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*JNCI J Natl Cancer Inst* (2022) 114(4): djac004

https://doi.org/10.1093/jnci/djac004
First published online January 20, 2022
Article

# Oral Contraceptive Use in *BRCA1* and *BRCA2* Mutation Carriers: Absolute Cancer Risks and Benefits

Lieske H. Schrijver, MSc,[1] Thea M. Mooij, MSc,[1] Anouk Pijpe, PhD,[1] Gabe S. Sonke, MD, PhD,[2] Marian J.E. Mourits, MD, PhD,[3] Nadine Andrieu, PhD,[4,5,6,7] Antonis C. Antoniou, PhD,[8] Douglas F. Easton, PhD,[8,9] Christoph Engel, MD,[10] David Goldgar, PhD,[11] Esther M. John, PhD,[12] Karin Kast, MD,[13] Roger L. Milne, PhD,[14,15,16] Håkan Olsson, MD, PhD,[17,†] Kelly-Anne Phillips, MD,[15,18,19] Mary Beth Terry, PhD,[20] John L. Hopper, PhD,[15] Flora E. van Leeuwen, PhD,[1,*] Matti A. Rookus, PhD[1]

[1]Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [3]Department of Gynecologic Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [4]INSERM U900, Paris, France; [5]Institut Curie, Paris, France; [6]Mines Paris Tech, Fontainebleau, France; [7]PSL Research University, Paris, France; [8]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [9]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK; [10]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany; [11]Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT, USA; [12]Department of Epidemiology & Population Health and Medicine, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA; [13]Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; [14]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia; [15]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia; [16]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia; [17]Department of Oncology, Lund University Hospital, Lund, Sweden; [18]The Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia; [19]Department of Medical Oncology, Peter MacCallum Cancer Centre, Victoria, Australia; and [20]Department of Epidemiology, Columbia University, New York, NY, USA

[†]Deceased.

[*]**Correspondence to:** Flora E. van Leeuwen, PhD, Department of Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, the Netherlands (e-mail: f.v.leeuwen@nki.nl).

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## Abstract

**Background:** To help *BRCA1* and *2* mutation carriers make informed decisions regarding use of combined-type oral contraceptive preparation (COCP), absolute risk-benefit estimates are needed for COCP-associated cancer. **Methods:** For a hypothetical cohort of 10 000 women, we calculated the increased or decreased cumulative incidence of COCP-associated (breast, ovarian, endometrial) cancer, examining 18 scenarios with differences in duration and timing of COCP use, uptake of prophylactic surgeries, and menopausal hormone therapy. **Results:** COCP use initially increased breast cancer risk and decreased ovarian and endometrial cancer risk long term. For 10 000 *BRCA1* mutation carriers, 10 years of COCP use from age 20 to 30 years resulted in 66 additional COCP-associated cancer cases by the age of 35 years, in addition to 625 cases expected for never users. By the age of 70 years such COCP use resulted in 907 fewer cancer cases than the expected 9093 cases in never users. Triple-negative breast cancer estimates resulted in 196 additional COCP-associated cases by age 40 years, in addition to the 1454 expected. For 10 000 *BRCA2* mutation carriers using COCP from age 20 to 30 years, 80 excess cancer cases were estimated by age 40 years in addition to 651 expected cases; by the age of 70 years, we calculated 382 fewer cases compared with the 6156 cases expected. The long-term benefit of COCP use diminished after risk-reducing bilateral salpingo-oophorectomy followed by menopausal hormone therapy use. **Conclusion:** Although COCP use in *BRCA1* and *BRCA2* mutation carriers initially increases breast, ovarian, and endometrial cancer risk, it strongly decreases lifetime cancer risk. Risk-reducing bilateral salpingo-oophorectomy and menopausal hormone therapy use appear to counteract the long-term COCP-benefit.

In the general population, use of combined-type oral contraceptive preparations (COCP) greatly reduces the risks of ovarian and endometrial cancer compared with never users (typical relative risk [RR] = 0.50) (1,2). In contrast, current COCP use is associated with a small increased risk of breast cancer (RR = 1.17-1.27) (3-6). The increases and decreases in relative risk are

**Received:** June 26, 2021; **Revised:** October 11, 2021; **Accepted:** January 10, 2022

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amplified with longer durations of COCP use and attenuate after stopping COCP use (1-6).

Carriers of pathogenic *BRCA1* and *BRCA2* mutations are at high lifetime risk of developing breast and/or ovarian cancer. To help *BRCA1* and *BRCA2* mutation carriers make informed decisions regarding COCP use, absolute cancer risk-benefit estimates are needed, specifically for breast, ovarian, and endometrial cancer.

## Methods

### Statistical Analysis

For a hypothetical cohort of 10 000 *BRCA1* or *BRCA2* mutation carriers, we used lifetable methods to estimate the absolute risks and benefits of COCP use with respect to breast, ovarian, and endometrial cancer cumulative incidence. Absolute and age-specific COCP-associated increases (or decreases) of cumulative incidences throughout life were calculated for each cancer type by subtracting the age-specific cumulative incidence among nonusers of COCP (= absolute background incidence) from the cumulative incidence among COCP users. We summed the age- and cancer-specific increased and decreased cumulative incidences of the 3 cancer types to calculate the overall risk-benefit outcome.

We examined 18 scenarios (A-R; see Table 1) with varying duration of COCP use (continuous use: 5, 10, and 15 years; 10-year interrupted use: 5-year use, 5-year no use, and 5-year use), age at first COCP use (age at start 15 or 20 years) and uptake of prophylactic surgeries (no prophylactic surgery, only risk-reducing bilateral salpingo-oophorectomy [RRSO] at age 40 years, both risk-reducing bilateral mastectomy [RRM] and RRSO at age 40 years, or RRM at age 30 years and RRSO at age 40 years). By definition, there was no loss to follow-up during COCP use. For all scenarios, the reference group consisted of non-COCP users.

The absolute cumulative incidence estimates were derived from 1) incidence rates of breast, ovarian, and endometrial cancer in *BRCA1* and *BRCA2* mutation carriers; 2) survival rates of breast, ovarian, and endometrial cancer; 3) competing mortality due to death from other causes; and 4) relative risks for the associations between COCP use and risks of breast, ovarian, and endometrial cancer. The risk-benefit calculation is explained in detail in the Supplementary Methods (available online).

### Model Parameters

Age-specific breast and ovarian cancer incidence rates for mutation carriers were estimated using data from the *BRCA1* and *BRCA2* Cohort Consortium [personal communication AC Antoniou (7)], adjusted for the underlying exposure to COCP use (Supplementary Table 1, available online). For endometrial cancer, we used national incidence rates from the Netherlands Cancer Registry, because there is no convincing evidence of an increased risk in mutation carriers yet (8). For survival after breast, ovarian, and endometrial cancer, we used data for the Dutch general population, stratified on age at diagnosis and time since diagnosis (8). The population at risk decreased during follow-up, because of ovarian cancer mortality in the calculations for breast and endometrial cancer and because of mortality from breast cancer in the calculations for ovarian and endometrial cancer, based on *BRCA1*-, *BRCA2*-, and COCP-specific breast and ovarian cancer incidences and corresponding survival rates (Supplementary Table 2, available online). For the decreasing population at risk due to other causes of death during follow-up, we used age-specific mortality rates from the Dutch general population, excluding the mortality of breast, ovarian, and endometrial cancer [2011-2015; Statistics Netherlands (9); Supplementary Table 3, available online].

