

# Risk of secondary malignancies in patients with ovarian cancer: a systematic review and meta-analysis

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**Objective:** This study was performed to systematically assess the risk of secondary malignancies in patients with ovarian cancer. **Methods:** A systematic search was conducted in PubMed, Web of Science, and Scopus databases up to September 2019. In this study, the overall standardized incidence ratio (SIR) was calculated applying fixed/random-effects models. Sixteen cohort studies, including 122715 ovarian cancer patients with 4458 secondary malignancies were included. **Results:** Combined SIRs showed an increased risk of secondary malignancies prevalence (SIR = 1.81, 95% CI 1.58–2.03). The most common malignancies were cervical cancer 11.57 (6.94–16.21), endometrium 6.31 (4.18–8.44), leukemia 3.33 (2.23–4.43), connective tissue 2.61 (1.56–3.66), bladder 2.13 (1.77–2.50), renal 1.43 (1.11–1.74), intestine 2.36 (1.11–3.61), colorectal 1.73 (1.44–2.02), pancreatic 1.42 (1.13–1.71), breast 1.34 (1.5–1.18), and thyroid 1.59 (1.13–2.04) cancers. **Conclusion:** Some malignancies were found to be highly prevalent in patients with ovarian cancer compared to the general population, including endometrial cancer, leukemia, connective tissue malignancy, and bladder cancer. Therefore, efforts for early detection, which could lead to improved survival should be taken in these patients.

## Keywords

Ovarian cancer; Secondary malignancy; Secondary cancer; SIR; Meta-analysis

## 1. Introduction

Ovarian cancer is the 18th most common cancer worldwide with 295414 new cases diagnosed in 2018 [1]. The 5-year survival rate is 30–50% [2]. In the United States, ovarian cancer is the second common and the most lethal gynecologic cancer [3]. Major advances in treatment of ovarian cancer, including screening, surgery, and chemotherapy have

improved survival rate in recent years. However, risk of secondary malignancies, which endanger the patients' lives, are causing concerns [4–6].

There are some suggested screening methods for early detection of ovarian cancer, including measurement of cancer antigen 125 (CA 125) [7], transvaginal ultrasound [8], and multimodal test (measuring CA-125 and transvaginal ultrasound) [9, 10]. Screening is recommended after assessing the risk of ovarian cancer. High-risk patients with a family history of ovarian cancer and possible hereditary ovarian cancer syndrome are screened to detect ovarian malignancy [11, 12]. However, there is no evidence on the effectiveness of screening in low-risk patients who have positive family history of ovarian cancer without a hereditary pattern [13].

Women with ovarian cancer are at higher risk for developing secondary malignancies [14]. Some of these malignancies (e.g., leukemia, bladder, and rectum) are associated with the side effects of chemotherapy or radiation therapy. On the other hand, some cancers, including breast, colorectal, and stomach are linked to genetic and environmental factors [15–19]. In adults, malignant ovarian cancers are mostly of epithelial cell origin and have lower survival rates when compared to other cell types [20]. Studies on malignant ovarian tumors in children and young adults have shown that most of the ovarian neoplasms are of germ cell origin [21]. These tumors are categorized as germinomas and non-germinomas which are recognized as tumors with an excellent prognosis and the 5- and 10-year survival rates are 91.7% and 91.4%, respectively [21].

