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CANCER FREQUENCY VARIATIONS AMONG AND WITHIN FAMILIES

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SUMMARY

Comprehension of etiologic factors in cancer requires precise recording of tumor histology, genealogy, medical history, and potential environmental carcinogens. With this approach and in a prospective and retrospective survey, two cancer-prone and two cancer-resistant families are described. Genetic factors, in cancer predisposition and in cancer resistance are hypothesized.

Cancer is not uniformly distributed in the population. There are marked variations in cancer incidence at different anatomic sites, in different populations, and in different areas of the world. Numerous etiologic differences account for such variations in cancer incidence, including differences in genotypes, environmental exposures, habit patterns, occupations, socioeconomic status, and educational factors (Lynch 1967, Stewart 1968). A comprehensive exploration of cancer etiology involves integrated consideration of all potentially mitigating factors, not only individually, but also collectively as they interact with each other (Lynch 1967, Gianferrari and Morganti 1957, Beolchini et al. 1956, Beolchini et al. 1957, Serra and Soini 1959).

As we studied families with significantly increased incidences of cancer, compared to the general population, we observed significant paucities in occurrences of the cancers in certain branches of these families and in a number of other families, some of which included the kin of spouses of patients in high-incidence families. We concluded that some kindreds may be characterized by unusual resistance or decreased susceptibility to cancer, just as other kindreds may be characterized by unusual cancer-proneness. This observation is not surprising because significant differences in cancer resistance have been well established in inbred strains of a variety of animals (Jacobs 1969, Stern and Goldfeder 1969, Waters and Burmester 1961). Recent studies in tumor immunology have revealed a crucial relationship between an animal's immune defense system and its response to carcinogens as well as to transplanted cancer cells (Moore 1968, Hellström et al. 1968). Stephenson et al. (1971) have discussed spontaneous regression of tumors in humans in relation to tolerance and/or resistance to malignancy.

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We present here our observations of two extended families, or kindreds, which show strikingly increased incidences of cancers (Hauser and Weller 1936, Lynch et al. 1966, Lynch and Krush 1967, Lynch and Krush 1971) and two other families whose incidences of cancer are far fewer than those found in the general population (Table I). These family data comprise part of an ongoing prospective study.

TABLE I
CANCER INCIDENCE IN CANCER-SUSCEPTIBLE AND CANCER-FREE FAMILIES

Family	All ages			Over age 40			Multiple primary lesions
	N	With cancer		N	With cancer		
		n	%		n	%	
G	675	95	14.0	250	80	32.0	13
N	619	53	8.6	431	47	11.0	8
A	255	5	2.0	113	3	2.7	—
B	613	16	2.6	355	15	4.0	1

A standard protocol for the study of cancer occurrence and distribution in families was used in the study of these four families (Lynch et al. 1966). This involved a complete medical-genetic history with pathological verification of all malignant neoplasms. Personal interviews and evaluations of patients and/or their relatives were made whenever possible.

CANCER-PRONE FAMILY (FAMILY "G" OF WARTHIN)

Figure 1 is a schematic pedigree of Family G which depicts the occurrence and distribution of cancer in 675 descendants of the progenitor. Of these patients, 95 developed one or more malignant neoplasms; 13 had multiple primary malignant neoplasm (Table II).

TABLE II
CANCER INCIDENCE IN CANCER-SUSCEPTIBLE FAMILY G

Branch of family	All ages			Over age 40			Multiple primary lesions
	N	With cancer		N	With cancer		
		n	%		n	%	
A	171	12	7.6	55	12	22.0	—
B	158	26	16.0	63	20	32.0	5
C	27	5	19.0	8	4	50.0	2
D	37	—	—	20	—	—	—
E	46	3	6.5	15	3	20.0	—
F	64	13	20.0	27	13	48.0	1
G	43	9	19.0	14	6	43.0	1
H	78	5	6.4	18	4	22.0	1
I	61	23	38.0	29	18	62.0	3

Certain family lines are significantly cancer-prone, with incidence ranging from 32% to 62% in branches B, G, C, and I, respectively. Relatively less cancer appeared in lines A and H, 22% in each, while line D has remained cancer-free throughout its history. Line E was cancer-free until recent occurrences of sarcoma and leukemia in three members (Fig. 1).

