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Evaluating Genetic Association among Ovarian, Breast, and Endometrial Cancer: Evidence for a Breast/Ovarian Cancer Relationship

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Summary

The possibility of a genetic relationship between ovarian, breast, and endometrial cancer was investigated in data from a large multicenter, population-based, case-control study, the Cancer and Steroid Hormone Study conducted by the Centers for Disease Control (CDC). Age-adjusted relative risks (RRs) for mothers and sisters of 493 ovarian cancer cases, 895 breast cancer cases, and 143 endometrial cancer cases versus 4,754 controls were calculated. Significantly elevated age-adjusted RRs were found for ovarian cancer (RR = 2.8; 95% confidence interval [CI] = 1.6–4.9) and breast cancer (RR = 1.6; 95% CI = 1.1–2.1) among relatives of ovarian cancer probands and for breast cancer (RR = 2.1; 95% CI = 1.7–2.5) and ovarian cancer (RR = 1.7; 95% CI = 1.0–2.0) among relatives of breast cancer probands. Relatives of endometrial cancer probands had an elevated RR for endometrial cancer only (RR = 2.7; 95% CI = 1.6–4.8). The genetic relationship between ovarian, breast, and endometrial cancer was tested using a multivariate polygenic threshold model developed by Smith (1976), which was modified to accommodate three classes of probands. Estimates of heritability for ovarian, breast, and endometrial cancer were 40%, 56%, and 52%, respectively. There was a significant genetic correlation between ovarian and breast cancer (R_{12} = .484). Evidence for significant genetic overlap between endometrial cancer and either ovarian or breast cancer was not found. These results suggest the existence of a familial breast/ovarian cancer syndrome. Endometrial cancer, while heritable, appears to be genetically unrelated.

Introduction

It has been postulated that there may be a genetic relationship between ovarian, breast, endometrial, and colon cancer. Cancer family syndromes involving one or more of each of these cancers have been cited (Lynch et al. 1982; Go et al. 1983; Bailey-Wilson et al. 1986). Lynch et al. (1982) distinguished three different types of family clusters involving epithelial ovarian cancer: (1) a site-specific ovarian cancer syndrome, (2) a breast/ovarian cancer syndrome, and (3) a cancer family syndrome that involves ovarian carcinoma in association with carcinomas of the breast, endometrium, and colon and in association with other adenocarcinomas. In the families reported, the possibility of chance clustering of cancer cannot be ruled out. Cancers of the colon and endometrium have been reported to be the main phenotypically expressed sites in nine pedigrees (Bailey-Wilson et al. 1986). Another study produced evidence for a breast/ovarian cancer syndrome inherited in an autosomal dominant fashion (Go et al. 1983). Go et al. (1983) also found evidence suggesting that endometrial cancer and breast cancer are expressions of the same autosomal dominant gene.

Elevated relative risks (RRs) for multiple primary cancers in different organs have been cited as evidence of a common and possibly genetic etiologic basis for these cancers (Strong 1977). Greater-than-chance oc-

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currences have been reported for multiple primary cancer for various combinations—namely, ovarian and breast cancer, ovarian and colon cancer, breast and endometrial cancer, and endometrial and colon cancer—of the four cancer sites (Shottenfeld and Berg 1971; Newell and Krementz 1977; Schoenberg 1977; Reimer et al. 1978; Prior and Waterhouse 1981).

Epidemiologic case-control studies have found a significantly increased risk for epithelial ovarian cancer in association with family history of cancer of the ovary, breast, endometrium, and colon in first-degree relatives (Hildreth et al. 1981; Cramer et al. 1983; Schildkraut and Thompson 1988*a*, 1988*b*). However, not all results were consistent in these studies. For example, associations with family history of breast and endometrial cancer were each statistically significant in only one of these studies. Kelsey et al. (1982) also found an increased risk for endometrial cancer among those with a family history of endometrial cancer or ovarian cancer. However, in neither instance was the association statistically significant. Salmi (1979) found evidence for an increased risk of endometrial cancer among those with a family history of breast cancer. Again, the association was not statistically significant.

