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The Genetic Epidemiology of Early-Onset Epithelial Ovarian Cancer: A Population-Based Study

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Summary

We conducted a population-based study to determine the contribution of germline mutations in known candidate genes to ovarian cancer diagnosed at age <30 years. Women with epithelial ovarian cancer were identified through cancer registries. DNA samples were analyzed for mutations in BRCA1, the "ovarian cancer–cluster region" (nucleotides 3139–7069) of BRCA2, and the mismatch-repair genes hMSH2 and hMLH1. Probable germline mutations in hMLH1 were identified in 2 (2%; 95% confidence interval 1%–8%) of 101 women with invasive ovarian cancer diagnosed at age <30 years. No germline mutations were identified in any of the other genes analyzed. There were no striking pedigrees suggestive of families with either breast/ovarian cancer or hereditary nonpolyposis colorectal cancer (HNPCC). There was a significantly increased incidence of all cancers in first-degree relatives of women with invasive disease (relative risk [RR] = 1.6, *P* = .01) but not in second-degree relatives or in relatives of women with borderline cases. First-degree relatives of women with invasive disease had increased risks of ovarian cancer (RR = 4.8, *P* = .03), myeloma (RR = 10, *P* = .01), and non-Hodgkin lymphoma (RR = 7, *P* = .004). Germline mutations in BRCA1, BRCA2, msh2, and mlh1 contribute to only a minority of cases of early-onset epithelial ovarian cancer. Our data suggest that early-onset ovarian cancer is not associated with a greatly increased risk of cancer in close relatives.

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Introduction

Inherited mutations of BRCA1 (MIM 113705), BRCA2 (MIM 600185), and the mismatch-repair genes are known to confer predisposition to ovarian cancer (Ford and Easton 1995). Of these genes, BRCA1 is thought to be responsible for the disease in the majority of families with breast/ovarian and site-specific ovarian cancer (Narod et al. 1995). Approximately 5% of ovarian cancers diagnosed at age <70 years are due to germline mutations of BRCA1 (Stratton et al. 1997). Early age at onset of cancer is often regarded as an indicator of underlying inherited predisposition to cancer, most notably for breast and large-bowel cancer. Of breast cancers diagnosed in women of age <30 years, 15% arise as a result of inherited mutations in BRCA1 (Fitzgerald et al. 1996; Langston et al. 1996; Krainer et al. 1997). Whittemore et al. (1997), using data from three U.S. population-based case-control studies, estimated that 18% of epithelial ovarian cancers occurring at age >30 years were due to germline BRCA1 mutations, whereas Ford et al. (1995) derived a more conservative estimate, 6%, from population-based British data. Perhaps it is somewhat surprising, therefore, that only one study has reported epithelial ovarian cancer that developed at age <30 years in a BRCA1-mutation carrier (Rubin et al. 1996). The scarcity of reports of early-onset epithelial ovarian cancer in women with BRCA1 mutations may be the result of ascertainment bias toward early-onset breast cancer, in the ascertainment of families for genetic study. To determine the contribution of known ovarian-cancer–predisposing genes to early-onset ovarian cancer, we set up a retrospective population-based study for the identification of all cases of early-onset epithelial ovarian cancer during a 10-year period. We collected information on cancer incidence among first- and second-degree relatives, to determine whether their relatives were at increased risk

of cancer and whether there was evidence of a particular pattern of cancers among family members.