Predominant tumors were adenocarcinoma of the colon (52), adenocarcinoma of the endometrium (18), and adenocarcinoma of the stomach (8). Although the age at onset of both colon and endometrial cancer was in many instances lower than that expected in the general population, the age of onset of carcinoma of the colon ranged from 20 to 82, and of endometrial carcinoma from 38 to 77. In both categories, the wide age-ranges are not shown by the relatively high average-ages at onset: 54.5 for colon cancer and 50.0 for endometrial cancer. No sex difference was noted in the total number of cancers. Vertical transmission was demonstrated, which is consistent with transmission of predisposition by a single autosomal dominant gene. For the most part, the above family characteristics fit the criteria for the " cancer family syndrome " which is characterized by: (1) increased incidence of adenocarcinoma of all varieties but predominantly adenocarcinoma of the colon, endometrium, and stomach; (2) increased incidence of multiple primary malignant neoplams; (3) earlier age of onset of cancer than that found in the general population; and (4) apparent autosomal dominant mode of inheritance.

CANCER-PRONE FAMILY (FAMILY "N")

In a second family which has been under our investigation for the past eight years, 53 of 619 ascertained members developed cancer. Of this number, 431 were aged 40 and over, which results in a figure of 11% of family members who developed cancer. However, Table III reveals that, when this family is considered according to its several separate branches, one branch has a marked paucity of cancer (7%), while three other branches have incidences of 33%, 33%, and 32%, respectively, when considering all members who have reached age 40 (an age chosen arbitrarily

TABLE III
CANCER INCIDENCE IN CANCER-SUSCEPTIBLE FAMILY N

Branch of family	All ages			Over age 40			Multiple primary lesions
	N	With cancer		N	With cancer		
		n	%		n	%	
A	178	21	11	60	19	32	8
B	126	17	13	48	16	33	—
C	45	6	13	18	6	33	—
D	295	9	3	121	9	7	—

as a beginning cancer-risk age). Eight individuals in one branch developed multiple primary malignant lesions (Table III). Tumors which occurred most frequently involved colon (20), endometrium (12), breast (3), stomach (3), and leukemia (3).

CANCER-RESISTANT FAMILY (FAMILY "A")

The schematic pedigree shown in Fig. 2 is noteworthy for a paucity of malignant neoplasms. Interestingly, longevity was rather advanced in many of its members. The average age at death of all members was 57.4 years. When deaths up to the age of 30 years were excluded, the average age at death was 70.3 years. Cardiovascular disease was responsible for 12 of the 32 recorded causes of death at ages which ranged from 53 to 86. Two family members are living in their eighties and 7 in their seventies. The histologic varieties of cancer in several patients, significantly, were usually associated with nongenetic factors, i.e., bronchogenic carcinoma in a heavy smoker; "youth cancer", which was probably leukemia, occurred in a 13-year-old child

TABLE IV
CANCER INCIDENCE IN CANCER-RESISTANT FAMILY A

Branch of family	All ages			Over age 40			Multiple primary lesions
	N	With cancer		N	With cancer		
		n	%		n	%	
1	17	1	8	5	—	—	—
2	62	1	2	18	1	6	—
3	19	1	5	10	—	—	—
4	8	1	12	8	1	12	—
5	22	—	—	22	—	—	—
6	20	—	—	6	—	—	—
7	19	—	—	7	—	—	—
8	30	—	—	14	—	—	—
9	20	1	5	11	1	9	—
10	20	—	—	5	—	—	—
11	4	—	—	2	—	—	—
12	25	—	—	6	—	—	—

(Table IV). This disease is of unknown etiology, possibly involving a virus, genetic factors, or both. Thus, in this family we see that among 255 relatives at risk for cancer, only 5 (2%) have developed malignant neoplasms. In considering those who reached the age of 40, 2.7% developed cancer (Table IV).

