Investigation on factors associated with ovarian cancer: an umbrella review of systematic review and meta-analyses

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Abstract
Following cervical and uterine cancer, ovarian cancer (OC) has the third rank in gynecologic cancers. It often remains non-diagnosed until it spreads throughout the pelvis and abdomen. Identification of the most effective risk factors can help take prevention measures concerning OC. Therefore, the presented review aims to summarize the available studies on OC risk factors. A comprehensive systematic literature search was performed to identify all published systematic reviews and meta-analysis on associated factors with ovarian cancer. Web of Science, Cochrane Library databases, and Google Scholar were searched up to 17th January 2020. This study was performed according to Smith et al. methodology for conducting a systematic review of systematic reviews. Twenty-eight thousand sixty-two papers were initially retrieved from the electronic databases, among which 20,104 studies were screened. Two hundred seventy-seven articles met our inclusion criteria, 226 of which included in the meta-analysis. Most commonly reported genetic factors were MTHFR C677T (OR = 1.077; 95% CI (1.032, 1.124); P-value<0.001), BSML rs1544410 (OR = 1.078; 95% CI (1.024, 1.153); P-value = 0.004), and Fokl rs2228570 (OR = 1.123; 95% CI (1.089, 1.157); P-value<0.001), which were significantly associated with increasing risk of ovarian cancer. Among the other factors, coffee intake (OR = 1.106; 95% CI (1.009, 1.211); P-value = 0.030), hormone therapy (RR = 1.057; 95% CI (1.030, 1.400); P-value<0.001), hysterectomy (OR = 0.863; 95% CI (0.745, 0.999); P-value = 0.049), and breast feeding (OR = 0.719, 95% CI (0.679, 0.762) and P-value<0.001) were mostly reported in studies. Among nutritional factors, coffee, egg, and fat intake significantly increase the risk of ovarian cancer. Estrogen, estrogen-progesterone, and overall hormone therapies also are related to the higher incidence of ovarian cancer. Some diseases, such as diabetes, endometriosis, and polycystic ovarian syndrome, as well as several genetic polymorphisms, cause a significant increase in ovarian cancer occurrence. Moreover, other factors, for instance, obesity, overweight, smoking, and perineal talc use, significantly increase the risk of ovarian cancer.

Keywords: Ovarian cancer, Risk factor, Protective factor, Nutritional factors, Genetic factors, Environmental factors

Background
Following cervical and uterine cancer, ovarian cancer (OC) has the third rank in gynecologic cancers. A woman’s risk of getting ovarian cancer during her lifetime is about 1 in 78. Mortality rate of ovarian cancer is about 1 in 108. (These statistics don’t count low malignant potential ovarian tumors.) It often remains non-diagnosed until it spreads throughout the pelvis and abdomen,
making its treatment even more difficult. At its early stages, when it is limited to the ovary, the treatment success has a higher rate. The silent tumor growth in OC increases its mortality rate and deteriorates its prognosis [1]. OC has a 46% five-year survival rate. Early detection is important. Most women with Stage 1 ovarian cancer have an excellent prognosis. Stage 1 patients with grade 1 tumors have a 5-year survival of over 90%, as do patients in stages 1A and 1B [2].

Besides the undetectable progress of this type of cancer, improper screening methods further delay its diagnosis [3]. Due to the low prevalence of ovarian cancer even amongst postmenopausal women (1:2500), an efficient screening tool requires high sensitivity (>75%) and extremely high specificity (99.7%) [4].

A significant increase is estimated in its mortality rate by 2040. Nonetheless, identification of the most effective risk factors can be helpful in prevention measures concerning OC [5]. Conflicting results can be found in the literature describing the role of several factors (e.g., nutritional, environmental, and genetic factors, as well as lifestyle, drug use, and medical history). Genetic predisposition is related to a higher risk of ovarian cancer that also tends to occur at a younger age. BRCA1 and 2 mutation carriers harbor significantly increased ovarian cancer risk (40–45% resp. 15–20%) by the age of 70. Risk of OC in the high risk women under 40 years old is low [6]. Several studies on ovarian cancer have been published that have examined various factors influencing the incidence, prevalence and mortality rate. Some of these studies were purely observational and some were meta-analyses. So far, no study has been published that has summarized and re-analyzed the results of various meta-analyses in this field, and this issue shows the importance of this study. The present study examined up to 50 factors (nutritional and genetic factors, drugs use, some diseases, breast feeding, smoking and physical activity) that other studies had examined and sometimes presented conflicting results.

The presented umbrella meta-analysis and systematic review is focused on any kind of risk factors on ovarian cancer among all women and aimed to summarize the available reviews and find the most important OC risk factors.

This study is focused on any kind of risk factors on ovarian cancer among all women.

Methods
A systematic review of systematic reviews was conducted to identify the associated factors with OC. This study was performed according to Smith et al. methodology for conducting a systematic review of systematic reviews [7].

Study question
What are the most important factors associated with ovarian cancer found in systematic reviews?

Literature search
A comprehensive systematic literature search was performed to identify all published systematic reviews and meta-analysis on associated factors with OC. Medline through PubMed, Scopus, Embase, Web of Science, Cochrane Library databases, and Google Scholar all were searched up to 17th January 2020 without time limitation.

