No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study

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BRCA1/2 mutation carriers are offered gynaecological screening with the intention to reduce mortality by detecting ovarian cancer at an early stage. We examined compliance and efficacy of gynaecological screening in BRCA1/2 mutation carriers. In this multicentre, observational, follow-up study we examined medical record data of a consecutive series of 888 BRCA1/2 mutation carriers who started annual screening with transvaginal ultrasonography and serum CA125 between 1993 and 2005. The women were annually screened for 75% of their total period of follow-up. Compliance decreased with longer follow-up. Five of the 10 incident cancers were interval tumours, diagnosed in women with a normal screening result within 3–10 months before diagnosis. No difference in stage distribution between incident screen-detected and interval tumours was found. Eight of the 10 incident cancers were stage III/IV (80%). Cancers diagnosed in unscreened family members had a similar stage distribution (77% in stage III/IV). The observed number of cases detected during screening was not significantly higher than expected (Standardized Incidence Ratio (SIR): 1.5, 95% confidence interval: 0.7–2.8). For the subgroup that was fully compliant to annual screening, a similar SIR was found (1.6, 95% confidence interval: 0.5–3.6). Despite annual gynaecological screening, a high proportion of ovarian cancers in BRCA1/2 carriers are interval cancers and the large majority of all cancers are diagnosed in advanced stages. Therefore, it is unlikely that annual screening will reduce mortality from ovarian cancer in BRCA1/2 mutation carriers.

British Journal of Cancer (2007) 96, 1335 – 1342. doi:10.1038/sj.bjc.6603725 www.bjcancer.com

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Keywords: ovarian carcinoma; BRCA1; BRCA2; screening; TVU; CA125

BRCA1/2 mutation carriers have a high lifetime risk of developing ovarian cancer (39% for BRCA1, 11–22% for BRCA2 at age 70 years) (Antoniou et al, 2003; Chen et al, 2006). To reduce the mortality of ovarian cancer, BRCA1/2 mutation carriers are currently being counselled for gynaecological screening and prophylactic bilateral (salpingo-) oophorectomy (BP(S)O). Although efficacy of BP(S)O has been demonstrated (Rebbeck et al, 2005), the efficacy of gynaecological screening with (bi)annual transvaginal ultrasonography (TVU) and the serum tumour marker CA125 (Karak et al, 1993; Burke et al, 1997) is still unclear. To summarise the literature on gynaecological screening of BRCA1/2 carriers, including overlap with the present study, eight interval cancers among 24 cancers were diagnosed among a total of 807 BRCA1/2 carriers (Table 1) (Laframboise et al, 2002; Liede et al, 2002; Scheurer et al, 2002; Fries et al, 2004; Kauff et al, 2005; Meeuwissen et al, 2005; Vassen et al, 2005; Gaarenstroom et al, 2006; Oei et al, 2006). Regrettably, most studies did not distinguish between prevalent and incident cases. Also, compliance with the intended screening protocol was generally unclear, whereas lack of compliance may interfere with the efficacy of screening.

Especially for BRCA1/2 carriers, more information on compliance and efficacy of gynaecological screening is urgently needed. Although compliance to the protocol may be higher for BRCA1/2 carriers than for other high-risk women, efficacy of screening may still be low. Ovarian tumours of carriers may have unfavourable clinical-pathological characteristics and a higher growth rate (Hogg and Friedlander, 2004). Moreover, carriers generally start screening well before menopause, when temporary abnormalities in TVU and CA125 for benign reasons are more common.

The purpose of this multicentre observational follow-up study was to investigate the efficacy of annual gynaecological screening taking compliance to the protocol into account. We compared numbers and stages at diagnoses of incident interval cancers with incident screen-detected cancers in a consecutive series of 888 BRCA1/2 carriers. In addition, we used two external comparisons:
### Annual ovarian cancer screening among BRCA1/2 carriers

**Clinical Studies**

**British Journal of Cancer (2007) 96(9), 1335 – 1342**

### Literature overview of studies concerning ovarian cancer detection in women at hereditary high risk and carriers of the BRCA1/2 mutation