Methods

Study Design

Women of age <30 years who had epithelial ovarian cancer diagnosed in 1984–93 were eligible to enter the study. Women with borderline tumors were included. Patients' names and their consultants' (hospital specialists) names were obtained from the following United Kingdom cancer registries: East Anglian, Thames, Trent, Wessex, Oxford, South Western, West Midlands, Mersey and Cheshire, Wales, West of Scotland, Scottish, and Northern Ireland. We wrote to the patients' consultants to obtain their permission to contact their patients, if the patients were still alive, and to provide us with the names and addresses of the patients' general practitioners (GPs). For patients who had died, we asked their consultants to provide us with details of their histological type of cancer, clinical staging, type of surgery undertaken, adjuvant therapy, and duration of follow-up. We also requested pathology reports and pathology material from these individuals. For patients who were alive, we wrote to their GPs to obtain their permission to contact their patients and, also, to request their help in obtaining a blood sample. When we received permission from the patients' GPs, we contacted the patients by letter, telling them about the study and asking whether they would be willing to participate. Patients who agreed to enter the study were asked to complete a questionnaire giving details of their medical history, including parity and oral contraceptive use. Participants were also asked to complete a table giving the names, dates of birth, vital status, and dates of death of all their first- and second-degree relatives and to indicate which individuals had cancer develop, including type of cancer and age at diagnosis. We requested that one 20-ml blood sample be obtained from each patient; this was taken either by the patient's GP or by a practice nurse and was collected in two 10-ml containers that we provided. If either the patient or the GP was unwilling for a blood sample to be drawn, a mouth swab was requested instead. The patients' consultants were sent the same questionnaire described previously for patients who had died. We also requested pathology reports and pathology material. All nonresponders (consultants, GPs, and patients) to any of the letters were sent a single reminder. We attempted to trace lost patients and GPs through the National Health Service Central Registry and the Family Health Services Authorities.

Ethics

One hundred five ethics committees located throughout the United Kingdom and Northern Ireland districts covered by the cancer registries, as well as the British Medical Association Central Ethical Committee, approved the study protocol. Ethical approvals were obtained by collaborators in their regions. Written, witnessed consent was obtained from all participating women. Participants were also asked to indicate whether they wished to be informed of the results of the mutation analysis.

Statistics

Comparison of the observed and expected incidence of cancers in first- and second-degree relatives was performed by use of the PERSON-YEARS program, version 1.21 (Coleman et al. 1989). Expected numbers of cancers were calculated from age-, sex-, and period-specific incidence rates for England and Wales (Electronic Database of Cancer Incidence in Five Continents).

For each relative, the date of entry into the cohort was defined as either the date of birth (estimated where unknown) or January 1955, whichever came later. The date of exit was either the date of cancer diagnosis or, if there was no cancer, either the date of death or the date last seen, as appropriate. For living relatives, date last seen was assumed to be January 1, 1997, whereas deceased relatives without a date of death were given a date on the basis of their relationship to the index case—for example, deceased grandparents without reported illnesses were assumed to have lived 75 years from their date of birth. Relatives whose dates of birth were unknown were assigned dates of birth on the basis of their relationship to the index case—for example, grandparents were assigned a date of birth 25 years before the date of birth of the relevant parent of the index case. Relatives born before 1890 and relatives who had died or who had developed cancer before 1955 were excluded from the analysis. The analysis was performed twice—once with individuals being censored on their 85th birthday and once with the earlier censoring age, 60 years. Analyses were performed separately for the relatives of index cases with invasive cancer and the relatives of index cases with borderline tumors. Significance levels were calculated on the basis of both the Poisson assumption and age.

Pathology

Ten 5-μm sections were cut from all paraffin-wax tumor blocks received and were mounted on glass slides. One slide was hematoxylin-eosin–stained and was reviewed by one of two reference pathologists, in

conjunction with the histology report, where available.

Mutation Analysis

Genomic DNA was extracted from blood or from mouth swabs, by standard methods, by an Extragen automated DNA extractor.

BRCA1.—Twenty-eight primer pairs were used to amplify the entire BRCA1 coding sequence and intron-exon boundaries for screening by multiplex heteroduplex analysis. DNA fragments were subsequently electrophoresed through 20-cm × 20-cm × .1-cm, nondenaturing 1 × MDE gels (Flowgen), by use of the Protean II™ vertical-slab-gel apparatus (Bio-Rad). Electrophoresis was performed for 12 h at a constant 250 V, with gels cooled to 10°C. All gels were stained with silver nitrate, according to standard procedures (Gayther et al. 1995, 1996; Glavac and Dean 1995; Rossetti et al. 1995).