Observed associations (measured in terms of relative risk) between COCP use and risks of breast and ovarian cancer do not appear to differ between mutation carriers and women in the general population (10,11). Therefore, we applied relative risks derived from meta-analyses of studies in the general population (1-6). For breast cancer, we conducted a new meta-analysis on all studies that were large enough to examine the interaction between recency and duration of COCP use and risk of breast cancer (1-6,10,11) (current use, duration <7 years: RR = 1.17; current use, duration ≥7 years: RR = 1.27; <5 years ago: RR = 1.14; ≥5 years ago, RR = 1.11; see Supplementary Methods, available

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**Table 1.** Scenarios for absolute risk calculations, varying duration, and age at first use of oral contraceptive preparations (COCP) and uptake of prophylactic surgeries by 10 000 *BRCA1* and 10 000 *BRCA2* mutation carriers[a]

| Scenario | COCP duration | Age at COCP use, y | Age at RRM, y | Age at RRSO, y |
|---|---|---|---|---|
| A | 5 y continuous | 20-24 | No surgery | No surgery |
| B | 10 y continuous | 20-29 | No surgery | No surgery |
| C | 10 y interrupted | 20-24 and 30-34 | No surgery | No surgery |
| D | 10 y continuous | 15-24 | No surgery | No surgery |
| E | 15 y continuous | 15-29 | No surgery | No surgery |
| F | 5 y continuous | 20-24 | No surgery | 40 |
| G | 10 y continuous | 20-29 | No surgery | 40 |
| H | 10 y interrupted | 20-24 and 30-34 | No surgery | 40 |
| I | 10 y continuous | 15-24 | No surgery | 40 |
| J | 15 y continuous | 15-29 | No surgery | 40 |
| K | 5 y continuous | 20-24 | 40 | 40 |
| L | 10 y continuous | 20-29 | 40 | 40 |
| M | 10 y interrupted | 20-24 and 30-34 | 40 | 40 |
| N | 10 y continuous | 15-24 | 40 | 40 |
| O | 5 y continuous | 20-24 | 30 | 40 |
| P | 10 y continuous | 20-29 | 30 | 40 |
| Q | 10 y interrupted | 20-24 and 30-34 | 30 | 40 |
| R | 10 y continuous | 15-24 | 30 | 40 |

[a]COCP= combined-type oral contraceptive preparations; RRM = risk-reducing bilateral mastectomy; RRSO = risk-reducing bilateral salpingo-oophorectomy.

online). For ovarian and endometrial cancer, we used the findings of the Collaborative Group on Epidemiological Studies of Ovarian Cancer and the Collaborative Group on Epidemiological Studies of Endometrial Cancer, respectively, showing a risk reduction that was larger and lasted longer with longer durations of COCP use (Supplementary Table 4, available online). We further assumed that the relative risks of the 3 types of cancer are independent.

In many Western countries, the majority (70%-75%) of *BRCA1* and 2 carriers nowadays opt for RRSO between ages 35 and 40 years, after childbearing is completed. We assumed that RRSO reduced the incidence of ovarian cancer in the years after RRSO by 80% (12). Furthermore, we assumed that RRSO did not reduce breast cancer incidence in *BRCA1* mutation carriers, whereas RRSO reduced the risk by 50% from 5 years after RRSO in *BRCA2* mutation carriers (13).

Compared with the uptake of RRSO, the uptake of RRM for *BRCA1* and 2 mutation carriers is much lower (2.7%-36.6%) and varies widely between countries (13). In the risk-benefit calculations including the uptake of an RRM, the incidence of breast cancer for *BRCA1* and *BRCA2* mutation carriers was reduced by 95% in the years following the RRM (14). We assumed that ovarian cancer incidence was not altered following an RRM and the risk of endometrial cancer was not affected by the uptake of RRSO or RRM.

### Sensitivity Analyses

Sensitivity analyses included scenarios accounting for 1) use of menopausal hormone therapy following RRSO; 2) assuming a different COCP-association for triple-negative breast cancer (TNBC; *BRCA1*); 3) absolute cumulative risk-benefit calculation of mortality; 4) uptake of hysterectomy together with RRSO; 5) no breast cancer risk reduction following RRSO (*BRCA2*) (15-17); 6) a larger ovarian cancer risk reduction after RRSO (18); and 7) improved *BRCA1*- and *BRCA2*-specific breast and ovarian cancer survival (19,20).

Sensitivity analysis 1 included scenarios with 5- or 10-year menopausal hormone therapy use (estrogen and progestogen [E + P], estrogen only [E-only], and tibolone) following RRSO. Relative risks were based on associations reported for the general population (21-24) (Supplementary Table 5, available online).

Breast tumors of *BRCA1* mutation carriers are often TNBC (25). In a meta-analysis for the general population, Li et al. (26) showed that the odds ratio (OR) for COCP (ever/never) comparing TNBC with other breast cancer subtypes was 1.31 (95% confidence interval [CI] = 1.18 to 1.45). We used this estimate for sensitivity analysis 2.

For sensitivity analysis 3, we expanded the absolute cumulative incidence model to a mortality model, where mortality is estimated by multiplying the numbers of breast, ovarian, and endometrial cancer cases per 5-year age category by cancer- and survival time-specific rates.

## Results

### Main Results

For a hypothetical cohort of 10 000 *BRCA1* mutation carriers, 10 years of continuous COCP use (no prophylactic surgeries; scenario B) resulted in 99 additional cases of breast cancer by age 35 years, in addition to the 572 cases expected for women with no COCP use (Figure 1). In contrast, by age 35 years, 32 fewer cases of ovarian cancer occurred in 10 000 *BRCA1* mutation carriers with 10 years of COCP use (20-30 years) compared with the 52 expected cases with no COCP use. No case of endometrial cancer was expected for women aged 35 years, irrespective of their COCP use. Taken together, by age 35 years, a maximum of 66 additional cases of COCP-associated cancers occurred compared with the 625 expected for women with no COCP use. From age 35 years onward, the excess number of cancers associated with COCP use decreased and became a deficit of cancers. By age 70 years, 907 fewer COCP-associated cancers occurred compared with 9093 expected cases for women with no COCP use (Figures 1 and 2).

Because of the underlying differences in cancer incidence, the maximum increased and decreased cumulative incidences due to COCP use shifted to older ages for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers. For *BRCA2* mutation carriers, a maximum of 80 additional COCP-associated cancer cases occurred at age 40 years compared with the 651 cases expected for women with no COCP use (Figures 1 and 2). By age 70 years, 382 fewer cancers occurred compared with an expected number of 6156 for the 3 cancer sites for women with no COCP use.

For comparison, for women in the general population, 5 additional COCP-associated cancer cases occurred in COCP users by age 40 years, compared with the 71 expected in nonusers (Figure 1). By age 70 years, 55 fewer cases occurred in COCP users compared with the 1021 expected.

