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Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer

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Abstract

Objective. Women at high risk of ovarian cancer are currently offered two options: either surveillance or prophylactic bilateral salpingo-oophorectomy. The efficacy and outcome of surveillance remain unclear.

Methods. We performed a retrospective study. Between 1994 and 2000, we screened 383 high-risk women, of which 152 were BRCA1/2 mutation carriers. Surveillance consisted of annual gynecological examination, transvaginal ultrasound, and serum CA125 measurement. Exploratory or prophylactic surgery was performed in selected cases.

Results. There were no screen-detected primary ovarian cancers. Abnormal results at surveillance were observed in 74 (19.3%) of women; in 47 (63.5%), the abnormalities disappeared spontaneously. Exploratory surgery was performed in 20 (27.0%) women in whom one malignancy was found (metastatic breast cancer in the ovary). A rising CA125 value prompted further (non-surgical) evaluation in three women with a history of breast cancer: recurrent breast cancer was diagnosed in two women; in the third, a chondrosarcoma was found. 133 women opted for prophylactic bilateral salpingo-oophorectomy, whereby two unexpected malignancies were found (fallopian tube cancer and metastatic breast cancer). One interval primary ovarian cancer occurred, presenting as papillary serous carcinoma of the peritoneum 14 months after prophylactic bilateral salpingo-oophorectomy. Complications of prophylactic surgery were encountered in 15 (11.5%) women.

Conclusions. Ovarian cancer surveillance has limited sensitivity, and a high number of false positive findings. This can lead to unnecessary surgical interventions, possibly resulting in surgery-related complications. It is important to inform high-risk women of these limitations. For now, prophylactic bilateral salpingo-oophorectomy remains the optimal risk-reducing strategy for women at high risk.

Keywords: Ovarian cancer; Screening; Serum markers; CA125; Transvaginal ultrasonography; Familial ovarian cancer; Brca genes

Introduction

It is estimated that 5% of all cases of ovarian cancer are caused by hereditary factors. BRCA1/2 mutation carriers have a highly increased risk of breast and ovarian cancer. The cumulative lifetime risk of developing ovarian cancer for these women is estimated to be 13–63% [1–8]. Family cancer clinics have been instituted worldwide to provide counseling, genetic testing, surveillance programs, and prophylactic surgery, aiming at early detection or prevention of ovarian (and breast) cancer in these high-risk women. Surveillance protocols for ovarian cancer vary between clinics, but at minimum consist of transvaginal ultrasound and CA125 measurements. Many reports on the efficacy of surveillance for ovarian cancer have been published [9–16]. However, it remains unclear whether surveillance results in a reduction of the mortality and/or morbidity rate of ovarian cancer. Moreover, negative effects such as unnecessary surgical

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intervention and related complications are rarely taken into account. In this report, we describe the first results of the surveillance program for ovarian cancer in high-risk women, as performed between 1994 and 2000 at the family cancer clinic of our institution. The outcome of the surveillance program for breast cancer in this population has been reported elsewhere [17–19].

Patients and methods

Patient selection and counseling

In a historic cohort study, we analyzed the data from all women at high risk of ovarian cancer due to a genetic predisposition or family history, who were screened at the Rotterdam Family Cancer Clinic, from January 1, 1994 until December 31, 2000. All women with a personal history of ovarian cancer were excluded. All participants were members from hereditary breast and/or ovarian cancer families [HB(O)C], as defined by the criteria shown in Table 1. Women were counseled with regard to their estimated cancer risk. Genetic testing was offered to all women from families with a 10% likelihood of finding a BRCA1/2 mutation. If wanted, this was first performed in "affected" women (with a history of breast or ovarian cancer) since they were considered 100% risk mutation carriers. In case a mutation in BRCA1/2 was identified in the family, all women considering surveillance were offered presymptomatic genetic testing [19]. Surveillance for ovarian cancer was offered to all BRCA1/2 mutation carriers and all 50% risk mutation carriers from hereditary breast and ovarian cancer (HBOC) or hereditary ovarian cancer (HOC) families (or 25% risk mutation carriers in case of paternal transmission). In the period 1994–1999, female 50% risk mutation carriers from hereditary breast cancer (HBC) families were also offered surveillance (or 25% risk mutation carriers in case of paternal transmission). After this time, gynecological surveillance in HBC families was only offered to BRCA1/2 mutation carriers.

Table 1
Definitions of family risk-group assessment (minimal present in pedigree)

- □ Hereditary breast and ovarian cancer (HBOC)
  - ■ ≥1 case(s) of ovarian cancer and ≥1 case(s) of breast cancer ≤55 years (or in 1 woman)
- □ Hereditary ovarian cancer (HOC)
  - ■ ≥2 cases of ovarian cancer
- □ Hereditary breast cancer (HBC)
  - ■ ≥2 cases of breast cancer, average age 2 youngest affected members ≤45 years
  - ■ ≥3 cases of breast cancer, at least 3 cases ≤50 years (in cases of bilateral breast cancer, the age at onset was considered lower)

Note. Cancer cases were first-degree relatives of each other (or second degree in case of paternal transmission) and were present in at least two generations.

According to national guidelines, gynecological surveillance started at 30–35 years of age, or 5 years earlier than the youngest case of ovarian cancer in the family. Surveillance consisted of gynecological examination, transvaginal ultrasound investigation, and serum CA125 measurement. It was performed biannually before 1998, and annually thereafter (because of altered regional guidelines). The surveillance protocol was similar for pre- and postmenopausal women, and the annual control was continued after prophylactic bilateral salpingo-oophorectomy (PBSO). The option of a PBSO above the age of 40 years was discussed with BRCA1/2 mutation carriers and with 50% risk mutation carriers from HBOC and HOC families, if genetic testing did not identify a BRCA1/2 mutation.

Transvaginal ultrasound

All women underwent ultrasound investigation using a 5-MHz transvaginal transducer. In the study analysis, findings were categorized as "simple cyst" (a thin walled unilocular cyst, 3–5 cm, without papillary formations) or as "complex cyst" (any multilocular cyst, or cyst with papillary formations), according to the description given by the gynecologist. As of 2000, a standard description method was used [20]. Ascites was noted as present or absent. In postmenopausal women, non-visualized ovaries were considered to be normal. In case of an abnormal ultrasound, a return visit was scheduled within 4–12 weeks. After PBSO, any visible mass in the true pelvis was considered to be abnormal.

Laboratory tests

Serum CA125 measurement was performed at each surveillance visit, or within a period of 3 months before or after the visit (1994–1999 using an IRMA, Cis Biointernational, France/2000- measured on an Elecsys 2010 system, Roche). A value of 35 IU/L or less was considered normal for both pre- and postmenopausal women. In case of an increased value, measurement was repeated within 1–3 months. If CA125 was repeatedly increased, and showed an increasing trend, in a woman with a BRCA1/2 mutation and/or history of breast cancer, dissemination examination for recurrent breast cancer was performed by the medical oncologist. This included physical examination, laboratory tests, bone scan, and any other investigation considered necessary in a given case (CT/MRI), to find evidence for, or rule out the presence of eventual recurrent breast cancer.

Surgical methods

PBSO was preferably performed by laparoscopy. Before 1998, removal of the fallopian tubes was not routinely performed at PBSO. As of 1998, both ovaries and the extrauterine parts of the fallopian tubes were completely resected.