Cancer risk variation in BRCA1/2 mutation families

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Chapter 5

Inverse birth cohort effects in ovarian cancer: Increasing risk in BRCA1/2 mutation carriers and decreasing risk in the general population

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Abstract

Objective
BRCA1/2 carriers are at increased risk of ovarian cancer, and some reports suggest an increasing risk in more recent birth cohorts. In contrast, decreasing incidences have been observed in the general population. The aim was to assess the birth cohort effect on ovarian cancer risk in BRCA1/2 carriers relative to their background general population.

Methods
Data on ovarian cancer incidence was collected for a cohort of 1,050 BRCA1/2 mutation carriers ascertained by our regional clinic and retrieved from the general Dutch population cancer registry. Birth cohorts were categorized as pre-1935, 1935-1953, post-1953. Birth cohort effects on the ovarian cancer risk were estimated using hazard ratios (HRs) in BRCA1/2 carriers and Poisson rate ratios in the general population. Standardized incidence ratios (SIRs) were calculated to compare populations. HRs were adjusted for mutation position and family history.

Results
Compared to the pre-1935 cohort, BRCA1 carriers in the 1935-1953 and post-1953 cohorts had an increased ovarian cancer risk of HR_adjusted 1.54 (95%CI 1.11-2.14) and 2.40 (95%CI 1.56-3.69), respectively. BRCA2 carriers in the 1935-1953 cohort had an HR_adjusted of 3.01 (95%CI 1.47-6.13). The SIRs for the 1935-1953 and post-1953 cohorts were 1.7 and 2.7, respectively, for the BRCA1 carriers and 1.6 times and 2.4 times, respectively, for BRCA2 carriers.

Conclusions
Mutation carriers, particularly BRCA1 carriers, born in the most recent cohorts, have the highest additional ovarian cancer risk as compared to the general population.
Inverse trends in the ovarian cancer risks of BRCA1/2 carriers and the general population

Introduction

Women in the general population have a 1.1-1.7% cumulative lifetime risk (CLTR) of developing ovarian cancer (OC).1-3 About 10-15% of epithelial OC cases are associated with a mutation in the BRCA1 or BRCA2 gene.4,5 Two large meta-analyses have estimated the OC risk by age 70 to be 39% (95%CI 18–54%)6 and 40% (95%CI 35- 46%)7 for BRCA1 mutation carriers and 11% (95%CI 2.4–19%)6 and 18% (95%CI 13- 23%)7 for BRCA2 mutation carriers. However, higher risk estimates were derived in the Family Cancer Clinic in our region which covers the Northern-Netherlands: 59% (95%CI 54-64%) for BRCA1 carriers and 35% (95%CI 25-44%) for BRCA2 mutation carriers.8 For BRCA1 carriers this higher risk (59%, 95%CI 43-76%) was also observed in a prospective analysis in an UK clinic-based cohort, but estimated figures were lower for BRCA2 carriers (17%, 95%CI 8-34%).9

In BRCA1 carriers, an increased risk of breast cancer (BC) is observed in more recent birth cohorts compared to older birth cohorts.2,10,11 However, studies on birth-cohort effects on OC risk have produced contradictory results. For BRCA1 carriers, all studies show an increasing trend in more recent birth cohorts, but the effect size and significance differ. No significant birth cohort effect has yet been reported for BRCA2 carriers.10-13 Recent reports on the general population in several countries actually present a reverse trend of gradually decreasing OC risk: a lower risk in younger birth cohorts compared to older birth cohorts.1,14

We wondered whether these inverse OC risk trends could be confirmed in our population, and what the relative risk of developing OC was for BRCA1/2 mutation carriers compared to the general population when these inverse cohort trends were taken into account. Our aim was to assess the effect of birth cohorts on the OC risk in BRCA1/2 mutation carriers, as well as in their background general population, and to assess the birth-cohort-specific added risk for OC in mutation carriers.

Methods

Mutation carriers

This study included female carriers of a pathogenic BRCA1 or BRCA2 mutation seen at the Family Cancer Clinic of the University Medical Centre Groningen.15,16 Women could be included in the cohort if they were born in 1910 or later.