The most prevalent patterns of COCP use of Dutch *BRCA1* and *BRCA2* mutation carriers (27) are 10 years of COCP use at 20-30 years combined with prophylactic surgeries (scenarios G, L, P). The maximum additional number of COCP-associated cancers had the same magnitude and timing after prophylactic surgeries, if these took place at age 40 years (scenarios G and L; see Figures 3 and 4; Supplementary Figure 1, available online). In the longer term, the uptake of RRSO at age 40 years reduced the risk of ovarian cancer and, thereby, decreased the benefits from COCP use. For *BRCA1* mutation carriers, COCP use followed by an RRSO at age 40 years resulted in 324 fewer COCP-associated cancer cases than the 6762 expected among women with no COCP use (scenario G), COCP use followed by RRSO and RRM at age 40 years decreased incidence by 332 cases (2688 expected; scenario L), and COCP use not followed by prophylactic surgeries (scenario B) led to a deficit of 907 cases (9093 expected). For *BRCA2* mutation carriers, 73 fewer COCP-associated cancer cases occurred (3408 expected for women who never used COCP) when COCP use was followed by RRSO at age 40 years (scenario G). An RRM at age 40 years in addition to the RRSO did not change the estimates (61 fewer cases than 1287 expected with no COCP use; scenario L). For comparison, COCP use with no prophylactic surgery (scenario B) decreased the incidence of COCP-associated cancer by 382 cases (6156 expected without COCP use). An RRM at age 30 years (scenario P) resulted in a smaller maximum increase of COCP-associated cancer cases (*BRCA1*: ≥45, expected without COCP use: 187; *BRCA2*: ≥22, expected without COCP use: 97) and a larger decrease (*BRCA1*: <440, expected without COCP use: 1818: *BRCA2*: <122, expected without COCP use: 791) of COCP-associated cancer cases.

The pattern that COCP use increased the absolute cumulative incidence in the early years following COCP use, but decreased the long-term risks, was qualitatively similar for other scenarios in which the duration of use and age at first COCP use were varied (Figures 3, B, and 4, B; Supplementary Figure 2 and Supplementary Tables 7 and 8, available online). For a longer duration of COCP use and for first use at older ages, both the absolute increased cumulative incidences in the early years

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| Scenario B: 10 years COCP use, start age 20 years, no prophylactic surgeries | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Attained age, y | | | | | | | | | | |
| Population at risk (n = 10 000) | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| **General population** | **Absolute cumulative incidence** | | | | | | | | | | |
| Breast cancer | | | | | | | | | | | |
| Never users | – | 1 | 8 | 28 | 66 | 135 | 248 | 393 | 527 | 684 | 859 |
| COCP users | – | 1 | 10 | 33 | 75 | 144 | 257 | 402 | 536 | 693 | 867 |
| Difference | – | 0 | 2 | 5 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Ovarian cancer | | | | | | | | | | | |
| Never users | – | 1 | 2 | 3 | 5 | 7 | 12 | 20 | 32 | 47 | 67 |
| COCP users | – | 0 | 1 | 1 | 2 | 3 | 6 | 11 | 17 | 33 | 47 |
| Difference | – | 0 | -1 | -2 | -3 | -4 | -7 | -10 | -14 | -17 | -20 |
| Endometrial cancer | | | | | | | | | | | |
| Never users | – | 0 | 0 | 0 | 1 | 2 | 6 | 15 | 34 | 62 | 95 |
| COCP users | – | 0 | 0 | 0 | 0 | 1 | 2 | 7 | 15 | 32 | 51 |
| Difference | – | 0 | 0 | 0 | -1 | -2 | -4 | -9 | -24 | -38 | -44 |
| Total hormonal cancer | | | | | | | | | | | |
| Never users (baseline) | – | 2 | 10 | 31 | 71 | 144 | 266 | 428 | 593 | 793 | 1021 |
| COCP users | – | 2 | 11 | 34 | 76 | 147 | 265 | 419 | 569 | 755 | 966 |
| **Total difference** | **–** | **0** | **1** | **3** | **5** | **3** | **-1** | **-9** | **-24** | **-38** | **-55** |
| ***BRCA1* mutation carriers** | **Absolute cumulative incidence** | | | | | | | | | | |
| Breast cancer | | | | | | | | | | | |
| Never users | – | 33 | 184 | 572 | 1167 | 1960 | 2888 | 3774 | 4476 | 4956 | 5264 |
| COCP users | – | 39 | 230 | 671 | 1324 | 2106 | 3032 | 3937 | 4678 | 5204 | 5558 |
| Difference | – | 6 | 46 | 99 | 157 | 147 | 144 | 162 | 202 | 249 | 293 |
| Ovarian cancer | | | | | | | | | | | |
| Never users | – | 1 | 3 | 52 | 286 | 873 | 1488 | 2116 | 2729 | 3300 | 3758 |
| COCP users | – | 1 | 1 | 21 | 112 | 416 | 745 | 1154 | 1569 | 2127 | 2587 |
| Difference | – | 0 | -1 | -32 | -174 | -457 | -744 | -962 | -1160 | -1173 | -1170 |
| Endometrial cancer | | | | | | | | | | | |
| Never users | – | 0 | 0 | 0 | 1 | 2 | 6 | 14 | 29 | 49 | 70 |
| COCP users | – | 0 | 0 | 0 | 0 | 1 | 2 | 6 | 14 | 27 | 41 |
| Difference | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -15 | -23 | -30 |
| Total hormonal cancer | | | | | | | | | | | |
| Never users (baseline)[a] | – | 34 | 187 | 625 | 1454 | 2835 | 4382 | 5904 | 7234 | 8305 | 9093 |
| COCP users | – | 29 | 232 | 691 | 1437 | 2523 | 3779 | 5097 | 6260 | 7358 | 8186 |
| **Total difference[a]** | **–** | **5** | **45** | **66** | **-17** | **-312** | **-603** | **-807** | **-974** | **-947** | **-907** |
| ***BRCA2* mutation carriers** | **Absolute cumulative incidence** | | | | | | | | | | |
| Breast cancer | | | | | | | | | | | |
| Never users | – | 19 | 94 | 286 | 640 | 1171 | 1815 | 2537 | 3304 | 4041 | 4765 |
| COCP users | – | 22 | 117 | 336 | 726 | 1253 | 1891 | 2607 | 3375 | 4124 | 4872 |
| Difference | – | 3 | 23 | 50 | 87 | 82 | 76 | 71 | 71 | 83 | 108 |
| Ovarian cancer | | | | | | | | | | | |
| Never users | – | 1 | 3 | 5 | 10 | 26 | 109 | 499 | 1028 | 1245 | 1307 |
| COCP users | – | 1 | 1 | 2 | 4 | 12 | 55 | 289 | 613 | 801 | 856 |
| Difference | – | 0 | -1 | -3 | -6 | -14 | -55 | -210 | -415 | -443 | -451 |
| Endometrial cancer | | | | | | | | | | | |
| Never users | – | 0 | 0 | 0 | 1 | 2 | 6 | 15 | 32 | 57 | 85 |
| COCP users | – | 0 | 0 | 0 | 0 | 1 | 2 | 7 | 15 | 29 | 46 |
| Difference | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -18 | -28 | -39 |
| Total hormonal cancer | | | | | | | | | | | |
| Never users (baseline)[a] | – | 20 | 97 | 292 | 651 | 1199 | 1930 | 3050 | 4365 | 5343 | 6156 |
| COCP users | – | 23 | 119 | 336 | 731 | 1265 | 1948 | 2903 | 4003 | 4955 | 5774 |
| **Total difference[a]** | **–** | **3** | **22** | **46** | **80** | **66** | **18** | **-147** | **-362** | **-388** | **-382** |

<50 increased number of cases per 10 000 women
≥50 increased number of cases per 10 000 women
<50 decreased number of cases per 10 000 women
≥50 decreased number of cases per 10 000 women

**Figure 1.** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 women (general population, *BRCA1* and *BRCA2* mutation carriers, attributable to 10 years of continuous COCP use starting at age 20 years with no uptake of prophylactic surgeries (scenario B). The numbers in the chart do not always add up because of rounding. COCP = combined-type oral contraceptive preparations. [a]These are the values displayed in Figures 3 (*BRCA1*) and 4 (*BRCA2*).

