High Risk for Ovarian Cancer in a Prospective Series Is Restricted to BRCA1/2 Mutation Carriers

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Abstract

Purpose: Inherited ovarian cancer carries a serious prognosis. Prophylactic oophorectomy has been advocated. The degree to which inherited ovarian cancer is restricted to BRCA mutation carriers is not fully known. We wanted to determine the prevalence of BRCA mutation carriers in women at high risk from ovarian cancer.

Experimental Design: Healthy women who were found to be at increased risk judged by family history were followed prospectively. Full BRCA1/2 mutation analysis was conducted on all patients who contracted pelvic cancer.

Results: We identified 1,582 women at risk during 5,674 person-years. Forty infiltrating epithelial ovarian cancers, six peritoneal cancers, and one fallopian tube cancer were diagnosed. All but one of these patients (98%) had a BRCA mutation, a frequency that was significantly higher than for the 3 patients with borderline ovarian cancers, who were all mutation negative (P = 0.0002). Eighty-two percent of the detected mutations belonged to one of the 10 Norwegian founder mutations previously reported. At prophylactic bilateral salpingo-oophorectomy, cancer was found in 18 of 345 (5.2%) of mutation carriers compared with none in the 446 mutation negative (P = 0.0000).

Conclusions: In healthy women with a family history of ovarian cancer, high risk for ovarian cancer was restricted to BRCA1/2 mutation carriers. A woman at risk for ovarian cancer according to her family history should have access to full BRCA1/2 mutation testing before deciding on prophylactic bilateral salpingo-oophorectomy.

Family clusters of ovarian cancer may be caused by BRCA1 or BRCA2 mutations. The high risk for the healthy female relatives in the kindreds has been one of the main concerns in clinical cancer genetics for the last two decades. Mortality is high when ovarian cancer is diagnosed at an advanced stage, whereas detection at an early stage is associated with a more favorable outcome. Efforts have been undertaken to identify women at high risk and to follow them with examinations for an early diagnosis and treatment. Several studies have disputed the value and effectiveness of screening (1–3). The advice in Norway has shifted from surveillance to prophylactic bilateral salpingo-oophorectomy (PBSO).8

We report here the prospective findings of pelvic cancers in our total series of women at risk from ovarian cancer as identified from 1988 onwards to have increased risk of ovarian cancer. This is to our knowledge the largest collection of prospectively detected ovarian cancers described. All cases were tested for mutations in the BRCA genes.

Materials and Methods

Included in these series are all prospectively detected pelvic tumors demonstrated in healthy women identified to be at risk for ovarian cancer and subjected to follow-up or PBSO, from the start of the activities from 1988 onwards until February 1st 2007. The criteria were two or more relatives with ovarian cancer at any age or second-degree relatives through a male. After the BRCA1/BRCA2 syndrome was detected in 1994/1995, we included women in families with breast and ovarian cancer as well, criteria being one or more relatives with ovarian cancer and one or more relatives with breast cancer beyond age 60 y, each of the being first-degree relatives or second-degree relatives through men, women with only one first-degree relative with both ovarian cancer and breast cancer at any age, and finally, women with an identified BRCA1/2 mutation. All pelvic cancers having occurred in the cohort are reported irrespective of mode of detection. The families were ascertained by family history (1, 4) including 1,582 women from the Section of Inherited Cancer, Rikshospitalet University Hospital (series 1). In that series, 45 ovarian cancer cases were observed. In a similar series from the Centre of Medical Genetics and Molecular

8 http://www.legeforeningen.no/asset/34023/1/340231.pdf
Medicine, Haukeland University Hospital, and Institute of Clinical Medicine, University of Bergen, nine prospective cases were observed. The exact total number of healthy at-risk women included in that series is not detailed. In the combined series, all but two cases detected after the first controls were diagnosed at the planned screening controls. In this report, the two interval cancers were grouped together with those detected at the planned examinations. Women who emigrated or withdrew from the study were censored on the day they were lost to follow-up examinations.

The follow-up program included annual transvaginal ultrasound and determination of CA125 level in blood. PBSOs were done in 791 women at risk and included cytology of pelvic lavage and close inspection/histology of removed ovaries and salpinges.