Information was collected up to September 2011, with follow-up information for 1,050 carriers (49,742 person years) from 364 BRCA1/2 families.8,17,18 Data were collected about mutation carrier status and type and location of the mutation and the following relevant dates: birth, death, last moment of contact, BC, OC, risk-reducing mastectomy and risk-reducing salpingo-oophorectomy (RRSO). Data were retrieved from patients’ medical records and entered into a separate, anonymous, password-protected database. According to Dutch law, this meant no further approval from our Medical Ethical Committee was needed.
General population
For the general population of the Netherlands, information was collected on the age-related OC incidence in the diagnosis periods 1960-1962, 1978-1982, 1983-1987, 1986-1988, and 1988-1992, which were available from the database of the International Agency for Research on Cancer, and in the diagnosis years 1989-2014, which were available from the Dutch Cancer Registry, the Netherlands.19,20

Outcome and independent variables
Birth cohorts were defined similarly for BRCA1/2 carriers and the general population. To define birth cohorts with sufficient group size and to maximize the follow-up time in each of the birth cohorts, three birth cohorts were defined: pre-1935, 1935-1953, and post-1953. Using this definition, CLTRs could be assessed up to age 55 for all birth cohorts, because all the cohorts included at least some women with follow-up to age 55. In addition, for the two oldest birth cohorts, the CLTRs up to age 70 could be assessed.

For BRCA1/2 carriers, mutation location definition was based on the OC cluster region (OCCR): 5 prime to OCCR, within OCCR, and OCCR to 3 prime.17,21,22 Family history of BC and OC was defined by two variables: (1) having any first- and/or second-degree relative with BC or not and (2) having any first- and/or second-degree relative with OC or not.

For the general population, age-specific incidences for each birth year were calculated using data on the incidence per 5-year age-group per year of diagnosis. By combining all data, an average incidence per age per birth year could be derived. For example, the incidence in the age group 50-54 for 2010 provided data for women born between 1956 and 1960, and similarly, for 2011, this age category consisted of women born between 1957 and 1961.

Statistical analysis
For mutation carriers, the effect of birth cohort on the CLTR of OC was assessed using Cox regression survival analysis and expressed as hazard ratios (HRs). The effect of birth cohort was adjusted for mutation location and family history. In the Cox models, robust standard errors were calculated to take the familial clustering into account. The proportionality of the HRs was examined using log-minus-log plots and Schoenfeld residuals. The CLTRs per birth cohort were calculated using Kaplan-Meier survival analyses. In the survival analyses, right-censoring was applied at the woman’s age at RRSO, or the last moment of follow-up, or age at death, or at age 70. To correct for ascertainment and genetic-testing bias, all these analyses were also performed with the inclusion of a proportion of untested FDRs (N=690; 35,553 person years) of mutation carriers, because these FDRs have no genetic-testing bias among them. We did not correct for bias by excluding the index cases, because this would have resulted in low numbers and because the vast majority of index cases were born in the 1935-1953 birth cohort. The proportion of FDRs was calculated based on the ratio of positive DNA tests of all presymptomatically tested women per age group and incident cancer status (i.e. cancer diagnosis after DNA testing in order to avoid overestimating the proportion due to genetic-testing bias). The calculated proportion reflects the proportion of assumed mutation carriers among the untested FDRs.23
For the general population, CLTRs and the effect of birth cohort on the CLTRs (age-adjusted Poisson rate ratios (PRRs)) were assessed by applying Poisson regression analyses.

For a direct comparison between the birth-cohort-specific incidence in mutation carriers and the general population, standardized incidence ratios (SIRs) were calculated and corrected for bias by including the proportion of assumed mutation carriers among the untested FDRs.

The analyses were performed using IBM SPSS statistics version 22 and R, and statistical significance was defined as $p < 0.05$. Continuous data is presented with a median and interquartile range (IQR), i.e. 25$^{th}$ percentile – 75$^{th}$ percentile.

### Results

**Mutation carriers**

In total, we included 656 $BRCA1$ carriers and 445 untested FDRs (consisting of both carriers and non-carriers) from 220 $BRCA1$ families, and 394 $BRCA2$ carriers and 245 untested FDRs from 144 $BRCA2$ families were included. $BRCA1$ carriers were followed until a median age of 48.2 years (IQR 38.4-57.3) and $BRCA2$ carriers until 49.5 years (IQR 40.1-59.5). In total, 136 (21%) $BRCA1$ and 43 (11%) $BRCA2$ carriers developed OC, at a median age of 49.4 years (IQR 43.9-56.1) and 57.8 years (IQR 52.2-62.7), respectively. RRSO was performed in 214 (33%) of the $BRCA1$ and 126 (32%) of the $BRCA2$ carriers at a median age of 43.9 years (IQR 39.9-50.9) and 47.8 years (IQR 39.1-53.3), respectively.