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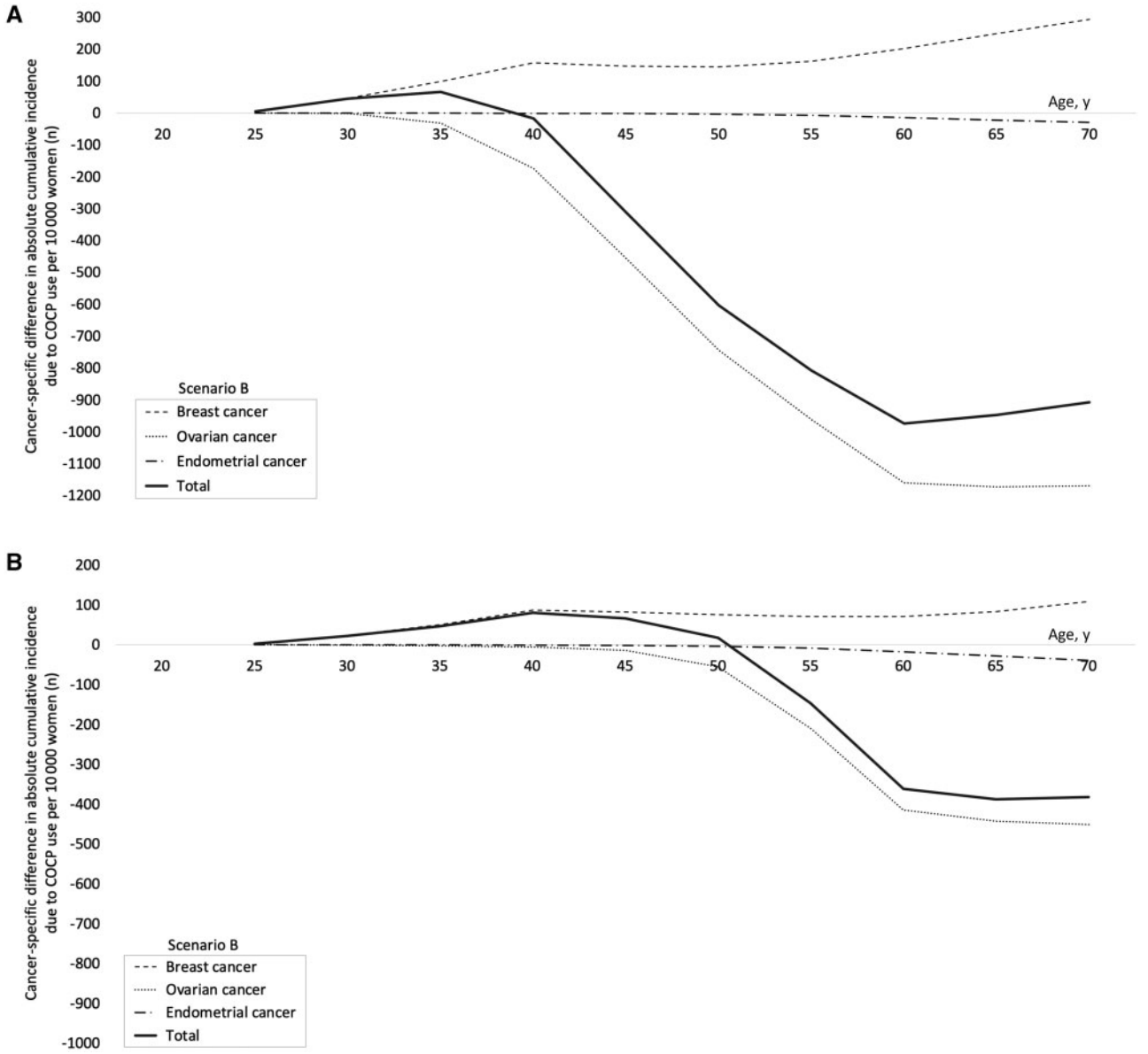


**Figure 2.** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 *BRCA1* **(A)** or *BRCA2* **(B)** mutation carrier, attributable to 10-year continuous COCP use and no prophylactic surgeries and stratified by type of cancer. COCP = combined-type oral contraceptive preparations; RRM = risk-reducing bilateral mastectomy; RRSO = risk-reducing bilateral salpingo-oophorectomy.

following COCP use and the absolute decreased long-term incidences were larger. In all scenarios, prophylactic surgeries reduced the long-term benefit of COCP use.

The breast cancer risk difference attributable to COCP use increased throughout life, even many years after stopping COCP use (eg, *BRCA1*: from 202 cases by age 60 years to 293 cases by age 70 years; Figure 1). This increase was caused by the extra person-years for COCP users because of the COCP-associated protection against ovarian cancer (age-group 65-70 years: hypothetical cohort at risk for breast cancer in the nonuser group 2969 women vs 3397 women in the COCP-user group; scenario B; data not shown).

## Sensitivity Analyses

With regard to hormone therapy (HT) after RRSO, 10 years of HT use (age 40-51 years; E + P, E-only, or tibolone) not only counteracted the long-term benefit of 10-year COCP use but also substantially increased the absolute long-term COCP-associated cancer incidence compared with no COCP and no HT use (Table 2; sensitivity analysis 1). Among 10 000 women, 10-year COCP use followed by RRSO resulted in 324 (*BRCA1*) and 73 (*BRCA2*) fewer cases diagnosed throughout life (scenario G; expected without COCP use: *BRCA1* = 6762, *BRCA2* = 3408). However, if COCP use was followed by RRSO and 10-year E + P HT use, then 1586 (*BRCA1*) and 970 (*BRCA2*) additional COCP-associated cancer cases occurred throughout life. If RRSO was followed by 10-year E-only (+hysterectomy) HT use, 853 (*BRCA1*) and 533 (*BRCA2*) additional COCP-associated cancer cases occurred; after 10-year tibolone use, 1010 (*BRCA1*) and 614 (*BRCA2*) additional COCP-associated cancer cases occurred. With 5-year HT use, the long-term absolute increased risk was smaller but still cancelled out the benefit of 10-year COCP use.

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**A**

| *BRCA1* mutation carriers at risk (n = 10 000) | Attained age, y | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| **Scenario B (Duration: 10 years, Start age: 20 years, RRM: No, RRSO: No)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 6 | 46 | 99 | 157 | 147 | 144 | 162 | 202 | 249 | 293 |
| Ovarian cancer | – | 0 | -1 | -32 | -174 | -457 | -744 | -962 | -1160 | -1173 | -1170 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -15 | -23 | -30 |
| **Total[a]** | – | 5 | 45 | 66 | -17 | -312 | -603 | -807 | -974 | -947 | -907 |
| **Scenario G (Duration: 10 years, Start age: 20 years, RRM: No, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 6 | 46 | 99 | 157 | 147 | 139 | 137 | 140 | 147 | 154 |
| Ovarian cancer | – | 0 | -1 | -32 | -174 | -231 | -293 | -347 | -403 | -424 | -441 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -17 | -26 | -37 |
| **Total[a]** | – | 5 | 45 | 66 | -17 | -86 | -157 | -218 | -280 | -303 | -324 |
| **Scenario L (Duration: 10 years, Start age: 20 years, RRM: age 40 years, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 6 | 46 | 99 | 157 | 127 | 156 | 156 | 156 | 157 | 157 |
| Ovarian cancer | – | 0 | -1 | -32 | -174 | -231 | -293 | -348 | -407 | -429 | -449 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -17 | -28 | -40 |
| **Total[a]** | – | 5 | 45 | 66 | -17 | -75 | -140 | -200 | -267 | -300 | -332 |
| **Scenario P (Duration: 10 years, Start age: 20 years, RRM: age 30 years, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 6 | 46 | 49 | 52 | 52 | 52 | 53 | 54 | 55 | 56 |
| Ovarian cancer | – | 0 | -1 | -32 | -174 | -231 | -295 | -351 | -412 | -434 | -455 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -18 | -28 | -41 |
| **Total[a]** | – | 5 | 45 | 17 | -123 | -181 | -246 | -307 | -376 | -408 | -440 |