BRCA2.—BRCA2 was screened for mutations in the ovarian cancer–cluster region (nucleotides 3139–7069), by means of the protein-truncation test (PTT). PTT was performed with the TNTT rabbit reticulocyte-lysate system (Promega), incorporating [^{35}S] methionine for protein detection (Foster et al. 1996; Friedman et al. 1997; Gayther et al. 1997).

hMSH2 and hMLH1.—The entire coding regions of both these genes were amplified and were screened by combined single-stranded conformation and heteroduplex analysis (SSCA/HA) on 0.6 × MDE gels (Flowgen), by use of the Protean II™ vertical-slab-gel apparatus (Bio-Rad). Electrophoresis was performed for 12 h at a constant 150–170 V, with gels cooled to 10°C. All gels were stained with silver nitrate, according to standard procedures (Glavac and Dean 1993; Borresen et al. 1995; Han et al. 1995, 1996; Moslein et al. 1996). All variants were characterized by DNA cycle sequencing, with the use of Ampli*Taq*-FS DNA polymerase (Applied Biosystems) on an Applied Biosystems 373A automated sequencer.

Results

For the purposes of this study, we identified 663 women through the cancer registries. Of these women, 140 were known to be dead and 7 were untraceable. Of the 516 women still possibly alive, we did not receive, from their hospital specialist, permission to proceed in 43 cases, and we were unable to identify the patient's current GP in 36 cases. A further 38 GPs did not respond to our letter, and 27 refused permission to contact their patients. A further 59 GPs who replied were unable to give permission to proceed with the study, since they had lost contact with their patients. This left 313 women who were contacted to take part in the study. Two women were subsequently excluded when pathology review revealed them to have germ-cell tumors. Of these 311 women, clinical details were obtained for 198, family-history information for 172, blood samples for 191, mouth swabs for 5, and archival pathology material for 121. Age range at diagnosis in the 198 women was 13–29 years, with a median of 25 years. Of the 140 women known to have died, clinical details for 96 were obtained through their consultant, and pathological material was obtained for 60. The age range at diagnosis in this group was 11–29 years, with a median of 25 years.

Family History

Results of the PERSON-YEARS analysis are presented in table 1. Results for borderline and invasive tumors are shown separately, since it is unclear whether they are part of the same disease process. Because of the greater likelihood of cancer sites being misreported among second-degree relatives and because familial effects are likely to be stronger among first-degree relatives, we analyzed the familial risks in first- and second-degree relatives separately. The lack of excess of cancers overall, in either first- or second-degree relatives of women with invasive and borderline tumors taken together, suggests that there is no significant recall bias.

First-degree relatives of women with invasive ovarian cancer had a marginally increased risk of cancer overall (30 vs. 19, RR = 1.6, $P = .01$ (table 1). They had a significantly increased risk of ovarian cancer (RR = 4.8, $P = .03$) if followed to age 85 years, but this was not significant in the smaller subset of relatives of age <60 years. Although slightly more cases of breast cancer were observed than were expected, the difference was not significant. There was, however, an excess of non-Hodgkin lymphoma (4 vs. 0.6, RR = 7, $P = .004$) and multiple myeloma (2 vs. 0.2, RR = 10, $P = .01$).

Among second-degree relatives of women with invasive cancer, there was a greater-than-expected incidence of both lung cancer (26 vs. 16, RR = 1.6, $P = .01$) and liver cancer at age <60 years (2 vs. 0.1, RR = 20, $P = .01$); however, these findings cannot be interpreted with confidence, since a report of "lung cancer" or "liver cancer" unconfirmed by medical evidence may reflect metastatic disease. First-degree relatives of women with borderline cancers had increased risks of prostate cancer (3 vs. 0.3, RR = 10, $P = .002$) and Hodgkin lymphoma (2 vs. 0.2, RR = 10, $P = .02$), which were not present in relatives of women with invasive cancer. Second-degree relatives of women with borderline tumors had increased risks of both cancer of the larynx (3 vs. 0.6, RR = 5, $P = .02$) and ovarian cancer at age <60 years (4 vs.