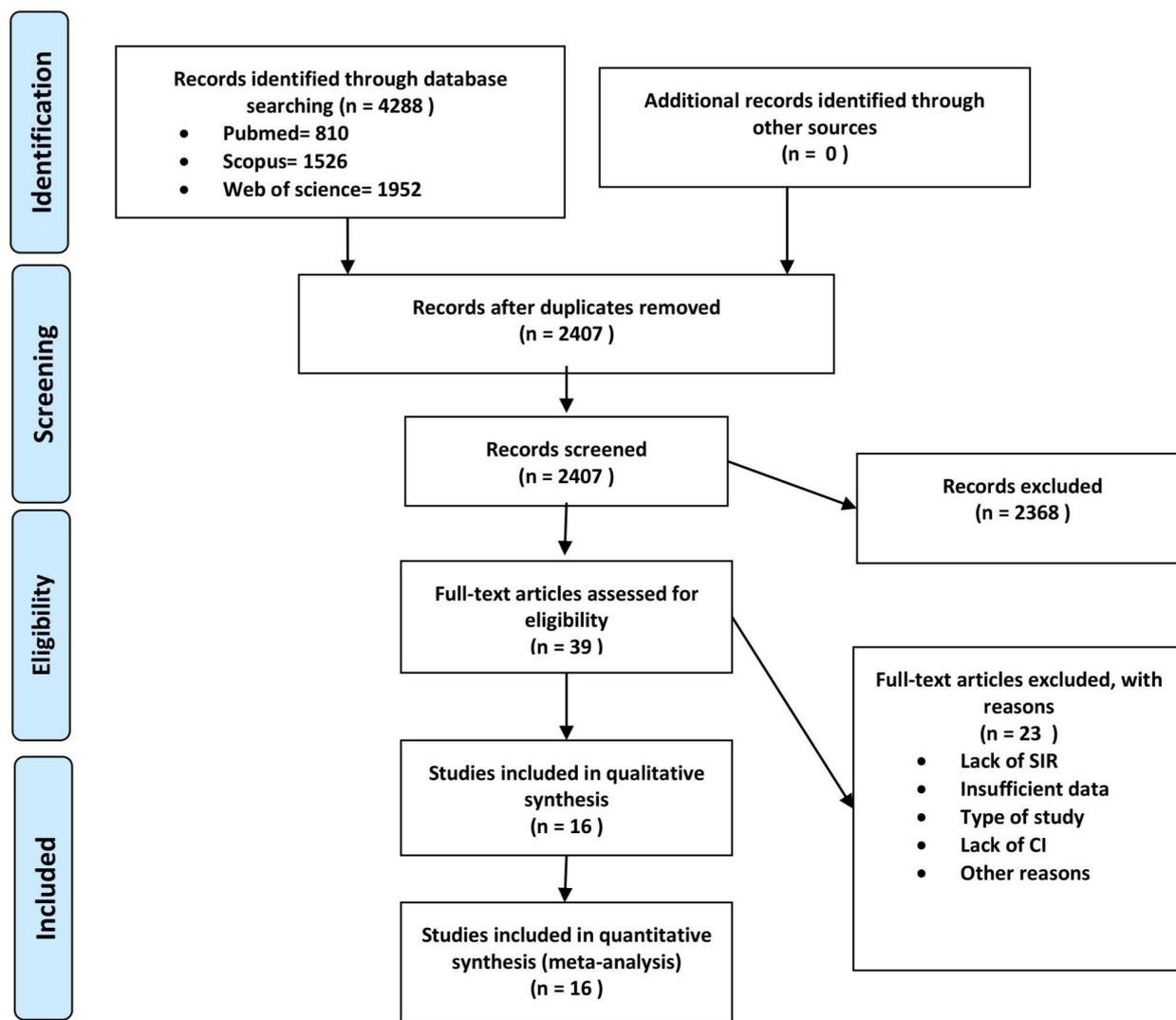


Fig. 1. PRISMA flowchart for study selection process.

Our search did not find any systematic review on risk assessment of secondary malignancies in patients with ovarian cancer. However, Zikry *et al.* performed a meta-analysis on the risk of melanoma in patients with ovarian teratoma [22]. We conducted a systematic review and meta-analysis on risk assessment of secondary malignancies in patients with ovarian cancer.

## 2. Materials and methods

### 2.1 Information sources

This systematic review and meta-analysis was conducted on cohort studies through searching PubMed, Scopus, and Web of Science up to September 2019.

### 2.2 Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for study design, search protocol, screening, and reporting. The search was done in PubMed, Scopus, and Web of Science using the following keywords: ovarian neoplasm, incidence, second,

secondary, after, and neoplasm.

### 2.3 Eligibility criteria

The criteria for selecting the papers were as follows: Cohort studies that included patients with ovarian cancers.

Studies that reported standardized incidence ratio (SIR), or that reported data that could be used to calculate SIR.

Studies published in English before September 2019.

No limitations were considered about study location.

All non-cohort studies, including case series, case-control, and case reports were omitted.

All animal and experimental studies were excluded.

### 2.4 Study selection

At this stage, duplicates were removed by Endnote software, then, two researchers separately screened the remaining papers for eligibility criteria. In case of disagreement, a third researcher helped to resolve the problem.

