Effect of Paternal and Maternal Cancer on Cancer in the Offspring: A Population-based Study[1]

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Abstract

The Family-Cancer Database was constructed from the nationwide Swedish registries to include more than 30,000 cancers in offspring diagnosed at ages 15–51 years and their parents. Cancer risk in the offspring was increased about 1.10 times when the father had cancer, whereas no increase was noted when the mother had cancer. If both parents had cancer, the risk for sons was 1.39 and for daughters, 1.34. Familial aggregation between parents and offspring was observed for 5 concordant and 14 discordant cancer sites and 10 parental sites at which all cancer was increased in the offspring. The concordant sites between the parent and offspring were colorectum, breast, melanoma, skin (squamous cell carcinoma), and thyroid. The aggregation at discordant sites in the parents and the offspring included stomach-breast, colorectum-salivary glands, colorectum-breast, colorectum-lymphoma, colorectum-leukemia, liver-breast, pancreas-breast, breast-melanoma, ovary-breast, prostate-breast, prostate-cervix, prostate-multiple myeloma, kidney-melanoma, and nervous tissue-melanoma. In most of these combinations, cancer in the second parent increased the risk to the offspring. The present results on young and middle-aged adults suggest that cancer in both parents increases cancer risk in the offspring at many sites. Chance and environmental effects may explain some of the results, whereas true genetic factors probably contribute to most of the findings. The molecular genetic explanation may be that rare dominant single genes increase susceptibility at many sites or that overlapping sets of genes control susceptibility at multiple sites.

Introduction

The study of familial clustering of cancer has been fundamental to the understanding of heritable components in cancer and the discovery of the genes involved (1, 2). The concept of tumor suppressor genes that has evolved along with analysis of familial cancers and family studies has been germane to the mapping and characterization of most of the cancer susceptibility genes identified to date (2, 3). Although only 5% of cancer is thought to be due to highly penetrant single-gene mutations in the germ line, a much larger proportion of cancer may involve somatic mutations in these genes in sporadic forms of cancer (2, 4). Additionally, it has become increasingly evident that the hereditary cancer syndromes often entail an increase in the risk of cancer at many sites other than the "index" sites, although at lower risk in the nonindex than in the index site.

Familial clustering of cancer has been studied most commonly after clinical identification of probands (5, 6). This approach has been very productive in terms of understanding cancer genetics. Many forms of cancer in which a single gene poses a high risk have been identified. Some 200 single-gene traits are known in which cancer is a recognized complication (7). Another approach to the study of familial cancer has been to analyze cancer risks of the relatives of the index case in analytical epidemiological studies (8, 9). Twin studies offer a third alternative for genetic epidemiology of cancer. Dissection of heritable and environmental components is possible in such studies, and the risk estimates should be robust, but the rareness of twinning impedes this approach (10–13). The fourth approach to genetic epidemiology of cancer is a population-based study in which all cancers are registered and family relationships can be reconstructed. The power is in large numbers and unbiased risk estimates. These in turn allow estimation of familiality at multiple sites. For gene-mapping purposes, the family units afford a possibility of applying allele-sharing methods that require large population bases but are useful when many genes operate in the disease (14, 15). Population-based studies have been carried out in a few geographic areas, including those on the Mormon population in Utah, which have been based on existing genealogy (16, 17). In Denmark and Iceland, cancer cases have been obtained from the nationwide cancer registry, and family relationships have been constructed from other national registers (18–20).

