Inherited mutations in BRCA1 and BRCA2 (BRCA1/2) are associated with an increased risk of developing breast and ovarian cancer (1,2). However, there is substantial interindividual variability in both the age at diagnosis and site of cancer occurrence in BRCA1/2 mutation carriers. A number of lines of evidence suggest that additional modifying factors influence cancer penetrance among BRCA1/2 mutation carriers. Cancer occurrences vary even among members of the same family who carry the same BRCA1/2 mutation (3). Begg et al. (4) reported that biases may exist in penetrance estimates (eg, lifetime cancer risk) if relevant covariables are ignored in estimating penetrance and concluded that modifiers are likely to exist that affect BRCA1/2-associated cancer penetrance. These observations suggest that modifiers of cancer risk may exist that could improve risk assessment in this high-risk population.

Specific factors have been reported to be associated with modified cancer risk. Genetic variation at other loci affects breast or ovarian cancer penetrance in women who carry an inherited BRCA1/2 mutation (5–15). Studies of many of these factors have been undertaken using large samples and validated using state-of-the-art genome-wide-association approaches. These loci are very likely to be valid modifiers of cancer risk in BRCA1/2 mutation carriers. A variety of exposures and lifestyle factors have been proposed to modify breast and ovarian cancer risk in BRCA1/2 mutation carriers (16). These modifiers of cancer risk include reproductive history and exposures such as smoking, alcohol consumption, or exogenous hormones. However, many of the studies published to date involve small sample sizes, “convenience” samples of BRCA1/2 mutation carriers, retrospective evaluation of risk factors, and other study design limitations. Many of these reports have not been validated using epidemiologically appropriate independent study samples. Thus, it remains unclear which (if any) of the putative modifiers of risk may truly influence a woman’s breast or ovarian cancer risk if she has inherited a BRCA1/2 mutation.

Given the importance of accurate risk assessment information in this high-risk population, it is critical to understand the role that risk modifiers may contribute to the risk assessment process.
Therefore, we undertook a systematic review of the literature regarding cancer risk modifiers in BRCA1/2 mutation carriers and have performed a meta-analysis of relevant data. Our results should inform the use of risk modifiers in cancer risk counseling, as well as highlight areas of research that are needed to resolve questions about modifiers that have been inadequately studied to date.

Methods

Search Strategy

Our literature search strategy is presented in Figure 1. We conducted a literature search consistent with the Cochrane Collaboration criteria of the PubMed and Web of Science databases for articles published through September 1, 2013. We searched on relevant terms, including BRCA1 and BRCA2, with selected nongenetic exposures, including abortion, age first birth, alcohol, breastfeeding, coffee, diet, fertility, infertility, HRT, hormone replacement therapy, reproductive, mammography, contraceptives, menarche, oophorectomy, parity, smoking, tubal ligation, weight, weight change, BMI, and tamoxifen. Articles included those that examined the risk of breast and ovarian cancer in association with these exposures in women who inherited BRCA1/2 mutations. In addition, we manually reviewed reference and citation lists of all relevant publications found by this search (including review articles) to identify additional articles.

We included only original peer-reviewed research reports that studied women with deleterious (diseased-associated) BRCA1 or BRCA2 mutations and that reported results for BRCA1 and

![Diagram](image-url)

**Figure 1.** Strategy used to identify literature for synopsis and meta-analysis. AFLB = Age at first live birth; HRT = hormone replacement therapy use; QOL = quality of life.
BRCA2 carriers separately; articles that only reported results for
BRCA1/2 carriers combined together were excluded. We excluded
studies that considered women who did not carry a deleterious
BRCA1/2 mutation (in the case or control group) or if the analysis
incorporated untested individuals or tested negative women.

Only studies that evaluated breast or ovarian cancer risk
were included. Studies that reported only on other BRCA1- and
BRCA2-related malignancies (eg, male breast cancer, pancre-
atic cancer, endometrial cancer, and melanoma) were excluded.
In addition, in vivo animal models, simulation studies, articles
reporting mutation prevalence, and studies of attitudes, reac-
tions, screening practices, and other behavioral or psychosocial
outcomes in BRCA1/2 mutation carriers were excluded. Articles
reporting only on the prevalence of cancer in carrier populations
were also excluded. Summaries, comments, reviews and a few
meta-analyses were reviewed but were not included in our sta-
tistical analysis. All potentially eligible articles were reviewed
in detail to confirm that the above-mentioned inclusion/exclusion
criteria were met.

The search generated a list of 2112 articles published between
September 1, 1982, and September 1, 2013. After removing dupli-
cate publications found in the primary search, 1575 unique articles
remained. After applying the exclusion criteria mentioned herein
(Figure 1), an additional 1427 titles were removed from consid-
eration. The remaining 148 articles were reviewed in detail. Upon
further review, 104 additional articles were excluded for the follow-
ing reasons: 28 contained non-BRCA1/2 carrier case patients and/
or control subjects, 20 only reported combined BRCA1/2 results,
22 were not primary analysis (ie, reviews, comments, etc), four
were meta-analyses, five reported on outcomes other than breast or
ovarian cancer, 14 were ineligible because of content area (eg, qual-
ity of life, simulation models), four were limited to a subset of the
applicable population (ie, only Jewish women), and seven did not
evaluate a relevant exposure for our analysis [eg, risk-reducing sur-
gery studies, on which large-scale systematic analyses have already
been reported (17)].

In the closer evaluation of potentially eligible articles, because
large collaborations are needed to study BRCA1/2 carriers, many
of the case–control and cohort studies had overlapping centers.
For example, the study sample of Andrieu et al. (18) in 2006 over-
lapped with the study sample of Antoniou (19) in 2006, and the
samples used in these two articles were included in the later article
of LeCarpentier et al. (20) in 2012. For a particular exposure, it
was noted whether a study sample overlapped or had been updated.
When two articles appeared to report results for risk factors with
overlapping data, only the data representing the most recent pub-
lication date or with the larger sample size (if reported in the same
year) were included in the meta-analysis. Although we made every
attempt to eliminate redundancy in the data represented in our
meta-analysis, we cannot rule out the possibility that a few indi-
nuals participated on more than one study.