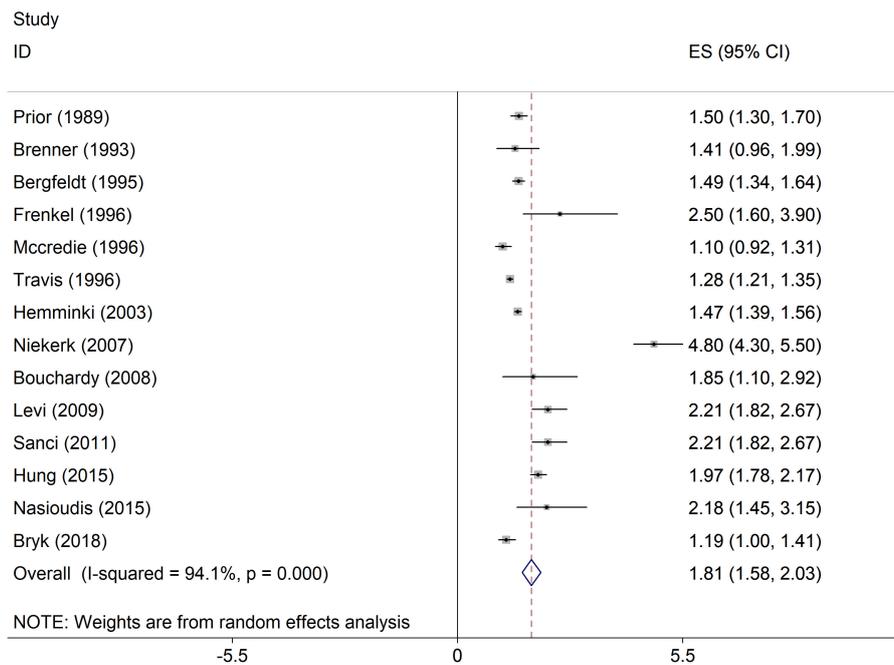


Fig. 2. Forest plot for pooling SIR of All cancer.

### 2.5 Quality assessment

The Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOS) was used for quality assessment. The studies were classified into three categories. Studies with scores 1, 2, and 3 were considered poor; scores 4, 5, and 6 were of fair quality and studies with scores 7, 8, and 9 were considered good.

### 2.6 Data extraction

Data was extracted by checking the full text of the papers. Information, including author name, publication year, mean age, SIR of secondary malignancies, and follow-up duration were extracted.

### 2.7 Statistical analysis

The studies heterogeneity was evaluated by the  $I^2$  test. The random/fixed-effect model was used to combine the results of the studies in case of  $I^2$  higher than 50%. Data were analyzed using STATA v11 and forest plot chart.

## 3. Results

### 3.1 Study selection process

A total of 4288 papers were found. After omitting duplicate papers and screening, 16 papers were entered into the meta-analysis. The PRISMA flow chart for the selection process is presented in Fig. 1.

### 3.2 Study characteristics

The sample size in studies ranged from 130 to 32,251 (n = 122,715). Secondary malignancies were diagnosed in 4,458 cases with ovarian cancer. The studies were performed in the U.S. (n = 3), Sweden (n = 2), Switzerland (n = 2), Germany (n = 1), Australia (n = 1), Israel (n = 1), Netherlands (n = 1),

Britain (n = 1), Turkey (n = 1), Taiwan (n = 1), and Finland (n = 1). In one study the location was not clear. Baseline characteristics of cohort studies are presented in Table 1.

### 3.3 Quality assessment

The methodological quality of the studies was evaluated using the NOS checklist. Eleven studies were found to be of good, and five studies were of fair quality.

### 3.4 Risk assessment of secondary malignancies after ovarian cancer

Based on cohort studies used in current meta-analysis, more than 40 secondary malignancy events were reported in patients with ovarian cancer.

Rare malignancies were found in only one study, including malignancies of the tongue, buccal, head and neck, gastrointestinal tract, larynx, ovary, vulva, eye, mesothelioma, bone, acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL).

Cancers that were reported in more than one study were mouth/pharynx, esophagus, stomach, small intestine, colon, rectum, colorectal, liver, pancreas, digestive system, lung, respiratory system, breast, endometrium, cervix uteri, genital, renal, bladder, melanoma, skin (excluding melanoma), urinary tract, brain, central nervous system, thyroid, endocrine glands, connective tissue, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and hematopoietic cancers.

In present meta-analysis, only secondary malignancies that were reported in more than one study were included.