Here, we present results from the population-based family database from Sweden. The size of the population (8.7 million in 1992) and the nationwide registration of cancer since 1958 (1.4 million registered tumors) offer unique possibilities for epidemiological studies of cancer. The availability of a family database on children born after 1940, including children and their parents in the Second Generation Register, permitted linkage to the Cancer Registry to form the Family-Cancer Database. We believe that this database will be a useful resource for genetic epidemiology of cancer and identification of new underlying genes. We analyze here the risks of cancer in adult offspring of the parents with or without cancer. We want to test the powers of the registered database in examining cancer risks across multiple sites and in families in which both

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Table 1 Cancer in offspring by parental cancer

	Parental cancer (father/mother)	No. of children	No. of cancers	Adjusted RR	95% CI
Sons					
	−/−	510,382	4,420	1.00	0.97–1.03
	+/−	121,771	1,251	1.12[a]	1.05–1.18
	−/+	99,918	872	0.97	0.90–1.03
	+/+	26,606	336	1.39[a]	1.23–1.54
	All	758,677	6,879		
Daughters					
	−/−	490,311	9,220	1.00	0.98–1.02
	+/−	116,548	2,532	1.07[a]	1.03–1.11
	−/+	95,724	1,865	0.98	0.93–1.02
	+/+	25,535	724	1.34[a]	1.23–1.44
	All	728,118	14,341		

[a] Ninety-five % CI does not include 1.00.

parents have cancer. We reason that modest inherited increases in offspring cancer risk should be augmented when contributed by both parents.

Subjects and Methods

Registers and Source of Subjects. Statistics Sweden maintains a Second Generation Register, in which the children born in Sweden in 1941 and later are registered with their biological parents as families. By 1995, more than 6 million individuals of the population of 8.8 million were in the register. However, the registration only took place for those children alive at the construction year of the register, 1992. In the 1940s and 1950s, each of the 5-year birth cohorts include more than 0.5 million children. Considering children born between 1941 and 1955, 97,600 of them were not included in the register because of death. Some other reasons for not being included in the present study were lack of one or both parents in the register (80,000 children deleted) and some apparent technical mistakes. The population of children (here called offspring) included consisted of 486,650 (born 1941–45), 527,755 (1946–50), and 472,390 (1951–55), a total of 1,486,795 children, together with their parents.

The Second Generation Register was linked by the individually unique national registration number to the Cancer Registry. For the present study, only those children were included who were diagnosed with cancer at of 15 years or older. The highest possible diagnosis age, 51, in the offspring is reached by those born in 1941 if they were diagnosed after their birthday during 1992; the common diagnosis ages for all of the three 5-year birth cohorts were 17–36 years.

The nationwide Swedish Cancer Registry includes cancer cases registered from 1958 and onward. Cancer registration is considered to be close to 100% currently (21). Basal cell carcinoma of the skin is not included in the registration. A four-digit diagnostic code according to the 7th revision of the International Classification of Diseases is used. Cancers are also recorded according to the first or subsequent primary cancer and cancer *in situ*. The persons entered in the present study were diagnosed for their first primary cancer during the years 1958–1992 at ages 15–51 years. Cancer *in situ* was not included. Children diagnosed for their first primary cancer before the age of 15 years were excluded from the study population.

Children born in 1941–1955 and alive at the end of 1992 were divided into four cohorts according to the cancer status of their both parents: −/−, neither parent had cancer; +/−, only the father had cancer; −/+, only the mother had cancer; +/+ both parents had cancer.

Analysis. The birth cohort-specific RRs[3] and the 95% CIs were calculated using the 5-year cohort-specific rate for offspring in group −/− as the reference. The birth cohort-adjusted rates ("adjusted RR") were calculated by the direct method. Each of the three 5-year birth cohorts received an equal weight, according to the method used for the truncated European standard population (22). Indirectly, this method also makes an adjustment for age.

The 95% CIs were calculated supposing that the number of cancer cases within a given time is Poisson distributed (22).