Table 1

Cancer Incidence in First- and Second-Degree Male and Female Relatives of Index Cases with Ovarian Cancer at Age <30 Years

	No. of Expected Cases/No. of Observed Cases			
	Invasive Tumor		Borderline Tumor	
Cancer Type in Index Case	First-Degree Relatives	Second-Degree Relatives	First-Degree Relatives	Second-Degree Relatives
Breast	5/3.5	12/11	2/2.2	11/8.6
Ovary	3*/.6	3/2.3	1/.4	4***/1.7
Pharynx	0/.4	1/.6	0/.2	1/1
Esophagus	1/.4	0/1.7	0/.2	0/1
Stomach	1/.8	8/5	1/.4	4/3
Colon	2/1.2	10***/6	0/.6	4/3.7
Rectum	1/.8	0/4	1/.4	0/2.5
Liver	0/.1	2***/.4	0/.05	0/.3
Pancreas	2***/.4	1/2.3	1/.2	0/1.4
Larynx	0/.2	2/.9	0/.1	3*/.6
Lung	1/2.9	26*/16	1/1.4	5/8.9
Bone	0/.09	0/.2	0/.06	0/.1
Connective tissue	0/.15	0/.4	0/.09	0/.3
Melanoma	0/.5	1/1.1	0/.3	0/.8
Cervix	2/.8	3/2.1	1/.5	0/1.7
Uterus	0/.4	1/2	0/.3	4***/1.4
Prostate	2/.6	4/4	3**/.3	0/2
Testis	0/.3	0/.4	0/.2	1/.3
Bladder	1/.9	0/4	0/.4	1/2.4
Kidney	0/.4	1/1.5	0/.2	0/1
Brain	0/.6	3/1.7	0/.4	1/1.2
Thyroid	1/.1	0/.3	0/.08	0/.2
Hodgkin	0/.3	1/.6	2*/.2	0/.4
Non-Hodgkin lymphoma	4**/.6	0/1.9	1/.4	0/1.2
Myeloma	2*/.2	0/.9	0/.1	0/.5
Leukemia	0/.6	0/1.7	0/.3	0/1.1
Other cancers	0/.4	0/1.6	0/.2	0/1
Unknown	0/.8	1/4	0/.4	0/2.5
All except nonmelanoma skin	30*/19	80/82	14/11	39/51
All except skin, breast, and ovary	22***/15	65/68	11/8	24/41

Note.—Number of male and female relatives at risk is 1,968.

* $P < .05$.

** $P < .01$.

*** $P < .1$.

1, RR = 3.8, $P = .02$), but they had no increased risk of cancer overall.

The possibility that some of these women with early-onset ovarian cancer might be members of families with a presumed breast/ovarian cancer syndrome was of obvious interest, as was the question of the risk of ovarian cancer at a young age in their siblings and the risk of second primary cancers in the patients themselves. There were no pedigrees with striking aggregates of early-onset cases. One family had a paternal aunt with bilateral breast cancer, at age 35 and at 45 years; there were no families with both a further case of ovarian cancer at any age and a further case of breast cancer at age <50 in close relatives. No woman had more than one relative with ovarian cancer; of the 13 cases of ovarian cancer reported in relatives, 4 were in first-degree relatives (at ages 28, 41, 66, and 72 years). The age range at diagnosis of the nine ovarian cancers in second-degree relatives was 28–65 years. Five patients were reported to have second primary cancers; one had an endometrioid adenocarcinoma of the ovary at age 25 years and a transitional-cell cancer of the bladder 8 mo later (both tumors were confirmed by histology), and one had a confirmed adenocarcinoma, in situ, of the uterus at age 28 years. The other primary cancers were basal cell carcinoma, at age 23 years; hydatidiform mole, at age 27 years; and astrocytoma of the spinal cord, at age 6 years.