Family histories were validated in the medical records of the treating hospitals and/or in the files of the Norwegian Cancer Registry for all healthy, at-risk persons initially included to follow-up. Either an affected member of each family or the healthy woman at risk were tested for the 4 most frequent Norwegian BRCA1/2 mutations (5, 6) and during the last 5 y for the 10 most frequent (4). All patients with prospective pelvic cancer shown were subjected to full BRCA1/2 mutation analysis with sequencing and MLPA if the mutation was not known before the diagnosis. Also, all families were considered for hereditary nonpolyposis colon cancer. This is because ovarian cancer is a part of this syndrome as well, and tumors from the affected were subjected to immunohistochemical examinations to uncover mismatch repair gene (MMR) mutations when appropriate (7). In families with a demonstrated BRCA mutation, women included were censored when found not to have the mutation of the family, as they were excluded from our health series.

All patients had asked for our health service or been referred by their doctors. All genetic testing was done according to national legislation, including pre-test and post-test genetic counseling and written informed consent. All data were held in the electronic filing systems at the two hospitals. The data, having been made anonymous, were exported from Haukeland University Hospital to be merged with anonymous data from Rikshospitalet University Hospital for the analysis. No research registry including patient name or date of birth was erected. Data were merged through Oracle, organized by Toad, exported, and analyzed by StatExact5 and Systat10.

Results

Series 1 in our study was suitable for considering cancer frequencies and annual incidence rates. Details are given in Table 1. Altogether, 1,582 healthy women (336 of them BRCA mutation positive) were subjected to 6,096 examinations. Of these, 1,168 women were examined twice or more and followed for a sum of 5,674 years. A total of 781 (345 BRCA mutation positive) women, either from the surveillance series or directly without an initial follow-up period, opted for PBSO.

| Table 1. Tumors detected at first round screening, at later follow-up, and after PBSO |
|------------------------------------------|-----------------|-----------------|-----------------|
| BRCA mutation | No mutation | Total |
| Surveillance: first round | | |
| Women included | 336 | 1,246 | 1,582 |
| Tumors detected | 8 (2.4%) | 3 (0.2%)* | 11 |
| Surveillance: later follow-up | | |
| Women examined twice or more | 205 | 963 | 1,168 |
| Follow-up years | 1,040 | 4,634 | 5,674 |
| Tumors detected (annual incidence rate) | 7 (0.7%) | 0 | 7 |
| Prophylactic PBSO | | |
| Women included | 345 | 446 | 781 |
| Tumors detected | 21 (6.4%)† | 1 | 22 |
| Cancers reported after PBSO | 5 § | 0 | 5 |

NOTE: Data from series 1 only (see text).
*All three borderline cancers.
†Including one tubal cancer, two Brenner tumors, one endometrial carcinoma, and one peritoneal mesothelioma.
§Infiltrating granulosa cell tumor.
§Including two cancers from remains of an ovary after PBSO (see text).

| Table 2. Tumors detected stratified on origin and histopathology and results of BRCA mutation analysis |
|------------------------------------------|-----------------|-----------------|-----------------|
| Organ | Histology | BRCA mutation | No mutation | Sum |
| Ovary, invasive | Undifferentiated | 6 | 0 | 6 |
| | Serous | 27 | 1 | 28 |
| | Endometroid | 5 | 0 | 5 |
| | Granulosa cell | 0 | 1 | 1 |
| | Mesonephroid | 1 | 0 | 1 |
| | Brenner tumor | 2 | 0 | 2 |
| Tube | Adenocarcinoma | 1 | 0 | 1 |
| Uterus | Adenocarcinoma | 1 | 0 | 1 |
| Peritoneum, at PBSO | Serous adenocarcinoma | 2 | 0 | 2 |
| | Mesothelioma | 1 | 0 | 1 |
| Peritoneum, after PBSO | Serous carcinoma | 3 | 0 | 3 |
| Sum | 49 | 5 | 54 |
All three borderline tumors were found at first screening round. One infiltrating ovarian cancer reported here was previously reported as borderline (1) but was later scored as infiltrating both by the treating hospital and the Norwegian Cancer Registry.

