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A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy

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HIGHLIGHTS

- Of 659 women who had preventive oophorectomy, two died of ovarian/peritoneal cancer (0.3%)
- Of the 1196 women who had ultrasound screening alone, 27 died of ovarian/peritoneal cancer (2.3%)
- Of the 9 ovarian cancer patients who were diagnosed at preventive oophorectomy the ten year survival was 80%.
- Of the 42 ovarian cancer patients who were diagnosed by ultrasound screening the ten year survival was 31%.
- Ultrasound screening is not a viable alternative to preventive salpingo-oophorectomy for women with BRCA1 mutations.

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ABSTRACT

Objective: To compare the survival experience of women with a BRCA1 mutation who enrolled in an ovarian cancer screening program with that of women who opted for preventive oophorectomy.

Methods: We followed 1964 women with a BRCA1 mutation and two ovaries intact in a prospective study. No women had ovarian cancer or had a bilateral oophorectomy prior to study initiation. There were 1814 women in the cohort who had at least one screening ultrasound. They were followed from the date of first ultrasound until the date of preventive oophorectomy, death or last follow-up. There were 659 women in the cohort who had preventive oophorectomy. They were followed from the date of preventive oophorectomy until death or last follow-up.

Results: Among the 1196 women who had one or more ultrasound examinations and no oophorectomy, there were 73 incident cancers detected and 27 deaths from ovarian/fallopian cancer. The ten year cumulative risk of death was 2.0%. Among the 659 women who had a preventive oophorectomy there were 12 incident cancers (9 detected at oophorectomy and 3 in the follow up period) and two deaths from ovarian cancer. The ten year cumulative risk of death was 0.5%. The hazard ratio for oophorectomy versus ultrasound was 0.23 (95% CI: 0.05 to 0.97; $p = 0.05$).

Conclusion: The survival of women diagnosed with ovarian cancer enrolled in an ultrasound screening program is relatively poor and screening is not a viable alternative to preventive oophorectomy.

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1. Introduction

Women with a BRCA1 mutation experience an increased risk of ovarian cancer from age 35 and by age 75 the cumulative risk reaches 40% [1]. The current recommendation for cancer prevention is salpingo-oophorectomy between ages 35 and 40 [2]. This has

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been shown to reduce the risk of death from ovarian/fallopian/peritoneal cancer by about 80% [2]. However, for women who wish to avoid surgery, or who wish to delay surgery until menopause, ultrasound screening is an option. There is little evidence to date to support screening for ovarian cancer in BRCA1 carriers, but the survival of cancer ovarian patients is inversely correlated with the stage at diagnosis and if we can identify cancer at an early stage there is potential to reduce mortality. The best evidence for screening effectiveness comes from randomised trials; alternatively, we can use data from observational cohort studies which compare women who do and who do not undergo screening for ovarian cancer-specific death. Other valid endpoints include a stage-shift among screen-detected cancers (down-staging) and a favorable ten-year survival experience of women who are diagnosed with cancer through screening. We can also use prospective data to compare screened women to those who opt for preventive surgery. It is important that women who decide to forego preventive surgery in favor of ovarian cancer screening have up-to-date information of the incidence and mortality of ovarian cancer associated with the two options.

In Poland, a program for women at high risk of developing breast and ovarian cancer was established in 1999 at the Pomeranian Medical University in Szczecin, financed by the Ministry of Health. Currently this program operates in 21 different centers. Patients with a BRCA1 mutation are invited by post, e-mail or telephone for an ultrasound examination of the reproductive tract (transvaginal ultrasound) and testing of the CA125 marker in blood (serum). During the clinic visit, surgical options are discussed, including preventive salpingo-oophorectomies. If abnormalities in the ultrasound image or if the serum CA125 is elevated, patients are referred for laparoscopic examinations and/or additional follow-up examinations.

