Familiality of Cancer in Utah

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ABSTRACT

The Utah Population Database allows examination of the genetic relationships among the 35.7% of all cancer cases in the state that have genealogical records. Familial clustering of cancer is measured by the Genealogical Index of Familiality and is examined by site, and within site by age of onset, histology, and gender. Most cancer sites examined show excess familiality for all cases considered together. Subsets of individuals with certain characteristics showed unusually high levels of familial clustering, specifically lymphocytic leukemias and especially chronic lymphocytic leukemia, lobular breast cancer, early lip cancer, early melanoma, and female lung cancers of alveolar/adenoma histology. These may represent characteristics of the most penetrant forms of inherited susceptibilities, those which are enhanced by environmental factors, chance aggregations, rare inherited syndromes, or a combination of these factors.

INTRODUCTION

Efforts to construct the UPDB\(^1\) began in 1974 (1–4). The UPDB is a unique combination of 3 Utah data sources including a genealogy, the Utah Cancer Registry, and the Utah death certificates. The core of this database is a genealogy of the Utah pioneers and their descendants with approximately one million individual records and 180,000 family records. The genealogical data have been linked to cancer records reported by the state, and to state death certificates by unique concordance of name and birth date. The death certificate files were not utilized for this analysis. The UPDB has made possible the investigation of the genetic relationships between individuals with given cancer characteristics within a defined population.

We have previously analyzed the database to estimate the degree of familial coaggregation of pairs of cancer sites using Utah Cancer Registry records from 1952 through 1982 (5–9). The record linking of the 10 most recent years of cancer data, through 1992, has nearly doubled the available records. This provides a view of 25 years of cancer in this population, allowing identification of cancer in more than one generation in many cases. We present the most recent analysis of the UPDB. Sample sizes are significantly increased, allowing comparison of more sites than have been described previously.

Much of the Utah population are descendants of the Utah pioneers who were mostly members of the LDS (or Mormons). Most members of the LDS abide by its proscriptions against consumption of coffee, tea, tobacco, and alcohol. LDS teachings encourage large, close-knit families and strict sexual mores. The average number of children per couple during the second half of the 19th century was 7.7 children for once-married women (3), and Mormons continue to have large families in this century. Polygamy was practiced by between 10 and 20% of male pioneers prior to 1890, which further increased the size of kindreds. There were approximately 10,000 founding pioneers, who were largely unrelated. Genetic studies of the population have shown that it is genetically representative of a Northern European population (10), and due to a continued influx of immigrants has normal levels of inbreeding (11).

Cancer rates in Utah for the years 1966 through 1990 are low when compared to the United States Third National Cancer Survey (12). Table 1 summarizes United States and Utah comparisons for data from 1966 to 1973. Utah males have a lifetime risk of developing cancer of approximately 20%, and Utah females have a lifetime risk of approximately 24%. Utah has the lowest overall cancer incidence in the Surveillance Epidemiology and End Results program of the National Cancer Institute. This is largely due to the much lower Utah rates for smoking-associated cancers; Utah has the lowest smoking rates of any state in national surveys. Cancer incidence comparisons between Mormons and non-Mormons have been described (13).

SUBJECTS AND METHODS

The Utah Population Database. Genealogical work is a key aspect of membership in the LDS. Members are encouraged to keep family group sheets for their immediate family and ancestors, and to submit them to the Genealogical Society of Utah. The society was established in 1894, and maintained a library of the 8 million-plus group sheets compiled, the source of the UPDB. All family group sheets which contained at least one birth, death, or marriage date in Utah or along the pioneer trail were obtained from the Society (3). Data on the individuals and marriages contained in these family group sheets have been computerized, and all the individuals have been linked into a genealogy representing the Utah descendants of the Mormon pioneers (1, 2). Each group sheet contains information on a full sibship and their parents, including for each individual: name, place and date of birth, marriage date, date of death, and spouse name. In addition, place of death and spouse death date are also available for the parents on each group sheet. The names of the grandparents are also included. Adopted individuals are noted, as are all births.

State-of-the-art methods for record linking have been implemented in the UPDB. A probabilistic record linking program, LNX, developed by R. Kerber, has been used to link cancer registry records through 1992 to the genealogy. The linking algorithm used by LNX is very similar to that pioneered by Newcombe and Kennedy (14), and implemented in the generalized iterative record linking system program (15).