Results

A total of 21,220 cancers, diagnosed between ages 15 and 51, were recorded in the Family-Cancer Database among persons born in 1941–1955. In the 5-year birth cohorts, 10,000 persons born in 1941–1945 had cancer, as compared to 7,086 and 4,134 persons in the subsequent 5-year cohorts. When the cancer risk was analyzed by the parental cancer status, a systematic trend was observed in all of the birth cohorts and in both sexes. If the father had cancer but the mother did not (the +/− group), the sons had a birth cohort-adjusted RR (adjusted RR) of 1.12 of contracting cancer (Table 1). The offspring of two cancer-free parents were the referents, with a RR of 1.00. Due to the large numbers, this increase was statistically significant. When the mother had cancer (the −/+ group), there was no excess risk in the offspring. When both parents had cancer, the risk was 1.39, highly significant statistically. Somewhat lower RRs were observed for the daughters. However, the increases in the (+/−) and (+/+) groups of 1.07 and 1.34 were statistically significant.

The parental cancers in the Family-Cancer Database distributed almost like all cancers in Sweden but with some skewing toward cancers detected at younger ages (21). The three most common paternal sites, based on the 7th revision of the International Classification of Diseases, were prostate, colorectum, and lung; common maternal sites were breast, colorectum, and cervix uteri. Due to the age truncation, 15–51 years, the common cancers in the offspring were different. For sons, the Family-Cancer Database included 1103 testicular cancers, 1063 melanomas, 858 lymphomas, 654 nervous system can-

[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

Table 2 Cancer in offspring by paternal cancer site and by maternal cancer status

Cancer in father	Cancer in offspring	Parental cancer status (father/mother)							
		Sons		Daughters		Both sexes			
		+/−	+/+	+/−	+/+	+/−		+/+	
		No. (RR)	No. (RR)	No. (RR)	No. (RR)	No. (RR)	95% CI	No. (RR)	95% CI
Stomach	Breast			59 (1.0)	25 (1.9)[a]	59 (1.0)	0.8–1.3	25 (1.9)	1.1–2.7[b]
Colorectum	Salivary glands	5 (4.8)	0	3 (2.6)	1 (3.7)	8 (3.6)	1.0–6.2[b]	1 (2.0)	
	Colorectum	13 (1.6)	9 (4.5)[a]	24 (2.0)[a]	4 (1.4)	37 (1.8)	1.2–2.4[b]	13 (2.7)	1.2–4.3[b]
	Breast			110 (1.1)	24 (1.1)	110 (1.1)	0.9–1.3	24 (1.1)	0.6–1.5
	Lymphomas	17 (1.1)	15 (4.4)[a]	11 (1.1)	1 (0.8)	28 (1.1)	0.7–1.5	16 (3.1)	1.5–4.7[b]
	Leukemias	2 (0.7)	1 (1.1)	2 (0.9)	1 (1.5)	4 (0.8)	0.0–1.5	2 (1.2)	
	All sites	150 (1.1)	58 (2.1)[a]	314 (1.1)	86 (1.4)[a]	464 (1.1)	1.0–1.2[b]	144 (1.6)	1.3–1.9[b]
Liver, bile	Breast			34 (1.5)	13 (2.6)[a]	34 (1.5)	1.0–2.0[b]	13 (2.8)	1.1–4.5[b]
	All sites	26 (0.9)	10 (1.4)	73 (1.1)	25 (1.8)[a]	99 (1.1)	0.8–1.3	35 (1.7)	1.1–2.3[b]
Pancreas	Breast			47 (1.7)[a]	9 (1.5)	47 (1.6)	1.1–2.1[b]	9 (1.5)	0.5–2.5
Lung	All sites	153 (1.3)[a]	37 (1.3)	277 (1.1)	77 (1.3)	430 (1.1)	1.0–1.2[b]	114 (1.3)	1.0–1.5[b]
Prostate	Breast			227 (1.2)[a]	73 (1.5)[a]	227 (1.2)	1.0–1.3[b]	73 (1.5)	1.2–1.9[b]
	Cervix uteri			68 (1.0)	27 (1.9)[a]	68 (1.0)	0.7–1.2	27 (1.9)	1.1–2.7[b]
	Multiple myeloma	11 (8.6)[a]	0	2 (1.7)	1 (4.4)	13 (5.4)	2.4–8.3[b]	1 (2.1)	
	All sites	287 (1.1)	82 (1.5)[a]	614 (1.1)[a]	180 (1.3)[a]	901 (1.1)	1.0–1.2[b]	262 (1.4)	1.2–1.5[b]
Kidney	Melanoma	6 (0.9)	2 (1.2)	21 (1.8)[a]	2 (0.7)	27 (1.5)	0.9–2.0	4 (0.9)	0.0–1.8
Melanoma	Melanoma	9 (2.5)	3 (4.3)	10 (1.6)	5 (3.7)	19 (2.0)	1.1–2.9[b]	8 (4.0)	1.1–6.8[b]
	All sites	25 (1.0)	9 (1.8)	54 (1.0)	17 (1.5)	79 (1.0)	0.8–1.3	26 (1.6)	1.0–2.3[b]
Skin	Skin	8 (6.5)[a]	0	2 (2.1)	0	10 (4.6)	1.7–7.5[b]	0	
Nervous system	Melanoma	8 (1.7)	1 (0.9)	15 (1.9)	5 (4.0)	23 (1.8)	1.1–2.6[b]	6 (2.6)	0.4–4.8
Thyroid gland	Thyroid gland	2 (11.7)	0	1 (1.5)	1 (11.0)	3 (6.5)		1 (5.5)	
Leukemias	All sites	38 (1.1)	10 (1.3)	68 (1.0)	28 (1.7)[a]	106 (1.0)	0.8–1.2	38 (1.5)	1.0–2.1[b]