In the current analysis we have attempted to assess formally the genetic relationship between cancers of the breast, ovary, and endometrium by using population data from a multicenter study conducted by the Centers for Disease Control (CDC). Genetic overlap with colon cancer could not be assessed formally here since the methods employed would require probands with colon cancer, and such a group was not included in the larger study.

Material and Methods

The data were obtained from a population-based case-control study, the Cancer and Steroid Hormone Study, conducted by CDC (Wingo et al. 1988). Incident cases of histologically confirmed cancers of the ovary, breast, and endometrium were ascertained among women 20–54 years of age, diagnosed between December 1, 1980, and December 31, 1982. The cases were obtained from eight population-based tumor registries that are part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI). Although ovarian cancer cases from all eight registries were available for this analysis, the only breast and endometrial cancer cases available were those from the state of Connecticut.

Controls were selected from the same eight geographic regions as were the cancer cases, by using Waksberg's method of random-digit dialing (Waksberg 1978). They were selected to be frequency matched to the age distribution of breast cancer cases within regions. The rates of cancers of the ovary, breast, and endometrium among the relatives of the controls from Connecticut represented the median of the rates from all eight centers. Therefore, controls from all eight centers were used, thereby increasing the precision of estimation. In the final study group there were 493 epithelial ovarian cancer probands, 895 breast cancer probands, 143 endometrial cancer probands, and 4,754 controls.

Data on family history of ovarian, breast, and endometrial cancer among mothers, sisters, daughters, maternal and paternal aunts, and maternal and paternal grandmothers were obtained from face-to-face interviews of the cases and controls. Age and age at onset were obtained for mothers, sisters, daughters, and grandmothers only.

Since direct interviews of relatives or reviews of medical records were not performed, we checked the correspondence between the observed number of reported cancers in relatives of controls and the number expected based on SEER registry data (Young et al. 1981). Possible cohort effects could not be taken into account since date of birth was not collected for deceased relatives. The standardized incidence ratios (SIRs) for mothers and sisters were 0.79, 0.74, and 1.80, for ovarian, breast, and endometrial cancer, respectively. Benign gynecologic conditions leading to hysterectomies may explain the greater-than-expected number of reported endometrial cancers in relatives. Owing to large differences in the SIRs for aunts and grandmothers as compared with first-degree relatives, and owing to generally less confidence regarding the accuracy of the reports for second-degree relatives, the analysis was restricted to first-degree relatives. Since daughters were too young to have experienced a substantial portion of the risk period, only sisters and mothers were used in the analysis.

Age-adjusted RRs and 95% confidence intervals (CIs) for breast, ovarian, and endometrial cancer among mothers, among sisters, and among mothers and sisters combined were calculated using Cox's (1972) proportional hazards model. The reference group for all comparisons consisted of the mothers and sisters of the population controls. The proportional hazards model compares age-specific incidence rates under the assumption that the hazard ratio for cases versus controls is constant throughout the risk period. If one assumes that the rate of underreporting is the same among the

cancer probands and controls, the hazard ratio remains the same. Therefore, both variable age at onset and underreporting are accommodated by this model.

The genetic relationship between ovarian, breast, and endometrial cancer was examined using maximum-likelihood estimation and a multivariate polygenic threshold model developed by Smith (1976). We modified Smith's model to accommodate three classes of probands. A trivariate normal distribution of cancer liability was assumed. The threshold model of disease liability is employed to estimate heritability and to determine genetic relationships by estimating the genetic correlation among traits. Thresholds are determined by the lifetime incidence in the general population (or a suitable control group). Because the risks for each cancer type were not higher among the case sisters than among mothers, only additive gene effects were assumed in the genetic model (i.e., dominance variance components were assumed to be zero).

Theoretically, there are eight different types of probands and relatives: those with all three cancers, those with each possible pair of cancers, those with each type of cancer alone, and those who have none of the three types of cancer. All of the probands were newly diagnosed as having primary cancer of one of the three sites (ovary, breast, and endometrium); therefore, we had four types of probands, including controls. In fact, the controls did not necessarily have no history of cancer. The only basis on which controls were excluded was if they had had cancer of the breast, ovary, or endometrium newly diagnosed within the 2-year period of the study. Therefore, the relatives of controls were assumed to be a random sample of the population—and not a sample of relatives of unaffected probands (although little difference results from this distinction).