#### Table 1

| Author                  | Number of women | Mean age (years) | Frequency | Combined/sequential TVU-CA125 (cutoff) | Number of screen-detected | Number of interval cases | Stage III | Stage III/IV | Stage IV | Stage I/II |
|-------------------------|-----------------|------------------|-----------|---------------------------------------|---------------------------|--------------------------|-----------|-------------|---------|-----------|
|                         |                 |                  |           |                                       |                           |                          |           |             |         |           |
| Ulfbrone et al. 2002    | 47              | 61               | NR        | Combined <35 kU ml                     | 0                         | 0                        | 0         | 0           | 0       | 0         |
| Leiden et al. 2002      | 290             | 62               | 129       | Combined (cutoff NR)                  | 6                         | 0                        | 0         | 0           | 0       | 0         |
| Schub et al. 2002       | 40              | 74               | 124       | Combined (cutoff NR)                  | 3                         | 0                        | 0         | 0           | 0       | 0         |
| Frys et al. 2002        | 46              | 61               | 42        | Combined (cutoff NR)                  | 7                         | 0                        | 0         | 0           | 0       | 0         |
| Veen et al. 2002        | 138             | 138              | 96        | Combined (cutoff NR)                  | 25                        | 0                        | 0         | 0           | 0       | 0         |
| Veen et al. 2002        | 383             | 383              | 99        | Combined (cutoff NR)                  | 25                        | 0                        | 0         | 0           | 0       | 0         |
| Kees et al. 2005        | 1135            | 1135             | 49        | Combined (cutoff NR)                  | 25                        | 0                        | 0         | 0           | 0       | 0         |
| Oei et al. 2006         | 512             | 512              | 45        | Combined (cutoff NR)                  | 25                        | 0                        | 0         | 0           | 0       | 0         |
| van der Voet et al. 2006| 269             | 269              | 40        | Annual                                 | 10                        | 0                        | 0         | 0           | 0       | 0         |
| Total                   | 2146            | 44               | 4965      |                                       | 28                        | 51                       | 7/5       | 1/1         | 6/5     | 5/1       |

NR = not reported. *Two of these cases had abnormal TVU at first screening and could be defined as prevalent screen-detected cases.**

### MATERIALS AND METHODS

#### Study population

For this multicentre observational follow-up study, we identified a consecutive series of all BRCA1/2 mutation carriers who started gynaecological screening in six University Family Cancer Clinics in the Netherlands (VU University Medical Centre, The Netherlands Cancer Institute, Erasmus University Medical Centre Rotterdam, University Medical Centre Groningen, and Leiden University Medical Centre) in the period 1993 – 2005. In total, 1035 women with a deleterious BRCA1 or BRCA2 mutation visited the gynaecologists. The specific mutations were not known by the gynaecologists, but the prevalence of BRCA1/2 mutations in the Netherlands have been presented by Hout van der et al (2006). Women presenting with complaints at first visit and women who visited the gynaecologist only once were excluded. Among the remaining 888 women, five prevalent cancers were detected at the first screening visit, leaving 883 women (683 BRCA1 and 200 BRCA2) for the evaluation of screening during follow-up.

For analyses on compliance and sensitivity, we had to restrict the study population to women who visited one of the three centres (VU University Medical Centre, The Netherlands Cancer Institute and Radboud University Nijmegen Medical Centre) where information on each single screening visit (N = 601 of the total group of 1035) was available, and to the 459 women who were 'annually screened', defined as having had at least one screening visit with both screening tools and another visit to create time of follow-up. Among the 459 women, two prevalent screen-detected cases were detected, leaving 457 women for evaluation of annual screening during follow-up.

#### Gynaecological screening

Since 1993, the national screening guideline implied annual visits at the gynaecologist, including pelvic examination, TVU and serum CA125 analysis (www.nvog.nl). From the late nineties onward annual visits have been introduced, though not systematically in all centres. For both BRCA1 and BRCA2 mutation carriers, the minimum age of entry into the surveillance programme was 35 years or 5 years earlier than the youngest age at diagnosis of ovarian cancer in the family.

TVU findings were classified as abnormal for ovaries or fallopian tubes, or normal including non-visualized ovaries. Serum CA125 levels above 35 kU l⁻¹ were scored as abnormal if the clinical decision based on these findings was an extra-screening visit or a diagnostic operation (laparoscopy or laparotomy). Prophylactic operation that followed a visit within 3 months, while at this visit abnormalities were detected, was coded as diagnostic operation (N = 8). Ovarian cancer cases were classified as prevalent screen-detected cases (diagnosed at the first screening visit), incident screen-detected cases (diagnosed at a regular screening visit) or as incident interval cases (diagnosed as a result of abdominal complaints, although no abnormalities were found at the previous screening visit). All tumours were reviewed by one pathologist (HvB).