[a] Significant increase (95% CI does not include RR = 1.00 of the −/− group).
[b] Ninety-five % CI does not include 1.00.

cers, and 455 colorectal cancers. For daughters, breast cancer dominated, 4860 cases, followed by cervical cancer (1801 cases), melanoma (1694 cases), and ovarian cancer (919 cases); for lymphoma, there were 497 cases (data not shown).

The site-specific risk of cancer in the offspring (sons and daughters separately and combined) was analyzed by 12 paternal and 15 maternal cancer sites. The cancer status of both parents was considered in the +/−, −/+, and +/+ groups. This produced large amounts of data, but many of the cells in this matrix were either empty or contained a few cases only. Some 37 statistically significant positive associations and 15 negative associations were found. Tables 2 and 3 contain those combinations of sites at which a statistically significant positive association was noted when the sons and the daughters were considered separately or combined. All of the rates shown in these tables are birth cohort-adjusted rates, and the (−/−) group is taken as a referent.

Site-specific cancer in the offspring was analyzed by site-specific paternal cancer in Table 2. There was an increased risk of cancer in the offspring for colorectal and skin (squamous cell) cancer, concordant with the paternal site. Several increases at discordant sites were observed, including father-offspring pairs for stomach-breast, colorectum-salivary glands, colorectum-lymphoma, liver-breast, pancreas-breast, prostate-breast, prostate-cervix uteri, prostate-multiple myeloma, kidney-melanoma, and nervous system-melanoma cancer sites.

An additional consideration in Table 2 was the modification of the cancer risk in the offspring by cancer status in the second parent (mother). In the +/− columns, mothers had no cancer, whereas in the +/+ columns, mothers had various types of cancer. There appeared to be a maternal enhancement of the effect at many father-offspring cancer site combinations. Enhancement of cancer risk was noted, *e.g.*, for father-son pairs in colorectal-colorectal (RR of 1.6 in the +/− group as compared to 4.5 in the +/+ group) and colorectal-lymphoma cancer sites (RR of 1.1 in the +/− group as compared to 4.4 in the +/+ group). A similar maternal effect was noted for father-daughter pairs in stomach-breast, liver-breast, prostate-breast, and prostate-cervix cancer sites.

