

Methods

For populations, genetic susceptibility is defined as the proportion of the population with either germline mutations of key genes, such as oncogenes or tumor suppressor genes, or with susceptibility genotypes. The proportion with susceptibility genotypes depends on the frequency of susceptibility alleles and the functional relationship between alleles. Consider a simple model for genetic susceptibility in an ethnic population: Genetic susceptibility arises from one gene with two alleles, with one allele, *N*, for nonsusceptibility and the second allele, *S*, for susceptibility. The alleles follow Mendelian inheritance in either a dominant or recessive pattern.

The proportion of the population with susceptibility genotypes depends upon whether the susceptible allele, *S*, is dominant or recessive. If it is dominant, as with tumor suppressor genes, both *SS* and *NS* genotypes will be susceptible and the proportion of susceptibles in the population will be given by $q(2-q)$, where q is the susceptible allele frequency. For the case where the susceptibility allele is recessive, only the *SS* genotype will be susceptible and the proportion of susceptibles in the population will be given by q^2 . For a susceptibility allele frequency of 10%, a dominant susceptibility allele will result in 19% being susceptible. Under a recessive model, only 1% of the population is susceptible. In the following models, the susceptible proportion will be used as the parameter for population genetic susceptibility.

In a comparison of rates in two ethnic groups, where RRe = ethnic relative risk, R_a = the disease risk in ethnic group *A*, and R_b = the disease risk in ethnic group *B*

$$RRe = \frac{R_a}{R_b}$$

is an accepted measure of ethnic variation in cancer risk.

In the simple case in which cancer risk is determined by inheritance of a mutation in a single tumor suppressor gene and ethnic differences in risk arise from differences in the allele distribution of this gene, the ethnic relative risk can be expressed as a ratio of disease risk between the two ethnic groups:

$$RRe = \frac{P_a(R_g - 1) + 1}{P_b(R_g - 1) + 1}$$

where P_a and P_b are the proportions of susceptibles in groups *A* and *B*, respectively, and R_g is the risk ratio for those with the susceptible genotype compared with those with the nonsusceptible genotype. Assumptions for this model are that baseline risks are equal in the two ethnic groups, and R_g is constant and independent of exposure or mutation spectrum.

Figures 1 and 2 illustrate the general form of the relationship among RRe , R_g , and the distribution of the proportion of susceptibles. For specific examples, we chose to examine the ethnic relative risk that could arise from differences in the proportion with cancer susceptibility arising from tumor suppressor genes with dif-

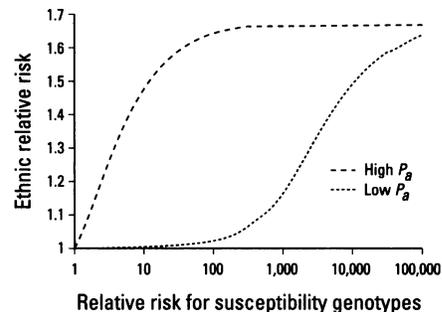


Figure 1. Relative risk comparing any two ethnic groups' asymptotic behavior for a fixed ratio of susceptibility genotype proportion.

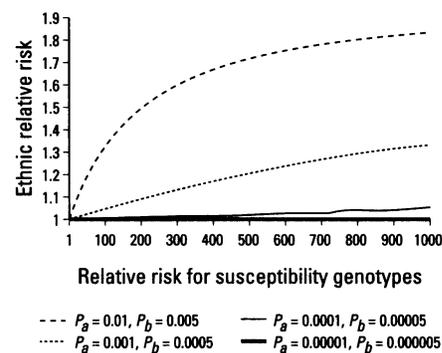


Figure 2. Relative risk comparing any two ethnic groups with differing proportions of susceptibility genotypes.

ferent characteristics, *p53* and *BRCA1*. The germline mutation frequency for *p53* is low, approximately 10^{-5} , but the cancer relative risk is high, in the 10^4 to 10^5 range (26). For *BRCA1*, the frequency is approximately 5 per 1000, but it has been found to show ethnic variation (16,17,25). The relative risk associated with *BRCA1* varies with age and is approximately 200 in women aged less than 45 years.

Results and Discussion

Figure 1 shows the general relationship between the ethnic relative risk (RRe), shown on the *y* axis, the relative risk for susceptibility genotypes, R_g , shown on the *x* axis, and two pairs of values for the susceptible proportions in two ethnic groups, denoted by P_a and P_b . The maximum value of the RRe will not exceed the ratio of susceptible proportions in the two groups, P_a/P_b . For example, if the proportion susceptible in ethnic group *A* is twice that in ethnic group *B*, the maximum RRe is 2. The maximum ethnic relative risk reflects the ratio of P_a and P_b , not the magnitude of R_g , the relative risk for susceptibility genotypes.

The rate at which the ethnic relative risk approaches its maximum value as R_g increases depends upon the magnitude of the proportion of susceptibles in the groups. To see this more concretely, consider two scenarios, both with a P_a/P_b ratio of 5, as shown in Figure 1. First, in the high P_a scenario half of group A is susceptible, so $P_a=0.5$ and one-tenth of group B is susceptible, so $P_b=0.1$, giving a P_a/P_b ratio of 5. Second, the low P_a scenario, where $P_a=0.05$ and $P_b=0.01$, again a P_a/P_b ratio of 5. As the relative risk for susceptibility genotypes increases, the ethnic relative risk increases to its maximum faster for the high P_a than for the low P_a scenario. Thus for a given susceptibility genotype, relative risk and P_a/P_b ratio, the higher the proportion of susceptibles, the higher the ethnic relative risk.

In consideration of plausible values of P_a and P_b and relative risks for susceptibility genotypes, Figure 2 shows the ethnic

relative risk on the y axis and the relative risk for susceptibility genotype on the x axis. The ranges of the relative risks for the genotype and the groups proportion of susceptibles were chosen for plausible values for tumor suppressor genes $p53$ and $BRCA1$.

Figure 2 shows a comparison of two ethnic groups with differing $BRCA1$ mutation frequencies, with RRe for a susceptible proportion of 1 in 100 versus 5 in 1000. The ethnic relative risk increases rapidly to 1.5 for a susceptibility genotype relative risk of 200. These values of the susceptibility proportion and genotype relative risks are in the ballpark for $BRCA1$ in young women from specific ethnic groups (16,17,25). Differences in $BRCA1$ frequency could explain ethnic relative risks for breast cancer in the 1.5 to 2 range for young women.

For a population with lower susceptibility proportions, such as that observed

for germline $p53$ mutations, the ethnic relative risk is small for plausible relative risks for susceptible genotypes. These values are in the range observed for several tumor suppressor genes, indicating that these genes are unlikely to explain even small ethnic differences.

In summary, ethnic differences in cancer occurrence may be a marker of differences in genetic susceptibility. For breast cancer, observed differences in the frequency of $BRCA1$ mutations could account for ethnic differences in rates for young women. However, the magnitude of ethnic relative risk is likely to more strongly reflect differences in the distribution of susceptibility genotypes between groups than the magnitude of the disease risk associated with the genotypes. For many scenarios, the ethnic relative risk arising from differences in susceptibility may be bounded by the ratio of the proportion of susceptible individuals in each group.

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