CANCER-RESISTANT FAMILY (FAMILY "B")

Among 613 members of Family B, 16 developed cancer (2.6%: Fig. 3 and Table V). Breast cancer occurred in 4 individuals (among whom 1 survived two primary breast lesions and died at age 76 of a CVA). Basal cell carcinoma occurred in 2 patients as did bladder cancer. The bladder cancer occurred in persons who were known to be cigar smokers. A cancer of the larynx occurred in a 56-year-old man who was known to have received X-ray treatment for acne during his adolescence. The late age of

TABLE V
CANCER INCIDENCE IN CANCER-RESISTANT FAMILY B

Branch of family	All ages			Over age 40			Multiple primary lesions
	N	With cancer		N	With cancer		
		n	%		n	%	
1	116	2	2	106	2	2	—
2	68	3	4	28	3	11	—
3	25	—	—	22	—	—	—
4	12	—	—	10	—	—	—
5	17	—	—	12	—	—	—
6	18	—	—	14	—	—	—
7	53	5	9	22	4	18	1
8	42	1	2	30	1	3	—
9	10	—	—	6	—	—	—
10	57	1	2	35	1	3	—
11	56	—	—	23	—	—	—
12	64	3	5	29	3	10	—
13	51	1	2	19	1	5	—

cancer onset is noteworthy in 4 individuals (i.e., 77, 79, 71, and 84). One child developed a brain tumor at the age of 6 years and died at the age of 9 years. The average age at death of 197 family members who died at any age was 52.2 but when only the 150 members who reached the age of 30 were considered, the average age at death was 65.1. Seven individuals are alive in their seventies and 14 in their eighties.

DISCUSSION

Discussions of the etiology of " cancer ", which is a generic term, are largely meaningless. If cancer is to be delineated further, through acquisition of information relevant to the circumstances surrounding onset, then it will be necessary to design studies of specific histologic varieties of cancer. Thus, for example, adenocarcinoma of the colon may occur as a result of excessive irradiation to the abdomen in treatment for

FIG. 1. *Schematic pedigree of cancer-susceptible family G depicting the occurrence of cancer by generation (and not by sibships in a generation). Note that in generations IV-VII sibship relationships are not recorded, but only total numbers in each branch.*

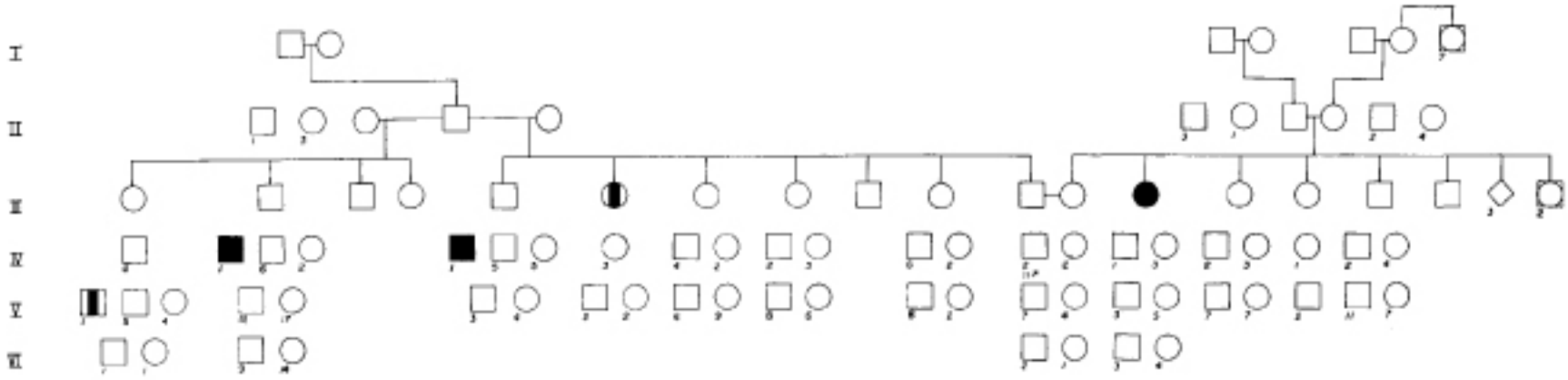

FIG. 2. *Schematic pedigree of cancer-resistant family A depicting the occurrence of cancer by generation (and not by sibships in a generation). Note that in generations IV-VI sibship relationships are not recorded, but only total numbers in each branch.*