Site-specific cancer risk in the offspring was analyzed by site-specific cancer in mothers (Table 3). Increased risk of cancer was noted for the following concordant sites: breast, melanoma, and thyroid gland. A large number of case pairs for breast cancer was noted: 229 and 90 for the breast-breast comparisons in the −/+ and +/+ groups, respectively. Increased risks at discordant sites (mother-offspring) were noted for colorectum-breast, colorectum-leukemia, pancreas-breast, breast-melanoma, and ovary-breast. The risk of the offspring was enhanced by paternal cancer in the mother-daughter pairs of, *e.g.*, colorectum-breast, pancreas-breast, breast-breast, and ovary-breast sites.

Discussion

This is the first site-by-site analysis of the nationwide Swedish Family-Cancer Database. The data are unique both in the size of the database and in its population-based structure. However, the Family-Cancer Database has two limitations because of the Second Generation Register. One is that the data are from those born in 1941 and later, causing truncation to persons ages 51 years and younger (Cancer Register was updated until 1992). Familial cancers are often recognized more clearly among relatively young adults, so the truncation does not invalidate the analysis (23). The second limitation was that the Second Generation Register lacked information from those born in 1941 or later who had died before 1992. This caused a deficit in fatal

Table 3 Cancer in offspring by maternal cancer site and by paternal cancer status

Cancer in mother	Cancer in offspring	Parental cancer status (father/mother)							
		Sons		Daughters		Both sexes			
		+/−	+/+	+/−	+/+	+/−		+/+	
		No. (RR)	No. (RR)	No. (RR)	No. (RR)	No. (RR)	95% CI	No. (RR)	95% CI
Stomach	Breast			21 (1.0)	6 (0.9)	21 (1.0)	0.5–1.4	6 (0.9)	0.2–1.7
Colorectum	Salivary glands	1 (1.1)	0	3 (3.5)	1 (2.9)	4 (2.4)	0.0–4.9	1 (1.6)	
	Colorectum	11 (1.7)	6 (2.8)	9 (1.0)	2 (1.1)	20 (1.3)	0.7–1.9	8 (1.8)	0.4–3.2
	Breast			54 (0.8)	38 (1.9)[a]	54 (0.8)	0.6–1.0	38 (1.9)	1.2–2.5[b]
	Lymphomas	19 (1.4)	6 (2.2)	4 (0.6)	2 (1.4)	23 (1.1)	0.6–1.6	8 (1.9)	0.5–3.4
	Leukemias	2 (0.9)	3 (3.1)	1 (0.5)	4 (6.2)	3 (0.7)	0.0–1.6	7 (4.4)	1.0–7.7[b]
	All sites	118 (1.1)	38 (1.5)	170 (0.8)	94 (1.5)[a]	288 (0.9)	0.8–1.0	132 (1.5)	1.2–1.8[b]
Liver, bile	Breast			22 (0.9)	8 (1.1)	22 (0.9)	0.5–1.2	8 (1.1)	0.3–1.8
	All sites	33 (1.0)	16 (1.7)	60 (0.8)	26 (1.2)	93 (0.9)	0.7–1.1	42 (1.3)	0.9–1.8
Pancreas	Breast			19 (1.0)	14 (2.3)[a]	19 (1.0)	0.5–1.5	14 (2.3)	1.0–3.5[b]
Lung	All sites	35 (1.0)	12 (1.3)	70 (0.9)	33 (1.6)[a]	105 (1.0)	0.8–1.2	45 (1.5)	1.0–1.9[b]
Breast	Breast			229 (1.5)[a]	90 (2.1)[a]	330 (1.5)	1.3–1.6[b]	91 (2.1)	1.6–2.5[b]
	Melanoma	42 (1.3)	15 (1.5)	51 (0.9)	22 (1.5)	93 (1.0)	0.8–1.3	37 (1.5)	1.0–2.0[b]
	All sites	223 (1.0)	78 (1.3)[a]	506 (1.1)	192 (1.5)[a]	729 (1.1)	1.0–1.1[b]	270 (1.4)	1.2–1.6[b]
Cervix uteri	All sites	38 (0.7)	18 (1.4)	118 (1.0)	43 (1.3)	156 (0.9)	0.8–1.1	61 (1.4)	1.0–1.7[b]
Corpus uteri	All sites	68 (1.2)	14 (1.0)	111 (0.9)	46 (1.5)[a]	179 (1.0)	0.9–1.2	60 (1.3)	1.0–1.7[b]
Ovary	Breast			42 (1.1)	22 (1.9)[a]	42 (1.1)	0.8–1.4	22 (2.0)	1.1–2.8[b]
	All sites	47 (0.9)	22 (1.6)	129 (1.1)	42 (1.4)	176 (1.1)	0.9–1.2	64 (1.4)	1.0–1.8[b]
Kidney	Melanoma	5 (1.1)	0	6 (0.9)	2 (0.8)	11 (1.0)	0.4–1.6	2 (0.5)	
Melanoma	Melanoma	11 (3.5)[a]	2 (2.0)	13 (2.4)[a]	5 (3.6)	24 (2.8)	1.7–3.9[b]	7 (3.1)	0.7–5.4
	All sites	30 (1.4)	6 (1.1)	57 (1.3)	14 (1.2)	87 (1.3)	1.0–1.6[b]	20 (1.1)	0.6–1.6
Skin	Skin	0	0	0	0	0		0	
Nervous system	Melanoma	4 (0.8)	0	10 (1.2)	4 (2.2)	14 (1.1)	0.5–1.7	4 (1.4)	0.0–2.8
Thyroid gland	Thyroid gland	5 (11.8)	1 (10.1)	6 (4.0)	3 (7.8)	11 (5.8)	2.3–9.3[b]	4 (8.3)	0.0–16.6
Leukemias	All sites	23 (1.1)	8 (1.2)	44 (1.0)	17 (1.4)	67 (1.0)	0.8–1.3	25 (1.3)	0.8–1.9

