

Age at Onset for Familial Epithelial Ovarian Cancer

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Objective.—To provide age-specific risks for ovarian cancer for relatives of ovarian cancer case patients. To characterize the age at onset for ovarian cancer for women with a single relative vs several relatives affected with ovarian cancer.

Design.—Three previous studies were reexamined. The cumulative probability of ovarian cancer in first-degree relatives of women with histologically confirmed epithelial ovarian cancer and matched control subjects who participated in the Cancer and Steroid Hormone (CASH) Study was determined. The age of onset of ovarian cancer in women with and without relatives with ovarian cancer in a Washington, DC, case-control study was contrasted with that of women with at least two first-degree relatives studied at the National Cancer Institute (NCI).

Results.—The CASH Study data showed that first-degree relatives of women with ovarian cancer had an increased risk for ovarian cancer, especially at older ages, when compared with relatives of control subjects. However, the median age at onset was the same among women in the Washington, DC, study with and without an affected relative. Among the women with an extensive family history of ovarian cancer studied at the NCI, the age at onset was considerably younger (47 years) than is typical for this disease (59 years). Of these, 17% had been diagnosed as having primary ovarian cancer by age 40 years.

Conclusions.—Women who have one first-degree relative affected by ovarian cancer are at greater risk for ovarian cancer but not at an age earlier than the general population. The small proportion of women who have several affected relatives are, however, at a greater risk of early onset of ovarian cancer. Prophylactic oophorectomy may be reasonable for these women.

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A FAMILY history is the strongest independent risk factor for ovarian cancer,¹ apart from age. Among US studies, the aggregate odds ratio is 3.6 for ovarian cancer in first-degree relatives of women with epithelial ovarian cancer.² A few rare genetic syndromes are associated with increased risk for ovarian tumors,³⁻⁵ but familial epithelial ovarian

cancer more often aggregates as a site-specific phenomenon or in association with breast⁶ or colon and endometrial cancers.⁷ Although the existence of at least a single locus on chromosome 17q greatly affecting susceptibility for breast and ovarian cancers is now well documented,^{8,9} the specific genetic defect and its relationship to risk for ovarian cancer in site-specific families remains unknown. In addition, other loci affecting susceptibility are postulated to explain disease aggregation in families not showing genetic linkage to markers in this chromosomal region.^{8,10}

At the present time, since we are generally unable to identify carriers of a

specific gene predisposing for ovarian cancer, epidemiologic studies must be relied on to estimate an individual's risk and to provide data for genetic counseling. The majority of women reporting a family history of ovarian cancer have only a single affected close relative, but guidelines for counseling and prophylactic oophorectomy have typically been generated from case series of families including many women affected by ovarian cancer.¹¹⁻¹⁴ Here, we compare results from three studies with different designs to develop risk estimates for counseling women, including those with only a single relative with ovarian cancer. Since early age of onset of cancer may reflect the degree of familial risk we studied the age of onset and age-specific risks for ovarian cancer in relatives of ovarian cancer case patients and control subjects and in families that included at least two close relatives with ovarian cancers.

MATERIALS AND METHODS

Data from three previous studies were reassessed. The Cancer and Steroid Hormone (CASH) Study involved women aged 20 to 54 years residing in eight US areas (Connecticut; Atlanta, Ga; Detroit, Mich; Iowa; San Francisco, Calif; Seattle, Wash; New Mexico; and Utah) with histologically confirmed primary ovarian cancer of all histologic types newly diagnosed between December 1, 1980, and December 31, 1982. Of the 785 eligible women, 548 (69.8%) were interviewed. Of the 5698 control subjects matched by age (in 5-year intervals) and locale, 4754 (83.4%) agreed to participate. Description of data collection¹⁵ and comparison of lifetime risk for ovarian cancer, breast cancer, and endometrial