<50 increased number of cases per 10 000 women
≥50 increased number of cases per 10 000 women
<50 decreased number of cases per 10 000 women
≥50 decreased number of cases per 10 000 women

**Figure 3.** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer attributable to COCP use per 10 000 *BRCA1* mutation carriers. **A)** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 *BRCA1* mutation carriers, attributable to 10 years COCP use at age 20 years, varying uptake of prophylactic surgeries. **B)** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 *BRCA1* mutation carriers, attributable to COCP use, varying both use of COCP and uptake of prophylactic surgeries. The numbers in the chart do not always add up because of rounding. COCP = combined-type oral contraceptive preparations; RRM = risk-reducing bilateral mastectomy; RRSO = risk-reducing bilateral salpingo-oophorectomy. [a]These are the values displayed in Figure 3, B.

Breast tumors of *BRCA1* mutation carriers are often TNBC (25). Using TNBC-specific relative risk estimates for 10-year COCP use by 10 000 *BRCA1* mutation carriers, we found an early increase of cumulative incidence of 196 cases by age 40 years (1454 expected), and we estimated 821 fewer cases by age 70 years (9093 expected) (see Table 2; scenarios B and G, sensitivity analysis 2).

Absolute COCP-associated cumulative mortality from breast, ovarian, and endometrial cancer showed similar patterns as the COCP-associated cumulative incidence of these tumor types (Table 2; sensitivity analysis 3). However, both risks and benefits following COCP use were delayed by 10 years and of smaller magnitude (Table 2; sensitivity analysis 3). Following 10 years of COCP use, the maximum number of additional deaths was 4 (*BRCA1*; expected 21) and 6 (*BRCA2*; expected 40). In the long term, the number of deaths was decreased by 681 (*BRCA1*; no prophylactic surgery), 203 (*BRCA1*; RRSO at age 40 years), 277 (*BRCA2*; no prophylactic surgery), and 42 (*BRCA2*; RRSO at age 40 years).

The results of the remaining sensitivity analyses were virtually similar to the results of the main analyses (Table 2; sensitivity analyses 4-7).

## Discussion

Our life table model, applied on a hypothetical cohort of 10 000 *BRCA1* and *BRCA2* mutation carriers, showed that COCP use initially increased breast cancer risk and decreased ovarian and endometrial cancer risk long-term. For breast, ovarian, and endometrial cancer combined, a substantial long-term decrease of the absolute cumulative incidence was estimated for COCP users compared with women who never used COCP. However, at young ages, an increase of the absolute cumulative incidence of the COCP-associated cancers was observed, which was attributable to an early increase of COCP-associated breast cancer risk. For *BRCA1* mutation carriers, by age 35 years we estimated a maximum increase of 1 extra COCP-associated cancer case per 152 women who used COCP between ages 20 and 30 years. For *BRCA2* mutation carriers, COCP use caused a greater short-term increased incidence (1 extra cancer case per 125 women by age 40 years for COCP use at 20-30 years), COCP use became protective at a later age and was less beneficial throughout life than for *BRCA1* mutation carriers. For both *BRCA1* and *BRCA2* mutation carriers, durations of COCP use longer than 10 years and COCP use at ages older than age 30 years resulted in larger

ARTICLE

**B**

***BRCA1* mutation carriers at risk (n = 10 000)**

| Parameters in calculation | | | | | Attained age, y | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario | Duration of COCP use, y | Age at first COCP use, y | Age at RRM, y | Age at RRSO, y | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | No | No | 1 | 34 | 187 | 625 | 1454 | 2835 | 4382 | 5904 | 7234 | 8305 | 9093 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| A. | 5 | 20 | No | No | – | 5 | 25 | 43 | -50 | -273 | -447 | -601 | -630 | -643 | -640 |
| B. | 10 | 20 | No | No | – | 5 | 45 | 66 | -17 | -312 | -603 | -807 | -974 | -947 | -907 |
| C. | 5+5 | 20 | No | No | – | 5 | 25 | 43 | 55 | -208 | -496 | -786 | -1027 | -1156 | -1231 |
| D. | 10 | 15 | No | No | 0 | 8 | 28 | 39 | -80 | -367 | -588 | -786 | -793 | -783 | -764 |
| E. | 15 | 15 | No | No | 0 | 8 | 48 | 69 | -15 | -309 | -597 | -799 | -967 | -40 | -902 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | No | 40 | 1 | 34 | 187 | 625 | 1454 | 2365 | 3436 | 4513 | 5455 | 6199 | 6762 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| F. | 5 | 20 | No | 40 | – | 5 | 25 | 43 | -50 | -98 | -139 | -181 | -201 | -222 | -241 |
| G. | 10 | 20 | No | 40 | – | 5 | 45 | 66 | -17 | -86 | -157 | -218 | -280 | -303 | -324 |
| H. | 5+5 | 20 | No | 40 | – | 5 | 25 | 43 | 55 | 75 | 67 | -41 | -144 | -226 | -295 |
| I. | 10 | 15 | No | 40 | 0 | 8 | 28 | 39 | -80 | -140 | -191 | -243 | -261 | -282 | -302 |
| J. | 15 | 15 | No | 40 | 0 | 8 | 48 | 69 | -15 | -83 | -154 | -215 | -277 | -300 | -322 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | 40 | 40 | 1 | 34 | 187 | 625 | 1454 | 1612 | 1797 | 2007 | 2233 | 2468 | 2688 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| K. | 5 | 20 | 40 | 40 | – | 5 | 25 | 43 | -50 | -95 | -135 | -181 | -208 | -238 | -267 |
| L. | 10 | 20 | 40 | 40 | – | 5 | 45 | 66 | -17 | -75 | -140 | -200 | -267 | -300 | -332 |
| M. | 5+5 | 20 | 40 | 40 | – | 5 | 25 | 43 | 55 | -12 | -88 | -163 | -245 | -319 | -390 |
| N. | 10 | 15 | 40 | 40 | 0 | 8 | 28 | 39 | -80 | -137 | -190 | -249 | -277 | -310 | -342 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | 30 | 40 | 1 | 34 | 187 | 256 | 522 | 685 | 878 | 1099 | 1338 | 1586 | 1818 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| O. | 5 | 20 | 30 | 40 | – | 5 | 25 | 3 | -86 | -130 | -171 | -218 | -246 | -277 | -306 |
| P. | 10 | 20 | 30 | 40 | – | 5 | 45 | 17 | -123 | -181 | -246 | -307 | -376 | -408 | -440 |
| Q. | 5+5 | 20 | 30 | 40 | – | 5 | 25 | 3 | -131 | -198 | -273 | -349 | -432 | -507 | -580 |
| R. | 10 | 15 | 30 | 40 | 0 | 8 | 28 | 0 | -115 | -173 | -226 | -287 | -316 | -349 | -383 |

<50 increased number of cases per 10 000 women
≥50 increased number of cases per 10 000 women
<50 decreased number of cases per 10 000 women
≥50 decreased number of cases per 10 000 women

**Figure 3.** Continued

short-term increases and long-term decreases of the cumulative cancer incidence. As expected, RRSO, which is associated with a substantial reduction of ovarian cancer risk, markedly reduced the long-term benefit of COCP use. If, in practice, HT use followed RRSO, the joint COCP and HT effect considerably increased cancer risk throughout life.