The search strategy included the use of Mesh terms and keywords related to subject and study design (ovarian; ovary; cancer; carcinoma; neoplasm; tumor; Malignancy; review; systematic review; systematic literature review; meta-analysis). The detailed search strategy for the Medline can be found in the supplementary, Table 1 S. The reference lists of selected articles were also manually searched to identify any additional related documents.

Study selection
This overview only included systematic reviews of factors associated with OC.

The articles which met the following criteria were included in our study: (1) systematic reviews or meta-analysis; (2) have evaluated risk factors of Ovarian cancer; (3) have at least abstracts in English. The articles that were narrative reviews or had assessed prognostic factors of OC or did not provide at least abstract in English were excluded. Characteristic of included studies are illustrate in Table 1.

Four authors (RR, MM, SL, and KT) independently screened the titles and abstracts of citations to identify potentially relevant studies. Then, the full texts of potentially eligible articles were obtained and reviewed for further assessment according to the inclusion and exclusion criteria. Controversies were resolved by consulting a third person (LJ).

Data extraction
Data were extracted from eligible studies using a pre-specified form in Microsoft Excel by four authors (RR, MM, SL, and KT) independently. The following information was collected: first author, year of publication, number of included primary studies, number of participants, age of participants, factors associated with OC, besides the measure of association (e.g., RR, OR), and its confidence intervals. Any discrepancy was resolved through discussion with a third author (LJ). EndNote X9 was used to extracting the records and removing duplicates (The EndNote Team. EndNote. EndNote X9 ed. Philadelphia, PA: Clarivate; 2013.).
| No. | Author          | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors                                      |
|-----|-----------------|------|-----------------|------------------------|--------------|----------------|--------------------------------------------------------|
| 1   | Yan Qiao        | 2018 | 21              | 309                    | -            | -              | Aspirin                                                |
| 2   | Hongmei Chen    | 2017 | 14              | 11,690                 | 4448         | 7242           | VDR rs2228570                                         |
| 3   | Li-Hui Yan      | 2018 | 46              | 84,772                 | 36,298       | 48,474         | BRCA2 N372H                                            |
| 4   | Jie Ruan        | 2018 | 24              | 1217                   | -            | -              | P16INK4a                                               |
| 5   | liang Tang      | 2018 | 13              | 13,064                 | 5461         | 7603           | HER2 and ESR2 polymorphisms                           |
| 6   | Ross Penninkilampi | 2018 | 27              | -                      | 14,314       | -              | Talc Use                                               |
| 7   | Chao-Huan Xu    | 2017 | 7               | 3016                   | 1,345        | 1,671          | Genetic polymorphisms                                  |
| 8   | Xu-Ming Zhu     | 2017 | 10              | 4621                   | 1930         | 2464           | Genetic polymorphisms                                  |
| 9   | JieNa Li        | 2017 | 9               | 4024                   | 1333         | 2691           | ERCC2 rs13181                                          |
| 10  | Jing Li         | 2017 | 7               | -                      | 1898         | -              | C-reactive protein                                     |
| 11  | Dongyu Zhang    | 2017 | 14              | 2,342,245              | 4184         | -              | Diabetes mellitus                                      |
| 12  | Xingxing Song   | 2017 | 15              | 493,415                | 7453         | 485,962        | Calcium Intake                                         |
| 13  | Wera Berge      | 2016 | 27              | 34,176                 | 15,154       | 19,022         | Talc Use                                               |
| 14  | Xin Zhan        | 2017 | 18              | 710,857                | 8,683        | 693,174        | Tea consumption                                        |
| 15  | A Darelius      | 2017 | 11              | -                      | -            | -              | Hysterectomy                                           |
| 16  | Zhiyi Zhou      | 2017 | 13              | 2,951,539              | 13,616       | 2,937,923      | Pelvic inflammatory disease                            |
| 17  | Yang Deng       | 2017 | 8               | 14,014                 | 6613         | 7401           | Androgen receptor gene                                 |
| 18  | Bania Christina | 2016 | 32              | -                      | 11,411       | -              | Coffee Intake                                          |
| 19  | Lihua Wang      | 2017 | 13              | 3,708,313              | 5534         | 3,702,779      | Diabetes mellitus                                      |
| 20  | lin h           | 2017 | 8               | 45,624                 | 19,260       | 26,364         | MTHFR C677                                            |
| 21  | Chunpeng Wang   | 2016 | 38              | 409,061                | 40,609       | 368,452        | Endometriosis, Tubal Ligation, Hysterectomy            |
| 22  | Chunyan Shen    | 2016 | 12              | 1235                   | 806          | 429            | Adenomatous polyposis coli (APC) gene                  |
| 23  | Xiuyue Xiao     | 2016 | 12              | 901                    | 612          | 289            | P16INK4a                                               |
| 24  | Fangfang Zeng   | 2016 | 7               | 33,456                 | 2011         | 31,445         | Inflammatory markers                                   |
| 25  | Dongyu Zhang    | 2016 | 23              | 499,950                | 15,163       | 484,787        | Aspirin                                                |
| 26  | Wenlong Qiu     | 2016 | 25              | 900,000                | 6612         | 893,388        | Dietary fat intake                                     |
| 27  | Qiang Wang      | 2016 | 9               | 740                    | 485          | 255            | CDH1 promoter                                          |
| 28  | Xiaoli Hua      | 2016 | 12              | 2,361,494              | 6,275        | 2,355,219      | Dietary Flavonoids                                     |
| 29  | Li-feng Shi     | 2015 | 12              | 2,353,945              | 8896         | 2,345,049      | Hormone therapy                                        |
| 30  | Christos lavazzo | 2016 | 4              | 725                    | 385          | 340            | Hypodontia                                             |
| 31  | Sang-Hee Yoon   | 2016 | 3               | 5,659,211              | 3509         | 5,655,702      | salpingectomy                                          |
| 32  | Wei Liu         | 2016 | 35              | 42,650                 | 19,527       | 23,123         | A1298C POLYMORPHISM                                    |
| 33  | Vida Mohammad   | 2019 | 7               | 381,810                | 3653         | 378,157        | flavonoids                                             |
| 34  | Lifeng Li       | 2016 | 9               | -                      | -            | -              | Metformin                                              |
| 35  | Arefe Farvareh  | 2019 | 13              | -                      | -            | -              | Quercetin                                              |
| 36  | Xiaowei Yu      | 2016 | 14              | 11,471                 | 3796         | 7675           | ERCC2 rs13181 - XRCC2 rs3218536                       |
| 37  | Rui Hou         | 2015 | 20              | 1,117,992              | 12,046       | 1,105,946      | Dietary fat                                            |
| 38  | Zhen Liu        | 2015 | 26              | 34,817                 | 12,963       | 21,854         | overweight, obesity                                   |
| 39  | N. Keum         | 2015 | 18              | -                      | 2636         | -              | Egg intake                                             |
| 40  | Liangxiang Su   | 2015 | 4               | 12,016                 | 2344         | 9672           | BRCA2 N372H                                            |
| 41  | Li-ping Feng    | 2014 | 12              | 629,453                | 3728         | 625,725        | Egg intake                                             |
| 42  | Xiaolian Zhang  | 2015 | 5               | 4233                   | 1791         | 2,196          | Vascular Endothelial Polymorphisms                    |
| 43  | Li-Ping Feng    | 2014 | 19              | 469,095                | 9438         | 459,657        | Breastfeeding                                          |
| 44  | collaborative Group | 2015 | 52             | 12,110                 | -            | -              | Menopausal hormone use                                 |
| 45  | Huang Yan-Hong  | 2015 | 13              | 1,996,841              | 3587         | 1,990,984      | alcohol consumption                                    |
| 46  | Ji-yi Hu        | 2015 | 8               | 305,338                | 3555         | 301,783        | cruciferous vegetables                                 |
| 47  | Jing Liao       | 2014 | 21              | 3117                   | 2842         | 4305           | progesterone receptor Polymorphisms                   |
Table 1  (continued)