After these exclusions were applied, we found a set of 44 articles
that met all of our criteria. These articles formed the basis for our
review and meta-analysis. We graded the risk factors from the 44
articles by using the protocol of Ioannidis et al. (21) to evaluate the
collective data for associations based on the amount of evidence,
replication, and potential for bias.

Evidence Grading Assessment
We applied the approach of Ioannidis et al. (21) to assess the cumula-
tive evidence for associations of variables reported in the 44 publica-
tions identified using the criteria described. This approach considers
three criteria for grading evidence for an association: 1) amount of
evidence, 2) replication, and 3) potential for bias. For each criterion,
we used the guidelines below to assign a grade of A, B, or C.

For amount of evidence, a grade of “A” was given if at least one
study with more than 1000 participants (even if only one study was
conducted) was reported. A grade of “B” was given if the largest
study reported was more than 100 participants but less than 1000.
A grade of “C” was given if a study was conducted with a total sam-
ple size of less than 100.

For replication, an “A” was given if three or more independent
(nonoverlapping) studies were reported and all reported results with
effects in the same direction (eg, direct or inverse association). A “B”
was given if two or three studies were reported and there was evidence
for non-statistically significant heterogeneity across studies. A grade
of “C” was given if only one independent study was reported or more
than one study was reported and these reported inconsistent results.

For protection from bias, a grade of “A” was given if multiple
prospective cohort or nested case–control studies generated from
prospective cohorts were reported. A grade of “B” was given if a
study was reviewed to have no obvious bias in terms of sample
selection or for variables that were unlikely to suffer from recall
bias even if evaluated in retrospective study. Studies that exhibited
potential for sampling bias (eg, retrospective studies, hospital-
based studies, low response rate), particularly those that reported
variables associated with potential recall bias, or studies for which
bias could not be adequately evaluated were given a grade of “C”.

Using these criteria, the authors created the following categories:

1. Insufficient evidence: Concluded if only one independent
   study of less than 1000 individuals was done and no meta-
   analysis could be performed. In addition, insufficient evidence
   was concluded if a grade of “C” was given for one or more of
   the three grading criteria.

2. Possible association: Concluded if our results produced a
   meta-estimate with borderline statistically significant results
   or if no true meta-analysis was possible because only a case–
   control and a cohort study were available and no formal meta-
   analysis of these two different designs was undertaken but two
   or more studies reported consistent results.

3. Probable null association: Concluded if our results produced
   a meta-analysis with null results, and each of the grading com-
   ponents could be made with grades of “A” or “B,” or if no true
   meta-analysis was possible because only a case–control and a
   cohort study were available and no formal meta-analysis of
   these two different designs was undertaken but two or more
   studies reported consistent null results.

4. Probable association: Concluded if our results produced a
   meta-estimate with statistically significant results, and the
   grading of the evidence had values of “A” or “B” for all criteria.

Statistical Analysis
Data were obtained from estimates as published in the original ar-
ticles. We undertook a fixed-effects meta-analysis using the hazard
ratios (HRs) and/or odds ratios (ORs) to estimate the pooled effect estimates and 95% confidence intervals (CIs). Hazard ratio and odds ratio estimates were meta-analyzed separately.

We identified variables that were presented in these articles for consideration in meta-analyses. In some categories, some adjustments were made to have comparable subgroups for a meta-analysis; for example ever vs never oral contraceptive use was not reported in one study (22), but it did report more than 1 year of use vs never use. Thus, coding inconsistencies limited the ability to combine study results. However, we used approximate overlapping groups such as more than 1 year of use vs never use into meta-analyses that considered ever/never analysis (see Supplementary Tables, available online, for detailed descriptions of these categories).

Figure 1 presents the variables that were considered for meta-analysis. We carried out separate meta-analyses in BRCA1 mutation carriers and BRCA2 mutation carriers for breast or ovarian cancer. All meta-analysis estimates are reported as effect size (ES) to represent the common metric of effect, whether they were based on odds or hazard ratios. A $\chi^2$ test of homogeneity among the individual risk ratio estimates of the identified studies was also performed. All analyses were conducted using STATA/MP version 12.1 (STATACorp, College Station, TX). $P$ values are based on two-sided hypothesis tests. A $P$ value of less than .05 was considered statistically significant.

## Results

The studies that formed the basis for this meta-analysis included case–control studies and prospective and retrospective cohort studies (Supplementary Table 1, available online). We have summarized the individual articles (where only a single eligible study was available) as well as the results of meta-analyses (when two or more eligible studies could be meta-analyzed). Figures 2 to 5 display the factors that may reduce or increase breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. Many of the factors studied showed a null effect. Any meta-estimate that was calculated in this article is presented in these figures, and in the situation where there was not more than one independent study and therefore a meta-analysis could not be performed, we reported the study estimate (either hazard or odds ratio) from the latest published study or that with the largest sample size for that particular risk factor. In addition, the Supplementary Tables (available online) report the complete list of studies and their main estimates.

Grading of evidence for association is presented in Table 1. These results clearly indicate the need for additional high quality studies of risk modifiers in BRCA1/2 mutation carriers. Only age at first live birth (AFLB) met the criteria for probable association. Although a number of factors met the criteria for possible associations (eg, breastfeeding, late age at menarche, oral contraceptive), many modifier risk factors had insufficient evidence for making inferences (eg, abortion, medical radiation) or no existing study met the inclusion criteria for analysis here (eg, obesity, exercise).

### BRCA1 and Breast Cancer

#### Reproductive Factors

The following reproductive factors were considered in relation to BRCA1 and breast cancer: AFLB, breastfeeding, age at menarche, and parity.