Some of the relatives were reported to have primary cancers of more than one site. We have no knowledge of the reliability of such information. To guard against the possibility of metastasis, we assessed the likelihood of metastasis of the cancers reported in these relatives, according to the chronology of their occurrence. The analysis was repeated after reclassifying the affected status for each of the cancer sites for which metastasis was likely. This reclassification affected a total of 18 cases. The results were not changed by this reclassification, so the results presented are from the analysis in which each cancer reported for a single relative was counted as a primary cancer.

The analysis was performed using the computer program COSEG (Risch 1986) in conjunction with the maximum-likelihood program MAXLIK (Kaplan and Elston 1972). The parameters of COSEG are the thresholds T_1, T_2, and T_3 (one for each disease category); the three heritabilities H_1, H_2, and H_3; the three correlations of the heritable components of liability, R_{12}, R_{13}, R_{23}; and the three correlations of the environmental components of liability, E_{12}, E_{13}, and E_{23}. In this analysis, the environmental correlations were not estimable because of our classification scheme of individuals with multiple cancers as described above. In all that follows, a subscript 1 corresponds to ovarian cancer, subscript 2 to breast cancer, and subscript 3 to endometrial cancer.

The usual input to COSEG is the frequency of each type of outcome in relatives for each type of proband. However, we had to deal with two problems: variable age at onset and underreporting. Both issues were resolved by using the following alternative approach: Instead of using actual frequencies, we used the log age-adjusted RRs for each type of cancer among the relatives of each type of proband obtained from the Cox (1972) regression analysis, along with their standard errors (SEs). There are nine risk ratios (three relative types for each of three proband types). We then created a sum-of-squared-deviations statistic, W, as follows:

$$W = \sum_{i=1}^{3} \sum_{j=1}^{3} [(\mathrm{OLRR}_{ij} - \mathrm{PLRR}_{ij})/\sigma_{ij}]^2 ,$$

where OLRR_{ij} and PLRR_{ij} are the observed and predicted log RRs, respectively, for a proband of type i and relative of type j and where σ_{ij} is the SE for the observed ijth log RR. The values of PLRR_{ij} are predicted from the multivariate threshold model described above. We then minimized W as a function of the parameters H_1, H_2, H_3, R_{12}, R_{13}, and R_{23}. If normality and independence of the log RR estimates are assumed, $-2W$ is equivalent to a log-likelihood function. This can be used as a goodness-of-fit test, as specification of the PLRRs to be equal to the OLRRs gives a value of 0 for W. The parameters T_1, T_2, and T_3 are not estimable in this approach but were fixed at values corresponding to the cumulative incidence from SEER registry data (Young et al. 1981) and, alternatively, to the lifetime risks in relatives of controls.

The within-person correlations obtained from the genetic model permit estimation of the probability that two specific types of cancer will occur in the same individual. In addition, for those probands who have had primary cancers of two of the three sites under investigation, the model can be used to predict the risk of each type of cancer in relatives. In the relatives of pro-

bands with multiple primaries, deviation of the observed risk from the predicted risk has potential implications for the mode of inheritance. Because of the small numbers of probands with multiple primaries, age-adjusted risks for those subgroups were calculated by the method of Risch (1983), using an age-at-onset function derived from the relatives of controls.

Results

Age-adjusted RRs and 95% CIs from the Cox regression analysis are listed in table 1 for the three proband types and for the three cancers sites for mothers and sisters combined. Since in no instance was the RR for mothers statistically different from the RR for sisters and since few sisters had undergone as large a portion of the risk period as the mothers, the data from mothers and sisters were combined. Both ovarian and breast cancer cases were found to have elevated rates of ovarian and breast cancer among their relatives. No association was observed between either of these sites and family history of endometrial cancer. Likewise, although there was an elevation of family history of endometrial cancer among mothers and sisters of endometrial cancer probands, evidence was not found for an elevated risk of either ovarian or breast cancer among the relatives of these probands.