Overall, the median year of birth was 1957 (IQR 1945-1969) for $BRCA1$ and 1957 (IQR 1946-1968) for $BRCA2$ carriers. Among the untested FDRs this was 1944 (IQR 1926-1963) and 1942 (IQR 1926-1962), respectively.

**Ovarian cancer risk in mutation carriers by birth cohort**

For $BRCA1$ carriers, the CLTR by age 55 was 18.9% (95%CI 9.8-27.2%) in the pre-1935 birth cohort, 28.6% (95%CI 21.1-35.4%) in the 1935-1953 birth cohort, and 43.4% (95%CI 26.5-56.3%) in the post-1953 birth cohort (Table 1). For $BRCA2$ carriers, the CLTR by age 55 was 6.8% (95%CI 0.0-13.9%) in the pre-1935 birth cohort, 7.8% (95%CI 2.4-12.8%) in the 1935-1953 birth cohort, and 25.2% (95%CI 0.0-45.5%) in the post-1953 birth cohort. CLTRs at other ages, and CLTRs for carriers including the assumed carriers among the FDRs, are presented in Table 1. The CLTRs and number of women included in the analyses are presented separately for mutation carriers and assumed carriers in Fig 1.
Table 1. Birth-cohort-specific crude cumulative lifetime risks (CLTRs) by ages 55 and 70 years in the BRCA1/2 mutation carriers and in the general population

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Carriers</th>
<th>Carriers &amp; FDRs</th>
<th>Carriers</th>
<th>Carriers &amp; FDRs</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55</td>
<td>N (events)</td>
<td>CLTR (95% CI)</td>
<td>N (events)</td>
<td>CLTR (95% CI)</td>
<td>N (events)</td>
</tr>
<tr>
<td>pre-1935</td>
<td>58 (15)</td>
<td>18.9 (9.8-27.2)</td>
<td>133 (15)</td>
<td>20.9 (14.7-26.6)</td>
<td>37 (3)</td>
</tr>
<tr>
<td>1935-1953</td>
<td>94 (46)</td>
<td>28.6 (21.1-35.4)</td>
<td>116 (60)</td>
<td>28.8 (22.2-34.9)</td>
<td>86 (8)</td>
</tr>
<tr>
<td>post-1953</td>
<td>4 (37)</td>
<td>43.4 (26.5-56.3)</td>
<td>4 (39)</td>
<td>40.1 (24.6-52.5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Age 70</td>
<td>N (events)</td>
<td>CLTR (95% CI)</td>
<td>N (events)</td>
<td>CLTR (95% CI)</td>
<td>N (events)</td>
</tr>
<tr>
<td>pre-1935</td>
<td>32 (29)</td>
<td>41.4 (28.2-52.2)</td>
<td>83 (61)</td>
<td>36.3 (28.4-43.3)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>1935-1953</td>
<td>6 (67)</td>
<td>56.5 (43.1-66.8)</td>
<td>13 (82)</td>
<td>52.1 (41.1-61.1)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>post-1953</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Number of women still at risk at the indicated age. Between brackets: the cumulative number of OCs from age 18 up to the indicated age.
Abbreviations: FDRs, first-degree relatives; NA, Not applicable.
Inverse trends in the ovarian cancer risks of *BRCA1/2* carriers and the general population

**Figure 1.** Cumulative life-time risk (CLTR) and 95% CI of ovarian cancer in *BRCA1* (A) and *BRCA2* (B) stratified by birth cohort and carrier status (i.e. carriers and assumed mutation carriers among FDRs).

*Abbreviations:* FDRs, first-degree relatives
Table 2. Effect of birth cohort on the CLTR of ovarian cancer by ages 55 and 70 years in (assumed) BRCA1/2 mutation carriers and in the general population