**Age at first live birth.** Four eligible articles (18–20,23), all cohort studies, examined the relationship between AFLB and breast cancer in BRCA1 mutation carriers. Comparing AFLB of 30 years or older vs less than 20 years, two studies (18,19) noted a decreased risk among parous BRCA1 women aged greater than 40 years vs nulliparous women (HR = 0.34; 95% CI = 0.16 to 0.70) but did not find a statistically significant result for women aged 30 years or older vs those younger than 20 years. Two cohort studies (18,20) both reported protection with later AFLB, particularly for women aged 30 years or older vs those aged 20 to 24 years (23), but results were not statistically significant in either study. In two of the cohorts (18,19), the samples overlapped and were later used in an analysis; therefore, only results from two cohorts (20,23) were used for a meta-analysis, which resulted in a statistically significantly reduced ES when comparing parity at age 30 years or older with parity at a younger age (<20 or 20–24 years) and parity at age 25 to 29 years with parity at a younger age (ES = 0.65, 95% CI = 0.42 to 0.99; ES = 0.69, 95% CI = 0.48 to 0.99, respectively).

**Breastfeeding.** Six eligible studies, four case–control studies and two cohort studies, examined breastfeeding (18,20,24–27). The samples of these studies overlap, so no meta-analyses could be performed. One study (26) reported a risk reduction with ever vs never having breastfed (OR = 0.76; 95% CI = 0.61 to 0.95), and all four case–control articles showed 32% to 50% decrease in risk if breastfeeding was greater than 1 year vs never.

**Age at menarche.** Four eligible articles examined age at menarche (25,27–29), but studies overlapped, and ages at menarche were not coded consistently across studies. Thus, we were not able to perform a meta-analysis, but both of the nonoverlapping articles each reported a reduced risk for later ages at menarche.

**Parity.** Seven articles reported on parity (18–20,23,27,30,31). Many of these articles overlapped substantially in terms of their study samples, and many reported inconsistent results. After removing studies with overlapping data, two cohort studies (20,23) were included in a meta-analysis of parous vs nulliparous women. The analysis revealed a null association (ES = 0.79; 95% CI = 0.59 to 1.06). Parity was also broken down into five subgroups: nulliparous, one live birth, two live births, three live births, and four or more live births. A meta-analysis of the cohort studies revealed a statistically significant reduction in risk for more than three live births vs nulliparity and for four or more live births vs nulliparity, and each additional birth revealed a risk reduction as well. (ES = 0.57, 95% CI = 0.39 to 0.85; ES = 0.56, 95% CI = 0.36 to 0.86; ES = 0.83, 95% CI = 0.75 to 0.92, respectively).

**Exposures.** The following exposures were considered in relation to BRCA1 and breast cancer: alcohol consumption, coffee/caffeine intake, mammography, radiation exposure, chest x-rays, oral contraceptive use, smoking, tamoxifen, and other exposures and factors.

**Alcohol consumption.** Three eligible articles studied alcohol consumption and breast cancer (32–34). The meta-estimate for the two nonoverlapping case–control studies showed a statistically significant reduction in risk for current alcohol consumption (ES = 0.84; 95% CI = 0.73 to 0.97). Alcohol consumption was also
Figure 2. Results of meta-analyses for specific risk factors: BRCA1 and breast cancer, estimates from eligible studies. A) By hazard ratio. B) By odds ratio. Black diamonds represent the effect sizes; horizontal lines are the 95% confidence intervals. *Loss of 10 lbs vs loss of less than 10 lbs to gain of 10 or less pounds; other findings were null. CBC = contralateral breast cancer; CI = confidence interval; ES = effect size; HRT = hormone replacement therapy. Vertical line represents the null hypothesis of no association.
broken down into three subgroups: low, medium, and high alcohol intake. Two case–control studies (32,34) both reported high alcohol intake vs none, and the meta-analysis suggested no statistically significant association (ES = 0.76; 95% CI = 0.55 to 1.04).

**Coffee/caffeine intake.** Coffee/caffeine intake was examined by three articles (25,35,36). Because of overlapping study samples, no meta-analysis could be performed. Of the three studies, only one article (36) reported a statistically significant risk

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**Figure 3.** Results of meta-analyses for specific risk factors: BRCA1 and ovarian cancer, estimates from eligible studies. A) By hazard ratio. B) By odds ratio. **Black diamonds** represent the effect sizes; **lines** are the 95% confidence intervals. **BC** = breast cancer; **CI** = confidence interval; **ES** = effect size; **HRT** = hormone replacement therapy.

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**Table A**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Category</th>
<th>Meta–analysis (META) or Single report (SR)</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives &gt;5 years vs never</td>
<td>SR</td>
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<tr>
<td>Tubal ligation</td>
<td>Ever vs never</td>
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<td>0.42 (0.22 to 0.80)</td>
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<td>Parity ≥4 vs nulliparous</td>
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<td>0.42 (0.20 to 0.88)</td>
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<tr>
<td>Oral contraceptives &gt;1–3 years vs never</td>
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<td></td>
<td>0.51 (0.28 to 0.93)</td>
</tr>
<tr>
<td>Breastfeeding ≥1 year vs never</td>
<td>SR</td>
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<td>0.52 (0.26 to 1.04)</td>
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<td>Menarche ≥15 vs ≤11</td>
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<td>0.66 (0.34 to 1.27)</td>
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<td>Breastfeeding ≤1 year vs never</td>
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<td>0.81 (0.52 to 1.26)</td>
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<tr>
<td>Parity 2 vs nulliparous</td>
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<td>0.87 (0.52 to 1.46)</td>
</tr>
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<td>HRT Ever vs never</td>
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<tr>
<td>Parity Parous vs nulliparous</td>
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<td>Breastfeeding Ever vs never</td>
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<tr>
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<td>Parity 3 vs nulliparous</td>
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**Table B**

