Ovarian cancer risk and nonisoflavone flavonoids intake: A systematic review of epidemiological studies

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Background: Although several studies have investigated the association between ovarian cancer risk and nonisoflavone flavonoids intake, these findings are inconsistent. This systematic review of published epidemiological studies was conducted to summarize and clarify the evidence on the association between ovarian cancer incidence and nonisoflavone flavonoids intake. Materials and Methods: PubMed, Scopus, Google Scholar, and EMBASE databases were searched based on MeSH term (ovarian neoplasm in combination with flavonoids) to identify related English and non-English papers published up to June 2016. We summarized the results of the relevant studies in this review. Results: In total, seven studies (four with cohort and three with case–control design) included in this review. The results of conducted cohort studies show no relation between ovarian cancer risk and total nonisoflavone flavonoids intake, and only one study reported a significant reduction between ovarian cancer incidence and kaempferol and luteolin intake. Similar to those in the cohort studies, also in case–control studies, no association was found between total nonisoflavone flavonoids intake and ovarian cancer risk, just an inverse association between flavonols intake and ovarian cancer was reported. Conclusion: Several studies investigated the relation of nonisoflavone flavonoids intake and ovarian cancer risk; none of them reported any association for total nonisoflavone flavonoids intake, but some reported an inverse association between certain subclasses or individual flavonoids. These findings are limited, and there is a need for further and more accurate researches to be confirmed.

Key words: Flavanones, flavonols, nonisoflavone flavonoid, ovarian neoplasm

INTRODUCTION

Flavonoids are polyphenolic chemicals found naturally in fruits, vegetables, and plant-derived foods and beverages. There are more than 5000 individual flavonoid compounds and at least ten subgroups of flavonoids. The most common subgroups in human diet are flavones, flavonols, flavanones (catechins), flavanones, isoflavones, and anthocyanidins. Flavonols (e.g., quercetin, kaempferol, and myricetin) are the most bountiful flavonoids in plant foods and are mainly present in leafy vegetables, apples, onions, broccoli, and berries. Flavones (e.g, apigenin and luteolin) and anthocyanidins are present in small quantities in grains, leafy vegetables, and herbs. Flavanols (e.g., catechin and epicatechin) are plentiful in tea, apples, grapes, chocolate, and red wine. Flavanones (e.g., naringenin and hesperetin) predominantly exist in citrus fruit and their juices. Isoflavones (e.g., daidzein and genistein) are mainly present in soybeans and soy-based products.

Ovarian cancer, cancer that begins in an ovary, is the fifth leading cause of cancer death in women, and...
unfortunately, its symptoms (such as abdominal pain and swelling) usually occur late in the disease process. In 2012, ovarian cancer occurred in 239,000 women and resulted in 152,000 deaths worldwide. This makes it the seventh most common cancer and the eighth most common cause of death from cancer among women. Ovarian cancer outcomes depend on the extent of cancer and its subtype. In comparison to North America and Europe, outcomes are worse in the developing world.

Nowadays, there is a growing body of evidences about the effects of phytochemicals and their sources on various health condition and cancers risk. This scientific evidence suggests that flavonoids possess several biological effects that may play a valuable role in cancer prevention, including antiestrogenic, antimutagenic, antiproliferative, anti-inflammatory, and antioxidant properties. These mentioned properties may involve in well-established association between fruits and vegetables high intake and lower cancers risk.

There are several systematic reviews that analyze the association between ovarian cancer and consumption of tea, wine, and isoflavonoids but based on our knowledge, there is no systematic review on the relation of ovarian cancer risk and nonisoflavone flavonoids intake; moreover, published evidences in this field are inconsistent. Therefore, we scrutinize the issue in this paper to clarify unknown aspects. This systematic review of published epidemiological studies was conducted to summarize and clarify the evidence on the association between ovarian cancer incidence and nonisoflavone flavonoids intake.

MATERIALS AND METHODS

We performed a systematic review of studies that evaluated the correlation between ovarian cancer risk and nonisoflavone flavonoids intake.

Search strategy


We found 348 papers, but after reading the titles and abstracts, most of them excluded based on our exclusion criteria: investigating molecular and biochemical aspects or working on animal models. Eligible (cohort and case–control studies) studies scanned based on their title, abstract, and their major aims in first-step and related studies assessed based on their full texts, except one article that we could not achieve its full text and our efforts to contact its authors were inconclusive. We also checked references of related studies to extract relevant studies.

RESULTS

Finally, we selected seven articles, which had our inclusion criteria (cohort and case–control studies) for systematic review. Figure 1 shows the pathway; we went through for selecting final articles.

In total, seven studies were included in the present review; four with cohort and three with case–control design. The articles, reviewed in this paper, were summarized in Table 1.