Among the 18 tumors detected in women participating in a surveillance program, 11 (61%) were shown at first round. Seven cases (39%), all infiltrating, were identified after first surveillance program, 11 (61%) were shown at first round. A family history of breast and ovarian cancer was described in all but three families with prospectively detected cancers (data not shown). In one family, four cases of ovarian cancer had occurred before. Two of the cases described were from families with breast cancer only, but in both, a BRCA1 mutation was shown before the ovarian cancer was found. These two women were tested because a mutation was found in the family.

Details on all cancers showed prospectively in the combined series from the two hospitals Rikshospitalet University Hospital and Haukeland University Hospital are specified in Tables 2 to 5. Among the 49 BRCA mutation carriers, 48 (98%) had a BRCA1 mutation and 1 (2%) had a BRCA2 mutation. Forty of the carriers (82%) had one of the 10 most frequent mutations in the Norwegian population (4).

In Table 2, the 54 malignant and nonmalignant pelvic tumors are displayed. Of these, 24 (44%) were found through the early detection program, 25 (46%) at PBSO, and 3 (5.6%) as peritoneal carcinomatosis after PBSO. Two (4.4%) ovarian cancers cases were found in remains of ovaries left behind at PBSO. Both patients believed that the one ovary had been removed previously, then decided to remove the other to reduce risk of cancer. They later contracted cancer in the remains of the first ovary that had not been completely removed. Besides 39 infiltrating epithelial ovarian cancers, the infiltrating cancers included six peritoneal cancers (five adenocarcinomas and one malignant mesothelioma), one fallopian tube cancer, one ovarian infiltrating granulosa cell tumor, one mesonephroid ovarian cancer, and one endometrial cancer (cancer corporis uteri). In addition, three borderline ovarian tumors and two Brenner tumors were diagnosed. Apart from three borderline tumors and the one granulosa cell tumor, all tumors were demonstrated in women with a germline BRCA mutation.

In the combined series, 47 of 54 (87%) of the tumors were invasive epithelial or mesothelial cancers, and among these, 46 (98%) had a demonstrated BRCA mutation (Table 2). All but one (98%) of the invasive epithelial or peritoneal cancers occurred from 35 years on, and 32 (68%) from 50 years on (Table 3).

A high proportion of the invasive cancers were either classified as International Federation of Gynecology and Obstetrics (FIGO) stage 3 or 4, or they were peritoneal cancers (32 of 47, 68%; Table 4). Among the ovarian cancers detected throughout the surveillance program, 17 of 21 (81%) of infiltrating ovarian cancers detected in the follow-up program were FIGO stages 3 or 4, or peritoneal cancers, compared with 11 of 22 (50%) of the ovarian cancers detected at PBSO. Only one woman with BRCA2 had invasive ovarian cancer detected prospectively, staged as FIGO4 (Table 5).

### Discussion

Our results indicate that in women considered to have an increased risk of ovarian cancer, according to family history, infiltrating epithelial ovarian cancer does not continue to occur at increased rate in the absence of a demonstrable BRCA mutation. If this were to be true, the advice of PBSO may be restricted to mutation carriers.

Most cancers found both in the surveillance program and at PBSO had spread at the time of diagnosis. This is in line with previous conclusions that current methods for early diagnosis of ovarian cancer are insufficient (8–11).

This study confirms the earlier finding that epithelial ovarian cancer is the main phenotype of pelvic cancers in women with...
BRCA mutation. Primary fallopian tube cancer, of which we reported only one case, is also seen as a part of the syndrome (12). Both retrospective and prospective studies, inclusive of the present report, have shown that women with BRCA mutations probably have no increased risk of endometrial carcinomas in the uterus (13, 14). None of the three borderline tumors found in this prospective material had developed in women with BRCA mutation, which is in line with the findings presented by Lakhani et al. (15).