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<th>Risk factor</th>
<th>Category</th>
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<td>Parity 2 vs nulliparous</td>
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</tr>
<tr>
<td>Parity Parous vs nulliparous</td>
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<td>0.67 (0.46 to 0.96)</td>
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<td>Smoking Ever vs never</td>
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<td>1.30 (0.80 to 2.30)</td>
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</table>
Figure 4. Results of meta-analyses for specific risk factors: BRCA2 and breast cancer, estimates from eligible studies. A) By hazard ratio. B) By odds ratio. Black diamonds represent the effect sizes; lines are the 95% confidence intervals. CBC = contralateral breast cancer; CI = confidence interval; ES = effect size.
A

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<th>Risk factor</th>
<th>Category</th>
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<th>ES (95% CI)</th>
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<td>Tubal ligation</td>
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<td>0.47 (0.18 to 1.21)</td>
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B

<table>
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<th>Risk factor</th>
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<th>Meta-analysis (META) or Single report (SR)</th>
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<td>&gt;5 years vs never</td>
<td>SR</td>
<td>0.37 (0.19 to 0.72)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Ever vs never</td>
<td>SR</td>
<td>0.39 (0.23 to 0.66)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>&gt;1–3 years vs never</td>
<td>SR</td>
<td>0.42 (0.20 to 0.88)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>&gt;1 year vs never</td>
<td>SR</td>
<td>0.56 (0.26 to 1.19)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>&lt;1 year vs never</td>
<td>SR</td>
<td>0.56 (0.28 to 1.10)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>Ever vs never</td>
<td>SR</td>
<td>0.63 (0.34 to 1.15)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Ever vs never</td>
<td>SR</td>
<td>0.72 (0.41 to 1.29)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>≤1 year vs never</td>
<td>SR</td>
<td>0.84 (0.45 to 1.58)</td>
</tr>
<tr>
<td>HRT</td>
<td>Ever vs never</td>
<td>SR</td>
<td>0.89 (0.29 to 2.39)</td>
</tr>
<tr>
<td>Parity</td>
<td>≥4 vs nulliparous</td>
<td>SR</td>
<td>2.32 (0.79 to 6.79)</td>
</tr>
<tr>
<td>Parity</td>
<td>2 vs nulliparous</td>
<td>SR</td>
<td>2.47 (1.02 to 5.97)</td>
</tr>
<tr>
<td>Parity</td>
<td>Parous vs nulliparous</td>
<td>SR</td>
<td>2.74 (1.18 to 6.41)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 vs nulliparous</td>
<td>SR</td>
<td>2.82 (0.97 to 8.17)</td>
</tr>
<tr>
<td>Parity</td>
<td>3 vs nulliparous</td>
<td>SR</td>
<td>3.84 (1.43 to 10.30)</td>
</tr>
</tbody>
</table>

Figure 5. Results of meta-analyses for specific risk factors: BRCA2 and ovarian cancer, estimates from eligible studies. **Black diamonds** represent the effect sizes; **lines** are the 95% confidence intervals. CI = confidence interval; ES = effect size; HRT = hormone replacement therapy.
<table>
<thead>
<tr>
<th>Factor</th>
<th>BRCA1</th>
<th>Ovarian cancer</th>
<th>Grade†</th>
<th>Inference‡</th>
<th>Grade†</th>
<th>Inference‡</th>
<th>Studies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion</td>
<td>ACB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(18,20)</td>
</tr>
<tr>
<td>Later age at first live birth</td>
<td>ABA</td>
<td>PA(−)</td>
<td>ABB</td>
<td>PN</td>
<td>BCB</td>
<td>IE</td>
<td>(18–20,23)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>ABB</td>
<td>PS(−)</td>
<td>ABB</td>
<td>PS(−)</td>
<td>BCB</td>
<td>IE</td>
<td>(32–34)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>ABB</td>
<td>PN</td>
<td>BCC</td>
<td>IE</td>
<td>BCB</td>
<td>IE</td>
<td>(18,20,24,25–27,62)</td>
</tr>
<tr>
<td>Coffee consumption</td>
<td>BBB</td>
<td>PN</td>
<td>BBB</td>
<td>PN</td>
<td>BBB</td>
<td>PN</td>
<td>(25,35,36)</td>
</tr>
<tr>
<td>Combined HRT* exposure</td>
<td>BCB</td>
<td>IE</td>
<td>BBB</td>
<td>PN</td>
<td>BBB</td>
<td>PN</td>
<td>(54,57,59)</td>
</tr>
<tr>
<td>Infertility treatment</td>
<td>ACB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(61)</td>
</tr>
<tr>
<td>Mammography</td>
<td>ABB</td>
<td>PN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3738)</td>
</tr>
<tr>
<td>Late age at menopause</td>
<td>ACB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(28)</td>
</tr>
<tr>
<td>Medical radiation</td>
<td>ACB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(39)</td>
</tr>
<tr>
<td>Late age at menarche</td>
<td>ABB</td>
<td>PS(−)</td>
<td>BCC</td>
<td>IE</td>
<td>BBB</td>
<td>PN</td>
<td>(25,27–29)</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>ABA</td>
<td>PS(+)</td>
<td>ABA</td>
<td>PS(−)</td>
<td>BAA</td>
<td>PS(+)</td>
<td>(18,22,35,45,58–60,68,70)</td>
</tr>
<tr>
<td>High parity</td>
<td>ACB</td>
<td>IE</td>
<td>ABB</td>
<td>IE</td>
<td>BBB</td>
<td>PN</td>
<td>(18–20,23,25,27,30,31,59,60)</td>
</tr>
<tr>
<td>Smoking</td>
<td>ACB</td>
<td>IE</td>
<td>BCC</td>
<td>IE</td>
<td>BAB</td>
<td>PS(+)</td>
<td>(25,33,46–50)</td>
</tr>
<tr>
<td>Tamoxifen (contralateral breast cancer)</td>
<td>BBB</td>
<td>PS(−)</td>
<td>BCC</td>
<td>IE</td>
<td>BBB</td>
<td>PS(−)</td>
<td>(51–53,59,63)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>BBB</td>
<td>PS(−)</td>
<td>BCC</td>
<td>IE</td>
<td>BBB</td>
<td>PN</td>
<td>(56,58,60)</td>
</tr>
<tr>
<td>Weight change</td>
<td>BCB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(55)</td>
</tr>
<tr>
<td>X-ray</td>
<td>ACB</td>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(33,40)</td>
</tr>
</tbody>
</table>

