Nutritional Factors in Ovarian Cancer Prevention: What Have We Learned in the Past 5 Years?

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Abstract: The recommendation of the American Cancer Society Nutrition and Physical Activity 2001 Guidelines regarding ovarian cancer prevention was that “there are no firmly established nutritional risk factors for ovarian cancer, though vegetable and fruit consumption may lower risk.” Since then, a number of studies have been published including several large cohort studies. The main objective of this review was to evaluate the literature from the past 5 yr and determine whether any more firm recommendations could be made at this point. Searches were conducted from 2000 to July 2006, and relevant citations were reviewed. Although population-based case-control studies have fairly consistently shown an increased risk with increase body mass, cohort data are inconclusive. The role of physical activity is also unclear. The current epidemiologic evidence for dietary factors is generally inconsistent to warrant public health recommendations regarding any of these factors.

Introduction

In the United States, cancer of the ovary is the second most common gynecologic cancer and the leading cause of death from gynecologic malignancies (1). An estimated 20,180 new cases and 15,310 new deaths were expected in the United States in 2006 (1). Early detection of ovarian cancer remains a major challenge because disease symptoms of abdominal discomfort and bloating, vaginal bleeding, gastrointestinal, or urinary tract symptoms are nonspecific, and no reliable screening and diagnostic tests are currently available (1). Only 19% of ovarian malignancies are detected at a localized stage when the disease can be cured successfully with 5-yr survival rate of 94% (1). In contrast, most patients are diagnosed with regional and distant disease, which have poor 5-yr survival rates of 69% and 29%, respectively (1). Thus, primary prevention of ovarian cancer through identification of modifiable lifestyle characteristics and early intervention is crucial to reduce ovarian cancer mortality.

Although the etiology of ovarian cancer is not well understood, genetic, hormonal, reproductive, and nutritional factors have been implicated. Family history of ovarian cancer is a risk factor, with approximately 90% of familial ovarian cancers attributable to mutations in the BRCA1 (breast cancer 1) and BRCA2 genes (2), with average cumulative risk by age 70 of 40% and 10%, respectively (3). However, fewer than 10% of ovarian cancers are hereditary. Other well-established risk factors for ovarian cancer include age and infertility, whereas increasing parity, oral contraceptive use, hysterectomy, and tubal ligation decrease risk (4). These epidemiological characteristics have given rise to several etiological hypotheses, most of which postulate a role of hormonal factors. The current evidence suggests a role of elevated androgens and estrogens and decreased progesterone in the pathogenesis of ovarian cancer (4). Insulin-like growth factor (IGF)-I and gonadotropins have also been implicated (4).

Nutritional factors, including diet, obesity, and physical activity, have also been suggested to influence ovarian cancer risk through hormonal and other mechanisms. Several scientific panels, such as the World Cancer Research Fund International (WCRF)/American Institute for Cancer Research (AICR) (5), the International Agency for Research on Cancer (IARC) (6,7), and the American Cancer Society (ACS) (8,9) have periodically reviewed the epidemiological evidence, but so far there are no firm recommendations for prevention of ovarian cancer. The 2001 ACS Nutrition and Physical Activity Guidelines for Cancer Prevention concluded that “there are no firmly established nutritional risk factors for ovarian cancer, though vegetable and fruit consumption may lower risk” (8). Since then, several population-based case-control studies and cohort studies have been published. In support of the revision of these guidelines (9), a review was conducted to evaluate and summarize the new epidemiological evidence from the past 5 years about the role of obesity, physical activity, major food groups, and nutrients in relation to ovarian cancer and determine whether more specific nutrition recommendations can be provided at this point for the prevention of this disease.
Methods

This review included all major recent reviews and reports from international agencies such as the WCRF/AICR 1997 Report (5), the 2002 IARC Monographs on Weight and Physical Activity (6), Fruits and Vegetables (2003) (7), and the Nutritional Oncology textbook (2006) (10). To identify the new evidence, recent meta-analyses and review papers published since 2000 in the peer-reviewed literature were also searched as well as individual studies evaluating any aspect of the role of nutrition, diet, and physical activity on ovarian cancer prevention.