| No. | Author               | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors                                                                 |
|-----|----------------------|------|-----------------|------------------------|--------------|----------------|-----------------------------------------------------------------------------------|
| 48  | Xingzhong Hu         | 2015 | 5               | 5884                   | 2336         | 3548           | RAD51 Gene 135G/C                                                                   |
| 49  | Jing Liu             | 2014 | 19              | -                      | -            | -              | Milk, Yogurt, and Lactose Intake                                                   |
| 50  | Jun Qin              | 2014 | 62              | 92,857                 | 42,315       | 50,542         | STK15 polymorphisms                                                                |
| 51  | Luliang Liu          | 2015 | 15              | 14,798                 | 7,450        | 7,348          | MMP-12-82 A/G polymorphism                                                         |
| 52  | X.Y. Shi             | 2015 | 3               | 7026                   | -            | -              | MTHFR A1298C polymorphism                                                         |
| 53  | M. Zhai              | 2015 | 4               | 10,169                 | 3565         | 6604           | Arg188His polymorphism                                                             |
| 54  | Yue-Dong Wang        | 2014 | 15              | 1653                   | 822          | 831            | serum levels of osteopontin                                                       |
| 55  | John A. Barry        | 2014 | 3               | 72,973                 | 919          | 72,054         | polycystic ovary syndrome                                                          |
| 56  | Xini Li              | 2014 | 10              | 72,054                 | 6127         | 65,927         | dietary lycopene intake                                                           |
| 57  | Yue-Dong Wang        | 2014 | 4               | 1133                   | 474          | 659            | Asn680Ser polymorphism                                                             |
| 58  | Shujing Shi          | 2014 | 13              | 16,230                 | 5,927        | 10,303         | RADS1 135 G>C and XRCC2 G>A (rs3218536)                                            |
| 59  | M. A. Alqumber       | 2014 | 12              | 2257                   | 993          | 1264           | 72 Arg Pro Polymorphism                                                           |
| 60  | Pei-yue Jiang        | 2014 | 15              | 889,033                | 6,087        | 882,946        | Fish Intake                                                                       |
| 61  | Danhua Pu            | 2014 | 7               | 7356                   | 3493         | 3863           | MTHFR Polymorphism                                                                |
| 62  | Xinwei Pan           | 2013 | 8               | 7724                   | 3,723        | 4,001          | Ala222Val                                                                       |
| 63  | Yulan Yan            | 2013 | 4               | 9108                   | 3,635        | 5,473          | XRCC3 Thr241Met polymorphism                                                      |
| 64  | Tracy E. Crane       | 2013 | 24              | 519,431                | 2091         | 517,340        | Dietary Intake                                                                   |
| 65  | Su Li                | 2014 | 14              | 10,964                 | -            | -              | VDR rs228570                                                                     |
| 66  | Dan Cheng            | 2014 | 22              | 15,343                 | 6836         | 8507           | RADS1 Gene 135G/C polymorphism                                                    |
| 67  | Bo Han               | 2014 | 11              | 379,868                | 4,306        | 375,562        | Cruciferous vegetables                                                            |
| 68  | Xin-Lan Qu           | 2014 | 10              | 297,892                | 4392         | 293,500        | Phytoestrogen Intake                                                              |
| 69  | Jin-Ze Du            | 2014 | 8               | 3940                   | 1,293        | 2,647          | COMT rs4680 Polymorphism                                                          |
| 70  | Li-Yuan Han          | 2014 | 10              | 6001                   | 2578         | 3423           | GST Genetic Polymorphisms                                                        |
| 71  | Da-Peng Li           | 2014 | 40              | 415,949                | 17,139       | 398,810        | Breastfeeding                                                                    |
| 72  | Yong-Jun Ma          | 2014 | 6               | 3839                   | 1,766        | 2,073          | Rs11615 (C>T)                                                                    |
| 73  | Jamal Poorolajal     | 2014 | 19              | 10,384                 | -            | -              | BMI                                                                              |
| 74  | Li-Min Zhou          | 2014 | 6               | 435,398                | 2983         | 432,415        | Recreational Physical Activity                                                    |
| 75  | Pyemeth Dilokthornsakul | 2013 | 34             | -                      | -            | -              | Meflornimin                                                                     |
| 76  | Chenglin Li          | 2013 | 18              | 227,859                | 5077         | 222,182        | Folate intake and MTHFR polymorphism C677T                                        |
| 77  | Susan J. Jordan      | 2013 | 22              | -                      | -            | -              | hysterectomy                                                                    |
| 78  | Nan-Nan Luan         | 2013 | 35              | 720,617                | 14,465       | 706,152        | Breastfeeding                                                                    |
| 79  | Xue Qin              | 2013 | 7               | 4,809                  | 1,977        | 2,832          | VDR                                                                             |
| 80  | Laura J. Havrilskay  | 2013 | 55              | 31,056                 | 10,031       | 21,025         | Oral Contraceptive                                                               |