* HRT = hormone replacement therapy.
† For grade, first letter is for amount of evidence, second letter is for replication, and third letter is for bias.
‡ IE = insufficient evidence; PA = probable association; PN = probable or possible null association; PS = possible association. For probable and possible associations, (−) indicates a protective effect of the factor on cancer, whereas (+) indicates a risk effect on cancer.
reduction in ever coffee drinkers vs never (OR = 0.61; 95% CI = 0.38 to 0.97).

**Mammography.** Two case–control studies (37,38) examined any mammography exposure. A null result was reported in both studies, and a meta-analysis showed a null result (ES = 1.0; 95% CI = 0.91 to 1.09).

**Radiation exposure.** Only one article that met inclusion criteria (39) reported an increased breast cancer risk after any diagnostic radiation exposure before age 30 years vs none (including but not limited to mammography) in BRCA1 mutation carriers (HR = 2.83; 95% CI = 1.59 to 5.04).

**Chest x-rays.** Two publications using overlapping sample sets (33,40) examined any exposure to chest x-rays vs none, and both showed a statistically significant increased risk of breast cancer for BRCA1 mutation carriers with exposure (OR = 4.12, 95% CI = 1.82 to 9.35; OR = 1.42, 95% CI = 1.00 to 2.00, respectively). In addition, one case–control study (41) reported a null effect of a history of diagnostic chest x-rays (excluding those for tuberculosis and pneumonia and not including mammograms) with breast cancer (OR = 1.16; 95% CI = 0.64 to 2.11).

**Oral contraceptive use.** Seven publications reported on oral contraceptive use (22,25,27,42–45). The meta-analysis of case–control studies suggested a null effect of ever vs never oral contraceptive use (ES = 0.78; 95% CI = 0.59 to 1.04). However, the combined hazard ratios for the cohort studies revealed an increased risk (ES = 1.59; 95% CI = 1.32 to 1.92) for ever users of oral contraceptives. Use of oral contraceptive was also categorized by duration of use: less than 1 year, 1 to 3 years, and more than 3 years. The meta-analysis for these subcategories produced null results.

**Smoking.** Seven original articles (25,33,46–50) investigated smoking. A meta-analysis of the two nonoverlapping case–control studies (49,50) noted a statistically significant increase in risk (ES = 1.15; 95% CI = 1.01 to 1.31); a meta-analysis of the two cohort studies (33,48) resulted in a decreased risk (ES = 0.69; 95% CI = 0.53 to 0.89) for ever smokers. Two subgroups were also examined: those who smoked 4 or more pack-years vs never smokers and those who smoked 20 or more pack years vs never smokers. The results of the meta-analysis of smoking on breast cancer risk in BRCA1 carriers did not reveal any consistent patterns.

**Tamoxifen.** Two eligible articles (51,52) evaluated the effect of tamoxifen on contralateral breast cancer. The two case–control studies reported a decreased risk of contralateral breast cancer with tamoxifen use, but the study samples overlapped. One study (63) presented a cohort study with two different study designs. The first was a cohort using combined retrospective and prospective data; this analysis showed a reduced risk of contralateral breast cancer (HR = 0.38; 95% CI = 0.27 to 0.55). The second design was restricted to only the prospective cohort, where a reduction in contralateral breast cancer was still observed, yet it was not statistically significant. A fourth study (53) showed a null effect of tamoxifen on the incidence of primary breast cancer in a small subset of eight BRCA1 participants (risk ratio = 1.67; 95% CI = 0.32 to 10.70).

**Other exposures and factors.** Other articles represent the only example of an association of a particular risk factor. One article (54) examined hormone replacement therapy. They reported that breast cancer risk of ever use of hormone replacement therapy compared with never use was statistically significantly reduced (OR = 0.58; 95% CI = 0.35 to 0.96). Another case–control study (55) examined the relationship between changes in body weight and breast cancer in mutation carriers; they reported that a loss of at least 10 pounds from age 18 to 30 years was associated with a reduced risk of breast cancer between age 30 and 49 years (OR = 0.47; 95% CI = 0.28 to 0.79). Overall weight gain and weight gain greater than 10 pounds to 20 pounds or less during the same age interval, as well as a gain of more than 20 pounds, were not statistically significant. No association of infertility treatment (54) or natural menopause (28) was found in the literature in BRCA1 mutation carriers. Two overlapping publications reported no relationship of abortion or miscarriage and breast cancer (18,20) in BRCA1 mutation carriers.

**BRCA1 and Ovarian Cancer**

Seven eligible articles examined the relationship between risk factors and ovarian cancer in BRCA1 mutation carriers (23,25,56–60). Reproductive history was the most widely reported area of inquiry.

**Reproductive Factors.** The following reproductive factors were considered in relation to BRCA1 and ovarian cancer: AFLB, breastfeeding, age at menarche and parity.

**Age at first live birth.** Two case–control studies (23,58) examined the relationship of AFLB in cohort studies, and null results were reported in each study. The meta-analysis combining the two case–control samples produced null results for AFLB of 30 years or greater vs younger (ES = 0.99; 95% CI = 0.58 to 1.71) and for AFLB of 25 to 29 years vs younger (ES = 1.00; 95% CI = 0.62 to 1.61).