Search Strategy and Selection Criteria

PubMed was searched with the terms ovarian cancer with diet, nutrition, anthropometry, body mass index, obesity, and physical activity as well as the individual dietary factors being reviewed (e.g., legumes, vegetables, carotenoids, etc.) from 2000 to July 2006. Included were peer-reviewed publications in English since 2000, but older papers considered key in that particular area of research were also included. These were identified through manual searches in bibliographies of published papers. Randomized controlled trials, prospective studies, and well-conducted, population-based, case-control studies with at least 100 ovarian cancer cases were prioritized. However, for some exposures, smaller studies or hospital-based case-control studies were also included if they were the only studies conducted for that particular exposure, but the study type is noted in the text.

Obesity

The WCRF/AICR 1997 Report (5) concluded that the evidence on body mass and ovarian cancer was "somewhat inconsistent" and "no judgement was possible." The IARC Report on Weight Control and Physical Activity (2002) (6) included 4 cohort studies and 10 case-control studies (5 of them population based) examining body mass index (BMI) and concluded that the evidence was inconsistent. A 2001 systematic literature review (11) identified 34 studies examining weight or BMI and ovarian cancer risk. They found significant heterogeneity and inconsistent results for hospital-based studies, whereas the 11 population-based studies identified consistently showed an increased risk, with a pooled odds ratio (OR) of 1.4 and a 95% confidence interval (CI) of 1.2 to 1.6 and no significant heterogeneity in high vs. low analysis. Five cohort studies were identified examining weight/obesity/BMI, and the pooled relative risk (RR) was 1.2 (95% CI = 1.1–1.3).

As Table 1 shows, a number of cohort studies have been published since 2001 (12–19), with inconsistent results. Higher BMI at baseline was associated with an increased risk in the Cancer Prevention Study (CPS) II (14) and the Netherlands Cohort study (16), whereas there was no association in the Nurses Health Study (13), the Iowa Women’s Health Study (18), and the Norwegian Cohort Study (17). In addition, a multicenter, nested, case-control study (12) within 3 cohort studies in New York, Umea (Sweden), and Milan (Italy), including 122 cases, found an inverse association with BMI (OR = 0.46; 95% CI = 0.23–0.92). Population-based studies published since 2001, shown in Table 2, have fairly consistently shown elevated risk for women in the highest category of BMI (20–28). The few studies that conducted stratified analysis by menopausal status suggested a stronger association in premenopausal women (11,13,20,28) and a weaker relationship (11) or no association in postmenopausal women (13,20,28).

However, these findings need replication, as the confidence intervals included the null value. Possible effect modification by histological subtype has also been shown in some studies, but the evidence is inconsistent to draw any conclusions.

As shown in Tables 1 and 2, higher BMI as a young adult (e.g., at age 18, 20, or adolescence) was found to increase risk in the Nurses Health Study (only in premenopausal women) (13), the Norwegian Cohort Study (17), and the Iowa Women’s Health Study (18) and in a population-based case-control study (21). In contrast, there was no association with BMI at age 20 in the Netherlands Cohort Study (16) or in several population-based case-control studies (25–27).

The role of central obesity on ovarian cancer etiology has received little attention. The Iowa Women’s Health Study suggested an increased risk for women with a waist to hip ratio (WHR) >0.89 compared to those with a WHR ≤0.78 (RR = 1.59; 95% CI = 1.05–2.40) (18). There was a suggestion of an increased risk with higher WHR in the multicenter nested case-control study described previously, but analyses had low statistical power (12) as well as in a population-based case-control study (25). In the Nurses Health Study (13), there was little evidence of an association, but there were only 4 cases with a WHR >0.89. An additional hospital-based study found an association (29).

In summary, the data for BMI are suggestive of an increased risk, but because prospective data have not been consistent, a firm conclusion cannot be drawn at this time. The role of central obesity deserves further examination.

