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 on 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.
### 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) |
| Cervix uteri(female) | 26         | 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 (Poonia) |
| Corpus uteri(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         | 16               | 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 (Poonia) |
| Hodgkin’s disease | 10          | Canada (Quebec)       | Japan (Miyagi) |
| Brain          | 9                | New Zealand (Polynesian Islanders) | India (Nagpur) |
| Larynx         | 8                | Brazil (Sao 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   | 36.6     | 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     |
| Gallbladder    | 0.8   | 0.8   | 1.5      | 6.9             | 1.2    | 1.5      | 1.4     | 1.4     |
| Lung/bronchus  | 82.1  | 116.6 | 32.7     | 14.2            | 60.2   | 49.4     | 39.1    | 108.2   |
| Skin melanoma  | 9.8   | 2.2   | 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        | 2.2   | 15.1  | 10.9     | 3.6             | 13.9   | 12.5     | 6.2     | 10.1    |
| Brain/nervous system | 7.3  | 4.3   | 4.9      | 3.9             | 3.0    | 3.1      | 3.4     | 3.1     |

Based on data from the Surveillance, Epidemiology, and End Results Program (SEER) (1996). Adapted from Parkin et al. (1997).

### 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   | 341.9   |
| 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     |
| Gallbladder    | 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   |
| Cervix uteri   | 8.8   | 19.7  | 17.1     | 20.0            | 10.5   | 5.6      | 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 (1996), adapted from Parkin et al. (1997).
(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, \( A \), 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:

\[
RRe = \frac{P_a(Rg - 1) + 1}{P_b(Rg - 1) + 1}
\]

where \( P_a \) and \( P_b \) are the proportions of susceptibles in groups \( A \) and \( B \), respectively, and \( Rg = \) 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 \( Rg = \) constant and independent of exposure or mutation spectrum.

Figures 1 and 2 illustrate the general form of the relationship among \( RRe \), \( Rg \), 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 different 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, \( Rg \), 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 \( Rg \), the relative risk for susceptibility genotypes.
The rate at which the ethnic relative risk approaches its maximum value as \( Rg \) increases depends upon the magnitude of the proportion of susceptibles in the groups. To see this more concretely, consider two scenarios, both with a \( P_s/P_d \) ratio of 5, as shown in Figure 1. First, in the high \( P_s \) scenario half of group \( A \) is susceptible, so \( P_s = 0.5 \) and one-tenth of group \( B \) is susceptible, so \( P_s = 0.1 \), giving a \( P_s/P_d \) ratio of 5. Second, the low \( P_s \) scenario, where \( P_s = 0.05 \) and \( P_s = 0.01 \), again a \( P_s/P_d \) ratio of 5. As the relative risk for susceptibility genotypes increases, the ethnic relative risk increases to its maximum faster for the high \( P_s \) than for the low \( P_s \) scenario. Thus for a given susceptibility genotype, relative risk and \( P_s/P_d \) ratio, the higher the proportion of susceptibles, the higher the ethnic relative risk.

In consideration of plausible values of \( P_s \) and \( P_d \) 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.