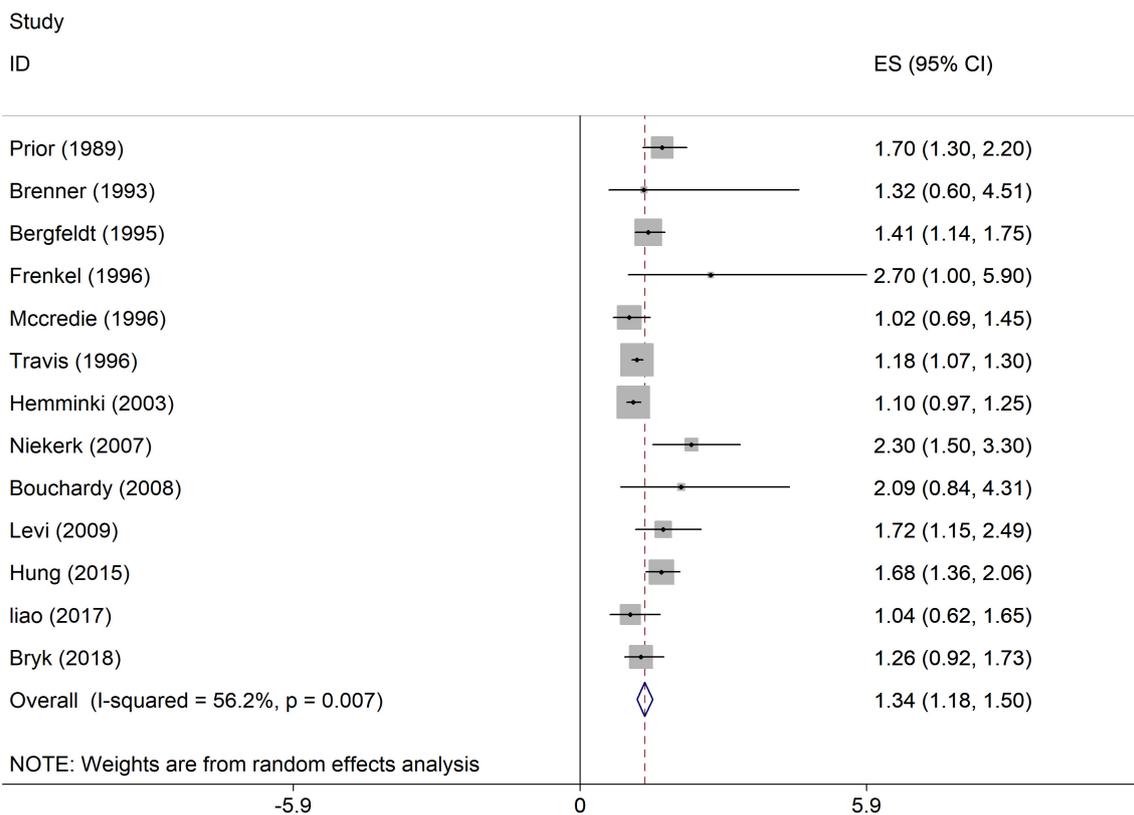
### 3.5 Risk of secondary malignancies

SIR for all secondary cancers in ovarian cancer patients was 1.81 (95% CI 1.58–2.03) ( $I^2 = 94.1%$ ) (Fig. 2).

**Table 1. Characteristics of studies entered into the meta-analysis.**

Author (Year)	Region	Follow-up	Person-years Follow up	Number of Participants	Total Mean age (range)	No. of Secondary cancer	Quality assessment Score (1 to 9)
Prior (1989) [58]	UK	6.5 Y	21446	7203	-	213	7
Brenner (1993) [59]	Germany	3 Y	19040	1745	-	32	7
Bergfeldt (1995) [60]	Sweden	6 Y	27848	5060	59 (1–80)	346	7
McCredie (1996) [61]	Australia	3.6 Y	18570	5170	59.5	126	7
Frenkel (1996) [62]	Israel	-	-	364	-	21	7
Travis (1996) [42]	USA	4.1 Y	133098	32251	58.8	1296	8
Weinberg (1999) [63]	USA	-	-	28832	-	300	7
Hemminki (2003) [64]	Sweden	-	156877	19994	61*	1104	8
Niekerk (2007) [65]	Netherland	-	-	5366	-	244	5
Bouchardy (2008) [66]	Switzerland	8.8	-	130	50.7 (17–92)	18	8
Levi (2009) [67]	Switzerland	-	-	304	-	31	5
Sanci (2011) [68]	Turkey	96.5 M	-	870	47 (19–79)	110	8
Nasioudis (2015) [69]	USA	-	-	806	15.4	28	6
Hung (2015) [70]	Taiwan	3.48 Y	56214	12127	50 (42–61)*	407	7
Liao (2017) [71]	UC	13.9	-	1507	22 (0–86)	45	6
Bryk (2018) [72]	Finland	-	-	986	-	137	5

\*Median; Y, Year; M, Month; UC, Unclear.



**Fig. 3. Forest plot for pooling SIR of Breast cancer.**

The SIR for breast cancer was 1.34 (95% CI 1.18–1.50)  $I^2 = 58.2$  (Fig. 3).