Physical Activity

The IARC Report on Weight Control and Physical Activity (2002) (6) included a narrative review on 5 studies examining physical activity and ovarian cancer, and the evidence was deemed inconsistent and inconclusive. Since then, 7 new cohort studies (18,30–35) and 3 population-based case-control studies (23,36,37) have been published. Overall, the evidence, reviewed by Weiderpass et al. (2006) (35), remains inconsistent. Only 1 of these 7 cohort studies (32) provided some indication of an inverse association with ovarian cancer risk for leisure time vigorous physical activity. In 2 of these cohort studies, the Iowa Women’s Health Study (18) and the Nurses’ Health Study (30), frequent and vigorous exercise was associated with an increased ovarian cancer risk.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort</th>
<th>No. of Cases</th>
<th>Cohort Size</th>
<th>Current BMI</th>
<th>BMI as a Young Adult</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lukanova et al. 2002 (12)</td>
<td>Northern Sweden Health and Disease Cohort, NYU Women's Health Study, ORDET Study</td>
<td>122</td>
<td>43,268; 14,275; 10,788</td>
<td>( \geq 28.4 \text{ vs } &lt;23.1 ) 0.46 (0.23–0.92)</td>
<td>( \geq 25 \text{ vs } &lt;20 ) 1.12 (0.77–1.63)</td>
<td>Multicenter nested-case control study. Premenopausal and postmenopausal women.</td>
</tr>
<tr>
<td>Fairfield et al. 2002 (13)</td>
<td>Nurses Health Study</td>
<td>402</td>
<td>109,445</td>
<td>( \geq 30 \text{ vs } &lt;21 ) 1.05 (0.73–1.51)</td>
<td>( \geq 25 \text{ vs } &lt;20 ) 1.12 (0.77–1.63)</td>
<td>Stratified analyses by menopausal status revealed an elevated risk for BMI at age 18 only for premenopausal women. Subtypes—limited power.</td>
</tr>
<tr>
<td>Rodriguez et al. 2002 (14)</td>
<td>CPS-II</td>
<td>1,511 deaths</td>
<td>300,537</td>
<td>( \geq 30 \text{ vs } &lt;25 ) 1.26 (1.07–1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonsson et al. 2003 (15)</td>
<td>Swedish Twin Registry</td>
<td>118</td>
<td>21,884</td>
<td>( &gt;30 \text{ vs. } 18.5–24.99 ) 0.30 (0.1–1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schouten et al. 2003 (16)</td>
<td>Netherlands Cohort Study</td>
<td>172</td>
<td>62,573</td>
<td>( \geq 30 \text{ vs } &lt;24.9 ) 1.69 (1.00–2.86)</td>
<td>( \geq 23 \text{ vs } &lt;20 ) 0.79 (0.48–1.32)</td>
<td>Postmenopausal women</td>
</tr>
<tr>
<td>Engeland et al. 2003 (17)</td>
<td>Norwegian Cohort Study</td>
<td>7,882</td>
<td>1.1 million</td>
<td>( \geq 30 \text{ vs } &lt;18.5 ) 0.98 (0.92–1.05)</td>
<td>( &gt;85 \text{ th vs } &lt;25 \text{ th–74 th percentiles in a U.S. reference population} ) 1.56 (1.04–2.32)</td>
<td>Premenopausal and postmenopausal. No differences by histologic subtype.</td>
</tr>
<tr>
<td>Anderson et al. 2004 (18)</td>
<td>Iowa Women's Health Study</td>
<td>223</td>
<td>41,836</td>
<td>( \geq 30 \text{ vs } &lt;25 ) 1.18 (0.83–1.69)</td>
<td>( \geq 30 \text{ vs } &lt;25 ) 1.83 (0.90–3.72)</td>
<td>Postmenopausal women</td>
</tr>
<tr>
<td>Niwa et al. 2005 (19)</td>
<td>Japanese Collaborate Cohort</td>
<td>38</td>
<td>36,456</td>
<td>25–29.9 \text{ vs } &lt;18.5–29.9 \ 2.24 (1.13–4.47)</td>
<td></td>
<td>Premenopausal and postmenopausal women</td>
</tr>
</tbody>
</table>

Note: 