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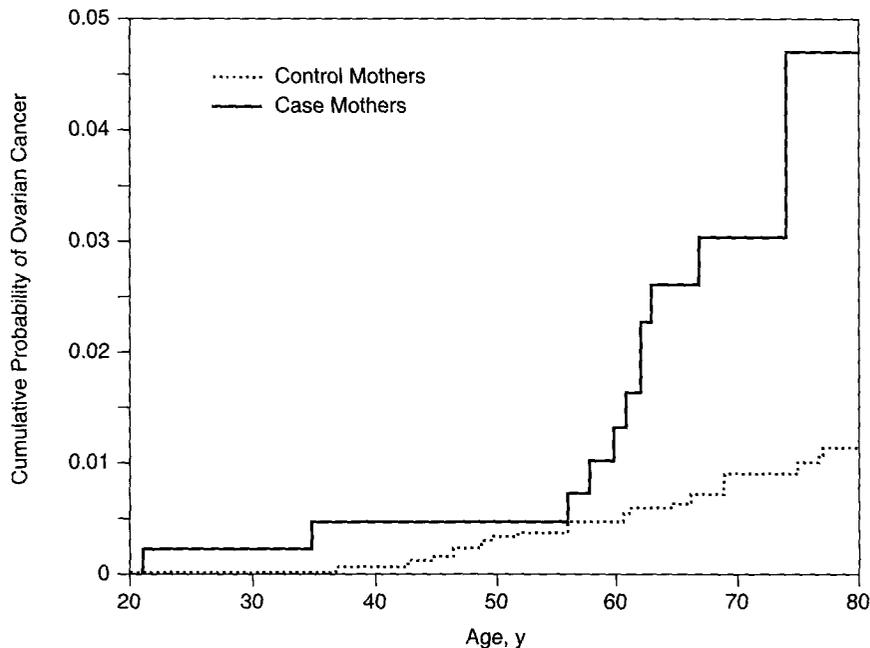
cancer in relatives of ovarian cancer case patients and control subjects^{1,16} have been reported. For this study we restricted analyses to the 449 case patients who had epithelial histologies on pathology review, their mothers, and their 685 sisters. Tumor behavior was characterized as borderline for 123 cases and invasive for 326 cases. Control subjects with prior primary breast or endometrial cancers were excluded, leaving 3868 control subjects, their mothers, and their 5866 sisters. We calculated cumulative risks separately based on whether the case patients or control subjects were younger than 50 years or were 50 years or older at examination.

We also used data from a case-control study of epithelial ovarian cancer conducted in Washington, DC,¹⁷ that included women aged 20 to 79 years who had a first histologically confirmed epithelial ovarian cancer during the period August 1978 to June 1981 and hospital control subjects. Of 400 identified case patients, 296 (74%) were interviewed. Family history of ovarian cancer in a mother, sister, or daughter was obtained.

Age at onset for ovarian cancer was also evaluated in 16 families referred to the National Cancer Institute (NCI) because of two or more first-degree relatives with ovarian cancer. In these families 63 ovarian cancers were clinically diagnosed, of which 53 were histologically confirmed. Three tumors of the omentum in women aged 51, 56, and 60 years, who had previously undergone oophorectomies, were included as were two tumors arising in the wolffian and müllerian ducts in women aged 34 and 57 years, respectively, and two fallopian tube tumors in women aged 34 and 43 years. Of the families in this analysis, five included at least three women with breast cancer and are identified as breast/ovarian-type families. Lynch cancer family syndrome II, or autosomal-dominant transmission of susceptibility for ovarian, endometrial, colon, and other adenocarcinomas, was not observed in any of these families, although stomach, lung, colon, and other cancers occasionally occurred in relatives.