Mutation Analysis

One hundred ninety-one women were screened for germline mutations in the entire coding region of

Table 2

Results of Mutation Analysis

Gene	No. of Cases Analyzed/No. of Mutations (95% CI)	
	Invasive	Borderline
BRCA1	109/0 (0%–4%)	77/0 (0%–5%)
BRCA2	98/0 (0%–4%)	74/0 (0%–6%)
hMLH1	100/2 (1%–8%)	64/0 (0%–6%)
hMSH2	100/0 (0%–4%)	64/0 (0%–6%)

Note.—There were five index cases analyzed for mutations in all of the genes but in which details on whether the tumors were borderline or invasive were unknown. In the computation of the 95% CIs, we allowed for a detection sensitivity of 70% for BRCA1 mutations. For the calculation of the confidence limits for BRCA2 mutations, we assumed that 73% of mutations in patients with ovarian cancer occur in the ovarian cancer–cluster region of BRCA2 and that the PTT has an 87% sensitivity (Hogervorst et al. 1995; Takahashi et al. 1996; Tavtigian et al. 1996; Gayther et al. 1997; Hakansson et al. 1997; Breast Cancer Information Core Data Base). In the computation of the confidence limits for the SSCP/HA analysis of the hMLH1 and hMSH2 genes, we assumed a sensitivity of 75%, which is the lowest reported sensitivity of the technique (Orita et al. 1989*a*, 1989*b*; Condie et al. 1993; Sheffield et al. 1993).

BRCA1; 177 women, for germline mutations in BRCA2 nucleotides 3035–6629; and 169 women, for germline mutations in MLH1 and MSH2. The age range of these women was 13–30 years, with a median of 25 years. The results are shown in table 2. No mutations were detected in BRCA1, BRCA2, or MSH2 genes, although the expected neutral variants were detected. Two patients had probable mutations in the hMLH1 gene. One patient had a Lys618Thr change in hMLH1, which has previously been reported as a mutation (Han et al. 1995). She presented with a mucinous adenocarcinoma of the ovary at age 27 years; among 27 first- and second-degree relatives, the only reported cancer was an unknown primary cancer seen in her paternal grandmother at age 71 years. The second woman also had a Lys618Thr change and, in addition, had an Asp304His variant in exon 11 of hMLH1. We could not determine whether this was on the same allele or on the opposite allele as the Lys618Thr change. This woman had endometrioid adenocarcinoma of the ovary diagnosed at age 25 years, and, 8 mo later, transitional-cell cancer of her bladder developed—a pattern that is consistent with the tissues known to be affected in families with HNPCC. No details of her family history were received. The Asp304His variant has not previously been reported. Both of the aforementioned changes affect residues conserved between man and rat; both changes are nonconservative and were not seen in 190 chromosomes screened from the general population.

Pathology, Stage, and Residual Disease

There were substantial differences in pathology between the women who were still alive at the time of the study (median time from diagnosis 7 years) and those who had died (tables 3 and 4). The group who had died had a significantly higher proportion of invasive adenocarcinomas of the ovary (20% vs. 6%, odds ratio [OR] 3.54, 95% confidence interval [CI] 1.6–7.7; $\chi^2 = 11.7$, $P < .001$) and other rare invasive histological subtypes (23% vs. 0%, $\chi^2 = 46$, $P < .001$), which most likely reflects a subgroup of tumors that have a worse prognosis. There were no significant differences, in the proportions of invasive serous, mucinous, and endometrioid tumors, between the living and dead groups, but the surviving group differed from the group who had died of their disease, with regard to the proportion with borderline tumors (41% vs. 1%, $\chi^2 = 52$, $P < .001$), with stage 1 disease (76% vs. 24%, $\chi^2 = 76.2$, $P < .001$), and with residual disease <1 cm after the initial operation (89% vs. 31%, $\chi^2 = 76.2$, $P < .001$).