| 81  | Ting-Ting Gong       | 2012 | 27              | 1,020,516              | 9859         | 1,010,657      | Age at menarche                                                                  |
| 82  | Yanling Liu          | 2013 | 6               | 10,768                 | 4,107        | 6,661          | VDR                                                                             |
| 83  | Louise Baandrup      | 2012 | 21              | 563,976                | 11,759       | 552,217        | NSAIDs                                                                          |
| 84  | Jung-Yun Lee         | 2012 | 19              | -                      | -            | -              | Diabetes Mellitus                                                               |
| 85  | Chengbin Ma          | 2013 | 10              | 18,628                 | 5,932        | 12,696         | MTHFR C677T polymorphism                                                         |
| 86  | Ying-Yu Ma           | 2013 | 6               | 3745                   | 1534         | 2211           | MDM2 309T.G Polymorphism                                                        |
| 87  | Gwan Gyu Song        | 2013 | 12              | 8775                   | 3716         | 5059           | VDR                                                                             |
| 88  | Ketan Gajjar         | 2012 | 5               | 3795                   | 1199         | 2596           | Cytochrome P1B1 (CYP1B1)                                                         |
| 89  | Xiaojuan Ni          | 2012 | 17              | 193,424                | 10,373       | 183,051        | NSAIDs                                                                          |
| 90  | Lu Liu               | 2012 | 4               | 7127                   | 3,496        | 3,631          | C677T and A1298C polymorphism                                                    |
| 91  | TN. Sergentanis      | 2012 | 11              | 5025                   | 1,680        | 3345           | Mspl and Ile462-Val and Thr461Asn                                                |
| 92  | Collaborative Group  | 2012 | 51              | 123,056                | 28,114       | 94,942         | Smoking                                                                         |
| 93  | Megan S Rice         | 2012 | 30              | 18,922                 | -            | -              | Tubal ligation and Hysterectomy                                                   |
| 94  | Matteo Rota          | 2012 | 27              | 15,762,134             | 16,554       | 15,745,580     | Alcohol drinking                                                                |
| 95  | Collaborative Group  | 2012 | 47              | 106,468                | 25,157       | 81,313         | Body Size                                                                       |
| No. | Author                | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors                      |
|-----|-----------------------|------|-----------------|------------------------|--------------|---------------|----------------------------------------|
| 96  | Su-Qin Shen           | 2012 | 18              | 7,368                  | 2,193        | 5,175         | TP53 Arg72Pro                           |
| 97  | Xiao-Ping Ding        | 2012 | 8               | 7,457                  | 3,379        | 4,078         | MTHFR C677T Polymorphism                |
| 98  | M.G.M. Braem          | 2011 | 150             | -                      | -            | -             | Genetic variants                        |
| 99  | M. Constanza Camargo  | 2011 | 18              | 21,973                 | 117          | 22,090        | Asbestos                                |
| 100 | David Cibula          | 2011 | 3               | -                      | -            | -             | Oral contraceptives                     |
| 101 | Sarah J. Oppeneer     | 2011 | 16              | -                      | 7,234        | -             | Tea Consumption                         |
| 102 | Lu Yin                | 2011 | 10              | 157,292                |              | -             | Circulating vitamin D                   |
| 103 | A Wallin              | 2011 | 8               | 754,836                | 2349         | 752,487       | Red and processed meat consumption     |
| 104 | D. Cibula             | 2011 | 13              | -                      | -            | -             | Tubal ligation                          |
| 105 | Ru-Yan Liao           | 2010 | 4               | 15,104                 | 5,532        | 9,572         | TGFBR1*6A/9A polymorphism               |
| 106 | Linda S. Cook         | 2010 | 20              | -                      | -            | -             | vitamin D                               |
| 107 | K. P. Economopoulos   | 2010 | 2               | 4,240                  | 2,049        | 2,191         | Meat, fish                              |
| 108 | Hee Seung Kim         | 2010 | 10              | 1,338,871              | 65,578       | 70,293        | Wine                                    |
| 109 | S-K. Myung            | 2009 | 9               | 169,051                | 3516         | 165,535       | Soy intake                              |
| 110 | BG Chittenden         | 2009 | 1               | 4,547                  | 476          | 4071          | Polycystic ovary syndrome               |
| 111 | Bo Zhou               | 2008 | 27              | 1,584,610              | 12,955       | 1,571,655     | Hormone replacement therapy             |
| 112 | HG Mulholland         | 2008 | 2               | -                      | -            | -             | Dietary glycemic index                  |
| 113 | Catherine M. Olsen    | 2007 | 12              | 2,778                  | 1,269        | 1,509         | Recreational Physical Activity          |
| 114 | J Steevers            | 2007 | 21              | -                      | 280          | -             | Tea and coffee drinking                 |
| 115 | C. M. Greiser         | 2007 | 42              | 48,153                 | 12,238       | -             | Menopausal hormone therapy              |
| 116 | Catherine M. Olsen    | 2007 | 28              | 1,640,615              | 53,182       | 1,587,433     | Obesity                                 |
| 117 | S. J. Jordan          | 2006 | 9               | 6,474                  | 910          | 5564          | smoking                                 |
| 118 | Stefanos Bonovas      | 2005 | 8               | 746,293                |              | 741,888       | Paracetamol                             |
| 119 | Susanna C. Larsson    | 2006 | 21              | -                      | -            | -             | Milk, milk products and lactose intake  |