[a] Significant increase (95% CI does not include RR = 1.00 of the −/− group).
[b] Ninety-five % CI does not include 1.00.

cancers, particularly those of lung, pancreas, and liver, and familiality in these cancers may not be recognized. However, this is not a cause of spurious positive associations. Another inherent limitation of the present kind of data is the inability to distinguish genetic and environmental effects. Families share many environmental causes of cancer, including diet, smoking habits, and many other lifestyle factors, warranting caution in the interpretation of the results.

Many cancer syndromes were initially recognized based on large excess risk at particular sites (23). However, extended studies often revealed increased risks at sites other than the "index" site, *e.g.*, Li-Fraumeni syndrome, and early-onset breast cancer (2, 4, 7, 23, 24). The molecular explanation for this has been the operation of the same susceptibility (tumor suppressor) gene, such as *Rb, p53, BRCA1,* and *BRCA2,* in several types of cancers (2, 5). Interestingly, large, population-based studies have revealed clear familial risks between discordant cancer sites, such as breast, colon, and prostate; nervous tissue and melanoma; and breast and thyroid in the Utah Population Database (17). Similarly, in the largest cancer study published on twins, there was an approximately 1.5-fold excess risk of all cancer in monozygotic as compared to dizygotic twins (13).

The cancer sites showing a statistically significant increase in the offspring if one or both parents had cancer (based on Tables 2 and 3) are listed in Table 4. The assumption of a familial component would be strengthened if the increased RRs were seen in both sexes and in several parental groups. Familial aggregation was evident in 19 pairs of cancer sites and in 10 combinations in which all cancer in the offspring was increased. Some combinations only appeared as solitary findings and may be spurious. Because many comparisons were done to produce Table 4, chance associations cannot be excluded. However, given that we observed a total of 37 positive associations and 15 negative associations, it appears prudent to assume that a large proportion of the associations has a biological basis.