Statistical Methods

Mean levels of quantitative measures were compared using a two-sample *t* test. We used a Kaplan-Meier estimator to obtain cumulative risks for ovarian cancer.¹⁸ Relative risks and confidence intervals (CIs) were obtained from fitting Cox proportional hazards models.¹⁹ For mothers, two separate models were fitted including person-years at risk either up to 60 years of age or aged 60 years and older. An exact test was used to compare medians.²⁰



	Person-Years of Follow-up in Interval, ×1000					
Control Mothers	38.5	38.0	36.5	32.2	22.2	9.1
Case Mothers	4.5	4.4	4.2	3.7	2.5	1.2

Fig 1.—Cumulative probability for ovarian cancer among mothers of ovarian cancer case patients (case mothers) and control subjects (control mothers), based on data from the Cancer and Steroid Hormone Study, 1980-1982.¹⁵

RESULTS

In the CASH Study, the mean ages of case patients and control subjects were similar (44 years), as were the numbers of sisters (1.5), years of education (13.4 years in control subjects vs 13.5 years in case patients), and income of the families (\$31 519 in control families vs \$30 224 in case families). A single control family and no case families reported more than one first-degree relative affected by ovarian cancer.¹

Cumulative probabilities for ovarian cancer among the case patients' and control subjects' mothers are shown in Fig 1. The median reported age at onset was 61 years in the 12 affected mothers of case patients (range, 21 to 74 years), while the median age at onset in the 27 affected mothers of control subjects was 56 years (range, 37 to 77 years). Overall, the cumulative probability of mothers of case patients to develop ovarian cancer was 3.9 times higher than that of mothers of control subjects (95% CI, 2.0 to 7.7). Until 60 years of age, the relative risk among mothers of case patients was only 2.1-fold higher (95% CI, 0.7 to 6.1), but this risk was 7.0-fold for mothers of case patients 60 years of age or

older (95% CI, 2.8 to 17.8). The cumulative probability of developing ovarian cancer for mothers of younger case patients (< age 50 years) was similar to that of older case patients (data not shown), but among mothers of case patients, the only two mothers with ovarian cancer before age 50 years occurred in the group of case patients diagnosed before age 50 years. Exclusion of patients with borderline histologic findings led to an overall relative risk to mothers of 5.0 (95% CI, 2.5 to 9.9); the risk was increased 2.8-fold among mothers of case patients until age 60 years (95% CI, 0.9 to 8.3) and 8.6 among older mothers (95% CI, 3.4 to 21.8).

For sisters of case patients and control subjects older than 50 years of age, respectively, 2687 person-years and 21 725 person-years were observed. Thus, only about one third as many person-years at risk for ovarian cancer were available for study in sisters compared with their mothers. Three of 449 case patients each reported an affected sister with ages at onset of 50, 55, and 71 years, while 15 of 3868 control subjects reported 17 affected sisters with a median age at onset of 40 years (range, 19 to 55 years). Sisters of control subjects