**Breastfeeding.** Two overlapping case–control samples (25,60) and one cohort study (58) investigated breastfeeding. Only one (25) reported a statistically significant reduction in ovarian cancer risk with ever vs never breastfeeding (OR = 0.74; 95% CI = 0.56 to 0.97) and for more than 1 year of breast feeding vs never (OR = 0.64; 95% CI = 0.47 to 0.91).

**Age at menarche.** Late age at menarche was reported in one study (58) with null results, and a borderline protective effect was reported in yearly increments in a second study (25) (OR = 0.90; 95% CI = 0.80 to 1.00). Because of nonoverlapping categories, no meta-analysis could be performed.

**Parity.** Three studies (23,58,60) reported on parity and two (25,59) reported on trend per birth. Inconsistent results were reported in these studies. We were able to perform a meta-analysis with the two nonoverlapping cohort studies (23,58) for any live birth vs nulliparous (ES = 0.90; 95% CI = 0.55 to 1.45), one live birth (ES = 1.25; 95% CI = 0.71 to 2.21), two live births (ES = 0.87; 95% CI = 0.52 to 1.46), and three live births (ES = 1.07; 95% CI = 0.60 to 1.91). A statistically significant risk reduction was only seen in women with four or more live births (ES = 0.42; 95% CI = 0.20 to 0.88).

**Exposures.** The following exposures were examined in relation to BRCA1 and ovarian cancer.

**Oral contraceptive use.** Five studies examined the relationship between oral contraceptives and ovarian cancer (25,56,58–60). Four of the studies (25,56,58,60) reported a decreased risk of ovarian cancer for BRCA1 mutation carriers with ever vs never use. In addition, four subgroups were formed for duration of use: 1 year vs never, 1 to 3 years, more than 3 years to 5 years, and more than 5 years. No meta-analysis could be performed because
of overlapping samples, but all studies that examined oral contraceptive use for more than 1 year showed a statistically significant decreased risk, ranging from 33% to 80% reduction.

**Other exposures.** Hormone replacement therapy was examined in three studies (57–59) with null effects reported in all three. There were no two independent studies for which to perform a meta-analysis. One article (25) studied coffee intake and smoking with null results in each category; and one study (59) reported a null effect of tamoxifen. Because of the limited data, no meta-analysis was performed for these exposures. Three studies evaluated tubal ligation (56,58,60). Although all three studies reported a reduction in risk in ever having a tubal ligation (OR = 0.39; 95% CI = 0.22 to 0.70; OR = 0.80, 95% CI = 0.59 to 1.08; HR = 0.42, 95% CI = 0.22 to 0.80), because of and different study designs no meta-analysis could be performed.

**BRCA2 and Breast Cancer**

**Reproductive Factors.** The data on modifiers of BRCA2-associated breast or ovarian cancer risk were far more limited. Twelve eligible studies reported on reproductive risk factors and breast cancer risk: seven case–control studies (24,27,29–31,61,62) and five cohort studies (18–20,23,28). In examining reproductive factors, few statistically significant associations were found. Meta-analysis was extremely limited because of overlapping studies and differences in study design.

**Age at first live birth.** Two cohort studies (20,23) reported on similar factors and were available for meta-analyses for AFLB and parity. The meta-analysis results were largely null. Null results were seen for AFLB of 30 years or older vs younger (ES = 0.99; 95% CI = 0.54 to 1.83) and for AFLB of 25 to 29 years vs younger (ES = 1.02; 95% CI = 0.64 to 1.63).

**Parity.** Less than three live births and any live birth vs nulliparous resulted in null meta-estimates, but three live births vs nulliparous showed a statistically significantly reduced risk of breast cancer (ES = 0.52; 95% CI = 0.30 to 0.86). Trend per birth also revealed a reduction in breast cancer risk (ES = 0.82; 95% CI = 0.70 to 0.96).

**Other reproductive factors.** Five eligible studies, three case–control (24,26,27) and two cohort studies (18,20), reported on breastfeeding and its relation to BRCA2 and breast cancer. All five studies reported null results and no meta-analysis was possible due to overlapping study samples. In addition, three studies (27–29) reported on the age at menarche and breast cancer in BRCA2 carriers. The published results were null and the three studies overlapped, therefore no meta-analysis was performed.

**Exposures.** The following exposures were considered in relation to BRCA2 and breast cancer: alcohol consumption, mammography, chest x-rays, oral contraceptives, smoking, tamoxifen, and other exposures and factors.

**Alcohol consumption.** Three studies reported on alcohol use (32–34), all of which reported null results, as did a meta-analysis of current vs never use (ES = 1.05; 95% CI = 0.81 to 1.35) and high vs never use (ES = 0.87; 95% CI = 0.50 to 1.23).

**Mammography.** Two nonoverlapping case–control studies reported on ever vs never mammography exposure (37,38). A meta-analysis showed a borderline reduction in risk (ES = 0.92; 95% CI = 0.84 to 1.00) for ever mammography exposure.

**Chest x-rays.** Two overlapping cohort studies (33,40) each reported a statistically significant increase in breast cancer risk with x-ray exposure (both not including mammograms) [HR = 2.33, 95% CI = 1.1 to 5.0 (40); HR = 5.43, 95% CI = 1.36 to 21.7 (33)]. More recently, one case–control study (56) reported a null effect of chest x-rays (excluding mammograms) with breast cancer (OR = 1.22; 95% CI = 0.62 to 2.42).

**Oral contraceptive use.** Five studies examined oral contraceptives and their effect on breast cancer in BRCA2 carriers: three case–control studies (22,27,43) and two cohort studies (44,45). When analyzing ever vs never use of oral contraceptives, meta-analysis of two of the case–controls studies (22,43) showed a null effect for ever users (ES = 1.04; 95% CI = 0.81 to 1.32), but pooling the two cohort studies (44,45) revealed a statistically significantly increased risk (ES = 1.85; 95% CI = 1.30 to 2.64) for ever users. We were also able to combine the odds ratio estimates from two case–control studies (22,27) to evaluate two subgroups of oral contraceptive use: 1 to 3 years vs never and more than 3 years vs never. Both of these analyses produced null results (ES = 1.15, 95% CI = 0.78 to 1.70; ES = 1.07, 95% CI = 0.78 to 1.37, respectively).