We also examined the risk of colorectal cancer in the relatives. We found that colorectal cancer was increased in frequency for mothers and sisters combined in each proband group. The crude odds ratios for family history of colorectal cancer among ovarian, breast, and endometrial cancer probands were 1.6 (95% CI = 1.0–2.7), 1.5 (95% CI = 1.0–2.3), and 1.6 (95% CI = 0.6–4.1), respectively. Age-adjusted RRs were not calculated, since age at onset of colorectal cancer in relatives was not reported.

The results for the genetic analysis using threshold values derived from the lifetime incidence from SEER are provided in table 2. Estimates of heritability of ovarian, breast, and endometrial cancer were approximately 40%, 56%, and 52%, respectively. There was a significant ($P < .01$) genetic correlation between ovarian and breast cancer ($R_{12} = .484$). A negligible and nonsignificant genetic correlation was found between ovarian and endometrial cancer ($R_{13} = .054$), and no genetic correlation between breast and endometrial cancer was found. We also analyzed the data by using threshold values derived from the lower cumulative lifetime incidences for each cancer type as reported by control probands for their relatives. The results were essentially the same, except that the heritability estimates were reduced by about 10%–20% of their initially estimated values, corresponding to the fact that, for a given RR, heritability decreases with decreasing population incidence. The values for R_{12}, R_{13}, and R_{23} remained essentially unchanged.

For the model given in table 2, $-2W = 2.91$, indicating a good fit of the model, assuming $-2W$ has a χ^2 distribution with 3 degrees of freedom (9 observations − 6 parameter estimates). Tests of fit of the model

Table 1

Age-adjusted RRs and 95% CIs for First-Degree Relatives (mothers and sisters), Calculated by Proband Type and Site of Cancer in Relative

Proband Type and Cancer Site	No. of Affected Relatives of Cases	RR (95% CI)
Ovary:		
Ovary	16	2.8 (1.6–4.9)
Breast	45	1.6 (1.1–2.1)
Endometrium	16	1.1 (.7–1.8)
Breast:		
Ovary	17	1.7 (1.0–2.9)
Breast	118	2.1 (1.7–2.5)
Endometrium	17	.9 (.6–1.3)
Endometrium:		
Ovary	1	.6 (.1–4.2)
Breast	14	1.2 (.7–2.2)
Endometrium	15	2.7 (1.6–4.8)

NOTE.—All RRs are calculated in comparison with those for the relatives of controls. The number of affected relatives of controls is 54, 297, and 160 for cancers of the ovary, breast, and endometrium, respectively.

Table 2

Heritability Estimates and Genetic Overlap for Ovarian, Breast, and Endometrial Cancer

Parameter[a]	Maximum-Likelihood Estimate	SE
T_1	2.090	...
T_2	1.303	...
T_3	1.774	...
H_1	.400	.090
H_2	.556	.061
H_3	.521	.118
R_{12}	.484	.131
R_{13}	.054	.139
R_{23}	.000	...

[a] 1 = Ovarian cancer; 2 = breast cancer; 3 = endometrial cancer; T = threshold based on cumulative incidence from SEER data; R_{ij} = correlation between H_i *and* H_j.

Table 3

Recurrence of Ovarian, Breast, and Endometrial Cancer among Relatives of Probands with Double Primaries of the Ovary and Breast

Cancer in Relative	*N*	No. Affected	Age-adjusted Risk (SE)	Model-predicted Risk
Ovary	33	0	.0 . . .	.03
Breast	33	6	.43 (.18)	.18
Endometrial	33	1	.06 (.06)	.03

by using data for mothers only and sisters only, data that are not presented here, were also not significant.

On the basis of the model in table 2, the within-person correlation of ovarian and breast cancer—or the probability of ovarian and breast cancer co-occurring within an individual—was estimated. From this result we estimated the RR of breast cancer in a woman with ovarian cancer, versus population incidence. This RR is the same as that of ovarian cancer in a woman with breast cancer. The risk of either ovarian or breast cancer given the other was estimated to be 2.3 times the probability of the independent occurrence of each cancer.