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Carriers</th>
<th>Carriers &amp; FDRs</th>
<th>Carriers</th>
<th>Carriers &amp; FDRs</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Birth cohort (crude)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pre-1935</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1935-1953</td>
<td>1.49 (0.81-2.76)</td>
<td>1.41 (0.97-2.06)</td>
<td>1.08 (0.28-4.15)</td>
<td>1.26 (0.48-3.34)</td>
<td>NA</td>
</tr>
<tr>
<td>post-1953</td>
<td>3.02 (1.66-5.48)</td>
<td>&lt;0.001</td>
<td>2.41 (1.57-3.69)</td>
<td>&lt;0.001</td>
<td>2.49 (0.55-11.3)</td>
</tr>
<tr>
<td>Birth cohort (adjusted)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-1935</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1935-1953</td>
<td>1.57 (0.84-2.90)</td>
<td>1.41 (0.97-2.07)</td>
<td>1.02 (0.28-3.78)</td>
<td>1.21 (0.45-3.23)</td>
<td>0.90 (0.87-0.92)</td>
</tr>
<tr>
<td>post-1953</td>
<td>3.14 (1.72-5.72)</td>
<td>&lt;0.001</td>
<td>2.40 (1.56-3.69)</td>
<td>&lt;0.001</td>
<td>2.22 (0.49-9.98)</td>
</tr>
<tr>
<td>Age 70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth cohort (crude)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-1935</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1935-1953</td>
<td>1.49 (0.95-2.34)</td>
<td>1.54 (1.10-2.15)</td>
<td>2.76 (1.05-7.27)</td>
<td>2.90 (1.44-5.62)</td>
<td>NA</td>
</tr>
<tr>
<td>post-1953&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.98 (1.76-5.04)</td>
<td>&lt;0.001</td>
<td>2.53 (1.65-3.86)</td>
<td>&lt;0.001</td>
<td>5.26 (1.11-24.8)</td>
</tr>
<tr>
<td>Birth cohort (adjusted)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-1935</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1935-1953</td>
<td>1.60 (1.01-2.53)</td>
<td>1.54 (1.11-2.14)</td>
<td>2.88 (1.03-8.02)</td>
<td>3.01 (1.47-6.13)</td>
<td>0.90 (0.87-0.92)</td>
</tr>
<tr>
<td>post-1953&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.15 (1.84-5.39)</td>
<td>&lt;0.001</td>
<td>2.51 (1.64-3.85)</td>
<td>&lt;0.001</td>
<td>5.03 (1.02-24.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The model of the BRCA carriers is adjusted for mutation position (OCCR) and family history of breast and ovarian cancer, while the model of the general population is adjusted for 5-year age-groups.

<sup>b</sup>In this birth cohort the maximum age of follow-up is approximately 55 to 57 years.

Abbreviations: Ref reference cohort; FDRs first-degree relatives; NA not applicable.
Birth cohort effect in mutation carriers

For BRCA1 carriers, the effect of birth cohort on the CLTRs by age 55 and age 70 was significant ($p < 0.001$) and the HRs were similar (Table 2). When compared to the pre-1935 birth cohort, the HRs adjusted for mutation location and family history by age 55 for the 1935-1953 and post-1953 birth cohorts were 1.57 (95%CI 0.84-2.90, $p = 0.156$) and 3.14 (95%CI 1.72-5.72, $p < 0.001$), respectively. When we included the assumed carrier-fraction of the FDRs, these HRs were 1.41 (95%CI 1.97-2.07, $p = 0.075$) and 2.40 (95%CI 1.56-3.69, $p < 0.001$), respectively (Table 2).

For BRCA2 carriers, the overall effect of birth cohort on the CLTRs by ages 55 and 70 was not significant (Table 2). However, by age 70 the risk was increased in the 1935-1953 birth cohort compared to the pre-1935 birth cohort. The adjusted HR was 2.88 (95%CI 1.03-8.02, $p = 0.043$), and with inclusion of assumed carriers among the FDRs, it was 3.01 (95%CI 1.47-6.13, $p = 0.002$).

Birth cohort effect in general population

In the general population, an opposite trend was observed with similar PRRs by ages 55 and 70 (Table 2). The PRRs by age 55 for the 1935-1953 and post-1953 birth cohorts were 0.90 (95%CI 0.87-0.92, $p < 0.001$) and 0.69 (95%CI 0.87-0.92, $p < 0.001$) compared to the pre-1935 birth cohort.