- **a**: Abbreviations are as follows: RR, relative risk; CI, confidence interval.
- **b**: Self-reported.
- **c**: Technician measurements.
Table 2. Recent Population-Based Case-Control Studies Evaluating the Association Between Body Mass Index (BMI) and Ovarian Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Cases</th>
<th>Controls</th>
<th>Current BMI</th>
<th>BMI as a Young Adult</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuper et al. 2002 (20)</td>
<td>United States</td>
<td>563</td>
<td>563</td>
<td>30 vs &lt; 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 vs &lt; 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Stratified analyses by menopausal status: Stronger association in premenopausal women</td>
</tr>
<tr>
<td>Lubin et al. 2003 (21)</td>
<td>Israel</td>
<td>1,269</td>
<td>2,111</td>
<td>22.9–35.2 vs &lt; 19.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22.9–35.2 vs &lt; 19.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Pike et al. 2004 (22)</td>
<td>United States</td>
<td>477</td>
<td>660</td>
<td>35 vs &lt; 25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.46 (0.87–2.44)</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Riman et al. 2004 (23)</td>
<td>Sweden</td>
<td>655</td>
<td>3,899</td>
<td>30 vs &lt; 22&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.37 (1.01–1.85)</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Pan et al. 2004 (24)</td>
<td>Canada</td>
<td>442</td>
<td>5,039</td>
<td>30 vs &lt; 25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.95 (1.44–2.64)</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Hoyo et al. 2005 (25)</td>
<td>United States</td>
<td>593</td>
<td>628</td>
<td>30 vs &lt; 25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4 (1.0–1.8)</td>
<td>Similar effect in African Americans and White women</td>
</tr>
<tr>
<td>Greer et al. 2006 (26)</td>
<td>United States</td>
<td>762</td>
<td>1,348</td>
<td>28.7 vs &lt; 21.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22 vs &lt; 18.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Rossing et al. 2006 (27)</td>
<td>United States</td>
<td>355</td>
<td>1,637</td>
<td>30 vs &lt; 25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 (0.9–2.4)</td>
<td>Premenopausal and postmenopausal women</td>
</tr>
<tr>
<td>Peterson et al. 2006 (28)</td>
<td>United States</td>
<td>700</td>
<td>5,943</td>
<td>30 vs &lt; 18.5–25.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 vs &lt; 18.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Premenopausal and postmenopausal women: Stronger association in premenopausal women</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Abbreviations are as follows: OR, odds ratio; CI, confidence interval.
<sup>b</sup>: Self-reported.
<sup>c</sup>: Technician measurements.

In premenopausal women, frequent vigorous activity may affect ovarian cancer risk by altering regular menstrual cycles and ovulation (30). It has also been proposed that physical activity may increase ovarian cancer risk by stimulating gonadotropin production in response to a reduction in circulating endogenous estrogen levels (30). At this time, the role of physical activity on ovarian cancer prevention is unclear.

**Dietary Factors**

A summary of selected results from recent studies reporting on dietary factors and ovarian cancer risk is shown in Table 3. Recent results for each dietary factor are described below.

**Dietary fat:** The WCRF/AICR 1997 Report (5) claimed that there was suggestion that total fat increased ovarian cancer risk, but the overall evidence was deemed insufficient. The evidence for fat subtypes was also found to be insufficient. A meta-analysis published in 2001 (38), based on 1 cohort study and 7 case-control studies, estimated a pooled RRs of 1.26 (95% CI = 1.11–1.42) for total fat, 1.20 (95% CI = 1.04–1.39) for saturated fat, and 1.70 (95% CI = 1.43–2.03) for animal fat. A more recent review (39) noted that the available evidence pointed to an inverse association for monounsaturated and polyunsaturated fat and a positive association for saturated fat. A pooled analysis of 12 cohort studies (40) failed to find an association for total fat, monounsaturated, polyunsaturated, transunsaturated, animal and vegetable fat, and cholesterol. In contrast, there was an indication of an increased risk with saturated fat intake with a pooled multivariate RR of 1.29 (95% CI = 1.01–1.66) for the highest versus the lowest decile. Results by histologic subtypes did not reveal any major differences. Overall, the evidence has been inconsistent, but the possible association with high levels of saturated fat deserves further investigation.

**Total carbohydrates:** Total carbohydrates or carbohydrate-rich foods have not been consistently associated to ovarian cancer (39). Dietary glycemic index and glycemic load were found to increase ovarian cancer risk in a hospital-based study conducted in Italy (41).