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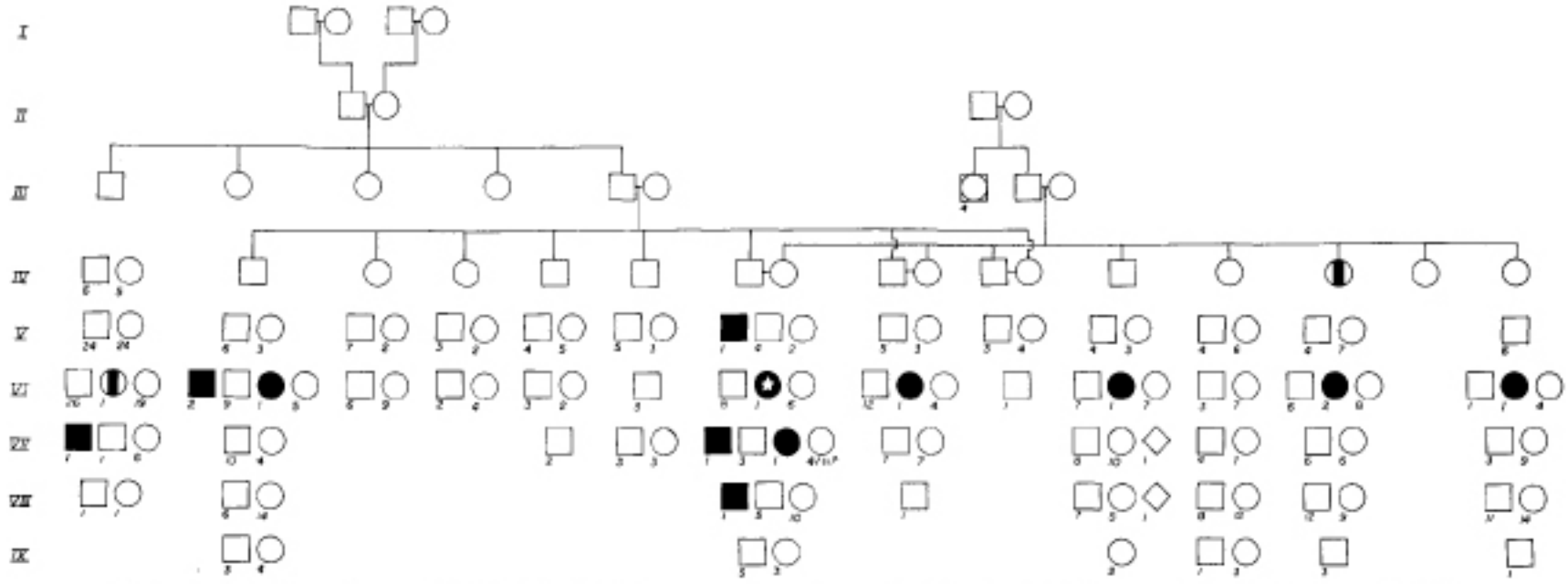

FIG. 3. *Schematic pedigree of cancer-resistant family B depicting the occurrence of cancer by generation (and not by sibships in a generation). Note that in generations V-IX sibship relationships are not recorded, but only total numbers in each branch.*

LEGEND

- Male
- Female
- Unknown sex
- Miscarriage or stillbirth
- Proband
- Carcinoma
- Carcinoma by reliable history
- Multiple primary malignant neoplasms
- Sarcoma, leukemia, lymphoma, or brain tumor
- Multiple primary malignant neoplasms, one a sarcoma
- $\square_{12}$, $\blacksquare_{1}$, etc. Number of unaffected, number of affected by carcinoma, etc.

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upon the individual's specific genetic and environmental circumstances. Thus, when environmental factors are more significant, the relative effects of hereditary factors will be less significant. Families like A and B (cancer-resistant) and G and N (cancer-prone) are associated with environments which are not strikingly different from each other. Mendelian genetic factors relevant to differences in cancer resistance are not yet identifiable.