| 120 | Grimes DA             | 2009 | 3               | 500                    |              | -             | Oral contraceptives                     |
| 121 | Stefanos Bonovas      | 2005 | 10              | 32,544                 | 3,803        | 31,764        | Nonsteroidal anti-inflammatory drugs    |
| 122 | L-Q Qin               | 2005 | 22              | 1,34,406               | 8,372        | 1,26,034      | Milk/dairy products consumption         |
| 123 | Sonya Kashyap         | 2004 | 10              | 1,34,800               | 3,624        | 9,856         | Assisted Reproductive Technology        |
| 124 | M. Huncharek          | 2003 | 16              | 11,933                 | -            | -             | Cosmetic talc                           |
| 125 | V Bagnardi            | 2001 | 235             | 1,17,471               | 235          | -             | Alcohol drinking                        |
| 126 | Michael Huncharek     | 2009 | 8               | 6,689                  | 2529         | 4,160         | Dietary Fat Intake                      |
| 127 | S. S. Coughlin        | 2000 | 15              | -                      | -            | -             | Estrogen replacement therapy            |
| 128 | Pushkal P. Garg       | 1998 | 9               | 259,794                | 4,392        | 2,55,402      | Hormone replacement therapy             |
| 129 | John F. Stratton      | 1998 | 15              | -                      | 6,077        | -             | Family history                          |
| 130 | Bowen Zheng           | 2018 | 13              | 142,189                | 5,777        | 136,412       | Dietary fiber intake                    |
| 131 | Hai-Fang Wang         | 2017 | 22              | 1,485,988              | -            | -             | Empirically derived dietary patterns    |
| 132 | Hui Xu                | 2018 | 19              | 567,742                | -            | -             | Dietary fiber intake                    |
| 133 | Dongyu Zhang          | 2018 | 14              | 180,833                | 7,500        | -             | Non-herbal tea consumption              |
| 134 | Yun-Long Huo          | 2018 | 6               | 81,791                 | 7,878        | 73,913        | antidepressant medication               |
| 135 | Massimiliano Berretta | 2018 | 9               | 787,076                | 3,541        | -             | Coffee consumption                      |
| 136 | Jiaqi Li              | 2018 | 7               | 65,754                 | -            | -             | vitamin D receptor                      |
| 137 | Xianling Zeng         | 2018 | 11              | 9,987                  | 4,097        | 5,980         | RAD51 135 G/C polymorphism              |
| 138 | Marieke GM Braem      | 2012 | 13              | 330,849                | 1,244        | 329,605       | Coffee and tea consumption              |
| 139 | Shanliang Zhong       | 2014 | 19              | 730,708                | 9,459        | -             | Nonoccupational physical activity       |
| 140 | Xiumin Huang          | 2018 | 17              | 149,177                | 7,609        | 73,168        | dietary fiber intake                    |
| 141 | Ting Liu              | 2013 | 17              | 16,363                 | 6,365        | 9,998         | Progesterone receptor PROGINS           |
| 142 | Yanyang Pang          | 2018 | 10              | 2354                   | -            | -             | Dietary protein intake                  |
| No. | Author                  | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors               |
|-----|-------------------------|------|----------------|------------------------|--------------|----------------|--------------------------------|
| 143 | Ke Wei Foong            | 2017 | 43             | 3,491,943              | -            | -              | Obesity                        |
| 144 | Lingling Zhou           | 2015 | 2              | 774                    | 389          | 385            | SNP rs763110                   |
| 145 | Rizzuto I               | 2013 | 25             | 182,972                | -            | -              | - ovarian stimulating drugs for infertility |
| 146 | Yanqiong Liu            | 2014 | 5              | 624                    | -            | -              | - Statin                       |
| 147 | Ahmad Sayasneh          | 2011 | 8              | -                      | 653          | -              | - Endometriosis                |
| 148 | Jia Li                  | 2018 | 25             | 957,152                | -            | -              | - Endometriosis                |
| 149 | Ho Kyung Sung           | 2016 | 32             | 530,950                | 7639         | 523,311        | Breastfeeding                  |
| 150 | Mahdieh Kamali          | 2017 | 17             | 10,817                 | 4464         | 6353           | XRC2 rs3218536                 |
| 151 | Menelaos Zafrakas       | 2014 | 16             | -                      | 17,445       | -              | - Endometriosis                |
| 152 | Dagfinn Aune            | 2015 | 28             | -                      | -            | -              | Anthropometric factors         |
| 153 | QIAO WANG               | 2015 | 4              | 1985                    | 627          | 1358           | circulating insulin           |
| 154 | Yihua Yin               | 2013 | 11             | 6192                    | 2,673        | 3519           | glutathione S-transferase      |
| 155 | Ximena Gianuzzi         | 2016 | 14             | 8130                    | 1,149        | 6981           | Insulin growth factor (IGF)    |
| 156 | Li-Ling Liu             | 2014 | 4              | 2675                    | 1073         | 1602           | transforming growth factor b receptor |
| 157 | Yong-qiang Wang         | 2012 | 4              | 580,581                 | 2,444        | 578,137        | TGFBR1 Polymorphisms           |
| 158 | Dongyang Li             | 2018 | 44             | 1,082,092              | 48,345       | 1,033,747      | - Dietary inflammatory index   |
| 159 | Si Huang                | 2018 | 10             | 4605                    | 2,394        | 2,211          | miR-502-binding site           |
| 160 | Eileen Deuster          | 2017 | 200            | -                      | -            | -              | - VDR                         |
| 161 | Ru Chen                 | 2017 | 28             | 3362                    | 2,171        | 1,191          | 유전자나열만화사                 |
| 162 | Joanna Kruk             | 2017 | 26             | -                      | -            | -              | - Dietary alkylresorcinols     |