To our knowledge, this is the first modeling study in *BRCA1* and *BRCA2* mutation carriers weighing the absolute increase and decrease of the cumulative breast, ovarian, and endometrial cancer risk associated with use of COCP, using various realistic scenarios. Scenarios differed with respect to timing and duration of COCP use and uptake of prophylactic surgeries (RRSO, RRM, or both). We aimed to present the results of the model including the most likely parameters and assumptions. The uncertainties were evaluated with various sensitivity analyses. The assumption that the relative risks of breast, ovarian, and endometrial cancer associated with COCP use represent causal relationships could not be evaluated in this modeling study.

The existing literature does not show clear evidence that relative risks of breast, ovarian, and endometrial cancer associated with COCP use differ for *BRCA1* and *BRCA2* mutation carriers and women in the general population (10,11,28). Therefore, in our *BRCA* models, we used relative risks reported for the general population. As *BRCA1* mutation carriers often develop TNBC (25), we conducted sensitivity analysis 1 using the TNBC-

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**A**

| *BRCA2* mutation carriers at risk (n = 10 000) | Attained age, y | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| **Scenario B (Duration: 10 years, Start age: 20 years, RRM: No, RRSO: No)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 3 | 23 | 50 | 87 | 82 | 76 | 71 | 71 | 83 | 108 |
| Ovarian cancer | – | 0 | -1 | -3 | -6 | -14 | -55 | -210 | -415 | -443 | -451 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -18 | -28 | -39 |
| **Total[a]** | – | 3 | 22 | 46 | 80 | 66 | 18 | -147 | -362 | -388 | -382 |
| **Scenario G (Duration: 10 years, Start age: 20 years, RRM: No, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 3 | 23 | 50 | 87 | 84 | 81 | 78 | 75 | 73 | 72 |
| Ovarian cancer | – | 0 | -1 | -3 | -6 | -8 | -16 | -47 | -92 | -100 | -103 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -18 | -29 | -42 |
| **Totala** | – | 3 | 22 | 46 | 80 | 75 | 62 | 22 | -35 | -56 | -73 |
| **Scenario L (Duration: 10 years, Start age: 20 years, RRM: age 40 years, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 3 | 23 | 50 | 87 | 86 | 86 | 86 | 85 | 85 | 85 |
| Ovarian cancer | – | 0 | -1 | -3 | -6 | -8 | -16 | -48 | -93 | -101 | -104 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -8 | -18 | -29 | -43 |
| **Total[a]** | – | 3 | 22 | 46 | 80 | 77 | 67 | 30 | -25 | -45 | -61 |
| **Scenario P (Duration: 10 years, Start age: 20 years, RRM: age 30 years, RRSO: age 40 years)** | | | | | | | | | | | |
| **Difference in absolute cumulative incidence** | | | | | | | | | | | |
| Breast cancer | – | 3 | 23 | 25 | 27 | 27 | 27 | 26 | 26 | 26 | 27 |
| Ovarian cancer | – | 0 | -1 | -3 | -6 | -8 | -16 | -48 | -94 | -102 | -105 |
| Endometrial cancer | – | 0 | 0 | 0 | -1 | -2 | -4 | -9 | -18 | -30 | -44 |
| **Total[a]** | – | 3 | 22 | 21 | 20 | 17 | 7 | -30 | -86 | -106 | -122 |

<50 increased number of cases per 10 000 women
≥50 increased number of cases per 10 000 women
<50 decreased number of cases per 10 000 women
≥50 decreased number of cases per 10 000 women

**Figure 4.** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer attributable to COCP use per 10 000 *BRCA2* mutation carriers. **A)** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 *BRCA2* mutation carriers, attributable to 10 years of COCP use at age 20 years, varying uptake of prophylactic surgeries. **B)** Increased or decreased absolute cumulative incidence of breast, ovarian, and endometrial cancer per 10 000 *BRCA2* mutation carriers, attributable to COCP use, varying both use of COCP and uptake of prophylactic surgeries. The numbers in the chart do not always add up because of rounding. COCP = combined-type oral contraceptive preparations; RRM = risk-reducing bilateral mastectomy; RRSO = risk-reducing bilateral salpingo-oophorectomy. [a]These are the values displayed in Figure 4, B.

specific relative risks of greater magnitude. Results showed that 1 extra cancer case per 51 *BRCA1* mutation carriers, which uses COCP between ages 20 and 30 years, would occur by age 40 years. Thus, the estimated 1 extra cancer per 152 women, according to our standard approach, may represent an underestimation. Clearly, more prospective research on COCP-associated risk of breast cancer subtypes is needed, especially in young mutation carriers during ages when COCP is used.

To evaluate the uncertainty of the relative risks, we repeated the calculations using the lower and upper limits of the 95% confidence interval of the relative risk estimates of COCP use and the risks of breast, ovarian, and endometrial cancer, respectively. From the 36 combinations possible, we took the most unfavorable one (the largest risk-increasing effect and the smallest risk-decreasing effects) and the most favorable one (the smallest risk-increasing effect with the largest risk-decreasing effects). Our standard approach showed an increased cumulative risk of the COCP-associated cancers of 66 additional cases at age 35 years for scenarios B and G (*BRCA1*). The most favorable and most unfavorable combinations of relative risk estimates result in a range of 19 fewer to 138 additional cases at age 35 years. For *BRCA2* mutation carriers, the increased cumulative risk of the COCP-associated cancers was 80 additional cases at age 40 years according to our standard approach, with a range of 6-124 at age 40 years using the most favorable and most unfavorable combinations of relative risk estimates. However, this range should not be interpreted as a 95% confidence interval.

In our life table method, we used Dutch general population reference rates for endometrial cancer, because there is no clear evidence of an increased risk in mutation carriers (8,9). The background risk of endometrial cancer in Europe (cumulative incidence by age 75 years: Netherlands = 1.6%, United Kingdom = 1.8%, France = 1.4%) and Australia (cumulative risk = 1.5%) (29) is lower than in the United States (cumulative risk = 2.4%), most probably because of a higher body mass index in the United States (30) [mean: Netherlands = 25.1 kg/m$^2$, United States = 28.7 kg/m$^2$ ; 2011-2015 (31)]. Therefore, in our absolute risk calculation, the contribution of endometrial cancer decreases because COCP use was minimal and will be somewhat larger in the United States.