Total SIR for mouth and pharynx malignancies was 1.7 (95% CI 0.31–3.09) (Supplement Fig. 1). Secondary esophagus and stomach malignancies were investigated in four and five studies, respectively (Table 2). High incidence of sec-

ondary esophagus (SIR = 0.81, 95% CI 0.38–1.24) and stomach (SIR = 1.22, 95% CI 0.94–1.50) malignancies were observed in this meta-analysis (Supplement Figs. 2,3). Small intestine cancer was reported in two cohort studies (SIR = 2.36, 95% CI 1.11–3.61) (Table 2 and Supplement Fig. 4).

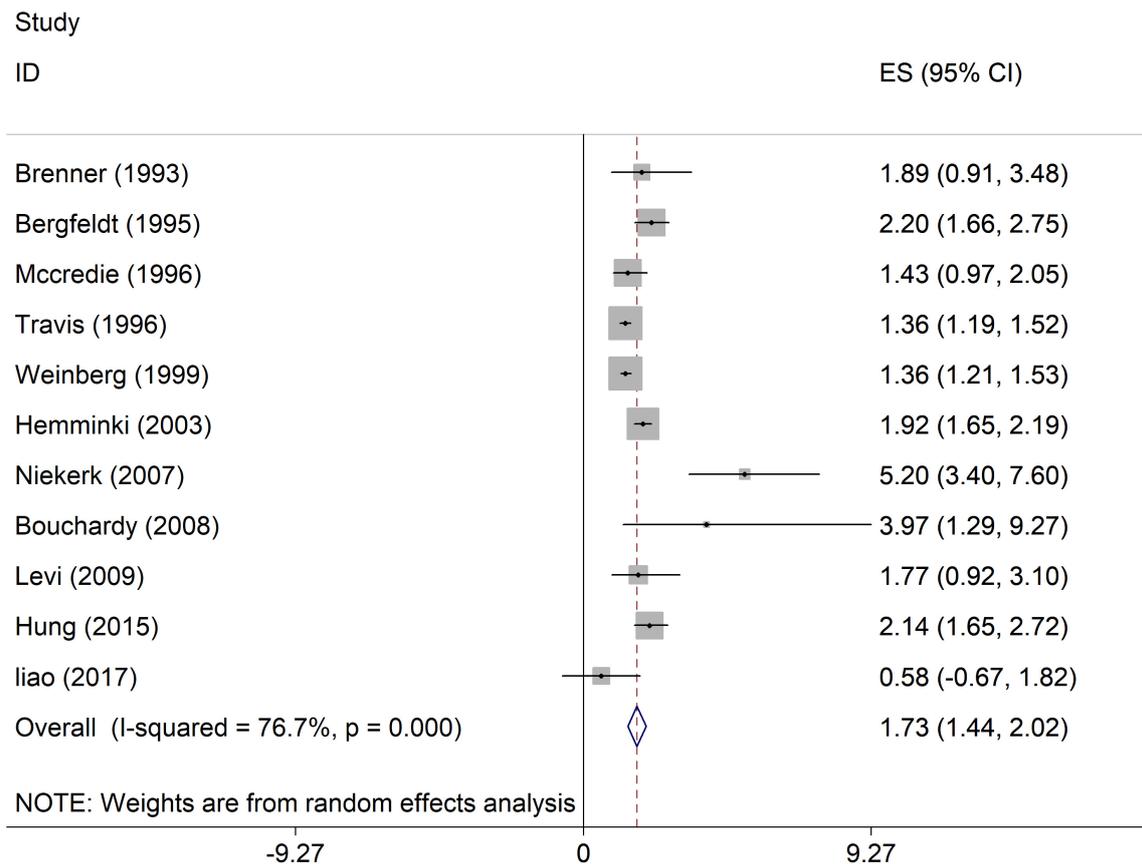


Fig. 4. Forest plot for pooling SIR of Colorectal cancer.

Cancers of the large intestine were reported separately in different studies. The SIRs for colon (1.68, 95% CI 1.12–2.24), rectum (1.61, 95% CI 1.35–1.87), and colorectal (1.73, 95% CI 1.44–2.02) cancers were found to be high (Fig. 4, Table 2 and Supplement Figs. 5,6).

The SIRs for liver and pancreatic cancers in patients with ovarian cancer was 1.07 (95% CI 0.78–1.35) and 1.42 (95% CI 1.13–1.71), respectively (Supplement Figs. 7,8). The meta-analysis indicated a SIR of 1.39 (95% CI 1.18–1.61) for digestive system cancers (Table 2 and Supplement Fig. 9).