Ten of the ovarian cancer probands had a prior history of breast cancer, and three of the breast cancer probands had a prior history of ovarian cancer. These double primary probands were combined into a single group of those with both ovarian cancer and breast cancer. The predicted risks, among the mothers and sisters of this double primary group, for cancers of each of the three sites are given in table 3. Although the sample size is small, table 3 indicates a very high risk of breast cancer in the relatives of ovarian/breast probands. In this case the rate is greater than the rate predicted by the model.

To investigate possible genetic heterogeneity for ovarian and breast cancer, other risk factors were examined. These include age at onset, menopausal status, nulliparity, use of oral contraceptives, and relative height for weight at age 18 years as quantified by the Quetelet index.

RRs for history of ovarian cancer and breast cancer in mothers and sisters of ovarian and breast cancer probands were calculated separately for relatives and probands with onset age at ⩽45 years and for those with onset age at >45 years. The data in table 4 suggest that, in both probands and relatives, familial occurrence of ovarian cancer is increased at later ages at onset. Also, breast cancer probands with an early age at onset exhibit a higher RR for early age at onset of breast cancer in relatives. Ovarian cancer probands with later age at onset also show increased risk of early age at onset of breast cancer in their relatives. The converse, however,

Table 4

Age-adjusted Population RR and 95% CI, by Type of Proband, Cancer Site, and Age/Age at Onset for Probands and for Mothers and Sisters

Proband Type and Cancer Site in Relative	Age at Onset in Proband (years)	RR (95% CI), by Age/Age at Onset (in years) in Mothers and Sisters	
		⩽45	>45
Ovary:			
Ovary	⩽45	2.0 (.4–9.4)	2.2 (.6–7.7)
	>45	.0 . . .	4.9 (2.4–10.1)
Breast	⩽45	1.8 (.8–4.4)	2.1 (1.2–3.8)
	>45	3.1 (1.7–5.7)	0.9 (.5–1.5)
Breast:			
Ovary	⩽45	.0 . . .	1.6 (.5–5.0)
	>45	2.4 (.7–7.7)	2.0 (.9–4.3)
Breast	⩽45	3.0 (1.6–5.5)	2.1 (1.3–3.4)
	>45	3.3 (2.1–5.4)	1.5 (1.1–2.1)

does not appear to be true, i.e., breast cancer probands with an early age at onset do not show an increase in late-onset ovarian cancer in relatives.

Ovarian cancer probands with first-degree family history of ovarian cancer only ($N = 14$) were compared with ovarian cancer probands with first-degree family history of breast cancer only ($N = 43$) for differences in other characteristics (see table 5). Likewise, breast cancer probands with family history of only ovarian cancer in first-degree relatives ($N = 15$) were compared with probands with family history of only breast cancer ($N = 111$) (see table 6). Mean age at onset in probands, age at first pregnancy, the Quetelet index, menopausal status, nulliparity, and history of use of oral contraceptives were compared between these two groups. None of the potential risk factors examined differed among the two groups, for either of the two types of probands.

Discussion

Estimates of the RRs demonstrate that there was a consistency in the patterns of the risk of cancer among relatives of the different proband types and support the validity of the comparisons, even though they are based only on reports of cancer history in relatives. The results suggest an incomplete overlap in the inheritance of breast and ovarian cancer in addition to site-specific inheritance of endometrial cancer. The heritability estimates for each of the three cancers were similar, with the heritability of ovarian cancer being somewhat lower than the heritabilities for the other two sites.

In this study we were limited to probands having cancers of the three sites described. However, we also examined the risk of colorectal cancer in the relatives of the probands. We found that there was an increased RR in each of the three groups. Hence, it appears that colorectal cancer may also share a genetic etiology with all three cancers described. However, because we did not have colorectal cancer probands, we could not address this possibility directly.