A heritability determination is an estimate of the proportion of the total phenotypic variance (i.e., individual differences) that can be attributed to genetic variation in a single generation of some particular population under one set of environmental conditions. The heritability of cancer may be defined as the extent to which variation in individual risk of acquiring cancer is due to genetic differences. A disease will show a greater-than-zero heritability if two or more segregating genetic alleles, which manifest different effects upon predisposition and resistance to the disease, occur on at least one chromosomal locus. Such a trait may show different heritabilities in different populations which are characterized by genotypic and/or environmental differences, because the manifestations of any particular gene depend upon interactions between that gene and the overall genotype as well as with nongenetic or environmental variables. An individual's predisposition or resistance to a particular disease process depends upon that individual's genetic norm or range of reaction and the environmental factors interacting with his genotype. A genetic factor may be manifested only by appropriate genotype-environment combinations. A gene's harmfulness or usefulness is determined by the bearer's environment. Thus, the genetic epidemiologist functions as an ecologist seeking significant correlations between a disorder and one or another variable from the great array of environmental influences. One's success in such research is related to the uniqueness of the variable and the directness of its effect, to the frequency of the disorder, and to the ease of diagnosing the disorder.

In Families G and N an autosomal dominant genetic factor has been postulated, but in Families A and B it is not possible to delineate a simple Mendelian pattern of genetic transmission for an alleged cancer resistance. Of the few cancers that have developed in kindreds A and B and the cancer-resistant line of Family N, most can be accounted for on an environmental basis. On the other hand, tumors in the cancer-prone branches of Families G and N indicate a pattern.

The available vital statistics in all of these families range from the early part of the nineteenth century to the present time. During the period before World War II, more persons died from infectious diseases, childbirth, etc., than at the present time. It is also relevant to consider the number who died or were killed during or after the major U.S. and foreign wars of the nineteenth and twentieth centuries. These conditions have all affected the longevity figures in the studied families.

For further testing of the above hypothesis, an analysis of cancer occurrences from the standpoint of families prone to the disease as well as families showing a paucity of malignant neoplasms is needed. Furthermore, additional analyses must be made of the particular varieties of cancer, given the known epidemiological factors perti-

nent to the specific malignant neoplasms. For example, smoking is associated with bronchogenic carcinoma; promiscuity, multiple matings, and poor female hygiene, are associated with carcinoma of the uterine cervix, etc. (Beolchini et al. 1958).

The cancer epidemiologist must constantly scrutinize all possible hereditary and environmental factors which could be of etiologic importance in the development of cancer. Unfortunately, many studies have concerned themselves only with single carcinogenic factors. Very few attempts have been made to relate nongenetic factors to host factors, e.g., cigarette smoking and family history (Tokuhata 1964), solar radiation and cancer induction in patients with xeroderma pigmentosum (Lynch et al. 1967*a*, Lynch et al. 1967*b*), etc. Few studies have been specifically concerned with cancer resistance in humans (Moore 1968, Hellström et al. 1968).

The present report has demonstrated the wide variation in tumor incidence among four extended families. Two of the four are noteworthy for the infrequent occurrence of cancer (Families A and B) and the others (Families G and N) are characterized by cancer-proneness in certain branches and less cancer in other branches. Biological variations structure the expectation that such distributions might occur in many families. Marked variations in life span exist between different species and between individuals within a given species. Goldstein (1971) stated that this phenomenon implicates genetic factors and suggested that an explanation for variations in the aging process resides " in genomes with either different genetic prgrams or specific rates of mutability ". Since cancer is generally an age-related disease, it is consistent with Goldstein's hypothesis that certain genetic programs " turn on " in different individuals in our population and thus elicit different diseases which partly account for variations in life expectancy of those individuals. Untreated patients with such classically inherited disorders as familial polyposis coli (Mendelian autosomal dominant) show a marked reduction in longevity due to the development of adenocarcinoma of the colon at a relatively early age as the result of an inherited cancer diathesis associated with the familial polyposis disease. Xeroderma pigmentosum is another example of a hereditary disease (Mendeliam autosomal recessive) which imposes a serious compromise on a patient's longevity. Other families are prone to coronary artery disease, either through inheritance of lipid or other metabolic abnormalities and/or gene-transmitted differences for factors yet undetermined but which predispose to coronary artery disease. Such individuals are additional examples of persons whose longevity may be seriously compromised by gene-transmitted constitutional characteristics. It is reasonable to postulate that genetic differences play prominent roles in the four families' cancer proneness and cancer resistance. This observation does not exclude the role of nongenetic factors such as the interaction of an oncogenic virus in a genetically and immunologically susceptible host whose constitution favors the development of malignant neoplasms.