**Vitamins:** The evidence in the 1997 WCRF/AICR Report (5) for Vitamin C and carotenoids was found to be
insufficient. A meta-analysis published in 2001 found a pooled OR of 0.84 (95% CI = 0.75–0.94) for highest vs. lowest categories of beta-carotene intake based on 5 observational studies (42). A few additional population-based case-control studies published since then seem to support a possible protective effect for carotenoids/β-carotene from dietary (43), supplement sources (44), or both (45). In contrast, prospective data have not confirmed these observations. In the Canadian National Breast Cancer Screening Study (46), a prospective study including 48,776 women and 264 ovarian cancer cases, there was no evidence of an association with total carotenoids or individual carotenoids including beta-carotene. Furthermore, a subsequent pooled analysis of 10 cohort studies failed to find an association with major carotenoids (total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) (47). Results were similar by histologic subtypes. Overall, prospective studies have provided little support for a relationship of ovarian cancer with vitamin A, vitamin C, or vitamin E (46,48,49).

Few epidemiologic studies have evaluated the association between dietary folate and ovarian cancer. In the Iowa Women’s Health Study (48) and a small hospital-based case-control study (50), there was some indication of an increased risk associated with folate intake. In the cohort study, the elevation in risk appeared to be attributable to folate from supplements. One additional population-based case-control study (43) and a hospital-based case-control study (51) did not find an association. In contrast to these findings, the Swedish Mammography Cohort reported a strong inverse relationship with folate intake, particularly for alcohol drinkers (52). The authors claimed that their discrepant results may have been attributed to a lower folate consumption in their study population of Swedish women. An interaction between alcohol and folate intakes was also found in the Iowa Women’s Health Study (53). A more recent report from the Nurses Health Study—including 80,254 subjects, among which 481 cases of ovarian cancer were identified during the 22 years of follow-up—provided little support for an association with folate, methionine, or vitamin B6 (54).

Overall, the epidemiologic data do not support a major role of vitamin intake on ovarian cancer prevention.

**Table 3. Results for Selected Dietary Factors in Major Recent Studies**

<table>
<thead>
<tr>
<th>Dietary Factor</th>
<th>Study</th>
<th>Contrast</th>
<th>Multivariate RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total vegetables</td>
<td>Pooling project(^b) (55)</td>
<td>Per 100 g</td>
<td>0.98 (0.94–1.01)</td>
</tr>
<tr>
<td>Total fruits</td>
<td>European Prospective Investigation into Cancer and Nutrition(^a) (57)</td>
<td>Per 80 g</td>
<td>0.92 (0.76–1.11)</td>
</tr>
<tr>
<td>Whole milk</td>
<td>Pooling project(^c) (68)</td>
<td>Per 250 g</td>
<td>0.98 (0.88–1.10)</td>
</tr>
<tr>
<td>Low-fat milk</td>
<td>Pooling project(^c) (68)</td>
<td>Per 250 g</td>
<td>1.04 (0.98–1.09)</td>
</tr>
<tr>
<td>Lactose</td>
<td>Pooling project(^c) (68)</td>
<td>&gt;30 g/day vs &lt;10 g/day</td>
<td>1.19 (1.01–1.40)</td>
</tr>
<tr>
<td>Total calcium</td>
<td>Pooling project(^c) (68)</td>
<td>350 mg</td>
<td>1.01 (0.99–1.02)</td>
</tr>
<tr>
<td>Dietary folate</td>
<td>Iowa Women’s Health Study (53)</td>
<td>100 IU</td>
<td>1.02 (0.99–1.04)</td>
</tr>
<tr>
<td>Dietary folate</td>
<td>Swedish Mammographic Cohort (52)</td>
<td>≥347 g vs &lt;238 µg/day</td>
<td>1.45 (0.83–2.53)</td>
</tr>
<tr>
<td>Total fat</td>
<td>Pooling Project(^a) (40)</td>
<td>Quartile 4 vs Quartile 1</td>
<td>1.08 (0.94–1.24)</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>Pooling project(^a) (40)</td>
<td>Quartile 4 vs Quartile 1</td>
<td>1.14 (0.97–1.34)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Pooling project(^a) (83)</td>
<td>≥30 g/day vs 0 g/day</td>
<td>1.12 (0.86–1.44)</td>
</tr>
</tbody>
</table>

\(^a\): Abbreviations are as follows: RR, relative risk; CI, confidence interval.