**Smoking.** A pooled estimate of two studies (49,50) showed an increased risk for more than 4 years of smoking vs never (ES = 1.97; 95% CI = 1.43 to 2.72), whereas an ever vs never meta-analysis of smoking produced null results (ES = 0.94; 95% CI = 0.74 to 1.19).

Three additional studies reported null results for smoking, but they were not included in the meta-analysis because of overlap (46,47) and study design incompleteness (33).

**Tamoxifen.** Three studies, two case–control studies and one cohort study, evaluated contralateral breast cancer and tamoxifen (51,52,63). The two case–control studies reported a null effect, and overlap prevented a pooled estimate. One cohort study (63) presented two different analyses. The first analysis combined retrospective and prospective data and showed a reduced risk of contralateral breast cancer in ever vs never tamoxifen use for a first breast cancer (HR = 0.33; 95% CI = 0.22 to 0.50). The second analysis was restricted to only the prospective cohort; a reduction in contralateral breast cancer was still observed, but it was not statistically significant. One large prevention study looking at incidence of breast cancer (53) also showed a null effect of tamoxifen on primary breast cancer for small group BRCA2 carriers (n = 11).

**Other exposures.** Two other exposures, body weight (27,29) and coffee consumption (35), had only one independent report each, both with null effects on breast cancer risk.

**BRCA2 and Ovarian Cancer**

Five eligible articles examined the relationship between risk factors and ovarian cancer in BRCA2 mutation carriers (23,56–58,60,64).

**Reproductive Factors.** Two studies (23,58) reported on the relationship of AFLB and ovarian cancer with null results in each primary analysis as well as in the meta-analysis. For AFLB of 30 years or older vs younger (ES = 0.57; 95% CI = 0.20 to 1.69) and for AFLB of 25 to 29 years vs younger (ES = 0.43; 95% CI = 0.17 to 1.09) null results were observed. For breastfeeding, two studies (58,60) reported no association for ever vs never, 1 year or less vs never, and more than 1 year vs never. A meta-analysis could not be performed because of differing study designs. Age at menarche was reported (58) with null results. Three studies (23,60) reported...
Exposures. Exposures have also been reported for BRCA2 and ovarian cancer in four different studies: three-case–control studies (56,57,60) and one cohort study (58). These studies reported on hormone replacement therapy (57,58), oral contraceptive use (56,58,60), and tubal ligation (56,58,60). A statistically significant reduction in risk, ranging from 58% to 63%, was reported with oral contraceptive use and ovarian cancer in two studies (56,60). However, because of lack of more than one independent study and consistent study design for any of the exposures mentioned, no meta-analysis could be performed.

Discussion

We have summarized the evidence for modifiers of breast and ovarian cancer risk in women who have inherited BRCA1 or BRCA2 mutations. These results suggest that the evidence for risk modifiers in BRCA1/2-associated cancers remains limited, although sufficient evidence is available for some factors to be considered in cancer risk assessment. Among those factors for which meta-analyses could be performed (ie, where multiple independent study samples were available), BRCA1-associated breast cancer was by far the best studied, whereas BRCA2 and BRCA1-associated ovarian cancer require substantially more data before risk modifiers are identified. In BRCA1-associated breast cancer, the only factor that both provided sufficient evidence from the grading analysis and for which a meta-analysis could be derived was protective effect of late age at first birth. Most of the other associations were deficient in one or more ways. As illustrated below, the inability to definitively identify incontrovertible associations points in the direction of research needs in this area.

Limitations in the existing data were observed across many studies. These include small sample sizes and accompanying limited statistical power to detect small effects. This limitation was particularly true for ovarian cancer. The mutation carriers included in this analysis represent carriers of many hundreds of BRCA1 and BRCA2 mutations, and no study has considered the potential role of mutational heterogeneity in risk. Most studies did not account for breast tumor characteristics such as estrogen or progesterone receptor status. The risk factors for tumors of different phenotypes may vary, but this level of information could not be assessed here. As suggested by the grading assessment, study designs were suboptimal in many cases: “convenient” samples of women identified from clinical series or research studies not specifically designed to address these questions were often used. It is also clear that ascertainment of families from clinic-based settings influences the absolute risk of cancer in BRCA1/2 mutation carriers (65). Although baseline risks may vary by study, there is no evidence to date that the relative risks conferred by a risk modifier may differ by ascertainment, but this concern has not been fully addressed in the literature. Limited prospective cohort data (including limited follow-up times in the limited prospective cohorts available) represent a major limitation for many of the risk factors of interest. This is particularly true for variables in which recall bias may be acting. Two results highlight this limitation and argue strongly for large prospective cohort studies to resolve the role of risk modifiers. First, meta-analysis from case-control studies of oral contraceptive use in mutation carriers resulted in no association with breast cancer risk. In contrast, meta-analysis from prospective cohort studies indicated an increase in breast cancer risk among mutation carriers. Thus, different study designs revealed inconsistent results. Moorman et al. (71) in a recent article in Journal of Clinical Oncology also reported on oral contraceptive use having a null effect on breast cancer; however, their review did not distinguish between case-control and cohort studies and combined these two types of studies in their meta-analysis. In our methods, because these are different study designs, we chose not to report on combined meta-analysis. In addition, we excluded studies where there was sample overlap. Second, meta-analysis from case-control studies of ever vs never cigarette smoking in BRCA1 mutation carriers resulted in an increased breast cancer risk for ever smoking. In contrast, meta-analysis from prospective cohort studies indicated that smoking was protective of breast cancer risk among BRCA1 mutation carriers. Given that recall bias and other study design limitations could have influenced these results, case-control study results of some factors remain suspect. A further limitation is that the reported studies did not all use the same adjustments for potential confounder variables. The inconsistent use of adjustment and matching factors further limits the comparability of studies, and may have resulted in varying levels of confounding across studies. Finally, studies have not used common definitions of some variables or used different cut points for the study of continuous variables (eg, duration or dosage). For example, medical radiation exposures include mammography, medical radiation, and x-ray, which potentially overlap. It was not possible from the articles to clearly delineate this or the dose or timing of these exposures. To evaluate this exposure class also required combining various related exposures, which is clearly suboptimal. These limitations limit our ability to make comparison of exposure across studies and to clearly define the actual exposure of interest in some cases.