#### Data collection

The data for this study comprised BRCA1/2 mutation status, first and last gynaecological screening visits, prophylactic and diagnostic operation and pathology, as recorded in gynaecological medical records and pathological reports. In three centres, detailed
data on each screening visit (date of visit, date of genetic testing, TVU, CA125, and reason to stop screening) were collected. Part of our pooled data was also used for earlier centre-specific publications (Table 1).

We used two external control groups. First, in two centres (Erasmus University Medical Centre Rotterdam and Netherlands Cancer Institute) pedigree information and the hospital-based cancer registry enabled us to trace anonymously tumours diagnosed in family members of the screened BRCA1/2 carriers. We evaluated those tumours diagnosed in the two centres before gynaecological screening started (before 1990). Second, we used BRCA1/2 reference curves of ovarian cancer derived as part of refitting the BOADICEA model of genetic susceptibility to breast cancer (Antoniou et al, 2002; Antoniou et al, 2004). Combined data were used from three UK population-based studies of breast cancer families (Peto et al, 1999; Angelian Breast Cancer Study Group, 2000; Laloo et al, 2003), with multiple cases of breast cancer and family data from BRCA1/2 carriers identified in 22 population-based studies of breast and ovarian cancer (Antoniou et al, 2003).

Statistical analysis
To calculate the Standardized Incidence Ratio (SIR), observed numbers of ovarian cancer were compared with expected numbers, based on the reference curves. Women were eligible for person-years analysis if no ovarian cancer was detected at the first screening visit. Starting date was defined as date of first visit, stopping date as date of diagnosis of ovarian cancer (end point), date of BP(S)O, or date of last screening visit, whichever was first. In the three centres with information on each single screening visit, the period of optimal annual screening was defined as the period during which the national guideline (‘complete screening visit’, i.e. visit with both TVU and CA125, every 13 months) was met. Here, stopping date was defined as date of diagnosis of ovarian cancer, date of BP(S)O, date of last complete screening visit plus 13 months, or date of last visit, whichever was first.

Women who decide to be tested may be more likely to have ovarian cancer than those who are not yet aware of their carrier status and, thus, are not eligible for the study (Klaren et al, 2003). If cancer events preceding the DNA test are included in the analysis, overestimation of the incidence rate may occur. We explored this potential testing bias by starting follow-up at date of first complete screening visit or date of BRCA1/2 mutation testing, whichever was later.

RESULTS
In total, 1035 BRCA1/2 carriers ever visited a gynaecologist for screening advice and 883 BRCA1/2 carriers were actually screened for 1473 women-years of follow-up. At first visit, the 683 BRCA1 carriers (77%, median age 40 years, range 21–76 years) were on average 3 years younger than the 200 BRCA2 carriers (23%, median age 44 years, range 25–77 years, Figure 1).

Compliance and quality of screening tools
Among the 601 women with full data on each single visit, 118 women (19.6%) visited the Family Cancer Clinic only once (Table 2), whereas 24 women with more visits were never screened with both TVU and CA125. Most women opted out of screening for valid reasons, like being too young (median age 28 years, range 20–34 years) or undergoing prophylactic operation (median age 44 years, range 26–75 years). Thus, the default rate was only 31/601 = 5% in the total group, and 6% including the women with missing data. Still, however, for 25% of the screening time (interval between starting and stopping dates) the interval between two complete screening visits was more than 13 months. This proportion of non-compliance increased with longer follow-up.

The sensitivity of TVU and CA125 assessed simultaneously was 71%, and the positive predictive value 23% (Table 3). As shown in Table 2, 311 of the 459 women (68%) opted for a BP(S)O and five occult tumours were diagnosed. Including these tumours, the sensitivity decreased to 42%.