In this meta-analysis, the overall SIRs for endometrium and cervix uteri cancers were 6.31 (95% CI 4.18–8.44) and 1.16 (95% CI 0.51–1.81), respectively (Supplement Figs. 10,11). Combination of SIRs in genital cancers was 1.13 (95% CI 0.46–1.79) (Table 2 and Supplement Fig. 12).

The SIRs for secondary renal and bladder malignancies were 1.43 (95% CI 1.11–1.74) and 2.13 (95% CI 1.77–2.50), respectively (Supplement Figs. 13,14). Total SIR for urinary system malignancies in ovarian cancer patients was 1.84 (95% CI 1.55–2.13) (Fig. 5).

Pooling SIRs were 3.33 (95% CI 2.23–4.43) for leukemia, 1.11 (95% CI 0.87–1.36) for lymphoma, and 2.05 (95% CI 0.86–3.24) for hematopoietic cancers (Table 2 and Supplement Figs. 15,16,17).

Total SIR for lung cancer was 1.09 (95% CI 0.94–1.23), and

for respiratory system cancers it was 1.23 (95% CI 0.43–2.02) (Table 2 and Supplement Figs. 18,19).

The SIRs for melanoma and non-melanoma skin cancers were 1.29 and 1.42 (95% CI 0.97–1.61; 95% CI 1.06–1.77), respectively (Table 2 and Supplement Figs. 20,21).

The meta-analysis resulted in SIR of 1.01 for brain and central nervous system malignancies (95% CI 0.69–1.33) (Supplement Fig. 22). Total SIR for Connective tissue malignancy was 2.61 (95% CI 1.56–3.66) (Supplement Fig. 23).

The SIRs for thyroid and malignancies of the endocrine system in women with ovarian cancer were 1.59 (95% CI 1.13–2.04) and 1.29 (95% CI 0.82–1.76), respectively (Table 2 and Supplement Figs. 24,25).

#### 4. Discussion

In this study, an increased risk of secondary malignancies was observed in ovarian cancer patients. Esophageal cancer was the least common malignancy in women with ovarian cancer when compared to the general population. On the other hand, central nervous system (CNS) neoplasms were as common as in the general population. The highest standardized incidence obtained was for the uterus, leukemia, endometrium, connective tissue, and bladder cancers.

Different factors can be involved in developing secondary malignancies in patients with ovarian cancer who had been treated. Genetic predisposition is among the major causes