The Utah Cancer Registry was initiated in 1958, made statewide in 1966, and includes cancer records dating back to 1952. All cancers except basal and squamous carcinomas of the skin must be reported to the Utah Cancer Registry by order of the Utah State Board of Health. In 1973, the registry became one of 11 population-based registries of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. The registry maintains abstracts of clinical records and follow-up information on all cases. There are currently 125,904 entries in the registry files (through August 1992) representing 117,407 individuals, 41,940 of whom linked to the UPDB genealogy (35.7%). The percentage of linked records is lower for females than males, as name changes reduce the probability of successfully linking a woman's record. The percentage of linked records reflects the fact that not all cancer cases are individuals who would be represented in the genealogy of the Utah pioneers. This is a result of 2 factors; a high percentage of cancer cases are non-Mormon, and the genealogy file is missing individual records for some Mormon individuals who have had cancer. The records are coded by site according to the International Classification of Diseases for Oncology (Third Revision) and...
contain detailed information on diagnosis, histology, treatment, and survival of patients. Definitions of cancer sites are by primary site and histology and behavior codes as described in The International Classification of Diseases for Oncology (16). The lymphoma site grouping is based on histology, not primary site, and includes all lymphoma histologies regardless of primary site. All other site groups exclude lymphoma histologies. A Technical Report summarizing cancer groupings is available upon request (17).

GIF. The GIF was initially developed to measure the degree of family clustering in the UPDB. The method measures the degree of relationship between all possible pairs of individuals in a group using the Malécot coefficient of kinship (18) to quantify the degree of relatedness between the 2 individuals. The coefficient of kinship for each pair is defined as the probability that randomly selected homologous genes from the 2 individuals are identical by descent from a common ancestor. Calculations of kinship were made by counting paths of common descent. Each path contributes an exponent of 1/2 to the total kinship; the value of the exponent is equal to the number of individuals along a path connecting a pair of cases. For instance, full sibs are connected by 2 routes, one through each parent; their kinship coefficient is the exponent of 1/2 to the total kinship; the value of the exponent is equal to the number of individuals along a path connecting a pair of cases. For instance, full sibs are connected by 2 routes, one through each parent; their kinship coefficient is the sum of 2 terms of exponent 3, giving 1/4. Half sibs are connected by only one path; their kinship is one term of exponent 3, or 1/8. By examining the distribution of all relationships by exponent, it is possible to detect whether an excess of familiality is due to an excess of close relationships or an excess of more distant relationships.

The mean of the coefficients of kinship between all pairs of cases is multiplied by 10^6 and presented as a single measurement of familiality called the GIF. The GIF and the breakdown by exponents for any set of individuals can be compared to the same measurement from a set of randomly selected, matched controls from the same population for meaningful interpretation of the observed familiality. Age-, sex-, and birthplace-matched controls are chosen at random from the UPDB. The distribution of kinship and the mean for the controls varies randomly, depending upon the actual controls chosen, so control groups are selected a number of times and the calculations are repeated. This repetition gives an empirical distribution for the control GIF. One hundred control sets were used in this analysis for each GIF measured.

This empirical method allows a significance test of excess familiality for any group considered. The P value displayed in the Tables represents the significance of the standardized case GIF:

\[
[p = \frac{\text{case GIF} - \text{mean control GIF}}{\text{control SD}}]
\]

when compared with a standard normal distribution. In addition, the GIF is shown in each Table. The MRG is a measure of how extreme the observed GIF of the cases is, taking into account the variability of the control GIFs, which is an important factor for groups with smaller sample sizes. We use the median of the ratio rather than the mean because the ratio of case GIF over control GIF is infinite in a few cases where small control sets contain no related individuals (i.e., control GIF = 0.0). Using the median instead of the mean makes the analysis robust to these cases.

The mean GIF for the controls is comparatively stable over all the cancer sites, with less variation than that noted between cancer sites. This is not unreasonable because for each cancer site the cases have similar year-of-birth distributions, and have approximately the same percentage of individuals born outside the state of Utah (15–20%); also kinship did not vary greatly in Utah for different time periods (5).