Cases of ovarian cancer
At the first screening visit, five women (four BRCA1 and one BRCA2) were diagnosed with a prevalent ovarian cancer (Table 4). Among the remaining 883 BRCA1/2 carriers 10 women (all BRCA1) were diagnosed with ovarian cancer during follow-up (incident cases). Nine of the 10 incident cases had been compliant to annual screening before diagnosis. In an efficiently screened population, the majority of cancers would be detected by screening instead of diagnosed following complaints. However, in our series five of 10 incident cancers were unexpectedly diagnosed as a result of abdominal complaints, although at the preceding visit no abnormalities had been found. The five incident screen-detected cases presented with both an abnormal TVU and CA125, although no abnormalities were detected at the preceding visit (Table 4, Figure 2). The family history of the 10 incident cases varied, three cases had a breast-only family, one case an ovarian-only family and six cases had both familial breast and familial ovarian cancer.

Seven cases (indicated in bold in Table 4) were diagnosed in the group of 459 women that underwent annual screening in one of the three centres with information on each screening visit. These 459 women came for 1116 screening visits during 690 annually screened women-years (2.4 visits/woman and 1.6 visits/year) (Figure 2). Abnormalities were detected in one or both of the screening tools, at 38 out of 1116 regular screening visits (3%). For 24 women (5%), the abnormal findings were followed by 32 extra visits at which 16 abnormalities persisted (50%). After normal regular screening visits, complaints resulted in 26 visits for 21 women (5%) at which four abnormalities were found (15%). In total, abnormalities were found in 40 women (9%) resulting in 26 diagnostic operations. No cancer was detected at nine operations that followed abnormal TVU only, two cancers were detected at six
operations that followed abnormal CA125 only (33%), and five cancers were detected at 11 operations (45%) that followed abnormal findings in both screening tools. Compared to the next to last visit, an exponential rather than progressive rise in serum CA125 levels from the individual baseline level occurred at the last visit for all incident screen-detected and interval cases (Figure 3).

Stages at diagnoses: interval vs screen-detected cancers

Advanced stages (III/IV) were diagnosed in all prevalent screen-detected cases. For the incident screen-detected cases, the stages at diagnosis were stage II (N=1), stage III (N=3) and stage IV (N=1), whereas for the incident interval cases, tumours were diagnosed at stage I (N=1), stage II (N=2) and stage IV (N=2). At a mean follow-up since diagnosis of 28 months, three of the 15 cases listed in Table 4 died of ovarian cancer. The five occult tumours detected at BP(S)O (Table 2) were diagnosed at stage I (N=4) and stage II (N=1). Premalignant lesions in prophylactically removed tissue were not the scope of this study, but were subject of separate hospital-based studies (e.g. Hermsen et al., 2006). In none of the women who were considered normal at surgery, evidence of tumour growth occurred during follow-up, so far.

Stages at diagnoses: comparison with cancers in unscreened family members

If screening were effective, ovarian cancer would be diagnosed at an earlier stage with better prognosis than would have been the case without screening. We evaluated this potential shift in stage by comparing the stages at diagnosis of the incident screen-detected tumours with tumours diagnosed in family members before gynaecological screening was available. In two centres, we could trace 26 family members with ovarian cancer diagnosed before 1990. Stages at diagnosis were stage I (N=3), stage II (N=3), stage III (N=19) and stage IV (N=1). For the subgroup of typed or obligate carriers (N=16), the numbers were: stage I (N=2), stage II (N=2), stage III (N=12) and stage IV (N=0). Thus, the stage distributions of the screened and unscreened groups were similar (stage III/IV: eight in 10 (80%) in the screened group vs 20 in 26 (77%) in the unscreened group).

Comparison with external reference curves

If screening were effective, the diagnosis would shift to an earlier age. We evaluated the lead-time by comparing the observed number of cases with the number expected from age- and mutation-specific external incidence curves, as estimated in an international data set, comprising women that most likely were less intensely screened (Antoniou et al., 2003). Given the rising incidence curve at the young ages of the screened group, one would expect the lead time to result in an increased SIR. However, based on 10 incident cases observed and 6.5 cases expected, the SIR was only 1.5 (95% confidence interval (CI) 0.7–2.8) (Table 5). Among BRCA1 carriers, the SIR was 1.7 (95% CI: 0.8–3.1) and among BRCA2 carriers the SIR could not be estimated with no event observed and 0.5 expected. The SIR was 1.6 (95% CI: 0.5–3.6) if the analysis was restricted to the optimally screened women.