The genetic basis of any common disease is a reflection of the genetic basis of health and that due to the interaction of the large number of relevant hereditary factors or genes and the large number of environmental factors which influence the liability of persons of any given constitution to the particular disease (Edwards 1963). The

first step in understanding the etiologic role of biological heredity is achievement of the realization that the genotype (i.e., total genetic material) of an individual, the chromosomal material derived from his parents, is a set of potentialities and not a set of already-formed or predetermined characteristics. The relative contributions of heredity and environment for a particular disease differ with different overall heredities (i.e., total genotypes) and with different environments.

The only unequivocally reliable approach to a nonexperimental system is deferment of any final determination of the relevant modes of genetic transmission until the responsible genes are individually recognizable. An alternative investigative approach involves comparative studies in members of high-risk versus those in low-risk or sporadic families (Morton 1969). Even if predisposition to a given disease category in most or many of the affected individuals may be associated with a simple Mendelian mode of genetic transmission, some cases within the disease category would be sporadic due to occurrence of phenocopies (i.e., the apparently same disease, characteristically associated with a particular gene or group of genes, brought about by special environmental conditions interacting with other genes), genocopies (i.e., the apparently same disease, characteristically associated with a particular gene or group of genes, brought about as a manifestation of other genes), diagnostic errors, etc.

The demonstration, for a particular cancer category, of both the occurrence of sporadic cases (as in Families A and B) and of familial cases (as in Families G and N) shows heterogeneity in data which were previously considered as if they were homogeneous. Such data even show that the risk in selected families is great enough to suggest a simple genetic hypothesis (Morton 1962) for transmission of major differences in predisposition to cancer, e.g., as indicated in Families G and N. The data have not established that any particular genotype is either necessary or sufficient for development of cancer. They do show, however, that certain types of cancer are particularly liable to develop in genetically predisposed individuals. Whether or not the disease actually develops in a genetically predisposed individual, or at what age it develops, and details of its symptomatology and severity, are determined by interactions with environmental variables and other genes. The happenings of nature are characterized by probability laws, rather than by simple causality (Reichenbach 1954). The cancer epidemiologist can define his best posits, but he never knows beforehand whether or not they will come true in any specific case.

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RIASSUNTO

La comprensione dei fattori eziologici nel cancro richiede che di un tumore si abbia una precisa conoscenza a livello istologico, genealogico, anamnestico e dei potenziali agenti carcinogeni ambientali: con tale tipo d'impostazione e su di un piano prospettico e retrospettivo, vengono descritte due famiglie predisposte al cancro e due famiglie resistenti. Vengono ipotizzati fattori genetici alla base della predisposizione o resistenza al cancro.

RÉSUMÉ

La compréhension des facteurs étiologiques du cancer demande un enregistrement précis, pour toute tumeur, des facteurs histologiques, généalogiques, anamnestiques, ainsi que des facteurs ambiants carcinogènes potentiels. Sur cette base, et sur un plan perspectif et rétrospectif, deux familles prédisposées et deux familles résistantes au cancer ont été décrites. L'hypothèse est avancée que des facteurs génétiques soient responsables de la prédisposition ou résistance au cancer.

ZUSAMMENFASSUNG

Um die Ätiologie des Krebses verstehen zu können, müssen die histologischen, genealogischen, anamnestischen Faktoren sowie die eventuellen krebserregenden Umweltsbedingungen eines jeden Tumors genau bekannt sein. Von diesem Standpunkt ausgehend werden die Vorgeschichten sowie die Zukunftsaussichten von zwei Familien mit Krebsneigung und von zwei krebsresistenten Familien beschrieben. Man nimmt an, dass diese Prädisposition oder Resistenz gegenüber dem Krebs erbbedingt sei.

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