| 163 | Xue-Feng Li             | 2017 | 11             | 33,209                  | 1,130        | 19,179         | IncRNA H19 polymorphisms      |
| 164 | Yan Jiang               | 2017 | 1              | 285                     | 165          | 120            | ARLT1 polymorphism             |
| 165 | Qiyuan Li               | 2017 | 7              | -                      | -            | -              | - BRCA2 rs144848 polymorphism  |
| 166 | Mohamed Hosny Osman     | 2017 | 1              | 2,116,029               | 4,724        | 2,108,905      | Cardiac glycodies              |
| 167 | Erjiang Zhao            | 2017 | 4              | -                      | -            | -              | Glutathione S-transferase      |
| 168 | Giuseppe Grosso         | 2017 | 4              | -                      | -            | -              | Diet                           |
| 169 | Limin Miao              | 2017 | 6              | 6027                    | 2,156        | 3871           | - BRCA1_P871L polymorphism     |
| 170 | Na-Na Yang              | 2017 | 4              | 2110                    | 944          | 1166           | XRCC1 polymorphism             |
| 171 | Giuseppe Grosso         | 2016 | 53             | -                      | -            | -              | - Dietary flavonoid            |
| 172 | Juan Enrique Schwarze   | 2017 | 4              | -                      | -            | -              | Reproduction technologies      |
| 173 | Rosanne M. Kho          | 2016 | 10             | -                      | -            | -              | Hysterectomy                   |
| 174 | K Robinson              | 2016 | 11             | -                      | -            | -              | Bisexual                       |
| 175 | Hong-Bae Kim            | 2016 | 6              | 1937                    | -            | -              | - Benzodiazepine               |
| 176 | Chuanjie Zhang          | 2017 | 3              | 2628                    | 1,276        | 1,352          | - NFκB-1-94 ins/del ATTG       |
| 177 | Minjie Chu              | 2016 | 2              | 18,540                  | 6,857        | 11,683         | H19 IncRNA                    |
| 178 | Duan Wang               | 2016 | 4              | 3036                    | 1,463        | 1,573          | - NFκB1 —94 ins/del ATTG       |
| 179 | Jun Wang                | 2016 | 19             | 3,87,71,388             | 13,116       | 38,758,272     | BMI                            |
| 180 | Yun-Feng Zhang          | 2015 | 1              | 549                     | 229          | 320            | IL-27 Genes                    |
| 181 | Ping Wang               | 2016 | 2              | -                      | -            | -              | MDM2 SNP285                    |
| 182 | Wenkai Xia              | 2015 | 4              | 1248                    | 497          | 751            | ESR2                           |
| 183 | Lei Chen                | 2016 | 2              | -                      | -            | -              | LSSM polymorphism              |
| 184 | Davide Serrano          | 2015 | 3              | 5456                    | 2,313        | 3,143          | VDR                            |
| 185 | Ranadip Chowdhury       | 2015 | 41             | -                      | -            | -              | - Breastfeeding                |
| 186 | Zhi-Ming Dai            | 2015 | 3              | 3530                    | 1,475        | 2,055          | VDR                            |
| 187 | Claudio Pelucchi        | 2014 | 4              | -                      | 2,010        | -              | - Dietary acrylamide           |
| 188 | Yu-Fei Zhang            | 2015 | 6              | 619,714                 | -            | -              | Tea consumption                |
| 189 | Jin-Lin Cao             | 2015 | 2              | 9245                    | 3102         | 6143           | TERT Genetic Polymorphism      |
| 190 | Myung-Jin Muna          | 2015 | 6              | -                      | 4107         | 6661           | VDR                            |
| No. | Author                  | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors                                                                 |
|-----|-------------------------|------|-----------------|------------------------|--------------|----------------|-----------------------------------------------------------------------------------|
| 191 | NaNa Keum               | 2015 | 6               | -                      | -            | -              | Weight Gain                                                                     |
| 192 | Sheng-Song Chen         | 2015 | 2               | 1185                   | 556          | 629            | MMP-12 82 A/G polymorphism                                                        |
| 193 | Bei-bei Zhang           | 2014 | 45              | 57,328                 | 28,956       | 28,372         | Genetic 135G/C polymorphism                                                        |
| 194 | Sara Raimondi           | 2014 | 5               | 97,275                 | 45,218       | 52,057         | BsmI polymorphism                                                               |
| 195 | Shang Xie               | 2014 | 15              | 11,644                 | 5873         | 5771           | LIG4 gene polymorphisms                                                          |
| 196 | Wen-Qiong Xue           | 2014 | 4               | ☐                      | 36,299       | 48,483         | BRCA2 N372H                                                                      |
| 197 | Patrizia Gnagnarella     | 2014 | 6               | 10,588                 | 4051         | 6537           | VDR                                                                              |
| 198 | Peter Boyle             | 2014 | 2               | -                      | -            | -              | Sweetened carbonated beverage consumption                                        |
| 199 | Tara M. Friebel         | 2014 | 5               | -                      | -            | -              | BRCA1 and BRCA2                                                                  |
| 200 | Xin Wang                | 2014 | 41              | 42,121                 | 17,814       | 24,307         | FAS rs2234767G/A Polymorphism                                                    |
| 201 | Yeqiong Xu              | 2013 | 7               | 11,009                 | 4210         | 6799           | VDR                                                                              |
| 202 | H S Kim                 | 2014 | 35              | 444 255                | -            | -              | Endometriosis                                                                    |