The concordant sites in the parents and in the offspring were colorectum, breast, melanoma, skin (squamous cell carcinoma), and thyroid gland (Table 4). Familiality is known at most of these sites, and some of the susceptibility genes have been discovered, including adenomatous polyposis coli and mismatch repair genes in colon cancer, *BRCA1* and *BRCA2* in breast cancer, *p16* in melanoma (25) and *ret* in thyroid cancer (26). In squamous cell carcinoma of the skin, *p53* is often involved, but other genes have yet to be identified.

The discordant sites, shown in Table 4, included colorectum-breast, ovary-breast, and prostate-breast, detected in several previous studies (16, 18, 23). Other combinations, colorectum-leukemia and nervous tissue-melanoma, showed familial aggregation also in the Utah study (16). The remaining discordant combinations, stomach-breast, colorectum-salivary glands, colorectum-lymphoma, liver-breast, pancreas-breast, breast-melanoma, prostate-cervix, prostate-multiple myeloma, and kidney-melanoma, may be novel.

This study was designed to examine the effect of paternal and maternal cancer individually and in combination on the cancer risk of the offspring. The combined parental effect on cancer risk in the offspring has seldom been a subject of study. One of the likely reasons is that in site-by-site analysis, most commonly exercised, the number of subjects is rarely large enough; another reason may be that many common cancers are

Table 4 Cancer sites where a familial effect or reinforcement of the effect by cancer in the second parent are noted, compiled from Tables 3 and 4

Cancer in parent	Cancer in offspring	Reinforcement
Same site		
Colorectum	Colorectum	Present
Breast	Breast	Present
Melanoma	Melanoma	Weak
Skin	Skin	No cases
Thyroid gland	Thyroid gland	No
Different site		
Stomach	Breast	Present
Colorectum	Salivary glands	Few cases
Colorectum	Breast	Present
Colorectum	Lymphoma	Present
Colorectum	Leukemia	Present
Liver, bile	Breast	Present
Pancreas	Breast	Weak
Breast	Melanoma	Present
Ovary	Breast	Present
Prostate	Breast	Present
Prostate	Cervix	Present
Prostate	Multiple myeloma	Few cases
Kidney	Melanoma	No
Nervous tissue	Melanoma	Weak
All cancer in offspring		
Colorectum	All cancer	Present
Liver, bile	All cancer	Present
Lung	All cancer	Weak
Breast	All cancer	Present
Cervix uteri	All cancer	Present
Corpus uteri	All cancer	Present
Ovary	All cancer	Present
Prostate	All cancer	Present
Melanoma	All cancer	Weak
Leukemia	All cancer	Present

sex specific, and analysis of a combined parental effect at a particular site is not relevant.

An interesting observation in this study was the increase in cancer risk in the offspring when both parents had cancer. The RR of all cancer was 1.39 for sons and 1.34 for daughters. The enhancement of risk in the offspring by cancer in both parents was observed for most of the sites listed in Table 4. The effect was observed for the parent-offspring combinations at the concordant sites, such as colorectum-colorectum and breast-breast, and at discordant sites.

The present data are in accordance with reports that there is a mechanistic link between sets of cancer sites, probably because the same gene/genes are involved. The tumor suppressor genes (and oncogenes) known to date act in a dominant fashion (1, 4). Assuming the operation of a single gene controlling cancer risk at a few sites, the results would be compatible with rare dominant alleles being inherited from both parents and thus causing an increase in a few sites in the offspring. The increase in risk would be rather small in this model and is unlikely to explain most of the findings in the present study. As another alternative, many partially overlapping dominant genes may control cancer at multiple sites. Thus, inheriting mutant alleles to any of this set of genes would cause an increase of cancer risk at multiple sites as observed. Further refinement of the data in the Family-Cancer Database should allow formal testing of such alternatives. The largeness of the database should also make segregation analysis and comparison of the models of inheritance possible for a number of cancer sites.

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