For the general population, several studies examined the absolute risk-benefit of COCP comparing the attributable risk of COCP use on lifetime cancer risk in Western countries (32-38). Studies that evaluated the risk-benefit throughout life

**B**

***BRCA2* mutation carriers at risk (n = 10 000)**

| Parameters in calculation | | | | | Attained age, y | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario | Duration of COCP use, y | Age at first COCP use, y | Age at RRM, y | Age at RRSO, y | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | No | No | 1 | 20 | 97 | 292 | 651 | 1199 | 1930 | 3050 | 4365 | 5343 | 6156 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| A. | 5 | 20 | No | No | – | 3 | 12 | 32 | 28 | 20 | -10 | -135 | -220 | -248 | -247 |
| B. | 10 | 20 | No | No | – | 3 | 22 | 46 | 80 | 66 | 18 | -147 | -362 | -388 | -382 |
| C. | 5+5 | 20 | No | No | – | 3 | 12 | 32 | 122 | 178 | 180 | -38 | -316 | -409 | -429 |
| D. | 10 | 15 | No | No | 0 | 4 | 14 | 33 | 29 | 18 | -19 | -182 | -268 | -297 | -297 |
| E. | 15 | 15 | No | No | 0 | 4 | 23 | 48 | 81 | 68 | 19 | -147 | -365 | -391 | -385 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | No | 40 | 1 | 20 | 97 | 292 | 651 | 921 | 1273 | 1749 | 2318 | 2855 | 3408 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| F. | 5 | 20 | No | 40 | – | 3 | 12 | 32 | 28 | 26 | 18 | -12 | -36 | -51 | -61 |
| G. | 10 | 20 | No | 40 | – | 3 | 22 | 46 | 80 | 75 | 62 | 22 | -35 | -56 | -73 |
| H. | 5+5 | 20 | No | 40 | – | 3 | 12 | 32 | 122 | 152 | 170 | 116 | 43 | 2 | -26 |
| I. | 10 | 15 | No | 40 | 0 | 4 | 14 | 33 | 29 | 25 | 16 | -22 | -49 | -68 | -83 |
| J. | 15 | 15 | No | 40 | 0 | 4 | 23 | 48 | 81 | 76 | 63 | 23 | -34 | -56 | -72 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | 40 | 40 | 1 | 20 | 97 | 292 | 651 | 682 | 736 | 866 | 1046 | 1177 | 1287 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| K. | 5 | 20 | 40 | 40 | – | 3 | 12 | 32 | 28 | 26 | 20 | -9 | -33 | -48 | -59 |
| L. | 10 | 20 | 40 | 40 | – | 3 | 22 | 46 | 80 | 77 | 67 | 30 | -25 | -45 | -61 |
| M. | 5+5 | 20 | 40 | 40 | – | 3 | 12 | 32 | 122 | 123 | 113 | 67 | 1 | -33 | -57 |
| N. | 10 | 15 | 40 | 40 | 0 | 4 | 14 | 33 | 29 | 26 | 17 | -19 | -46 | -65 | -81 |
| | | | | | **Baseline absolute cumulative incidence** | | | | | | | | | | |
| - | 0 | NA | 30 | 40 | 1 | 20 | 97 | 109 | 133 | 165 | 222 | 355 | 540 | 676 | 791 |
| | | | | | **Difference in absolute cumulative incidence** | | | | | | | | | | |
| O. | 5 | 20 | 30 | 40 | – | 3 | 12 | 12 | 10 | 8 | 1 | -28 | -52 | -67 | -78 |
| P. | 10 | 20 | 30 | 40 | – | 3 | 22 | 21 | 20 | 17 | 7 | -30 | -86 | -106 | -122 |
| Q. | 5+5 | 20 | 30 | 40 | – | 3 | 12 | 12 | 13 | 14 | 5 | -41 | -107 | -141 | -164 |
| R. | 10 | 15 | 30 | 40 | 0 | 4 | 14 | 13 | 10 | 8 | -1 | -38 | -65 | -85 | -101 |

<50 increased number of cases per 10 000 women
≥50 increased number of cases per 10 000 women
<50 decreased number of cases per 10 000 women
≥50 decreased number of cases per 10 000 women

**Figure 4.** Continued

concluded that before age 35-40 years the fraction of cancer cases attributable to COCP use was slightly increased, whereas lifetime cancer risk after COCP use was reduced. This pattern was comparable to our results for the general population (Figure 1). The Centers for Disease Control and Prevention (CDC) (34) also estimated the risk-benefit of COCP use for *BRCA1* and 2 mutation carriers. For a mean 5 years of COCP use at age 20-24 years, the CDC found larger long-term benefits (−917 cases [*BRCA1*] and −403 cases [*BRCA2*] per 10 000 women) than estimated in the present study (−640 cases [*BRCA1*] and −247 cases [*BRCA2*]; scenario A). Differences with our results for the mutation carriers may be explained by the fact that the CDC considered fixed effects of COCP use and by the larger contribution of endometrial cancer (see previous paragraph) (34).

The most important indication for COCP use is to prevent unwanted pregnancies. *BRCA1* and 2 mutation carriers and their clinicians have to judge what increased COCP-associated cancer risk is acceptable. In our risk-benefit estimations, the burden from breast, ovarian, and endometrial cancer was equally weighted. However, in terms of the impact on quality of life,

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**Table 2.** Sensitivity analyses: difference in absolute cumulative incidence or mortality of breast, ovarian, and endometrial cancer per 10 000 women with a *BRCA1* or *BRCA2* mutation carriers, according to various scenarios and assumptions

| Parameters in calculation | | | | | Attained age, y | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | Duration of COCP use, y | Age at first COCP use, y | Age at RRM, y | Age at RRSO, y | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| Sensitivity analysis 1: RRSO + menopausal hormone therapy[a] | | | | | | | | | | | | | | |
| *BRCA1* mutation carriers | | | | | | | | | | | | | | |
| Reference group: No COCP use | | | | | | | | | | | | | | |
| Scenario G, no HT use | 10 | 20 | No | 40 | 5 | 45 | 66 | −17 | −86 | −157 | −218 | −280 | −303 | −324 |
| Reference group: COCP use | | | | | | | | | | | | | | |
| Menopausal hormone therapy use: type; duration | | | | | | | | | | | | | | |
| E + P; 5 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 809 | 932 | 1013 | 1005 | 957 | 894 |
| E + P; 10 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 809 | 1830 | 1869 | 1799 | 1699 | 1586 |
| E; 5 y[b] | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 221 | 292 | 327 | 393 | 382 | 346 |
| E; 10 y[b] | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 221 | 644 | 783 | 838 | 862 | 853 |
| T; 5 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 341 | 412 | 457 | 511 | 496 | 456 |
| T; 10 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 341 | 916 | 1025 | 1057 | 1038 | 1010 |
| *BRCA2* mutation carriers | | | | | | | | | | | | | | |
| Reference group: No COCP use | | | | | | | | | | | | | | |
| Scenario G, no menopausal hormone therapy use | 10 | 20 | No | 40 | 3 | 22 | 46 | 80 | 75 | 62 | 22 | −35 | −56 | −73 |
| Reference group: COCP use | | | | | | | | | | | | | | |
| Menopausal hormone therapy use: type; duration | | | | | | | | | | | | | | |
| E + P; 5 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 258 | 322 | 403 | 460 | 497 | 509 |
| E + P; 10 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 258 | 662 | 784 | 872 | 938 | 970 |
| E; 5 y[b] | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 59 | 82 | 109 | 163 | 181 | 168 |
| E; 10 y[b] | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 59 | 204 | 297 | 377 | 461 | 533 |
| T; 5 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 99 | 131 | 170 | 226 | 249 | 241 |
| T; 10 y | 10 | 20 | No | 40 | 0 | 0 | 0 | 0 | 99 | 303 | 398 | 483 | 547 | 614 |
| Sensitivity analysis 2: COCP-associations for triple-negative breast cancer[c] | | | | | | | | | | | | | | |
| *BRCA1*: Difference in absolute cumulative incidence | | | | | | | | | | | | | | |
| Breast cancer | 10 | 20 | No | No | 12 | 86 | 210 | 371 | 341 | 315 | 311 | 332 | 366 | 402 |
| Ovarian cancer | 10 | 20 | No | No | 0 | −1 | −32 | −174 | −458 | −746 | −968 | −1170 | −1189 | −1192 |
| Endometrial cancer | 10 | 20 | No | No | 0 | 0 | 0 | −1 | −2 | −4 | −8 | −16 | −23 | −30 |
| Total | 10 | 20 | No | No | 12 | 84 | 177 | 196 | −119 | −435 | −664 | −854 | −846 | −821 |
| Sensitivity analysis 3: Increased or decreased absolute cumulative mortality of breast, ovarian, and endometrial cancer (scenarios B and G)[d] | | | | | | | | | | | | | | |
| Baseline absolute cumulative mortality | | | | | | | | | | | | | | |
| *BRCA1* | 0 | NA | No | No | 0 | 3 | 21 | 92 | 295 | 725 | 1410 | 2025 | 2786 | 3541 |
| *BRCA1* | 0 | NA | No | 40 | 0 | 3 | 21 | 92 | 295 | 561 | 900 | 1205 | 1626 | 2077 |
| *BRCA2* | 0 | NA | No | No | 0 | 2 | 11 | 40 | 103 | 220 | 430 | 797 | 1375 | 1852 |
| *BRCA2* | 0 | NA | No | 40 | 0 | 2 | 11 | 40 | 103 | 192 | 311 | 447 | 643 | 843 |

