Race and Cancer Genetics: Lessons From BRCA1

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The effect of a patient’s race or ethnicity on cancer incidence and mortality rates remains a neglected area of cancer research. However, with cancer statistics differing among various populations, research on racial and ethnic groups could provide clues to cancer trends.

Cancer incidence and mortality rates vary among ethnic and racial groups. These differences offer clues to the causes, risk factors, and forces that influence the development and progression of cancer. Although some authors have attributed varying rates to genetic differences, epigenetic influences on cancer are becoming more appreciated. Still, as cancer research seeks to explain why cancer statistics differ among various groups of people, practical details concerning research on racial and ethnic groups remain neglected.

Two questions are critical: (1) When is genetic research on a population appropriate? (2) How should researchers define a given population being studied? All research on ethnic groups must, in fact, address these two questions, even if investigators do not explicitly take them into consideration. Studies of Ashkenazi Jews and BRCA1/2, for instance, represent fairly concrete genetic analyses on a specific population. As such, an examination of these studies offers a simplified vantage point from which to dissect the practicalities of ethnic research as well as clarify what is necessary for research concerning all racial and ethnic groups.

When Is Genetic Research on a Population Appropriate?

The concept of "race" implies a genetic homogeneity among a group of people that correlates with skin hue or other physical characteristics. Yet modern genetic techniques have repeatedly demonstrated that the amount of variation within a racial group is greater than the difference between two groups.[1] Such findings are not surprising, given the arbitrary nature of definitions used to categorize people. For instance, in Virginia in 1750, a person was considered a member of the "Negro" race if born to a "Negro" mother. Later, the definition was changed, and a person was designated as Negro if he or she had "one drop of Negro blood."[2] Moreover, at varying times in the 20th century, immigrants from India have been categorized as white, Asian, and Indian. Clearly then, such definitions are political and unscientific. Dividing people into racial groups is more a consequence of social constructs than a reflection of biological reality.

"Ethnicity" is another term that is sometimes used interchangeably with "race." Yet, unlike race, ethnicity includes a variety of social factors and is not strictly a biological term.[3] As Bhopal defines it, ethnicity denotes "a group that people belong to because of shared characteristics, including ancestral and geographical origins, cultural traditions, and language."[4] Like race, however, ethnicity is a socially constructed phenomenon. Ethnic boundaries are based primarily on self-assessment, and are thus inherently imprecise and can change over time or depending on the specific context.[5]

Thus, it is not surprising that racial and ethnic groups do not represent a genetically homogeneous population. In some instances, however, a correlation exists between an ethnic group and a specific mutation, as can occur in situations of enforced segregation. For example, approximately 20% of Ashkenazi Jewish women with breast cancer carry mutations in BRCA1 or BRCA2—a finding that is 10- to 15-fold higher than in breast cancer patients who are not Jewish.[6] Specific mutations in both BRCA1 and BRCA2 are present at least 10 times more often in unaffected Ashkenazi Jewish women than in the general population.[7] Nevertheless, the Ashkenazi Jewish population does not monopolize the gene. The genetic mutations associated with cancer have been found in people of several races and ethnicities.[8]

Familial vs Racial Correlations

Although they have been associated with the entire Ashkenazi population, such genetic abnormalities should be considered familial and not racial. This is particularly true given the high rates of intermarriage among the American Jewish population; any genetic homogeneity that may have existed under the conditions of segregated ghettos in Eastern Europe has been and continues
to be diluted. This point is confirmed by looking at the prevalence of the 185delAG BRCA1 mutation among groups of Ashkenazi Jewish breast cancer patients, as was determined in 14 separate studies. When patients are unselected for family history of breast or ovarian cancer, prevalence rates range from 3% to 48% (Table 1).[6,7,9-19] When the same data, however, are stratified by degree of family history, prevalence rates become more consistent from study to study (Table 2).[6,7,9-19] These data suggest that it is not only being an Ashkenazi Jew that increases one’s risk of carrying the 185delAG mutation, but rather, being an Ashkenazi Jew with a positive family history of the mutation. As family history of breast or ovarian cancer increases, so does the risk of carrying the mutation.

It seems that this point is often overlooked. Soon after the higher rates of these genetic abnormalities were realized, the possibility of conducting community-wide screening within both the medical and Jewish communities was considered. It was ultimately determined that

> [i]n view of the low predictive value of positive mutation testing without strong family histories, together with the lack of effective primary and secondary breast cancer-prevention measures, screening and counseling measures may be best focused on high-risk women.[9]

That so much effort was initially expended in determining population-wide prevalence rates suggests that some researchers were naively assuming a genetic homogeneity among Ashkenazi Jews. Perhaps research efforts may have been directed more efficiently at Ashkenazi Jewish women who were unable to determine their family history, such as women with few female relatives or Holocaust survivors who had lost much of their family.