\(^b\): Pooled analysis of 12 cohort studies.

\(^c\): European Prospective Investigation into Cancer and Nutrition

\(^d\): Pooled analysis of 10 cohort studies.

**Vegetables and fruits:** The 1997 WCRF/AICR Report (5) suggested a “possible” decreased risk with vegetables and fruits based on data from 6 case-control studies. The IARC Report on Fruits and Vegetables (7) found the evidence suggestive of a decreased risk associated with vegetable intake, whereas for fruit, the evidence was less consistent. Given the few studies evaluating these exposures, meta-analyses were not conducted. A more recent review (39) including studies published up to June 2004 found 3 cohort studies and 13 case-control studies. They tended to support an inverse association with total vegetable intake, particularly green leafy vegetables, but not for fruit. In the Nurses Health Study (49), only adolescent fruit and vegetables consumption was associated with decreased risk, suggesting that perhaps early dietary exposure may be relevant. More recent prospective data do not support a relationship with vegetables and/or fruit consumption. In a recent report by the pooling project including 12 cohort studies (55) there was no indication of an association with total fruit, total vegetable, total fruit and vegetable, or any botanically defined subgroup. There was also little evidence of an association in the Netherlands Cohort Study on Diet and Cancer with fruit and vegetable consumption (56). The European Prospective Investigation into Cancer and Nutrition Study (57), which included 325,640 women among...
whom 581 cases of invasive ovarian cancer were identified, also failed to find an association with total vegetables and fruits, combined or separately, or any subgroup of vegetables, with the exception of allium vegetables. There was some suggestion that high intake of garlic/onion vegetables may decrease ovarian cancer risk. This needs to be replicated in other studies.

Overall, the current epidemiologic data do not seem to support a major role of fruit and vegetable consumption on ovarian cancer prevention.

**Legumes and phytoestrogens:** Pulses were mentioned in the WCRF/AICR 1997 Report (5), but the evidence was found to be insufficient to draw any conclusions. A 2004 review (39) identified 4 case-control studies evaluating pulses and legumes with inconsistent results. Moreover, there was no association for legumes (comprising tofu, beans, and peas) in the Nurses Health Study (49), but consumption levels were very low (≥0.5 servings per week was the highest category). There was no evidence of an association with legumes either in a case-cohort analysis of the Netherlands Cohort Study on Diet and Cancer, comprising 2216 cohort members and 252 invasive epithelial ovarian carcinomas (56).

There is a growing interest in the role of soy products and phytoestrogens on female hormonal cancers (58). One study in China (59,60) specifically examining the effect of soy and isoflavone intakes on ovarian cancer risk reported a strong inverse relationship for both. The OR for the highest quartile of intake of soybean products compared to the lowest was 0.5 (95% CI = 0.31–0.82). In the Western New York Diet Study (43), an inverse relationship was found with several phytochemicals, including total lignans primarily from fruits, vegetables, grains, and seeds (OR = 0.43; 95% CI = 0.21–0.85). Although these observations require replication in other studies, they suggest that phytoestrogens may have a beneficial effect on ovarian cancer. However, the data are insufficient at this time to issue any recommendations.

**Dietary fiber:** There was no mention of dietary fiber and ovarian cancer in the 1997 WCRF/AICR Report (5). A 2004 review of the literature (39) suggested an inverse association with fiber, with a 20–50% reduction in risk for high vs. low intake. It should be noted that fiber was not found to be associated with ovarian cancer in the Iowa Women’s Health Study (48). However, the range of fiber intake seemed to be narrow (7.3 g/day difference between Cut Point 3 and Cut Point 1) in that cohort, and analyses were based on only 139 ovarian cancer cases, which probably affected the study’s ability to detect an association. A large population-based case-control study also failed to find an association with dietary fiber (44).