Discussion

The most striking result is the failure to detect any germline mutations (*a*) in BRCA1 in 101 women, and (*b*) in a limited analysis of the ovarian cancer–cluster region of BRCA2 in 98 women with invasive ovarian cancer diagnosed at age <30 years; or (*c*) in either BRCA1 or BRCA2 in >70 women with borderline tumors. This result contrasts both with the experience in early-onset breast cancer (Fitzgerald et al. 1996; Langston et al. 1996; Krainer et al. 1997) and with the predictions, from epidemiological studies, that 6%–18% of ovarian cancers diagnosed at age <30 years would be attributable to mutations in BRCA1 (Ford and Easton 1995; Whittemore et al. 1997). Although the evidence for a higher familial relative risk at younger ages is much weaker for ovarian cancer than for breast cancer, the frequency of BRCA1 mu-

Table 3

Histological Diagnosis in 198 Living Women with Epithelial Ovarian Cancer Diagnosed at Age <30 Years, with Number of Each Subtype Analyzed for BRCA1 Mutations

Tumor Histology	No. of Tumors/No. of Tumors Analyzed	
	Invasive	Borderline
Serous	32/30	35/31
Mucinous	67/64	46/43
Endometrioid	4/4	2/2
Adenocarcinoma	11/11	1/1
Total	114/109	84/77

Table 4

Histological Diagnosis in 36 Deceased Women with Epithelial Ovarian Cancer Diagnosed at Age <30 Years

	No. of Tumors	
Tumor Histology	Invasive	Borderline
Serous	23	0
Mucinous	25	1
Endometrioid	5	0
Undifferentiated	5	0
Not specified	2	0
Adenocarcinoma	20	0
Small cell	14	0
Clear cell	1	0
Total	95	1

tations that we observed in cases of invasive cancer diagnosed at age <30 years was actually lower than that in our previous hospital-based series of consecutive cases of invasive cancer diagnosed at age <70 years (median age 53 years): 0/109 vs. 12/355 (P = .08).

This finding is consistent with the observations from the multiple-case families collected by the Breast Cancer Linkage Consortium (Hall et al. 1990; Narod et al. 1991, 1995; Easton et al. 1993, 1995, 1997; Wooster et al. 1994). Of the 277 confirmed cases of epithelial ovarian cancer in the entire set of families known to carry a mutation in BRCA1 or BRCA2, only 4 were diagnosed at age <30 years. Three of these have been shown to be phenocopies, and, in one, the BRCA-mutation status is unknown. The finding is also consistent with unpublished data from the United Kingdom Co-ordinating Committee on Cancer Research Familial Ovarian Cancer Register, which suggest that early age at diagnosis is not a feature of familial ovarian cancer: among 202 well-documented families with at least two confirmed diagnoses of invasive epithelial ovarian cancer in first- or second-degree relatives, only 15 (2.7%) of 556 cases of ovarian cancer for which data are available were diagnosed at age <35 years, and only 9 (1.6%) of 556 were diagnosed at age <30 years.