| 203 | Yazhou He               | 2014 | 7               | 69,524                 | 30,868       | 38,656         | XRCC2 Arg188His Polymorphism                                                     |
| 204 | Weifeng Tang            | 2014 | 14              | 27,269                 | 11,245       | 16,024         | Aurora-A V571 (rs1047972) Polymorphism                                           |
| 205 | Yeqiong Xu              | 2014 | 3               | 937                    | 457          | 480            | Polymorphisms                                                                    |
| 206 | Mengmeng Zhao           | 2014 | 42              | 39,505                 | 19,142       | 20,363         | RadS1 G135C                                                                      |
| 207 | Xiao Yang               | 2014 | 21              | 6127                   | 9238         | -              | NFKB1 -94ins/del ATTG Promoter                                                    |
| 208 | Bai-Lin Zhang           | 2014 | 7               | -                      | 9956         | -              | Blood Groups                                                                     |
| 209 | Ursula Schwab           | 2014 | -               | -                      | -            | -              | Dietary fat on cardiometabolic                                                  |
| 210 | Tie-Jun Liang           | 2013 | 21              | 8720                   | 3,400        | 5,222          | 137G>C polymorphism                                                             |
| 211 | Wei Wang                | 2013 | 39              | 41,698                 | 19,068       | 22,630         | RAD51 135 G/C Polymorphism                                                       |
| 212 | Lei Xu                  | 2013 | 47              | 43,295                 | 19,810       | 23,485         | FASL rs763110 Polymorphism                                                       |
| 213 | Jingxiang Chen          | 2013 | 19              | 48,670                 | 14,814       | 33,856         | TCF7L2 Gene Polymorphism                                                        |
| 214 | Monica Franciosi        | 2013 | 53              | 1,050,984              | -            | -              | Metformin                                                                        |
| 215 | Zhou Zhong-Xing         | 2013 | 41              | 42,169                 | 17,858       | 24,311         | FAS-1377 G/A (rs2234767) Polymorphism                                           |
| 216 | Zhibin Yu               | 2013 | 73              | 38,278                 | 15,942       | 22,336         | Interleukin 10 - 819 C/T Polymorphism                                           |
| 217 | Shangqian Wang          | 2013 | 2               | 1706                   | 794          | 912            | PAI-1 4G/5G Polymorphism                                                        |
| 218 | Li Li Li                | 2013 | 8               | 746,455                | -            | -              | Fertilization                                                                    |
| 219 | XIN XU                  | 2012 | 21              | 17,623                 | 8,415        | 9,208          | PAI-1 promoter                                                                  |
| 220 | Dominique Trudel        | 2012 | 22              | -                      | -            | -              | Green tea                                                                        |
| 221 | Tian-Biao Zhou          | 2012 | 6               | 2,658                   | 1,461        | 1,197          | Gene Polymorphism                                                                |
| 222 | Xin-Min Pan             | 2011 | 17              | 27,759                 | 13,691       | 14,068         | MLH1 -93 G>A polymorphism                                                       |
| 223 | Jane Green              | 2011 | -               | -                      | 4830         | -              | Height                                                                           |
| 224 | C. Pelucchi             | 2011 | 3               | -                      | 1594         | -              | Acrylamide                                                                       |
| 225 | Bo Peng                 | 2010 | 4               | 1240                   | 443          | 797            | Polymorphisms                                                                    |
| 226 | Bahi Takkouche          | 2009 | 10              | -                      | -            | -              | Hairdressers                                                                      |
| 227 | Bahi Takkouche          | 2005 | 2               | 556                    | 238          | 318            | Hair Dyes                                                                        |
| 228 | V. G. Kaklamani         | 2003 | 1               | 907                    | 659          | 248            | TGFB1*6A                                                                         |
| 229 | Song Mao                | 2018 | 3               | -                      | -            | -              | klotho expression                                                                |
| 230 | Mukete Franklin Sonia   | 2018 | 15              | 1 915 179              | 31,893       | 1,911,045      | Type 1 diabetes mellitus                                                         |
| 231 | Christine Schwarz       | 2018 | 4               | -                      | -            | -              | Night shift work                                                                 |
| 232 | Xiaoping Shi            | 2018 | -               | 1208                   | 604          | 604            | NME1 polymorphisms                                                              |
| 233 | H.J. van der Rhee       | 2006 | 2               | -                      | -            | -              | Sunlight                                                                          |
| 234 | Nadine Younes           | 2018 | 44              | -                      | 805          | -              | Polymorphisms                                                                    |
| 235 | Yue Xu                  | 2016 | 1               | -                      | -            | -              | BHMT gene rs3733890                                                             |
| 236 | Zhong Tian              | 2013 | 46              | 51,413                 | 22,993       | 28,420         | CYP1A2*1F Polymorphism                                                           |
Table 1 (continued)