The point then is that it is wrong to assume genetic similarities among people because they identify with a common group. Any trends that do exist within a given population can be attributed to specific families and not to the group as a whole.

**How Should Researchers Define a Population Being Studied?**

Given the arbitrary nature of racial and ethnic categorizations, one practical issue for research is how to define a given population. The US Office of Management and Budget (OMB) has designated five categories to be used at a minimum in collecting and presenting data on race and ethnicity: (1) American Indian or Alaska Native, (2) Asian, (3) black or African-American, (4) Native Hawaiian or other Pacific Islander, and (5) white. The OMB admits that these categories have no scientific or biological basis.[20]

Such categories also do little to facilitate the classification of individuals from multiethnic backgrounds. As Newton and Feit point out:

> How white is white? At what point in one’s ancestry does race change? Is a person who has only one grandparent of another race defined or categorized the same as one who has one great-grandparent or two great-grandparents? What happens if two grandparents are white, one is black, and another Asian?[21]

A definition of an Ashkenazi Jewish population must consider many of the same issues, particularly since individuals can convert to Judaism, and subsequently, be included in Jewish ethnic categories despite a dissimilar ancestry. Such potential for variation seems contrary to the carefully controlled methods of scientific investigation.

**Reporting of Ethnic Populations**

Several authors have pointed out the need for more attention to the way in which ethnic populations are being selected for research studies. For example, Huth argues that reports on trials that require ethnic identification of the subjects...

> could be expected to include statements on whether the investigators categorized persons according to ethnicity and on the definitions that were used, or on whether persons categorized themselves using their own terms or terms supplied by the investigators. Such information could be crucial for scientifically sound judgements about the apparent ethnic differences and the generalizability of the results.[1]

Similarly, Witzig suggests, "if ethnicity is to be clinically useful in medicine, a strict methodologic approach equal to that required for the study of other clinically relevant variables will be
necessary."[3] Senior and Bhopal also emphasize the need for researchers to detail how ethnic identifications were made.[5]

Nevertheless, it seems that such details are often left out of reports, and if included, lack adequate information to be useful. Of the 14 articles concerning Ashkenazi Jews and BRCA1 and BRCA2 mutations, 50% made no reference to the way in which the ethnicity of their subjects was determined. The remaining seven mentioned that patients identified their own ethnicities; of these, four required patients to identify themselves as "Jewish" and three required patients to identify themselves as "Ashkenazi Jewish." These observations are summarized in Figure 1, and the specific comments regarding this aspect of the studies are listed in Table 3. [6,7,9-19,22]

Only one study identified what comprised an acceptable ancestry, requiring that "participants were at least 50% Ashkenazi Jewish descent."[19] Having some type of "ethnicity standard" for study participants seems important, given that there is potential for a great deal of variation in the ancestry of the study participants and that 9 of the 14 studies used population samples of 50 individuals or less.

**Validity of Study Results**

Clearly, as ancestry requirements become more stringent, the more challenging it is for researchers to recruit study participants. Nevertheless, ignoring such obstacles leaves the validity of the results open to criticism. In addition, not specifying the ancestry required of study participants makes it difficult to compare results from different studies. When specifically examining genetic questions, it would be difficult to compare a study requiring 50% Ashkenazi Jewish heritage to one requiring 100% Ashkenazi Jewish heritage. Such detail is also relevant for determining the population to which the results are applicable.

Another issue concerns the validity of self-identification of ethnicity for research purposes. Self-identification is currently the most common means used to categorize people. It is a fairly straightforward method and is considered politically correct in that it does not impinge upon the autonomy of the research subject. Nevertheless, it seems that few efforts have been made to determine whether self-identification of ethnicity is a consistent and dependable research method. Indeed, this might be an important area for future research. It is potentially dangerous to assume that individuals possess a specific genetic background or health variable just because they assign themselves to a particular ethnic group.

**Conclusions**

Looking at cancer data stratified by ethnic groups has the potential to provide much important information on the effects of various environmental exposures. Still, it seems that using population groups as a research tool requires a great deal more care than has been taken in the past. Researchers must recognize the inherent heterogeneity within any ethnic or racial classification. Genetic studies are warranted only under rare circumstances in which genetic segregation has occurred. In addition, although definitions used to select various populations may not need to be consistent from study to study, they should at the very least be made explicit.

In the history of science, this certainly is not the first time that research efforts have been directed at racial groups. Many previous attempts at racial research, however, leave little to be commended because of the blatant bias with which investigators pursued their investigations. As a result, eugenics, phrenology, and similar efforts have been demoted to little more than pseudoscience. With foresight and extra attention to those areas most sensitive to bias and prejudice, today’s efforts hopefully will not suffer a similar fate in the eyes of future researchers.

**References:**