These study design limitations are not a surprise given the difficulty of obtaining large, well-designed, prospective cohorts of BRCA1/2 carriers on whom exposures were assessed before cancer development. Many women come to attention of these studies at the time of a cancer diagnosis and/or through referral testing clinics. Population-based assessment of BRCA1/2 mutation carriers has been generally unfeasible because of the high cost of genetic testing to date. Similarly, few independent replication sets are available for specific risk factors, and many study samples have been reported multiple times for the same risk factor, often with increasing sample sizes over time (but incorporating the older samples in each report). Given the limited availability of large numbers of prospectively identified BRCA1/2 mutation carriers, it is unlikely that many of these design limitations will be addressed in the near future. Therefore, it is of importance to identify those factors that are most likely to confer relatively large effects on risk, particularly those that are modifiable or over which women may have control.
Despite these limitations, a number of conclusions about risk modifiers can be made from our data. First, oral contraceptives remain an important exposure in BRCA1 mutation carriers. Although we were not able to undertake meta-analyses of the existing data, it is likely that oral contraceptives are associated with ovarian cancer risk reduction (60.66–69). Our analysis was equivocal about the use of oral contraceptives and increased breast cancer risk. Therefore, women and their providers will need to weigh the benefits of oral contraceptives (e.g., reduction in ovarian cancer risk, avoidance of unintended pregnancy, and other benefits) against the potential risks (e.g., blood clots).

Second, reproductive history affects both breast and ovarian cancer in BRCA1 mutation carriers, as well as breast cancer in BRCA2 mutation carriers. The association with parity is apparent across these groups, but additional research is required to fully evaluate the role parity plays in risk modification. The effect of parity may be influenced by a number of other reproductive factors, as well as use of preventive surgery. Two inconsistencies have emerged from our analyses. We reported that older AFLB was associated consistently with decreased breast cancer risk in BRCA1. This is inconsistent with the effect in the general population and can be explained by at least two hypotheses: 1) the effect of AFLB is different in BRCA1 mutation carriers than in the general population, or 2) the use of risk-reducing oophorectomy or bias in ascertainment may have affected these results. Additional research is required to determine whether these or other explanations can be given for this result. In addition, no reproductive factor (or any modifier) was unequivocally associated with risk modification in BRCA2 mutation carriers. Oral contraceptive use came closest to a clear-cut association. The lack of any association is likely to be a reflection of the very limited data in this group of women.

Third, most exposures have yet to be adequately studied as risk modifiers. Even though we report some consistent effects, the potential for bias and other design issues to have influenced these associations is great. For example, we report associations of alcohol consumption as protective of breast cancer in BRCA1 mutation carriers and an increase in breast cancer risk among BRCA2 ever smokers based on the meta-analyses undertaken here. However, the quality of the data, as assessed by our grading evaluation (Table 1), suggests these results may not be ready for translation to a clinical setting. Although knowledge of all variables may lead to improved understanding of cancer etiology, variables that may be of highest priority are those that may be modifiable. These include breast-feeding, oral contraceptive use, tubal ligation, alcohol intake, x-ray or mammography exposures, tamoxifen (and other selective estrogen receptor modulators) exposure, obesity, and physical activity.

Although our analyses did not identify a large number of risk factors of value to the clinical setting, there is evidence that some factors are unlikely to have a large effect on cancer risk in BRCA1/2 mutation carriers. Clear lack of association (including indication of very small effects that are unlikely to have clinical relevance) may help the field to focus on risk factors studies that are most promising in terms of potential clinical utility. Future research may not be needed to further pursue studies of these factors. These factors include those labeled possible protective or risk in Table 1. Although some of these factors are very likely to have minimal effect on risk, the variables reported in the literature may not be the most relevant with respect to risk modification. For example, existing data suggest that ever/never mammography use has no effect on breast cancer risk. However, these data do not address frequency of mammography or use of mammography at an early age (as may be experienced by some BRCA1/2 mutation carriers). Similar arguments may be made about complex exposures such as combined hormone replacement therapy use. Finally, some factors that are reported as probably null association using our objective criteria may still be understudied because of limited sample sizes for some groups. The most obvious example is that of BRCA2 and ovarian cancer, for which very limited data are available to date.

Despite the limitations of the data available to address what factors are associated with cancer risk, many of the associations reported here supported by the available data are largely consistent with the effects that would be predicted in the general population. In some cases, interventions designed to modify these exposures already exist (e.g., weight training, smoking cessation). Do these results provide clinically meaningful information that may help women and their providers to alter their clinical decision-making process and optimize surveillance or prevention? Many factors are associated with small magnitudes of effect (HR/OR >0.5 or <2), and are not easily modifiable. It is possible that many of these will not contribute to the decision-making process. However, many factors confer high relative risks (e.g., OR/HR <0.4 or >3). These include potentially modifiable factors such as body size, use of tamoxifen, use oral contraceptives, smoking, and radiation exposures (Figures 2–5). These modifiable factors with large effect may be the focus of counseling and decision-making for some women. There is a critical need for improved risk assessment for women with BRCA1/2 mutations and a need to reduce risk in this high-risk population. The data presented here may be of value in developing more meaningful risk assessment tools, including statistical models, and approaches for reducing cancer risk in BRCA1/2 mutation carriers.

References


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