**Table 2** Reasons not to start or to stop screening (at least annual screening with TVU and CA-125) for all 601 BRCA1/2 mutation carriers who visited the gynaecologist at the Family Cancer Clinic in three centres

| Status at end of follow-up | With follow-up | Without follow-up | Total number |
|----------------------------|----------------|-------------------|--------------|
| In screening               | N  | %   | N  | %   | N  | %   | N  | %   |
| Did not show up at appointment | 14 | 3.1 | 9  | 16.6 | 23 | 3.8 | 32 | 5.3 |
| Moved to other place/other gynaecologist | 7  | 1.5 | 2  | 16.6 | 9  | 1.5 | 18 | 2.9 |
| Too young                  | 3  | 0.7 | 4  | 16.6 | 7  | 1.2 | 10 | 1.6 |
| Too old                    | 1  | 0.2 | 0  | 0    | 1  | 0.2 | 0  | 0    |
| Prophylactic operation*    | 311| 67.8| 10 | 41.7 | 321| 68.0| 40 | 65.7|
| Missing                    | 1  | 0.2 | 0  | 0    | 1  | 0.2 | 0  | 0    |
| Diagnostic operation       | 25 | 5.4 | 0  | 0    | 25 | 5.4 | 0  | 0    |
| Total                      | 459| 100 | 24 | 100  | 483| 100 | 24 | 100  |

*Five occult tumours were detected (4 stage I, 1 stage II). *One woman had two diagnostic operations.

**Table 3** Quality of screening tools used during combined multimodal gynaecological screening of 459 BRCA1/2 carriers during 1116 regular screening visits

| Test                      | Number of cases* | Number of unaffected women | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---------------------------|------------------|---------------------------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| CA-125, irrespective of TVU | +                | 10 (10)                   | 42% (14–70)         | 99% (99–100)         | 33% (9–57)                       | 99% (99–100)                      |
|                           | –                | 7 (2)                     | 71% (38–100)        | 99% (99–100)         | 33% (9–57)                       | 100% (100–100)                    |
| TVU, irrespective of CA-125 | +                | 12 (12)                   | 25% (1–50)          | 99% (98–100)         | 20% (0–40)                       | 99% (99–100)                      |
|                           | –                | 9 (4)                     | 43% (6–80)          | 99% (98–100)         | 20% (0–40)                       | 100% (100–100)                    |
| CA-125 and/or TVU         | +                | 17 (17)                   | 42% (14–70)         | 99% (98–99)          | 23% (5–40)                       | 99% (99–100)                      |
|                           | –                | 7 (2)                     | 71% (38–100)        | 99% (98–99)          | 23% (5–40)                       | 100% (100–100)                    |

CI, confidence interval. *In italic: numbers and percentages without the five occult ovarian cancer cases, diagnosed during prophylactic operation, were included in the case group.
years. As only one case was tested for BRCA1/2 mutation after the
diagnosis of ovarian cancer, testing bias did not markedly confound the results (4% change of the SIR, data not shown).

DISCUSSION

We evaluated the actual gynaecological screening in a consecutive series of 888 BRCA1/2 mutation carriers. Although compliance was reasonably high (compliant for 75% of the follow-up), gynaecological screening did not seem to be effective, because (1) interval tumours comprised five out of 10 incident cancers, (2) all women diagnosed with an interval tumour had been compliant to annual screening, (3) eight of the 10 cancers were diagnosed at stage III/IV, (4) no difference in stage distribution between incident screen-detected and interval tumours was found, (5) no difference in stage distribution between incident screen-detected tumours and tumours diagnosed in family members before 1990 was found, and (6) in the total group as well as in the compliant group the observed number of ovarian cancers was not markedly higher than expected from reference curves, based on carriers of which the majority was most likely not screened. Thus, although we could not formally test efficacy with mortality as outcome, it is unlikely that annual gynaecological screening will reduce mortality of ovarian cancer in BRCA1/2 carriers.

Reported compliance of high-risk women to gynaecological screening proved to vary extremely among studies (Lerman et al., 2000; Scheuer et al., 2002; Botkin et al., 2003; Vasen et al., 2005). This may result from differences in definition of compliance, differences in the requested frequency of screening visits and differences in risk perception of the women and their physicians (Tinley et al., 2004). For instance, in a series of 112 high-risk women (29% BRCA1/2 carriers) adherence to annual TVUs was only 19%, whereas in a group of 62 BRCA1/2 carriers adherence was 68% to biannual screening with CA125 (Scheuer et al., 2002). We found that women were compliant for 75% of their follow-up, but valid reasons like pregnancies or breast cancer treatments may partly explain why these BRCA1/2 carriers missed or delayed their annual screening visits.