The incompleteness of genealogical records or the lack of appropriate genealogical record links will result in an underestimate of the mean coefficient of kinship among a set of individuals. It is therefore important to choose controls so that there is not an inherent difference in the standard of information between cases and controls. In order for a cancer case to be considered in this analysis, it must first be ascertained by the Utah Cancer Registry. This registry has essentially complete ascertainment (13) so that there should not be bias introduced simply by appearance in the registry. The cancer cases considered here must also be record-linked to the genealogy. This requires that a unique individual with exactly the same name and birth date as the cancer case must be found in the genealogy. For this reason, we also require the controls to have birth dates recorded in the genealogy. We have previously examined 3 different methods of control selection. The first method chooses age-, sex-, and birthplace-matched controls from the entire genealogy. The second chooses matched controls who do not have a death date before 1966 (when the Utah Cancer Registry became statewide). The third method required that a death certificate be available for the control and that death occurred after 1966. These 3 methods gave similar results consistent with the random variation inherent in the selection process (8). The first method of control selection was used in these analyses. Since a difference in the number of ancestors between cases and controls may affect the measures of familiality, we compared the average number of ancestors for controls to the average number of ancestors for cases and found no significant difference.

Our previous analyses using this method (5–9) considered only the shortest connecting path between any pair. In this analysis, we found all paths connecting all pairs of individuals and calculated both the total kinship and the breakdown by exponent. We have improved the algorithm for calculation of GIFs, and we present 100 sets of controls for each GIF, rather than the previously published 5 sets. We present an additional measure of familiality, the MRG, as discussed previously.

RESULTS

Familial Clustering of Cancer by Site. Excess risk for cancer for many anatomical sites has been shown in relatives of cancer cases (see review, Ref. 19). However, familiality of many of the less common cancer sites remains unexamined. All cancer sites represented in the Utah Cancer Registry are examined here. The results for the major cancer sites are shown in Table 2, in which sites are ranked by the GIF of cases. Tables 3–8 summarize the results of age-, gender-, and histology-specific subgroups by general site categories.

Each Table shows the cancer site, the number of cases from the state of Utah which linked to the genealogy, the GIF of the cases, the mean GIF of the 100 randomly selected control groups, the MRG, as defined previously and the significance value for the comparison of the case and control kinship. For those sites with at least 300 cases, subsets by age of onset and gender are also shown in Tables 3–8. For sites with a sufficient number of early onset cases, early onset is described as 50 years or younger. For those sites with under 100 cases diagnosed before age 50, the early onset group is comprised of the youngest tercile of all cases, and is termed "youngest." The age of the oldest individual in the set is shown for these "youngest" groups.

Table 2 shows that for all of the 24 sites considered, the case GIF exceeded the mean control GIF, but the excess was not significant for 6 sites: small intestine, gallbladder, kidney, liver, pancreas, and uterus. Cancers of the small intestine showed the highest GIF, but the
excess was not statistically significant ($P = 0.11$). Although the mean control GIF for this site did not differ from other sites, it has a much larger variance due to the small number of cases. The 4 sites with the highest measure of familiality are among the less common cancer sites, including small intestine, lip, testis, and thyroid. Of the more common cancers, melanoma ranks the highest, followed by leukemia, prostate, and colon cancer. Breast cancer, usually thought to be the most familial of the common cancers, is among the cancer sites with relatively low GIF.

Many of the cancer sites with the highest familiality are sites for which Utah incidence is higher than United States incidence. Table 1 shows Utah incidence compared to United States Caucasian incidence for females and males. The sites which have higher incidence in Utah than in United States Caucasians are lip, melanoma, thyroid, connective tissue, and acute leukemia for females; and lip, melanoma, testis, prostate, and connective tissue for males. All are among those cancer sites with the highest measured familiality in the UPDB.

Table 3 shows that cancer at 3 of the 4 female reproductive or genital sites examined demonstrate excess familiality; cancer of the uterus does not. For breast, ovarian, and cervical cancer, the measure of familiality is higher for the early onset cases than the late onset cases. The lobular breast cancer subgroup shows the highest excess familiality, which, although it is higher in the youngest group, appears to be present in both groups.

Table 4 reviews the urogenital and male reproductive sites. Each of the sites except kidney showed significant excess familiality compared to controls. The excess familiality for prostate cancer was observed in both the youngest third and the oldest two-thirds. Although bladder cancer showed excess familiality as a group, no subgroup had a significant excess.