2. Methods

We studied women between the ages of 20 and 70 at study entry and who had two ovaries intact at the time of study entry and who had not been diagnosed with ovarian or fallopian cancer prior to study entry. Only women positive for a BRCA1 mutation were eligible. The great majority of mutations were one of three Polish founder mutations (5383insC, 4153delA, C61G). One of these three mutations is responsible for 13.5% of unselected ovarian cancer in Poland [3]. Genetic testing has been done in the laboratory of the Pomeranian Medical University since 1998. All the women are enrolled in a comprehensive follow-up study which is designed to measure the impact of screening, exogenous hormones, lifestyle factors and preventive surgery on breast and ovarian cancer risk and mortality. Women complete a baseline questionnaire at study entry and a follow-up questionnaire every two years thereafter. They are asked if they ever had a screening ultrasound and if so, the date of first ultrasound, the date of last ultrasound and the total number of ultrasounds. Only ultrasounds at or before the diagnosis of ovarian/fallopian cancer were considered screening and were included in the calculation. The information on ultrasounds was updated with each follow-up questionnaire. The ultrasound interval was the mean time interval between ultrasound examinations and was calculated as the time from first ultrasound to the time to last ultrasound in years divided by the number of ultrasound less one. That is, if the woman had three ultrasounds over a two-year period, the mean interval between ultrasounds was one year. The time from previous ultrasound was the date of the most recent ultrasound minus the date of the penultimate ultrasound.

All incident cases of ovarian/fallopian cancer were confirmed by reference to pathology reports and medical records. The principal outcome was death from ovarian/fallopian cancer. Cause of death was determined by medical chart review and by consultation with the treating physician. The women who had a screening ultrasound and then had a preventive salpingo-oophorectomy were included in both cohorts for the analysis. The women in the ultrasound group were followed from the date of the baseline questionnaire until bilateral preventive oophorectomy, death from ovarian cancer, death from another cause or the date of the last questionnaire. The women in the salpingo-oophorectomy group were followed from the date of oophorectomy until death from ovarian, fallopian or peritoneal cancer, death from another cause or the date of the last questionnaire. The cumulative risk of ovarian cancer or death from ovarian cancer was calculated as the actuarial survival using the Kaplan-Meier method.

Of the 3747 Polish women in our total sample of female BRCA1 carriers, we excluded 585 women because they had ovarian cancer or fallopian cancer at baseline, 814 because they had a bilateral oophorectomy at baseline, 95 who were below age 20 at baseline and 43 who were over age 70 at baseline. We also excluded 33 women because they had a cancer (other than breast, DCIS, thyroid or skin) at baseline. In addition, 196 women were excluded because follow-up information was missing. 191 subjects who were missing data on ultrasound were excluded. After exclusions, 1964 women were eligible for the study.

The secondary outcome was incidence of ovarian/fallopian cancer; the women were followed from the date of the first ultrasound until bilateral preventive oophorectomy, ovarian cancer, fallopian cancer or the date of the last questionnaire. If no cancer was identified at the time of oophorectomy, the woman was censored as unaffected at that time. After oophorectomy, the women were followed until ovarian cancer, fallopian cancer, peritoneal cancer, death from another cause or the date of the last questionnaire.

For each cancer, we assigned a mode of detection as ultrasound detected, CA125 detected, clinically-detected, and detected at preventive surgery or means of detection missing. If the patient had a positive ultrasound test and a positive CA125 test, then the means of detection was defined as ultrasound detected. Stage was determined according FIGO classification. Vital status was ascertained by linkage to the Polish vital statistics registry. Cause of death was determined by chart review or correspondence with the treating physician.

3. Results

The 1964 subjects were followed for a mean of 7.3 years. There were 1814 women who had at least one screening ultrasound. 1196 women had an ultrasound screening test but not an oophorectomy (Table 1). 618 women had one or more screening ultrasound examinations followed by an oophorectomy. In total 659 women in the cohort had a preventive salpingo-oophorectomy. On average, the oophorectomy occurred 7.5 years after the first ultrasound, 41 women had an oophorectomy but never had an ultrasound and 109 women had neither an ultrasound nor an oophorectomy.

There were 86 ovarian/fallopian/peritoneal cancers (76 ovarian, 8 fallopian, two peritoneal) diagnosed in the follow-up period. There were 212 other cancers diagnosed (161 breast cancers, 51 other cancers). Details on the mode of diagnosis, CA125 levels at diagnosis, histology and stage are summarized in Supplemental Table 1.