**Red meat, fish, eggs:** The WCRF/AICR 1997 Report (5) found the evidence for red meat limited and inconsistent. The evidence was deemed insufficient but suggestive of decreasing risk for fish and suggestive of increasing risk for eggs. A 2004 review of the literature (39) came to the same conclusion for fish and eggs. However, the evidence for red meat was found to be suggestive of an increased risk with the 11 case-control studies and 3 of the 4 cohort studies identified reporting risk estimates above 1 (39). A recent report from the Swedish Mammography Cohort (61) found no association for meat, fish, or eggs. In the pooling project (40), there was no indication of an association with egg consumption. Results did not vary by histological subtypes.

**Dairy products and lactose:** The WCRF/AICR 1997 Report (5) found the evidence limited and inconsistent for milk consumption and suggested that diets high in galactose have no relationship with ovarian cancer risk. However, the data were deemed “too limited and inconsistent to make a judgement.”

The role of milk and other dairy products on ovarian cancer has been explored for more than 20 years. The increased ovarian cancer risk initially identified for butter and whole milk was attributed to galactose toxicity to oocytes (62). Galactose is primarily produced from the hydrolysis of lactose, which is found only in milk. However, 2 recent reviews did not provide much support for a role of consumption of milk/dairy products or galactose metabolism on ovarian carcinogenesis (39,63). An additional meta-analysis published in 2005, including 18 case-control and 3 prospective studies, concluded that prospective data, but not case-control data, suggested an increase risk of ovarian cancer associated with high intakes of dairy foods and lactose (64). The random effects summary RR derived from the 3 cohort studies identified (48,65,66) was 1.47 (95% CI = 1.17–1.84) for highest vs. lowest categories of lactose consumption. For total dairy foods, the summary RR for total dairy foods for 2 cohort studies (48,66) was 1.66 (95% CI = 1.19–2.31). Summary risk estimates from case-control studies were close to 1 for both lactose and dairy products. It should be noted that in the Nurses’ Health Study (65) and the Swedish Mammography Cohort (66), lactose consumption was associated with increased risk of serous ovarian cancer, but not with other subtypes, suggesting that future studies should consider histologic type when evaluating this association. In contrast, a report from the Netherlands Cohort Study of Diet and Cancer (67) reported no association with any dairy products or lactose and epithelial ovarian cancer or the serous subtype. Furthermore, there was no indication of an association with milk/dairy product or calcium consumption in a recent study pooling data from 12 cohort studies (68) and only a weak association with lactose intake at a level equivalent to 3 or more glasses of milk per day (RR = 1.19; 95% CI = 1.01–1.40 comparing ≥30 g/day vs. <10 g/day). In this study, there was no evidence of effect modification by histological subtype. Overall, although additional research may provide some clues regarding the impact of lactose on ovarian cancer risk, the evidence for dairy products/lactose is too inconsistent at this time to warrant any recommendations.

Tea: There is a growing interest in the role of tea, particularly green tea and ovarian cancer (70). Green tea contains many compounds including catechins, which have antioxidant, antimitogenic, and anti-inflammatory properties (71). A recent review of the literature concluded that although the evidence from experimental studies is very promising, the epidemiologic literature of tea and ovarian cancer is not very supportive of a relationship (70). However, most of the studies were conducted in Western populations where the prevalence of tea drinking is low. The 1 study conducted in China found an inverse association between green tea and ovarian cancer (72). Since then, an additional cohort study has been published (73). In this study, the Swedish Mammography Cohort Study including 301 cases of epithelial ovarian cancer, there was an inverse association between tea consumption and ovarian cancer. Compared to women who never or rarely consumed tea, the OR for those consuming 2 or more cups was 0.54 (95% CI = 0.31–0.91). Each cup of tea was estimated to reduce risk by 18%. The separate effect of green tea was not evaluated. The overall evidence is intriguing but insufficient to warrant any recommendations at this time.

Alcohol: Compared to other cancer sites, the relationship between alcohol and ovarian cancer has not been widely investigated (74). The 1988 IARC Report (75) concluded that there was no association between alcohol and ovarian cancer, whereas the relationship was not even mentioned in the 1997 WCRF/AICR Report (5). A meta-analysis (76) including 5 case-control studies computed elevated pooled ORs (95% CIs) of 1.11 (1.0–1.24), 1.23 (1.01–1.54), and 1.53 (1.03–2.32) for 25 g, 50 g, and 100 g of alcohol per day, respectively. A more recent meta-analysis including 7 population-based studies (77) computed a pooled risk estimate of 0.72 (95% CI = 0.54–0.97) for the highest level of consumption reported in each study.