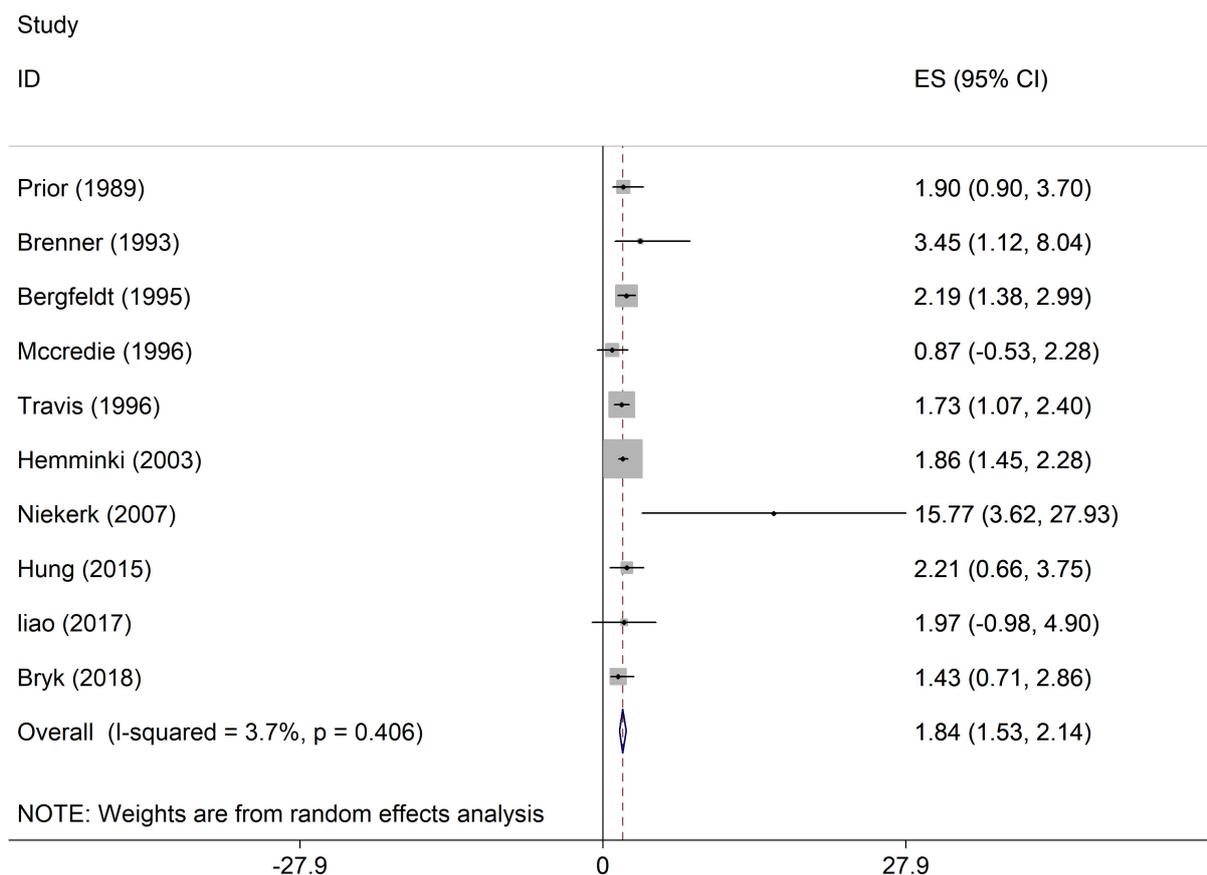


Fig. 5. Forest plot for pooling SIR of Urinary system cancers.

in these individuals. Extensive studies on the genetic background of ovarian cancer indicated several genetic factors that contribute to the development of this type of malignancy in women such as mutations in breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes or mutations in mismatch repair genes that lead to Lynch syndrome. In addition to ovarian cancer, the BRCA 1/2 gene is implicated in the pathogenesis of malignancies such as breast cancer [23–25], endometrial cancer [26–28], pancreatic cancer [26, 29, 30], gastric cancer, gallbladder cancer [29, 31], and colorectal cancer.

A meta-analysis of 14 case-control studies, showed that pathogenic variants of BRCA genes were associated with an increased risk of colorectal cancer [32]. BRCA gene mutation is also believed to be involved in development of ovarian cancer [23–25]. Besides, genetic mutations are still present after the treatment of ovarian cancer and could cause other cancers, so, elevated incidence of malignancies in which this gene is involved is expected. In current study, an increased incidence was observed in breast, endometrium, pancreatic, stomach, gallbladder, and colorectal cancers compared to the general population.

A rare syndrome called Lynch syndrome is caused by mutations in genes involved in repairing DNA mismatches. In patients with this syndrome, we observed an increased incidence of some cancers, including ovarian, colorectal, uri-

nary tract, stomach, and pancreas, which justifies present findings [33–35]. According to evidence, the most common extracolonic cancers in Lynch syndrome include cancers of the urinary tract and ovaries, followed by brain tumors, small intestine cancers, breast, and bile duct, which are less common [36]. If ovarian cancer is caused by Lynch syndrome, an increased risk of these cancers is expected; as in our study, we found an increased incidence of the uterus, skin (melanoma/non-melanoma), stomach, and colorectal cancers compared to the normal population.

Sporadic ovarian carcinoma is the most common type of this malignancy [37]. A review by Denlinger *et al.* [38] reported sporadic cases of ovarian cancer as a significant risk factor for colorectal cancer, which is in line with our findings.

Chemotherapy and radiation therapy treatments increase the risk of developing future malignancies [39, 40]. However, all patients are not at equal risk for secondary malignancies, and all secondary malignancies are not due to a history of chemotherapy. Alkylating agents, topoisomerase inhibitors, and anthracycline agents are among the common carcinogenic drugs used in cancer treatment regimens that further affect chemotherapy-sensitive cells such as bone marrow cells, hair follicles, and gastrointestinal epithelial cells [39].