Among women who had an oophorectomy group, there were 12 cancers diagnosed. Nine were diagnosed at the time of salpingo-oophorectomy (six ovarian and three fallopian) and three in the follow up period. The latter included a peritoneal cancer diagnosed in a 57-year old woman 1.1 years after the oophorectomy and a peritoneal cancer in a 45-year old woman 2.2 years after the oophorectomy and a fallopian cancer diagnosed in a 63-year old woman 3.5 years after the oophorectomy. The ten year cumulative incidence from ovarian/fallopian/peritoneal cancer in the oophorectomy group (including occult cancers) was 4.3%. The ten-year cumulative mortality of ovarian cancer was 0.5%. Two of the nine

Table 1
Comparison of the four groups according to surveillance scheme.

	Neither $N = 109$	Oophorectomy only $N = 41$	US only $N = 1196$	Both $N = 618$
Year of birth	1973.2	1960.0	1971.7	1961.9
Age at first US			33.0	40.1
Age at oophorectomy		49.4		47.6
Incident cancers				
Ovarian cancer	1	0	69	6
Fallopian cancer	0	1	4	3
Peritoneal cancer	0	0	0	2
Any of three	1	1	73	11
Age of diagnosis, years				
Mean (range)	50.1 (n/a)	56.3 (n/a)	49.2 (30.3 −70.3)	56.4 (45.0 −68.3)
≤50	0	0	42 (58.3%)	2 (18.2%)
>50	1 (100%)	1 (100%)	30 (41.7%)	9 (81.8%)
Missing	0	0	1	0
Means of detection				
US	0	0	42	0
CA125	0	0	11	0
Clinical	1	0	17	3
Oophorectomy	0	1	0	8
Missing	0	0	3	0
Cause of death				
Ovarian cancer	1	0	26	1
Fallopian cancer	0	0	1	0
Peritoneal cancer	0	0	0	1
Any of three	1	0	27	2
Breast cancer	0	1	1	0
Other cancers	0	0	2	0
Missing	0	0	0	0

women who had cancer diagnosed at preventive salpingo-oophorectomy died; one of these women died of ovarian cancer and one died of breast cancer. The characteristics of the patients diagnosed at preventive oophorectomy are in Table 2. The mean age of oophorectomy for these nine cases was 56.9 years.

There were 1814 women who had one or more screening ultrasound examinations. Among the women who underwent a screening ultrasound, the mean age at first ultrasound was 35.4 years and the mean period of follow-up from first ultrasound was 10.2 years. The mean number of ultrasounds among those who had an ultrasound was 8.2 ultrasounds and the mean interval between ultrasounds was 1.1 years. Of the 1814 women who had one or more ultrasounds 618 transferred to the oophorectomy group a mean of 7.5 years after the date of the first ultrasound.

Among the 1196 women who had one or more ultrasound but no oophorectomy there were 73 cancers detected. Of the 73 cancers detected, 42 were detected by screening ultrasound, 11 were detected by CA125, 17 were detected by clinical symptoms and for three cases the means of cancer detection was missing. The stage distribution is presented in Table 3. Of the 73 cases, 30 have died; 27 died of ovarian cancer, one died of breast cancer and for two women the cause of death was missing. The mortality rates from ovarian cancer for women in the ultrasound group are compared with women in the preventive surgery group in Fig. 1. The ovarian cancer-specific survival of the 73 women who were enrolled in the ultrasound program and who had ovarian/fallopian cancer diagnosed is 30.4% at ten years (Fig. 2).

On average, the women in the screening program had their first ultrasound at age 35.5 years and underwent eight screening ultrasounds over 8.5 years. Among the women in the ultrasound screening program, 73 ovarian/fallopian cancers were diagnosed, including 42 by ultrasound, 11 by CA125 and 20 clinical (or missing). There were 27 women in the screening program who died of ovarian cancer; 15 of these were detected by ultrasound, 11 by other means and one missing. In the 11 group 7 had a normal screening ultrasound in the one year period prior to diagnosis. Among the women with cancer in the screening cohort, ten-year survival was only 30%.

Among the 659 women who opted for oophorectomy, 12 women were diagnosed with cancer, including nine at oophorectomy and three in the follow-up period. The prevalence of ovarian cancer at oophorectomy was 1.8% overall, but it was 0% for 88 women who had the oophorectomy prior to age 40, was 0.3% for the 335 women who had the operation between age 40 and 50 and was 4.2% for the 236 women who had the operation between ages 50 and 70. Of interest is the very good survival experienced by the women with cancer detected through oophorectomy. Only one of the twelve women with occult fallopian/ovarian cancer died of ovarian cancer. These women were negative for both CA125 and ultrasound (if they were positive then they would have been clinically-detected). Based on this observation it is a reasonable goal to develop a screening test that is sensitive to early-stage ovarian cancer and that is positive prior to a positive CA125 or ultrasound. That is, if a test could identify cancer of similar stage to the occult cancers diagnosed in this series it might be possible achieve an acceptable survival rate.