Cohort studies

Cassidy et al. followed 171,940 Nurses’ Health Study and Nurses’ Health Study II participants to examine associations between consumption of total flavonoids and their subgroups (flavanones, flavonols, anthocyanins, flavan-3-ols, flavones, and polymeric flavonoids) and risk of ovarian cancer. During 16–22 years of follow-up, 723 cases of ovarian cancer were confirmed through medical records. In this cohort study, food frequency questionnaire was used
for collecting dietary data. They reported that in comparing top with the bottom quintile, total flavonoids intake was not significantly associated with ovarian cancer risk. However, participants in the highest quintiles of flavonol and flavanone consumption had modestly lower risk of ovarian cancer although the P-trend was not significant. Authors concluded that higher intakes of flavonols and flavanones might be associated with lower risk of ovarian cancer. Above authors conclusion, these findings were not statistically significant.

In another study, Wang et al.\(^{[22]}\) prospectively investigated the association between the intake of selected flavonoids (flavonols [quercetin, kaempferol, and myricetin] and flavones [apigenin and luteolin]) and flavonoid-rich foods (tea, apple, broccoli, onion, and tofu) and risk of ovarian cancer in the Women’s Health Study. A total of 131 incident ovarian cancer cases were identified during 11.5 years of follow-up among 38,408 women aged ≥45 years. Semi-quantitative food frequency questionnaire was used for collecting dietary data in this study. No significant association was found between total flavonoids consumption, the individual flavonoid, and flavonoid-rich foods and the incidence of ovarian cancer.

Gates et al.\(^{[23]}\) analyzed the association between intake of five common dietary nonisoflavone flavonoids from the flavonol and flavones subclasses (myricetin, kaempferol, quercetin, luteolin, and apigenin) and incidence of epithelial ovarian cancer among 66,940 women in the Nurses’ Health Study.

### Table 1: A summary of studies that reviewed in current article

<table>
<thead>
<tr>
<th>References/year Study design</th>
<th>Subjects/patients</th>
<th>Type of flavonoid</th>
<th>Follow-up duration (years)</th>
<th>Dietary assessment method</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassidy et al.(^{[21]})/ 2014 Cohort</td>
<td>723/171,940</td>
<td>Flavanones, flavonols, anthocyanins, flavan-3-ols, flavones, polymeric flavonoids</td>
<td>16-22</td>
<td>FFQ</td>
<td>No association between ovarian cancer risk and total flavonoids and the individual flavonoid intake. The highest versus lowest quintile of flavonol and flavanone intakes had modestly lower risk of ovarian cancer, but the P-trend was not significant.</td>
</tr>
<tr>
<td>Wang et al.(^{[25]})/ 2009 Cohort</td>
<td>131/38,408</td>
<td>Flavonols (quercetin, kaempferol, and myricetin), flavones (apigenin and luteolin), and flavonoid-rich foods (tea, apple, broccoli, onion, and tofu)</td>
<td>11.5</td>
<td>Semi-quantitative FFQ</td>
<td>No association between ovarian cancer risk and total flavonoids, the individual flavonoid, and flavonoid-rich foods intake.</td>
</tr>
<tr>
<td>Gates et al.(^{[23]})/ 2007 Cohort</td>
<td>347/66,940</td>
<td>Flavonol and flavone subclasses</td>
<td>18-19</td>
<td>Semi-quantitative FFQ</td>
<td>No association between ovarian cancer risk and total flavonoids and the individual flavonoid intake.</td>
</tr>
<tr>
<td>Chang et al.(^{[24]})/ 2007 Cohort</td>
<td>280/97,275</td>
<td>Isothiocyanates</td>
<td>8-9</td>
<td>FFQ</td>
<td>No association between ovarian cancer risk and isothiocyanates intake.</td>
</tr>
<tr>
<td>Rossi et al.(^{[26]})/ 2010* Case-control</td>
<td>- cases/ - control</td>
<td>Flavonols</td>
<td>-</td>
<td>-</td>
<td>Flavonoids intake was inversely associated to ovarian cancer.</td>
</tr>
<tr>
<td>Gates et al.(^{[25]})/ 2009 Case-control</td>
<td>1141 cases/1183 control</td>
<td>Flavonoids (myricetin, kaempferol, quercetin, luteolin, and apigenin)</td>
<td>-</td>
<td>FFQ</td>
<td>No association between total flavonoid intake and ovarian cancer risk. Only intake of apigenin was associated with a significant decrease in ovarian cancer risk.</td>
</tr>
<tr>
<td>Rossi et al.(^{[24]})/ 2008 Case-control</td>
<td>1031 cases/2411 control</td>
<td>Flavan-3-ols, flavonones, flavonols, flavones, anthocyanidins</td>
<td>-</td>
<td>FFQ</td>
<td>Inverse relation with significant trend in risk between ovarian cancer and flavonols.</td>
</tr>
</tbody>
</table>

\(^{[21]}\)For this study, we could not get access to full text, therefore, we could not mention the number of cases and controls. FFQ=Food frequency questionnaire.
In this cohort study, dietary information was collected using semi-quantitative food frequency questionnaire, and data were available from multiple time points during 18 years of follow-up. They observed no clear association between total intake of the five examined flavonoids and ovarian cancer risk. However, there was a significant 40% and 34% reduction in ovarian cancer incidence for the highest versus lowest quintile of kaempferol and luteolin intake, respectively. These data suggest dietary intake of certain flavonoids may reduce ovarian cancer risk.