There are several caveats in the interpretation of these results. The first two relate to the mutation analysis. This was subject to potentially serious selection bias, in that it was performed on blood samples and, therefore, on surviving patients. However, this may not have affected the results: the proportion of invasive serous tumors (which is the histological type most frequently associated with BRCA1 mutations) did not differ between survivors and nonsurvivors, and current data do not suggest that the selection of survivors would have biased against cases with BRCA mutations (Rubin et al. 1996; Brunet et al. 1997; Johannsson et al. 1997, 1998; Stratton et al. 1997). Second, the mutation analysis has limited sensitivity, and some mutations may therefore have been missed. This is addressed in more detail in table 2. A third caveat is that the pattern of histological types is markedly different between cases diagnosed at age <30 years and those diagnosed at age ⩾30 years. Of the 111 patients with invasive cancer who were analyzed for germline mutations, 66 (59%) had mucinous tumors, and only 30 (28%) of 109 had serous tumors. This compares with 58% invasive serous tumors in our previous hospital-based series of invasive ovarian cancers diagnosed at age <70 years. In the hospital-based series, 12 of the 13 BRCA1 mutations identified occurred within the 203 cases of invasive serous carcinoma. If the prevalence was similar, this would predict two mutations in our set of 30 invasive serous tumors diagnosed at age <30 years. This lies within the confidence limits of our observation that there are no mutations in this set. We therefore cannot make any firm conclusion about differences in the prevalence of BRCA mutations in invasive serous carcinomas in different age groups.

The possibility of bias due to selective study of surviving patients might conceivably affect the family-history analysis. However, with this reservation, the scarcity of cases of early-onset ovarian cancer in families with breast and ovarian cancer, the lack of strong excess risks of breast or ovarian cancer in the relatives of cases in the current study, and the mutation data all suggest that, in contrast to early-onset breast cancer, diagnosis of ovarian cancer at age <30 years is not a strong indicator of familial susceptibility to either breast or ovarian cancer.

If early-onset ovarian cancers are not, in general, part of the familial breast/ovarian cancer syndrome, do they have characteristics suggesting that at least some of them are distinct from the generality of epithelial ovarian cancer? One difference, mentioned earlier, is suggested by the pathology. The impression of a different spectrum of pathology in early-onset cases in the current study is confirmed by an analysis of all cases, irrespective of survival or our ability to trace them, in the East Anglian Cancer Registry. Among epithelial ovarian cancers recorded in this registry during 1987–96, 20 (39%) of 51 of those diagnosed at age <30 years were of borderline histology, compared with 121 (8%) of 1,466 of those in women of age 30–70 years at diagnosis ($P < .001$). Among the invasive cancers, mucinous histology was more frequent in cases diagnosed at age <30 years, occurring in 15 (48%) of 31, compared with 214 (16%) of 1,345 cases of invasive cancer diagnosed at age 30–70 years ($P < .001$).

Another possible clue to differences might come from the finding of distinct patterns of familial aggregation in early cases. In our series, we detected a

number of familial associations, the statistical significance of which is weakened by the large number of comparisons made. Apart from the expected slightly increased familial relative risk of ovarian cancer, the most striking finding was an excess risk of both non-Hodgkin lymphoma and multiple myeloma. Each of these associations involved only a very small number of cases and was not consistent between first- and second-degree relatives, which suggests that, until further confirmation is obtained, they should be treated with caution. We found two individuals with germline mutations in hMLH1, a finding that is consistent with the known involvement of some cases of ovarian cancer in the HNPCC syndrome; however, the upper confidence limits for the prevalence of mutations in hMSH2 and hMLH1 combined was only 12%.

In sum, our data suggest that ovarian cancers diagnosed at age <30 years differ from those diagnosed at later ages, in that they contain a higher proportion of both borderline cases and mucinous histology among invasive cases. In the great majority of cases, there is no evidence of strong hereditary predisposition. One of the motivations to perform this study was a series of clinical referrals of sisters of young women who had had invasive ovarian cancer diagnosed in their 20s, with the question of risk to the sisters and the advisability of prophylactic oophorectomy. The conclusion that we draw from our data is that, in the absence of a suggestive family history, the risks to such young women are probably not greatly increased and that drastic measures, such as oophorectomy, are unnecessary.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Breast Cancer Information Core Data Base, http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/

International Agency for Research on Cancer, World Health Organization, http://www-DEP.IARC.FR/dataava/globocan/globoJava.html

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for BRCA1 [MIM 113705] and BRCA2 [MIM 600185])

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