We also conducted a secondary analysis limited to women diagnosed with cancer prior to age 50 (data not shown). There were two women diagnosed with ovarian cancer before age 50 in the screening and oophorectomy group and both women were still alive at the end of follow-up (mean survival 3.1 years; range 3.0–3.16). Among the 42 subjects diagnosed with ovarian cancer before 50 in the ultrasound only group, 16 (38%) died of ovarian cancer and 26 (62%) were still alive at the end of follow-up (mean survival 4.3 years; range 0.3–14.3).

Table 2
Cancer discovered at preventive oophorectomy.

Case number	Age at study entry	Age at 1st ultrasound	Age at oophorectomy	Site	Vital status	Cause of death
15668	37	38	47	Fallopian	Alive	
15884	58	56	59	Fallopian	Alive	
16258	51	44	51	Ovarian	Alive	
16506	56	No US	56	Fallopian	Dead	Breast cancer
17220	53	54	54	Ovarian	Alive	
17439	52	48	57	Ovarian	Dead	Ovarian cancer
18522	52	53	59	Ovarian	Alive	
20430	61	60	61	Ovarian	Alive	
24079	65	67	68	Ovarian	Alive	

Table 3
Means of detection and stage of cancer at presentation.

Means of detection	N	Stage	N	Deceased from ovarian cancer
Any	86	I	5	2
		II	18	9
		III	26	12
		IV	2	1
		Missing	35	6
Ultrasound	42	I	4	2
		II	10	5
		III	13	6
		IV	2	1
		Missing	13	1
CA125	11	I	0	0
		II	4	2
		III	2	2
		IV	0	0
		Missing	5	0
Oophorectomy	9	I	1	0
		II	2	1
		III	2	0
		IV	0	0
		Missing	4	0
Clinical	21	I	0	0
		II	2	1
		III	8	4
		IV	0	0
		Missing	11	4

4. Discussion

In this study, we followed a large cohort of Polish BRCA1 mutation carriers for incidence and mortality from ovarian/fallopian/peritoneal cancer. Approximately one-third of the women had a bilateral prophylactic salpingo-oophorectomy and 61% had no oophorectomy but were followed by screening ultrasound. About 34% of the women left the screening program because they underwent a preventive salpingo-oophorectomy; these women were initially included in the screening and then transferred to the surgical cohort and were followed from the date of surgery. There were too few women with neither oophorectomy nor ultrasound screening to permit a robust comparison of screened versus unscreened women.

It is also important to note the ages of oophorectomy in the women who had occult ovarian cancer (Table 2). The oophorectomies in this subgroup were typically done in the fifties and sixties and it is reassuring that there were no occult cancers among 262 women who had the oophorectomy done before age 45. This observation supports our recommendation that for BRCA1 carriers, salpingo-oophorectomy should be conducted before age 40. However to do so may require that genetic testing in general for BRCA1 mutations be conducted at an early age.

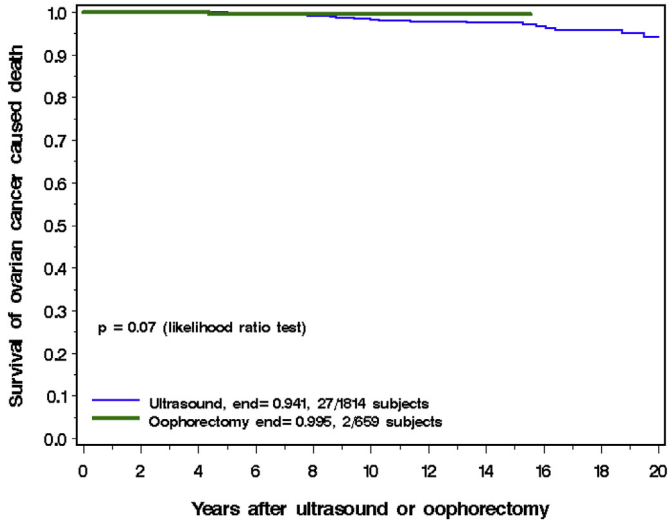

Fig. 1. Ovarian cancer free survival, ultrasound vs. oophorectomy.