The observed point estimate of the crude annual incidence rate of ovarian cancers in mutation carriers was 7 per 1,000 person-years, as expected for hereditary ovarian cancer (16). This is 10 times the highest age-specific rate for Norwegian women in general, which is 0.68 per 1,000 person-years for the age group 80 to 84 years. Median age at diagnosis of invasive cancers in this study population was 49 years (not including the three post PBSO cases), which is 15 years lower than the median age at diagnosis for ovarian cancer cases in general and lower than the reported penetrance estimates for the mutations (16). The young age at diagnosis in our series can probably be explained by an early age of onset in mutation carriers compared with noncarriers, and it may also reflect the fact that the majority of women seeking our health service are young and not necessarily representative for the population of mutation carriers. There may be an element of lead time bias as well. The finding was expected and has no bearings on our conclusions.

We have previously contributed to the reports showing that ovarian cancer may be a part of the Lynch syndrome (17). These reports indicated a slightly increased risk of ovarian cancer for mismatch repair gene mutation carriers. The combined effect of low probability for selecting such families by family history of ovarian cancer, and low absolute risk for women within such families to contract ovarian cancer, made us anticipate that prevalence of mismatch repair gene mutation carriers in the present series would be low, and indeed, we observed none. The only ovarian cancer case without a demonstrable BRCA mutation had no relative with colorectal or endometrial cancer.

We expected to see a few peritoneal cancers diagnosed after PBSO, as asymptomatic ovarian cancer may remain undiagnosed at PBSO. These examples underline the necessity of a complete and careful removal of the ovaries and salpinges to prevent cancer. It may be that one should look at the effect of age at PBSO and the method of PBSO, rather than calculate the overall annual incidence rates for peritoneal cancer post-PBSO (18).

More than half the cancers were seen at PBSO, and among the women being under surveillance, several of the cancers were seen at first round. Eight of 22 (36%) of cancers detected at PBSO were FIGO stages 3 to 4 (Table 5). These findings are in keeping with the notion that BRCA1-associated ovarian cancer develops slowly, may remain without symptoms even in advanced stages, and usually is not detectable in early stages (19). In general, ovarian cancer may be present for years before it is clinically diagnosed, and we suggest that PBSO should be considered from age 35 years onwards.

The rationale for PBSO is not only to prevent ovarian cancer but also to prevent breast cancer. In contrast to other forms of inherited or familial breast cancer, no substantial gain from early diagnosis and treatment has been documented in BRCA1-associated breast cancer (20). PBSO and prophylactic mastectomy are the only interventions documented to substantially reduce the risk of dying from breast cancer in BRCA1 mutation carriers (21–23).

Full BRCA mutation analysis is now available at a cost f – 1,000€. PBSO in Norway has a cost that is 4-fold. The maximum a priori risk for a healthy female first-degree relative to carry a mutation is 50%. Some ovarian cancer kindreds do not have a BRCA mutation, some have a male in-between the affected females and themselves in the family, rendering the woman at 25% a priori risk. Consequently far less than 50% of healthy women in ovarian cancer kindreds will have a mutation even in highly selected families with a high probability of having an underlying BRCA mutation. It will be cost effective to offer them full BRCA mutation testing and restrict PBSO to mutation carriers. The lower the a priori risk for a BRCA mutation in the family, the better the cost-benefit of a BRCA mutation analysis will be compared with PBSO. In addition, there is an ethical reason to avoid unjustified PBSO.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

7. Stormorken AT, Bowitz-Lothé IM, Noren T, et al. Immunohistochemistry identifies carriers of mismatch repair gene mutation carriers in the present series would be low, and indeed, we observed none. The only ovarian cancer case without a demonstrable BRCA mutation had no relative with colorectal or endometrial cancer.

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References

2. Tallor A, Bourne TH, Campbell S, Okokon E, Dew T, Collins WP. Results from an ultrasound-based familial ovarian cancer screening clinic: a 10-year observa-
cols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J Clin Oncol 2005;23:5588–96.
1713–7.
7. Stormorken AT, Bowitz-Lothé IM, Noren T, et al. Immunohistochemistry identifies carriers of mismatch repair gene defects causing hereditary non-
10. Olivier RL, Lubsen-Brandsma MA, Verhoef S, van Beurden M, CA125 and transvaginal ultrasound moni-
toring in high-risk women cannot prevent the diagno-


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