Table 5 reviews the familiality of cancer for hematopoietic sites. Some subgroups of the leukemias showed the highest familiality observed of all cancers considered. Both lymphocytic and granulocytic subgroups showed excess clustering; however, of the lymphocytic leukemias, the excess familiality is observed solely in the CLL cases. Both granulocytic subgroups (CGL and AGL) show excess familiality. In the subgroups examined, the significant excess familiality for lymphocytic leukemia is not observed in the youngest subgroups, but in all others. For granulocytic leukemia, the excess familiality is exclusively seen in the late onset and in the male subgroups. Since leukemias may be histologically subdivided to a greater degree, it would be of interest to see precisely which histological subgroups of CLL, CGL, and AGL are most responsible for this excess familiality. Among the lymphoma cases, it is interesting to note that the non-Hodgkins subgroup shows excess familiality, but not the Hodgkins group. Among the non-Hodgkins subgroups, the excess familiality is observed in all except the early cases. The excess of familiality observed for myeloma is due primarily to the more common late onset and is high for both males and females.

Table 6 summarizes the results for all gastrointestinal sites examined. Of these sites, in addition to cancers of the colon and rectum, which have been long recognized to have a familial component, only stomach cancers also show an excess of familiality. All subgroups of colon cancer show excess familiality, the measure of familiality is highest in the early cases.

Table 7 reviews the familiality for cancers of the skin and connective tissues. Lip cancer is the site with the highest significant excess of familiality (Table 2). Care has been taken in the registry to differentiate between lip cancer and squamous cell skin cancer, which
is reported differently. Melanoma of all sites has been considered as a single group, as well as subdivided into melanoma of the skin, ocular melanoma, and lentigo maligna. Most of the excess familiality observed for melanoma is due to the cases of melanoma of the skin rather than ocular melanomas and lentigines, which are less common.

Cancers of the connective tissues show excess familiality as a whole, and for the male subgroup.

Table 8 summarizes familiality for the remaining cancer sites, including brain, thyroid, and lung. The late and female subgroups appear to contribute most of the excess familiality observed for brain cancer. For lung cancer, which as a whole showed excess familiality, there are 4 histological tumor types considered. All except small cell types show familiality in excess of that expected. The squamous and small cell subtypes are those most strongly associated with lung cancer due to smoking.

Several different graphical presentations have been made, displaying different aspects of the measures. Fig. 1 shows the breakdown of the GIF by kinship exponent, with the contribution from each exposure value displayed for the case GIF, the median control GIF, and the 5th and 95th percentiles of the control GIFs shown for all cancer cases. Fig. 2 shows the breakdown of the GIF by kinship exponent similarly to Fig. 1 for all cancer sites considered separately. Fig. 3
Table 8 Familiality of cancer for brain, lung, and endocrine sites with gender, age of onset, and histology subgroups