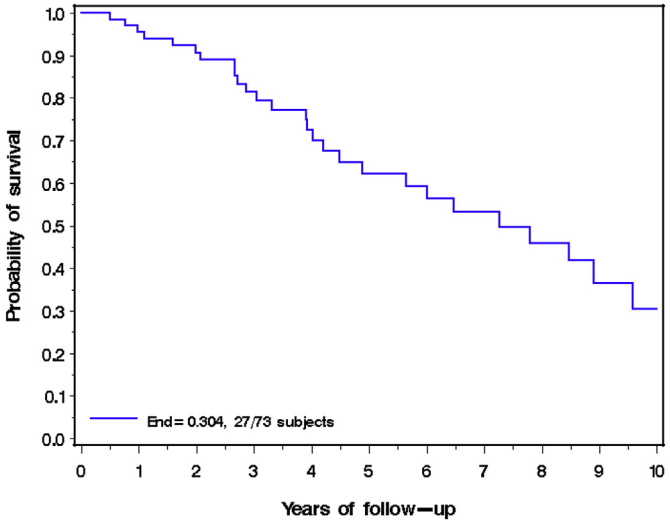

Fig. 2. Survival after ovarian cancer, ultrasound group.

This is the first study of ovarian screening in BRCA1 carriers with ovarian cancer death as an endpoint. Rosenthal et al. conducted a screening trial of women at high risk in the United Kingdom [4]. They conducted CA125 tests every four months and annual transvaginal ultrasounds. There were 377 women with a BRCA1 mutation in the study and 24 of these developed high grade serous cancers. A favorable stage shift was noted but no data on ovarian cancer survival were given. A second study was conducted in the USA [5]. Skates et al. followed 3692 women with the same protocol. They identified 19 incident cancers, but eight of these were detected at preventive surgery. There were four cancers detected in the BRCA1 carriers; two of the four had a positive ultrasound and three of the four were detected at stage II. Again, survival rates were not provided.

The principal strength of our study is the large number of BRCA1 carriers enrolled in the study, the length of the follow-up period and the high number of ultrasounds performed (8.0 per person). There were 86 incident cancers and the length of follow-up was sufficient to estimate the ten-year survival. This is the only screening study of BRCA1 carriers to report on survival among patients diagnosed with cancer in the cohort. Weaknesses include the data on ultrasound was derived from a patients questionnaire and there was no formal protocol for recording and assessing the result of each ultrasound examination. We did not record ultrasound examinations that gave rise to a negative surgical procedure. We had limited data on CA125 and we did not record the actual level of CA125 or the date of the corresponding blood draw. We did not have details on treatments received or the extent of residual disease post-surgery and we had limited data on stage. Because there were so few women with no ultrasound examination we were unable to provide a direct comparison of those who did and did not attend ultrasound screenings.

We were able to compare the survival experience of women by mode of detection. Of the 42 women who had the cancer detected by ultrasound, the ten-year ovarian cancer specific survival was 29.7%, of the 32 women who had the cancer detected by other means the ten year survival was 30.3%. Of the nine women who had (occult) cancer detected at the time of oophorectomy the ten year survival was 80%.

Survival in ovarian cancer is dependent on several factors other than stage, such as the use of neo-adjuvant versus post-surgical

chemotherapy and the route of delivery of chemotherapy (intravenous or intraperitoneal) [6,7]. Optimum survival is achieved when the surgeon reaches the stage of no residual disease [6]. It may be that screening works better in scenarios where the surgeon intensifies efforts to achieve a stage of no residual disease and when patients with no residual disease are treated with intraperitoneal chemotherapy. We did not have information on means of treatment or extent of residual disease post-surgery. This study was conducted in a few medical centers in Poland and the results may not be generalisable to other countries or other hospitals. In conclusion, this observational study of trans-vaginal ultrasound, preventive oophorectomy and ovarian cancer mortality in BRCA1 carriers suggests that, at present, ultrasound screening is not a rational alternative to preventive salpingo-oophorectomy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.08.034.

Author contributions

Conceptualization: SAN, JL.
Data analysis: PS.
Patient material/Clinical information: JG, JC, TH, CC, JM, MS, MS.
Writing draft Review & Editing: All authors.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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