From the estimates of the components of the phenotypic variance of ovarian cancer and breast cancer, it was estimated that, when one of these types of cancer

Table 5

Comparison of Characteristics of Ovarian Cancer Probands with Only a Family History of Ovarian Cancer vis-à-vis Those with Only a Family History of Breast Cancer in First-Degree Relatives

Variable	Family History of Cancer		
	Ovary		Breast
Age at onset:			
Mean	46.9		44.4
N	14		43
Difference (95% CI)		2.5 (−12.4 to 17.4)	
Age at first pregnancy >6 mo:			
Mean	23.2		22.2
N	13		32
Difference (95% CI)		1.0 (−2.4 to 4.4)	
Quetelet's index at age 18 years:			
Mean	2.0		2.1
N	14		43
Difference (95% CI)		.1 (−0.3 to 0.5)	
Premenopausal:			
%	42.9		53.4
N	14		43
Odds ratio (95% CI)		.7 (.2–2.2)	
Nulliparous:			
%	7.1		25.6
N	14		43
Odds ratio (95% CI)		.2 (.0–1.9)	
Oral contraceptive user:			
%	50.0		41.9
N	14		43
Odds ratio (95% CI)		1.4 (.4–4.7)	

Table 6

Comparison of Characteristics of Breast Cancer Probands with Only a Family History of Ovarian Cancer vis-à-vis Those with Only a Family History of Breast Cancer in First-Degree Relatives

Variable	Family History of Cancer		
	Ovary		Breast
Age at onset:			
Mean	46.6		45.4
N	15		101
Difference (95% CI)		1.2 (−13.8 to 16.2)	
Age at first pregnancy >6 mo:			
Mean	22.3		23.7
N	11		81
Difference (95% CI)		−1.4 (−9.9 to 7.1)	
Quetelet's index at age 18 years:			
Mean	2.1		2.0
N	15		101
Difference (95% CI)		.1 (−.4 to .6)	
Premenopausal:			
%	33.3		39.6
N	15		96
Odds ratio (95% CI)		.8 (.2–2.7)	
Nulliparous:			
%	26.7		18.8
N	15		101
Odds ratio (95% CI)		1.6 (.4–6.2)	
Oral contraceptive user:			
%	26.7		46.1
N	15		101
Odds ratio (95% CI)		.4 (.1–1.6)	

was present, there was a 2.3-fold increased risk for the other. Therefore, the observed tendency of these two cancers to occur in the same individual is consistent with a genetic causation. The predicted RR of 2.3 is of about the same magnitude as the estimated RR calculated on the basis of studies that have focused specifically on the incidence of multiple primary cancers (Shottenfeld and Berg 1971; Newell and Krementz 1977; Schoenberg 1977; Reimer et al. 1978).

Among the small group of probands who had both ovarian and breast cancer, the risk of breast cancer was higher than what was predicted by the model. This elevated risk suggests the possibility of a major-locus effect.

The fact that the genetic correlation between ovarian and breast cancer (R_{12} = .484) was significantly >0 but <1.0 suggests the possibility of genetic heterogeneity, i.e., shared gene(s) and unique gene(s) for the two cancers. Early age at onset has been implicated in the familial form of several cancers, including retinoblastoma and breast cancer (Anderson 1977; Murphree and Benedict 1984). Our data confirm the importance of early age at onset in familial breast cancer but suggest that late-onset ovarian cancer may be more familial than early-onset ovarian cancer. However, age at onset, as dichotomized at age 45 years, does not provide a clear separation of syndromes. The number of affected relatives was small for both ovarian cancer probands and breast cancer probands, and, therefore, precise measures of the RRs could not be obtained.

Other than age at onset, none of the five additional risk factors examined was found to distinguish between ovarian cancer probands who had a family history of ovarian cancer and those who had a family history of breast cancer. Similarly, none of these five risk factors was found to distinguish between breast cancer probands who had a family history of ovarian cancer and those who had a family history of breast cancer. However, owing to small sample sizes, only large differences would have been detectable in this study.

The observed relationship between familial ovarian cancer and breast cancer suggests that the genetic fac-

tors influencing breast cancer are complex. The results indicate that in future pedigree studies of familial breast cancer it may also be worthwhile, in analyzing patterns of inheritance, to include relatives with ovarian cancer. Additional factors, such as age at onset (Williams and Anderson 1984; Schwartz et al. 1985; Bishop et al. 1988; Newman et al. 1988), need to be studied further to delineate other possible sources of heterogeneity for familial breast cancer.

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