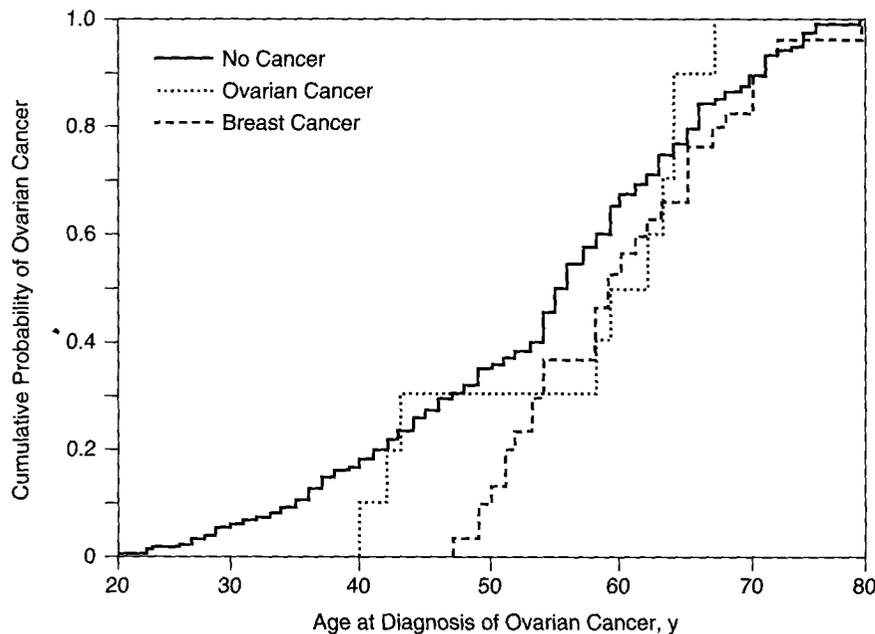


Fig 2.—Age at diagnosis for ovarian cancer cases by family history of ovarian or breast cancer, based on data from case-control study, Washington, DC, 1978-1981.¹⁷

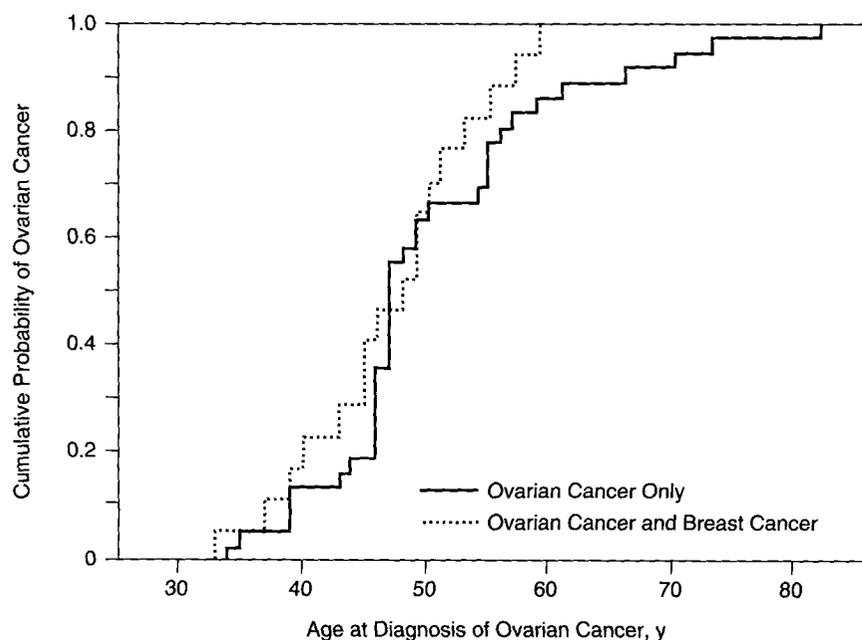


Fig 3.—Age at diagnosis for ovarian cancer cases in 16 high-risk pedigrees.

had an equivalent risk for ovarian cancer compared with their mothers ($P>.40$), as did sisters of case patients with their mothers ($P>.90$), although the latter comparison is based on a small number of events.

Similar findings from the Washington-based study are reported in Fig 2. Among the 10 case patients who reported one first-degree relative affected by ovarian cancer, the median age at diag-

nosis was 60 years, while among the 256 case patients reporting no family history of either ovarian cancer or breast cancer, the median age was 55.5 years. The median age at diagnosis among the 30 case patients who reported breast cancer but not ovarian cancer in a first-degree relative was 59 years. These differences were not significant. Analysis including only mothers and aunts and excluding daughters and sisters (who

have not experienced their full period of risk) showed similar results, with no difference in median ages for the three groups. No families reported more than one first-degree relative with ovarian cancer, but two reported first-degree relatives separately affected by breast and ovarian cancers.

Figure 3 shows the age at diagnosis of women from 16 families studied by the NCI. Age at diagnosis for ovarian cancer ranged from 33 to 82 years, and the median age at onset for case patients from both the ovarian and the breast/ovarian cancer families was 47 years. By age 40 years, 17% of the affected women had been diagnosed as having ovarian cancer.