REFERENCES

1. Fraumeni J Jr, Devesa S, Hoover R, Kinlen L. Epidemiology of cancer. In: Cancer: Principles and Practice of Oncology, Vol 1 (DeVita V Jr, Hellman S, Rosenberg S, eds). Philadelphia:J.B. Lippincott, 1994:150–183.
2. Parkin D, Muir C, Whelan S, Gao Y, Ferlay J, Powell J, eds. Cancer Incidence in Five Continents, Vol 6. IARC Scientific Publications No 120. Lyon:International Agency for Research on Cancer, 1992.
3. Tomatis L, Aitio A, Day N, Heseltine E, Kaldor J, Miller A, Parkin D, Riboli E, eds. Cancer: Causes, Occurrence and Control. IARC Scientific Publications No 100. Lyon: International Agency for Research on Cancer, 1990.
4. Poleidnak A. Host Factors in Disease: Age, Sex, Racial and Ethnic Group, and Body Build. Springfield, IL:CC Thomas, 1987.
5. Polendak A. Racial and Ethnic Differences in Disease. New York:Oxford University Press, 1989.
6. MacMahon B, Pugh T. Epidemiology: Principles and Methods. Boston:Little Brown, 1970.
7. Pearce N, Maros E, Vainio H, Boffetta P, Kogevinas M, eds. Occupational Cancer in Developing Countries. IARC Scientific Publications No 129. Lyon:International Agency for Research on Cancer, 1994.
8. U.S. Bureau of the Census. Census of the Population 1990: Social and Economic Characteristics. Final Report. New Mexico. CP 2-33. Washington:U.S. Government Printing Office, 1990.
9. Schottenfeld D, Fraumeni JF. Cancer Epidemiology and Prevention. Philadelphia:W.B. Saunders, 1982.
10. Jones L, ed. Minorities and Cancer. New York:Springer-Verlag, 1989.
11. Doll R, Peto R. The Causes of Cancer. Oxford:Oxford University Press, 1981.
12. Harris C. Tumor suppressor genes, multistage carcinogenesis and molecular epidemiology. In: Mechanisms of Carcinogenesis in Risk Identification (Vainio H, Magee P, McGregor D, McMichael A, eds). IARC Scientific Publications No 116. Lyon:International Agency for Research on Cancer, 1992:67–85.
13. Knudson A. The genetic predisposition to cancer. Birth Defects Orig Artic Ser 25:15–27 (1989).
14. Knudson A. Hereditary cancer, oncogenes, and antioncogenes. Cancer Res 45:1437–1443 (1985).
15. Shields P. Pharmacogenetics: detecting sensitive populations. Environ Health Perspect 102(Suppl 11):81–87 (1994).
16. Inoue R, Fukutomi T, Ushijima T, Matsumoto Y, Sugimura T, Nagao M. Germline mutation of \( BRCA1 \) in Japanese breast cancer families. Cancer Res 55:3521–3524 (1995).
17. Ford D, Easton D, Bishop D, Narod S, Goldgar D. Risks of cancer in \( BRCA1 \)-mutation carriers. Breast Cancer Linkage Consortium. Lancet 343:692–695 (1994).
18. Johannsson O, Ostermeyer E, Hakansson S, Friedman L, Johannsson U, Sellberg G, Brundum-Nielsen K, Selc V, Olson H, King M-C et al. Founding \( BRCA1 \) mutations in hereditary breast and ovarian cancer in southern Sweden. Am J Hum Genet 58:441–450 (1996).
19. Struwing JP, Abellovic D, Peretz T, Avishai N, Kackab MM, Collins FS, Brody L.C. The carrier frequency of the \( BRCA1 \) 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet 11:198–200 (1995).
20. Barkardottir RB, Arason A, Egilsson V, Gudmundsdottson J, Jonassdottr A, Johannesdottir G. Chromosome 17q-linkage seems to be infrequent in Icelandic families at risk of breast cancer. Acta Oncol 34:657–662 (1995).
21. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W et al. A strong candidate for the breast and ovarian cancer susceptibility gene \( BRCA1 \). Science 266:66–71 (1994).
22. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. Breast Cancer Linkage Consortium. Am J Hum Genet 52:678–701 (1993).
23. Szabo CI, King MC. Inherited breast and ovarian cancer. Hum Mol Genet 4:1811–1817 (1995).
24. Ford D, Easton DF. The genetics of breast and ovarian cancer. Br J Cancer 72:805–812 (1995).
25. Goldgar DE, Reilly PR. A common \( BRCA1 \) mutation in the Ashkenazim. Nat Genet 11:113–114 (1995).
26. Knudson A. Antioncogenes and human cancer. Proc Natl Acad Sci USA 90:10914–10921 (1993).