Table 3. Birth-cohort-specific standardized incidence ratios (SIRs) with 95% confidence intervals for BRCA1/2 mutation carriers

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-1935</th>
<th>1935-1953</th>
<th>Post-1953*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR (95%CI)</td>
<td>SIR (95%CI)</td>
<td>SIR vs. SIR&lt;sub&gt;1935&lt;/sub&gt;</td>
</tr>
<tr>
<td>SIR vs. SIR&lt;sub&gt;1935&lt;/sub&gt;</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>43.8 (22-78)</td>
<td>61.2 (35-99)</td>
<td>0.351</td>
</tr>
<tr>
<td>45-54</td>
<td>51.1 (33-75)</td>
<td>108.2 (78-146)</td>
<td>0.002</td>
</tr>
<tr>
<td>55-70</td>
<td>27.3 (17-41)</td>
<td>58.5 (37-88)</td>
<td>0.012</td>
</tr>
<tr>
<td>Total 20-55</td>
<td>48.7 (35-67)</td>
<td>81.5 (62-105)</td>
<td>0.012</td>
</tr>
<tr>
<td>Total 20-70</td>
<td>37.6 (29-48)</td>
<td>73.5 (59-91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>6.7 (0-37)</td>
<td>5.7 (0-32)</td>
<td>0.917</td>
</tr>
<tr>
<td>45-54</td>
<td>15.8 (5-37)</td>
<td>29.3 (14-55)</td>
<td>0.265</td>
</tr>
<tr>
<td>55-70</td>
<td>12.3 (5-25)</td>
<td>65.4 (39-102)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total 20-55</td>
<td>12.3 (5-27)</td>
<td>19.3 (9-35)</td>
<td>0.376</td>
</tr>
<tr>
<td>Total 20-70</td>
<td>12.3 (7-2)</td>
<td>35.5 (24-51)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Maximum age of follow-up in this birth cohort is 55 to 57 years

Abbreviations: NA, Not applicable because there were no women at risk
Comparison of incidence carriers and general population

For BRCA1 carriers, the SIRs by age 55 for the pre-1935, 1935-1953, and post-1953 birth cohorts were 57.3 (95%CI 32-95), 93.5 (95%CI 69-125) and 160.9 (95%CI 113-222), respectively. In comparison with the pre-1935 birth cohort, SIRs were significantly higher in the 1935-1953 ($p<0.001$) and post-1953 ($p=0.012$; Table 3) birth cohorts.

For BRCA2 carriers, the SIRs by age 55 were not significantly different for the pre-1935, 1935-1953, and post-1953 birth cohorts: 12.3 (95%CI 5-27), 19.3 (95%CI 9-35) and 29.2 (95%CI 11-64), respectively. However, significantly increased SIRs were seen from age 55 onwards for the pre-1935 and 1935-1953 birth cohorts: 12.3 (95%CI 5-7) and 35.5 (95%CI 24-51), respectively ($p=0.001$).

Discussion

Increased OC risks were observed for BRCA carriers born in the two more recent birth cohorts. Compared to carriers born pre-1935, the HRs by age 55 were 1.41 (95%CI 0.97-2.07) for BRCA1 carriers born between 1935 and 1953, and 2.40 (95%CI 1.56-3.69) for those born post-1953. For BRCA2 carriers, these HRs were 1.21 (95%CI 0.45-3.23) and 2.51 (95%CI 0.75-8.37), respectively. Over the same time span, the OC risk decreased in more recent birth cohorts in the general background population, leading to higher additional risks for OC in carriers born more recently. Compared to pre-1935, the SIRs by age 55 were 1.7 times ($p=0.012$) and 2.7 times ($p<0.001$) higher in BRCA1 carriers born between 1935 and 1953 and post-1953, and these SIRs were 1.6 times ($p=0.376$) and 2.4 times ($p=0.152$) higher in BRCA2 carriers born between 1935 and 1953 and post-1953. Thus, this trend only reached statistical significance in BRCA1 carriers.

Our findings on the increased risk of developing OC in BRCA1 mutation carriers born more recently are in line with several previous clinic-ascertained studies that indicated a higher OC risk for BRCA1 carriers from more recent birth cohorts.[10-13] One study, which included the index cases, detected significant differences in birth-cohort-specific CLTR in BRCA1 carriers by ages 40 and 60.12 The CLTR by age 40 was 4 times higher in a birth cohort post-1958 compared to pre-1958, and by age 60 it was 2.5 times higher in birth cohort post-1940 compared to pre-1941. Another study, which excluded the index cases, showed similar but non-significant trends for BRCA1 carriers. Compared to pre-1920, the HRs by age 70 for a 1920-1939 and post-1939 cohorts were 1.8 (95%CI 0.6-5.6) and 3.7 (95%CI 0.9-15.8), respectively.11

For BRCA2 carriers, no significant effect of birth cohort on the OC risk has been observed thus far.10-13 This could be due to the smaller numbers of BRCA2 carriers and of OCs, in combination with the later onset of OC in BRCA2 carriers compared to onset in BRCA1 carriers. The study that included the index cases found no effect by age 40 for birth cohort (pre-1958 vs. post-1958).10 We did find a significantly increased risk in more recent birth cohorts, which is probably due to the longer follow-up time in our study, since we only detected a significant effect by age 70 and not by age 55.