In a study by Chang et al., [24] the association between consumption of some phytochemical compounds including isothiocyanates and ovarian cancer risk has been investigated. Among 97,275 women participated in the California Teachers Study, 280 women developed invasive or borderline ovarian cancer. Food frequency questionnaire was used for gathering dietary data, but in this study, usual dietary intake was assessed only at one point. Intake of isothiocyanates or foods high in isothiocyanates was not associated with ovarian cancer risk.

In general, the results of conducted cohort studies in this field are diverse. Remarkable point is that no study shows a significant relation between ovarian cancer risk and total flavonoids intake, [21–24] and only one study reported a significant 40% and 34% reduction in ovarian cancer incidence for the highest versus lowest quintile of kaempferol and luteolin intake (flavonoids subgroups), respectively. [23]

**Case–control studies**

In a network of case–control studies from Italy, Rossi et al. [20] assessed the relation of total flavonoids, flavanones, flavonols consumption, and ovarian cancer risk. They expressed that just flavonols intake (odds ratio = 0.63) was inversely associated with ovarian cancer.

In another study, Gates et al. [25] evaluated the association between ovarian cancer risk and intake of five common dietary flavonoids (myricetin, kaempferol, quercetin, luteolin, and apigenin), as well as total intake of these flavonoids, for 1141 cases and 1183 frequency-matched controls. In this study, food frequency questionnaire was used for gathering flavonoid intake. No association was observed between total flavonoid intake and ovarian cancer risk. In analyses of each individual flavonoid, only intake of apigenin was associated with a significant decrease in ovarian cancer risk.

Another study by Rossi et al. [26] investigated the relation of six classes of flavonoids (flavan-3-ols, flavanones, flavonols, flavones, anthocyanidins, and isoflavones) with ovarian cancer risk. The study included 1031 cases with confirmed epithelial ovarian cancer and 2411 controls. Food frequency questionnaire was used for collecting data. In this study, an inverse relation was found between ovarian cancer and flavonols intake, which had a trend toward significance.

Similar to those in the cohort studies, also in case–control studies, no association was found between total flavonoids consumption and ovarian cancer; just Rossi et al. reported an inverse association between flavonols intake and ovarian cancer. [20] and in another study, an inverse relation with significant trend was found between ovarian cancer risk and flavonols intake. [26]

**DISCUSSION**

In this systematic review of epidemiological studies, we investigated the relationship between ovarian cancer risk and nonisoflavone flavonoids and their subgroups intake. For this purpose, we systematically reviewed the related cohort and case–control studies. Based on the present evidences, it seems that there is no association between ovarian cancer risk and total nonisoflavone flavonoids intake, but if the members of flavonoids subgroups considered individually, there is a significant adverse association between some of them and ovarian cancer risk.

Based on scientific evidence, there is a well-established association between high fruits and vegetables consumption and reduced cancers risk. Their phytochemicals content has been suggested for these effects. [12–14] As you know, like other phytochemicals, flavonoids and its subgroups have several biological effects, including antiestrogenic, antimutagenic, antiproliferative, anti-inflammatory, and antioxidant properties, that may play a valuable role in cancer prevention. [1, 5] Certain flavonoids, including quercetin, luteolin, and apigenin, appear to decrease inflammation through inhibiting cyclooxygenase-2 and inducible nitric oxide synthase which are important mediators of inflammatory reaction. [1, 26, 29]

Despite the considerable strengths of cohort studies, including their large size, prospective exposure assessment, and effective complete case ascertainment, there are several limitations to take into account. For example, Chang et al. [24] evaluated dietary intake only at one point, and their study has a wide age range, so the effects of dietary intake during some other age or period or accumulative effects or change in dietary habits over time are not considered.

Reviewed cohort studies are also subject to the limitations of all observational studies that assessed dietary intake. For instance, food frequency questionnaires were used for collecting data in all studies that have a limited capacity to gather detailed information about food and nutrient content.
consumption. The semi-quantitative food frequency questionnaire used in some studies was not specifically designed to estimate flavonoid intake; as a result, not all dietary sources of flavonoids were included in the questionnaire.

In addition, we assessed case–control studies, and these data need to be explicated watchfully because of the retrospective collection of dietary data and the long common period of cancer development.

In the present paper, we reviewed cohort and case–control studies, which evaluated the association of nonisoflavone flavonoids and its subgroup components consumption and ovarian cancer risk. According to the results of reviewed studies, there is no association between ovarian cancer risk and total nonisoflavone flavonoids intake, unanimously. However, some studies reported an inverse association between certain nonisoflavone flavonoids subclasses (flavonols20,26) or individual flavonoids (kaempferol and luteolin20,26 and apigenin20,26) and ovarian cancer risk. These results provide limited support for an association between nonisoflavone flavonoids intake and ovarian cancer risk, and we should be aware that there is a need for further and more accurate researches to be confirmed.

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Conflicts of interest
There are no conflicts of interest.

AUTHORS’ CONTRIBUTIONS
VM and SD contributed in the conception of the work, conducting the study, searched all target databases and merged the results, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. BL and LA contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. All steps were under supervision of LA.

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