COMMENT

We compiled data from a number of sources to evaluate age-specific risks for relatives of patients with ovarian cancer and the age at onset based on family history of the disease. Because of the rarity of the disease, estimates of familial risk remain imprecise even when obtained from large studies such as the CASH Study. The CASH data suggest that having one first-degree relative with ovarian cancer increases risk at all ages, but does not shift the age at onset to younger ages. Data from the Washington, DC, case-control study¹⁷ showed no difference in age at onset among case patients with or without an affected first-degree relative. These results, along with those from a previous case series,²¹ suggest that having a single affected relative generally is not predictive of the occurrence of ovarian cancer at an age earlier than that seen in the general population.

Prophylactic oophorectomy has been recommended by some for women with a strong family history of ovarian cancer and considered for women from lower-risk families. Data are not available addressing the frequency of prophylactic oophorectomies in the United States, but a recent survey²² of British gynecologists and obstetricians showed 44% would perform prophylactic oophorectomy in women with a strong family history of ovarian cancer. The data we have compiled suggest that for women who have only a single affected first-degree relative, a conservative approach for ovarian cancer prevention among premenopausal women should be taken. The estimate to age 50 years of risk to mothers of case patients was about 0.5%, and this hardly seems sufficient to warrant this procedure. In addition, the risks of cardiovascular disease and osteoporosis after removal of the ovaries must be considered.²³ In women aged 50 years and older with a single affected relative,

the risk is substantially higher. A recommendation about the efficacy of prophylactic oophorectomy in this group is not warranted at this time, however, since these estimates are based on only one study and need to be replicated.

On the other hand, because the efficacy of screening modalities for ovarian cancer remains unclear, prophylactic oophorectomy may be a reasonable choice for women from rare families with multiple affected relatives.^{12,24-25} Approximately 20% of case patients from high-risk families studied at the NCI had an age of onset younger than 40 years, and the median occurred at age 47 years. We did not see any variation in age at onset for ovarian cancer among women with or without an additional family history including breast cancer as has been previously suggested.²⁷ Families that have been referred to the NCI are likely to have been referred in part because of their early age at onset for ovarian cancer. Results from all of these family studies must therefore be interpreted with caution as they may not be representative of the age-at-onset distribution among women from unselected pedigrees. However, recommendations that women from these high-risk pedigrees should consider prophylactic oophorectomy after they have completed child-bearing and/or by age 35 years^{12,24,25} seem warranted. Ideally, risk estimates for women in high-risk pedigrees are needed to validate these conclusions but may not be possible from population-based

studies because of the rarity of these families; only 0.2% of the families of control subjects and 0.6% of the case patients in the CASH Study reported at least two first-degree or one first-degree and one second-degree relative affected by ovarian cancer.¹

The limited data that are available are not sufficient to provide clear guidelines for separating all families into high-risk and low-risk categories. An autosomal-dominant model with reduced penetrance might explain the inheritance pattern in families with a history including several epithelial ovarian cancers. Under this scenario, women who report two first-degree relatives with ovarian cancer, an affected mother and an affected maternal second-degree relative, or an affected sister or daughter and any second-degree relative should be considered at high risk. Women with a family history that includes several affected relatives, the closest being of third degree, could be classified into a lower risk category. Recommendations are difficult to formulate when considering families with multiple other tumors, such as breast, colon, and endometrial cancers, although in some rare families susceptibility for these cancers may be governed by a single factor, as has previously been suggested²⁷; segregation of a susceptibility gene through individuals affected by cancers other than ovarian should be considered. For the few rare families that include many relatives with ovarian and/or breast cancer, oophorectomy may be beneficial un-

til more effective screening modalities become available. In this population, however, intra-abdominal carcinomatosis has been reported following oophorectomy,²⁸ and screening may still be needed after oophorectomy.

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