**Table 2. Summarized Pooled SIRs of Considered Secondary malignancies.**

Secondary Malignancy	Number of study	I-square	P value	SIR (95% CI)
Digestive system	9	57.1	0.017	1.39 (1.18–1.61)
Mouth and pharynx Cancers	4	0.0	0.820	1.70 (0.31–3.09)
Esophageal cancer	4	0.0	0.598	0.81 (0.38–1.24)
Stomach cancer	5	13.9	0.326	1.22 (0.94–1.50)
Cancer of Small intestine	2	0.000	0.328	2.36 (1.11–3.61)
Colon cancer	4	84.2	0.000	1.68 (1.12–2.24)
Rectal cancer	4	9.6	0.345	1.61 (1.35–1.87)
Cancer of Liver and gallbladder	4	0.0	0.848	1.07 (0.78–1.35)
Pancreas cancer	6	0.0	0.523	1.42 (1.13–1.71)
Reproductive system	6	75.7	0.001	1.13 (0.46–1.79)
Cancer of Endometrium	7	98.0	0.000	6.31 (4.18–8.44)
Cancer of Cervix uteri	5	25.0	0.255	1.16 (0.51–1.81)
Urinary System	10	3.7	0.406	1.84 (1.55–2.13)
Kidney cancer	8	43.8	0.087	1.43 (1.11–1.74)
Urinary bladder cancer	7	0.0	0.578	2.13 (1.77–2.50)
Hematopoietic system	4	61.6	0.050	2.05 (0.86–3.24)
Leukemia	8	64.4	0.006	3.33 (2.23–4.43)
Lymphoma	6	0.0	0.651	1.11 (0.87–1.36)
Endocrine system	2	24.7	0.249	1.29 (0.82–1.76)
Thyroid carcinoma	5	14.1	0.324	1.59 (1.13–2.04)
Other cancers	-	-	-	-
Melanoma	6	0.0	0.878	1.29 (0.97–1.61)
Skin cancer (non-melanoma)	4	0.0	0.512	1.42 (1.06–1.77)
Cancer of CNS	4	0.0	0.398	1.01 (0.69–1.33)
Lung cancer	5	17.2	0.305	1.09 (0.94–1.23)
Connective tissue malignancy	4	0.0	0.506	2.61 (1.56–3.66)

SIR, Standardized incidence ratio.

Progress in chemotherapy protocols has dramatically increased survival in these patients. Before 1990, standard ovarian cancer treatment protocols included cisplatin, doxorubicin, and cyclophosphamide, which significantly increase the risk of secondary malignancies after 20 years [39, 41, 42]. Today, depending on the stage of ovarian cancer, treatment regimens such as cisplatin + paclitaxel and carboplatin + paclitaxel are used. In advanced stages, tamoxifen and gemcitabine are the most common choices of treatment [43–47].

According to the present meta-analysis, after treatment of ovarian cancer, there is elevated risk for secondary malignancies such as endometrial and bladder cancers and leukemia. Currently, screening and surveillance are performed for early detection of these malignancies. For instance, physicians inform women at increased risk for endometrial cancer [48]. Symptomatic endometrial cancers are seen in 75%–90% of the cases [49, 50], so, the risk symptoms (e.g., abnormal uterine bleeding) are taught to high-risk patients, and they are advised to follow the symptoms and visit their physician if any unusual symptoms were observed [48].

Bladder cancer is one of the most common cancers of

the urinary tract, and there is paucity of information about screening methods for this malignancy. However, micro hematuria [51, 52], urinary cytology [53], urinary biomarkers [54], and cystoscopy [55] are suggested to be beneficial. Another common malignancy in women with improved ovarian cancer is leukemia. Genomic examination of patients is used for screening and early detection of leukemia [56]. During this procedure, the patient's genome is examined, and the expression of genes that are effective in cancer is evaluated. However, cancer screening is one of the most controversial issues in medicine. For many cancers, the benefits and harms of available screening tests are not studied well, and there is still no agreement on an appropriate test confidence interval and the cut-off for a positive diagnosis, so screening programs vary in different countries [57].

## 5. Conclusions

This systematic review and meta-analysis showed that patients with ovarian cancer had a wider range of malignancies than the general population. Leukemia, endometrial cancer, connective tissue, and bladder malignancies are among the most common secondary malignancies in these patients. Further comprehensive studies are needed to corroborate cur-

rent findings and investigate the various aspects affecting the incidence of secondary malignancies in these patients. Moreover, if economically feasible, high-risk malignancies can be included in the screening program of these patients in order to diagnose common secondary cancers, which hopefully will lead to diagnosis and treatment at early stages of the disease.

### Author contributions

KH, AS and PL determined the search strategy. KH, PH, NS and AZK conducted the selection of relevant studies and data extraction separately. DS and AS evaluated the quality of each study independently. KH and RAN did the analyses and outcomes. KH, DS, AS, PL, PH and SR drafted the manuscript. All authors revised and approved the final version of the manuscript.

### Ethics approval and consent to participate

The proposal of this systematic review and meta-analysis has been registered in research committee of Mazandaran University of Medical Sciences with the Ethic number: IR.MAZUMS.REC.1398.1265.

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### Conflict of interest

The authors declare no conflict of interest.

### Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://ejgo.imrpess.com/EN/10.31083/j.ejgo.2021.02.2238>.

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