In the Dutch general population, we found decreasing CLTRs in more recent birth cohorts, irrespective of age. When compared to the pre-1935 birth cohort, the relative
Inverse trends in the ovarian cancer risks of BRCA1/2 carriers and the general population

Risks of OC were statistically significantly lower in more recent birth cohorts (PRRs were 0.9 (p < 0.001) and 0.7 (p < 0.001) for the 1935-1953 and post-1953 birth cohorts, respectively). A decreasing trend was also reported for some North American and Western European populations.1,2

The uptake of RRSO among our BRCA1/2 mutation carriers is lower (i.e. 32-33%) than seen in recent cohorts with uptakes up to 87%.25 This is because our carrier cohort included women born in 1910 or later whereas the uptake of RRSO started to increase gradually over the last 2 decades following the discovery of BRCA1/2. And it is only since 2009 that RRSO is advised proactively, following the reports showing the ineffectiveness of screening in reducing ovarian/tubal cancer mortality.26-28

A number of reproductive and hormonal factors are known to have impact on the risk of both BC and OC in more recent birth cohorts.29 These factors include fewer full-term pregnancies, an older age at first full-term pregnancy, less breastfeeding, and more hormonal replacement therapy.29-32 However, the use of oral contraceptives is associated with an increased BC risk but a decreased OC risk. For BC, the risk-increases over time in both the general population as well as in the BRCA carriers are concordant.2,10,11 Both trends can be attributed to changes in reproductive and hormonal factors, an unhealthier lifestyle (e.g. alcohol consumption, physical activity, BMI), and an increase in BC screening; factors which will play a role in both populations.33-37

The opposite trends in OC risk in the general population and in BRCA mutation carriers are difficult to explain from an underlying genetic or environmental mechanism, as it is expected that both populations have in general a similar distribution of risk factors other than BRCA. Such an explanation could not be assessed in this study because those data were not available, and data on interaction between these risk factors and BRCA mutations is scarce. However, since 1970, oral contraceptives have increasingly been used in the general population, which is seen as the major explanation for the decreased OC risk.38 This suggests at least one possible explanation for the divergent risks: if BRCA carriers use oral contraceptives less often than women in the general population because oral contraceptives increase their risk of BC, then BRCA carriers would not benefit from the protective effect provided by oral contraceptives for OC. No data is currently available to explore this hypothesis.

To our knowledge, this is the first study to assess the effect of birth cohort on the OC risk in both BRCA mutation carriers and their background general population. The follow-up time in this study was long enough to present risks by age 55 for all birth cohorts, and by age 70 for the two older birth cohorts. At both ages the risk was increased similarly, which indicates that the risk curve did not shift due to an earlier age at diagnosis. Though, the HRs up to age 70 in the post-1953 cohort should be interpreted carefully as only a few women in this cohort were older than age 55. The actual decrease in the OC risk in non-carriers is likely to be even a little stronger than that seen in the Dutch cancer registry general population data, since carriers are also included in this population data. We did not adjust for this in the analyses, as this requires multiple uncertain assumptions regarding the age- and birth cohort related percentage of BRCA-related OC.39,40 No registry data was available before calendar year 1960 or for the period 1963-1977, and the average incidence in the adjacent years was used. We assume that this did not affect our results, since PRRs were stable over time.
and the SIRs showed the expected age-related variation. The data from the mutation carriers was collected in the Northern Netherlands, whereas the data on the general population was not specific for this region as only national data was available for older calendar years. However, the population of The Netherlands is relatively small and population incidence rates of OC are comparable throughout the country.

In conclusion, there are inverse trends in the OC risk in BRCA1/2 mutation carriers compared to the general population. Mutation carriers born in more recent birth cohorts have a substantially higher additional risk for OC, and this is especially true for BRCA1 carriers. It is difficult to explain the inverse trends in the OC risk in BRCA carriers compared to the general population, indicating that further analysis of the influence of lifestyle, hormonal and reproductive factors is needed.

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References


38. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll
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