TVU and serum CA125 lack adequate sensitivity apart or together (15–71% for TVU/CA125) (Laframboise et al., 2002; Botkin et al., 2003; Vasen et al., 2005). We used our finding of 42% for TVU/CA125 in accordance with these findings.

The external reference population that we used to calculate the expected number of ovarian cancer, consisted of family members of a largely population-based index case series, who were tested positive in a research setting. Most of these women may not have been aware of their carrier status and thus, might be less intensively screened than the BRCA1/2 carriers in our study. However, this assumption is not the only reason why the estimated SIR should be interpreted with caution. Oral contraceptives strongly protect against ovarian cancer (Antoniou et al., 2003; Whittemore et al., 2004), and use of oral contraceptives might
differ between our study sample and the reference population. With these limitations in mind, the SIRs suggest that the lead-time is very limited in the total and compliant group.

In evaluating efficacy of screening, several factors hamper the comparison among various studies, (1) compliance to the intended screening procedure has not been examined in combination with efficacy, (2) generally, no distinction is made between prevalent and incident screen-detected cases, (3) the screening protocol may differ, such as the frequency of screening, the cutoff level of CA125 (15–35 U ml⁻¹) (Bourne et al, 1994; Jacobs et al, 1999; Kauff et al, 2005; Meeuwissen et al, 2005; Olivier et al, 2006), and the combined or sequential order of applying the screening tools (Jacobs et al, 1999; Scheuer et al, 2002; Meeuwissen et al, 2005; Stirling et al, 2005; Olivier et al, 2006), and (4) quality measures of screening tools, like sensitivity, are typically reported including occult tumours, while the proportion of women opting for a screening procedure has not been examined in combination with the frequency of screening, the cutoff level of CA125, and incident screen-detected cases, (3) the screening protocol may differ, such as the frequency of screening, the cutoff level of CA125 (15–35 U ml⁻¹) (Bourne et al, 1994; 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taking three new biomarkers into account. The sensitivity of the combination of apolipoprotein A1, transthyretin, H4 and CA125 was higher than CA125 alone (Zhang et al, 2004). A combination of four other proteins was identified with microarray analysis (Mor et al, 2005). However, clinical implementation of such early findings will need confirmatory and prospective studies in larger groups. In the general population, there are two major randomised controlled trials being undertaken to assess the impact of screening on ovarian cancer mortality; the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States (Andriole et al, 2004; Menon, 2004, respectively).

For now, it is unlikely that annual gynaecological screening with TVU and CA125 will reduce mortality from ovarian cancer in BRCA1/2 mutation carriers. Prophylactic removal of the ovaries and fallopian tubes has proven its value as a risk-reducing strategy for ovarian cancer as well as breast cancer (Kauff et al, 2002; Rebbeck et al, 2002; Finch et al, 2006) and should therefore be the cornerstone in the management of BRCA1/2 mutation carriers, as long as no other effective screening tool is available.

ACKNOWLEDGEMENTS

We thank FE van Leeuwen for her valuable advice. This study was partly supported by the Biocare Foundation (Grant no. 02-22).

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Table 5 SIR calculated for the total group of 883 BRCA1/2 mutation carriers and for the subgroup of 457 BRCA1/2 mutation carriers, known to be annually screened.

| Women-years | Number of women | Number of women-years | Observed | Expected* | SIR (95% Confidence Interval) |
|-------------|-----------------|-----------------------|----------|-----------|-------------------------------|
| All women-years, six centres | 883 | 1473 | 10 | 6.5 | 1.5 (95% CI: 0.7 – 2.8) |
| All women-years, three centres | 457 | 921 | 5 | 3.9 | 1.3 (95% CI: 0.4 – 3.0) |
| Exclusively annually screened women-years, three centres | 457 | 690 | 5 | 3.2 | 1.6 (95% CI: 0.5 – 3.6) |

Cl, confidence interval; SIR = Standardized Incidence Rates. *In three of the six centres, data were available for each screening visit, which enabled the selection of women who were at least some time annually screened, that is, a visit with both TVU and CA125 and some time of follow-up. **Reference data: age- and mutation-specific risk of ovarian cancer among BRCA1/2 mutation carriers, as modelled by Antoniou et al (2002, 2004).
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