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>Case GIF</th>
<th>Mean control GIF</th>
<th>MRG*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>571</td>
<td>3.58</td>
<td>2.75</td>
<td>1.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Early</td>
<td>135</td>
<td>3.59</td>
<td>2.62</td>
<td>0.58</td>
<td>0.859</td>
</tr>
<tr>
<td>Late</td>
<td>435</td>
<td>4.55</td>
<td>2.89</td>
<td>1.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>255</td>
<td>4.76</td>
<td>2.74</td>
<td>1.83</td>
<td>0.004</td>
</tr>
<tr>
<td>Male</td>
<td>316</td>
<td>3.35</td>
<td>2.71</td>
<td>1.26</td>
<td>0.133</td>
</tr>
<tr>
<td>Thyroid</td>
<td>584</td>
<td>4.43</td>
<td>2.61</td>
<td>1.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early</td>
<td>297</td>
<td>4.79</td>
<td>2.69</td>
<td>1.89</td>
<td>0.0002</td>
</tr>
<tr>
<td>Late</td>
<td>287</td>
<td>4.95</td>
<td>2.69</td>
<td>1.97</td>
<td>0.0009</td>
</tr>
<tr>
<td>Female</td>
<td>418</td>
<td>4.16</td>
<td>2.60</td>
<td>1.65</td>
<td>0.0003</td>
</tr>
<tr>
<td>Male</td>
<td>166</td>
<td>4.02</td>
<td>2.51</td>
<td>1.79</td>
<td>0.062</td>
</tr>
<tr>
<td>Lung</td>
<td>2477</td>
<td>3.33</td>
<td>2.77</td>
<td>1.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Youngest (64 yrs)</td>
<td>824</td>
<td>3.95</td>
<td>2.81</td>
<td>1.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oldest</td>
<td>1653</td>
<td>3.20</td>
<td>2.78</td>
<td>1.15</td>
<td>0.007</td>
</tr>
<tr>
<td>Female</td>
<td>510</td>
<td>3.50</td>
<td>2.82</td>
<td>1.25</td>
<td>0.043</td>
</tr>
<tr>
<td>Male</td>
<td>1967</td>
<td>3.37</td>
<td>2.78</td>
<td>1.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alveolar/adenocarcinoma</td>
<td>477</td>
<td>3.67</td>
<td>2.72</td>
<td>1.36</td>
<td>0.008</td>
</tr>
<tr>
<td>Youngest</td>
<td>159</td>
<td>2.86</td>
<td>2.80</td>
<td>1.14</td>
<td>0.479</td>
</tr>
<tr>
<td>Oldest</td>
<td>318</td>
<td>4.71</td>
<td>2.72</td>
<td>1.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>163</td>
<td>6.51</td>
<td>2.73</td>
<td>2.60</td>
<td>0.0007</td>
</tr>
<tr>
<td>Male</td>
<td>314</td>
<td>3.80</td>
<td>2.71</td>
<td>1.42</td>
<td>0.031</td>
</tr>
<tr>
<td>Large cell</td>
<td>635</td>
<td>3.34</td>
<td>2.75</td>
<td>1.23</td>
<td>0.031</td>
</tr>
<tr>
<td>Youngest</td>
<td>212</td>
<td>1.39</td>
<td>2.83</td>
<td>0.51</td>
<td>0.950</td>
</tr>
<tr>
<td>Oldest</td>
<td>423</td>
<td>3.69</td>
<td>2.86</td>
<td>1.30</td>
<td>0.074</td>
</tr>
<tr>
<td>Female</td>
<td>128</td>
<td>1.63</td>
<td>2.89</td>
<td>0.70</td>
<td>0.762</td>
</tr>
<tr>
<td>Male</td>
<td>507</td>
<td>3.30</td>
<td>2.75</td>
<td>1.21</td>
<td>0.093</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>762</td>
<td>3.84</td>
<td>2.74</td>
<td>1.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Youngest</td>
<td>253</td>
<td>5.28</td>
<td>2.76</td>
<td>2.01</td>
<td>0.0004</td>
</tr>
<tr>
<td>Oldest</td>
<td>509</td>
<td>3.55</td>
<td>2.68</td>
<td>1.33</td>
<td>0.032</td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
<td>0.85</td>
<td>2.61</td>
<td>0.47</td>
<td>0.734</td>
</tr>
<tr>
<td>Male</td>
<td>699</td>
<td>3.74</td>
<td>2.75</td>
<td>1.36</td>
<td>0.002</td>
</tr>
<tr>
<td>Small cell</td>
<td>296</td>
<td>3.53</td>
<td>2.83</td>
<td>1.29</td>
<td>0.137</td>
</tr>
</tbody>
</table>

* Median of the distribution of the ratio of the case GIF to the control GIFs.

The UPDB is a unique database which has allowed the hypothesis of familial clustering of a genetic nature to be examined. Previous analyses on a much smaller data set (8) showed a very similar ranking of cancer sites by familiality to that presented here. More sites have been examined here, and some of these less common sites have taken places high in the site ranking of Table 2. These include cancer of the testis, thyroid, and myeloma, which now rank among the top 6 sites for significant excess familiality. The only significant kinship difference in sites which have been previously reported occurred for ovarian cancer, which ranked as the third most familial of sites previously and has now dropped to the level of breast cancer. The number of ovarian cancer cases has increased from 435 to 966. If there are only a few clusters of close relatives among cases, then in the presence of the new samples the effect of these few clusters would be reduced. Table 3 shows that there is still significant excess familiality among the 195 ovarian cases diagnosed before age 50.