The Iowa Women’s Health Study (48) and several population-based studies (77–80) examining the relationship between alcohol and ovarian cancer risk have suggested a decreased risk associated with drinking levels below 3 drinks/day. One additional case-control study suggested an elevated risk for drinkers of more than 3 drinks/day (81). There was no indication of an association among participants in the Netherlands Cohort Study (82) or in the pooling project (83). The 2 cohort studies that evaluated the possible interaction between alcohol and folate intakes reported an inverse association between folate and ovarian cancer among alcohol drinkers (52,53).

Two recent case-control studies (80,84) have suggested that the effect of alcohol on ovarian cancer risk might vary by histology. One of these studies (84) reported an elevated risk only for mucinous tumors, with an OR for those consuming more that 24 g/day ethanol of 1.93 (95% CI = 1.02–3.65). In contrast, another study (80) found similar risk estimates for mucinous and nonmucinous tumors but reported a strong protective effect for total alcohol only for invasive epithelial ovarian cancer (OR = 0.36; 95% CI = 0.19–0.70) and an elevated risk for borderline serous tumors associated with the consumption of spirits (OR = 2.66; 95% CI = 1.46–4.85). However, a large case-control study found an inverse association between alcohol consumption and ovarian cancer, which was of similar magnitude for all histologic types (77). In the pooling project, there was no association with alcohol for any histological subtype (83). Although the findings are not conclusive, they suggest that future ovarian cancer studies should examine the effect by histologic type.

Overall, these results, although inconsistent, tend to indicate that moderate levels of alcohol drinking might be associated with a reduced risk of ovarian cancer. There is no consistent evidence that any particular source of alcohol may be more beneficial or detrimental than another, but in general, there is a tendency for studies to show reduced risk for wine consumption and elevated risk estimates for beer and liquor. The high content of antioxidants and resveratrol in wine has been proposed to explain these findings (77). If alcohol drinking is related to ovarian cancer, current rather than lifetime drinking seem to be the relevant factor (80).

Discussion

Ovarian cancer is a cancer site difficult to study for several reasons. First, because it is a rare disease, studies have typically included few cases, which resulted in limited the statistical power, particularly to study histological subtypes. Second, cases tend to be very sick when they are diagnosed, and a number of them die before they can be interviewed in case-controls studies. Third, ovarian cancer is difficult to diagnose early, and this is particularly true among obese women, which may have resulted in some undetected ovarian cancer cases in cohort studies.

Nevertheless, as some of the major cohort studies have aged, they have accumulated enough cases, and there have been several cohort studies published in the past 5 yr that bring additional scientific evidence since the American Cancer Society Nutrition and Physical Activity Guidelines issued in 2001 (8). In support of the revision of these guidelines (9), the evidence accumulated since then was reviewed and summarized here. Unfortunately, at this time, the evidence for most nutrition/dietary factors remains inconsistent. Current evidence (55,57) does not seem to support a role of fruit and vegetable consumption for ovarian cancer prevention. The association with milk/dairy products and galactose metabolism has been widely explored with inconsistent results (39,40,63). Unlike for other cancers, the role of obesity and physical activity on ovarian cancer risk is unclear. Several studies have suggested that obesity during adolescence may increase premenopausal ovarian cancer, again pointing out
to a possible role of early nutritional influences. Some studies have suggested that ovarian cancer histological subtypes (serous, mucinous, endometrioid, and clear cell tumors) may be affected by different factors, and if so, studies may have offered inconsistent results because they typically combined all these subtypes. These are currently active areas of research, and future studies may help clarify the impact of diet and nutrition on ovarian cancer.

In conclusion, despite a considerably recent growth in the literature on diet/nutrition and ovarian cancer, the epidemiologic evidence remains insufficient and inconclusive to warrant any firm dietary guidelines specific to ovarian cancer prevention.

Acknowledgments and Notes

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