(continued)

**Table 2.** (continued)

| Parameters in calculation | | | | | Attained age, y | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | Duration of COCP use, y | Age at first COCP use, y | Age at RRM, y | Age at RRSO, y | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| Difference in absolute cumulative mortality | | | | | | | | | | | | | | |
| BRCA1 | 10 | 20 | No | No | 0 | 0 | 4 | 3 | −37 | −145 | −336 | −483 | −637 | −681 |
| BRCA1 | 10 | 20 | No | 40 | 0 | 0 | 4 | 3 | −37 | −65 | −95 | −133 | −178 | −203 |
| BRCA2 | 10 | 20 | No | No | 0 | 0 | 2 | 6 | 13 | 18 | −1 | −90 | −227 | −277 |
| BRCA2 | 10 | 20 | No | 40 | 0 | 0 | 2 | 6 | 13 | 20 | 21 | 5 | −27 | −42 |
| Sensitivity analysis 4: RRSO + hysterectomy at age 40 y | | | | | | | | | | | | | | |
| BRCA1 | 10 | 20 | No | 40 | 5 | 45 | 66 | −17 | −85 | −154 | −210 | −264 | −278 | −288 |
| BRCA2 | 10 | 20 | No | 40 | 3 | 22 | 46 | 80 | 76 | 65 | 30 | −18 | −28 | −32 |
| Sensitivity analysis 5: No breast cancer risk reduction following RRSO for BRCA2 mutation carriers[e] | | | | | | | | | | | | | | |
| BRCA2 | 10 | 20 | No | 40 | 3 | 22 | 46 | 80 | 73 | 57 | 14 | −45 | −67 | −82 |
| Sensitivity analysis 6: Stronger ovarian cancer risk reduction following RRSO[f] | | | | | | | | | | | | | | |
| BRCA1 | 10 | 20 | No | 40 | 5 | 45 | 66 | −17 | −63 | −110 | −152 | −196 | −217 | −237 |
| BRCA2 | 10 | 20 | No | 40 | 3 | 22 | 46 | 80 | 76 | 66 | 39 | −1 | −20 | −37 |
| Sensitivity analysis 7: BRCA1- and BRCA2-specific breast and ovarian cancer survival[g] | | | | | | | | | | | | | | |
| BRCA1 | 10 | 20 | No | No | 5 | 45 | 66 | −18 | −315 | −616 | −836 | −1023 | −1009 | −980 |
| BRCA2 | 10 | 20 | No | No | 3 | 22 | 46 | 80 | 66 | 17 | −150 | −370 | −401 | −401 |

[a]Relative risks were based on associations reported for the general population. CI = confidence interval; COCP = combined-type oral contraceptive preparations; E = estrogen; P = progesterone; HR = hazard ratio; RR = relative risk; RRM = risk-reducing bilateral mastectomy; RRSO = risk-reducing bilateral salpingo-oophorectomy; T = tibolone.

[b]Hysterectomy at age 40 years. The uptake of a hysterectomy reduced the risk of endometrial cancer by 100%.

[c]20-24 year: RR = 1.37, 25-29 year: RR = 1.49 (Supplementary Table 7, available online).

[d]Mortality is estimated by multiplying the numbers of breast, ovarian, and endometrial cancer cases per 5-year age category by cancer- and survival-time specific rates.

[e]In the default, breast cancer incidence was assumed to be reduced by 50% for *BRCA2* mutation carriers after 5 years following RRSO.

[f]RRSO: ovarian cancer risk: HR = 0.12.

[g]Survival rates of general population are modified for breast cancer (RR = 0.58, 95% CI = 0.41 to 0.82 [*BRCA1/2*]) and for ovarian cancer (RR = 0.78, 95% CI = 0.69 to 0.87 [*BRCA1/2*]).

social impact, and costs to health systems, other options may be preferable. For thrombosis [cumulative incidence 20 per 10 000 per 10-year use (39)], an absolute increased incidence of around 85 per 10 000 during 10-year COCP use containing desogestrel, gestoden, and drospirenon was reason to prioritize a levonorgestrel-containing COCP [increased risk around 40 per 10 000 women during 10-year COCP use (39)]. The increased risk of cancer per 10 000 women (*BRCA1*: 66 cases, age 35 years; TNBC-specific: 196 cases, age 40 years; and *BRCA2*: 80 cases, age 40 years) for 10 years of COCP use (at ages 20-30 years) may or may not be judged differently against the already high background risk for *BRCA* mutation carriers who did not use COCP (cumulative risk of breast, ovarian, and endometrial cancer of 625 at age 35 years, 1454 at age 40 years [*BRCA1*], and 651 at age 40 years [*BRCA2*] per 10 000 women), compared with women in the general population (5 additional cancer cases after COCP use at age 20-30 years, whereas 71 cases were expected for women who never used COCP; Figures 2-4).

To conclude, COCP use by *BRCA1* and *2* mutation carriers appears to reduce the combined breast, ovarian, and endometrial cancer long-term risk. However, this long-term benefit is preceded by an increased cumulative COCP-associated cancer incidence, implying 1 extra COCP-associated cancer diagnosis per 50-150 women for 10 years of COCP use. The temporal increased risk is higher for durations of use longer than 10 years and for use at ages older than 30 years. The long-term benefit is much smaller after RRSO and is canceled out by 5 or more years of HT use following RRSO.

## Funding

This work was supported by Pink-Ribbon/Dutch-Cancer-Society (2014-187.WO76) and Transcan-JT (2012/Cancer-12-054). KAP is an Australian National Health and Medical Research Council Leadership Fellow.

## Notes

**The role of the funders:** The funders had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclosures:** We declare no competing interests.

**Author contributions:** Conceptualization: MAR, FEL, TMM, and AP conceived the study. Formal analysis: MAR, TMM, AP, and LHS. Methodology: All authors. Writing-original draft: LHS and MAR. Writing-review & editing: All authors.

**Acknowledgements:** We acknowledge the work on breast cancer subtypes of Andrea Valles.

**Prior presentations**: BRCA Symposium 2021, Canada (virtual; Proffered paper 2 [S7-PP2]).

## Data Availability

Parameters used for the hypothetical cohort are shared within the supplementary methods (available online). For additional questions, the corresponding author can be contacted.

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