It is interesting that many of the sites showing highest familiality are also those for which incidence in Utah is higher than United States incidence. There may be an excess of these sites in Utah due to the presence of a susceptibility gene or genes in earlier generations which are now manifesting themselves in many descendants. Exposure to an additional risk factor in an individual with an inherited susceptibility might also be responsible, e.g., the excess sun exposure in Utah could result in a higher percentage of individuals with a lip cancer susceptibility gene actually expressing the cancer.

It is well recognized that breast and ovarian cancer have a familial component; however, cervical cancer is thought of primarily as a nongenetic disease of viral origin. It appears that only the subgroup of early cervical cancer is responsible for the excess familiality observed.
The distribution of GIF by exponent (Fig. 2) shows that the excess of familiality is observed out to the level of exponent 5, indicating that the excess of familiality is not just due to close relationships.

Lung cancer showed excess familiality (Table 2), and 3 of the 4 histological tumor types still showed excess familiality when considered separately (Table 8). This finding may simply represent the effect of the familiality of smoking; it may represent the interaction of a susceptibility gene for lung cancer and another environmental variable such as smoking; or it may be the result of an inherited lung cancer susceptibility which is entirely unrelated to smoking, but is expressed in a histologically similar manner. Individuals represented in the UPDB do not necessarily practice the LDS’s teachings prohibiting tobacco use. Further studies of these families are necessary to resolve these alternative explanations.

The familiality among the leukemia cases was second only to that observed for lobular breast cancer. Leukemia alone was the seventh most familial of all cancer sites (Table 2), and when examined by histological type, much higher familialities were observed (Table 5). Lymphocytic leukemias clustered more than all leukemias together, and when leukemias were separated into CLL and ALL, only CLL showed excess familiality. Granulocytic leukemias alone showed excess familiality, and showed even further excess when divided into chronic and acute subgroups. This may indicate that there are unique susceptibility genes for each of these leukemia types.

It has been widely reported that cancer which appears at an early age is more likely to be due to an inherited predisposition; however, most of these studies are based on rare kindreds and not on a population. This hypothesis can be tested appropriately by exam-
been reported. The results presented here support the hypothesis of prostate cancer, for which supportive linkage results have not yet existence of more than one susceptibility locus for some cancers, have been hypothesized for other sites including lung cancer and have not yet been isolated (for review, see Ref. 20). Major genes other cancer susceptibility loci have been identified, but the genes effect which leads to higher penetrance in females. The difference may indicate a different gene/environment interaction ef cancer observed are due to an inherited susceptibility, the gender cancer showed excess clustering for males only. If the clusters of lung showed greater excess clustering for females; squamous cell lung cancer was subdivided, the alveolar/adenocarcinoma type thyroid, males showed excess familiality and females did not. When cancers, breast cancer, ovarian cancer, and melanoma all showed higher GIF in early than late onset cases. Although some of this effect may be due to earlier screening and diagnosis in the relatives of young probands, this result also supports the observations of clusters of cancer occurring at very early age which are probably due to rare inherited susceptibility loci. Leukemia and lymphoma both showed much higher familiality in the late onset group than in the early onset group. This late age onset familiality held true for many of the subgroups analyzed. The sites for which only one of the sexes showed a statistically significant excess include kidney, rectum, lip, melanoma of all sites, connective tissue, brain, and thyroid. For all except kidney, brain, and thyroid, males showed excess familiality and females did not. When lung cancer was subdivided, the alveolar/adenoacinaroma type showed greater excess clustering for females; squamous cell lung cancer showed excess clustering for males only. If the clusters of lung cancer observed are due to an inherited susceptibility, the gender difference may indicate a different gene/environment interaction effect which leads to higher penetrance in females.

Many cancer susceptibility genes have already been isolated, and other cancer susceptibility loci have been identified, but the genes have not yet been isolated (for review, see Ref. 20). Major genes have been hypothesized for other sites including lung cancer and prostate cancer, for which supportive linkage results have not yet been reported. The results presented here support the hypothesis of an inherited basis to cancer of almost all sites, and supports the existence of more than one susceptibility locus for some cancers, since subsets of individuals with certain characteristics show excess clustering. These may represent characteristics of individuals with the most penetrant forms of inherited susceptibilities. It remains unclear what fraction of cancer of any particular site is due to an inherited component. Studies of common cancer susceptibilities in the Utah population (21–22) support the similarity to other populations, and suggest that the results should be generally applicable to populations of similar origin.

REFERENCES


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