| No. | Author                   | Year | No. of Articles | No. of Patient (total) | No. of Cases | No. of Control | Evaluated Factors                          |
|-----|--------------------------|------|-----------------|------------------------|--------------|----------------|--------------------------------------------|
| 237 | Yu Wang                  | 2018 | 1               | 79,988                 | -            | -              | Renal transplants                         |
| 238 | T. O. Yang               | 2014 | -               | 453,023                | 2009         | 451,014        | Birth weight                               |
| 239 | Lanhua Tang              | 2017 | -               | -                      | -            | -              | Night work                                 |
| 240 | Steven M. Koehler        | 2012 | 8               | -                      | -            | -              | BMP-2                                      |
| 241 | Yan Zhang                | 2013 | 9               | 5632                   | 2,331        | 3,301          | VDR                                        |
| 242 | Ivana Rizzuto            | 2013 | 25              | 182,972                | -            | -              | Stimulating drugs for infertility          |
| 243 | Xiao-san Zhang           | 2018 | 7               | 105,507                | 6783         | 98,724         | Bisphosphonates use                        |
| 244 | Yun Ye                   | 2018 | 10              | 1045                   | -            | -              | B7-H4 expression                           |
| 245 | Junga Lee                | 2018 | 34              | -                      | -            | -              | Physical activity                          |
| 246 | Huijun Yang              | 2019 | 26              | 1,174,527              | 11,410       | 1,163,117      | Age at menarche                            |
| 247 | M. Kadry Taher           | 2019 | 27              | 214,447                | 15,303       | 199,144        | Perineal use of talc powder                |
| 248 | Yanjun Wu                | 2019 | 13              | 2,471,030              | 19,959       | 2,451,071      | Age at last birth                          |
| 249 | A. Moazeni-Roodi         | 2019 | 19              | 37,036                 | 13,562       | 23,474         | MDM2 40 bp indel polymorphism              |
| 250 | Fateme Shafei (2018)     | 2019 | 22              | 40,140                 | 8568         | 31,572         | Caffeine                                   |
| 251 | Lindsay J. Wheeler       | 2019 | 11              | 13,591                 | 4,484        | 9,107          | Intrauterine Device Use                    |
| 252 | Yuhang Long              | 2019 | 16              | 437,689                | 4,553        | 433,136        | vitamin C intake                           |
| 253 | M. Arjmand (2020)        | 2019 | 16              | 4184                   | 1106         | 3078           | Circulating omentin levels                 |
| 254 | Claudia Santucci         | 2019 | 37              | -                      | 70,646       | -              | smoking                                    |
| 255 | A. Salari-Moghaddam      | 2019 | 14              | -                      | 4434         | -              | Caffeine                                   |
| 256 | M. Karimi-Zarchi         | 2019 | 11              | 12,720                 | 4990         | 7730           | MTHFR 677 C>T Polymorphism                 |
| 257 | Fan Yang                 | 2019 | 2               | 445                    | -            | -              | ERCC1 gene polymorphisms                  |
| 258 | Tingting Yang            | 2019 | 3               | -                      | -            | -              | Work Stress                                |
| 259 | Youxu Leng               | 2019 | 14              | -                      | 4597         | -              | vitamin E                                  |
| 260 | Jalal Choupani           | 2019 | 4               | 9532                   | 843          | 110            | mir-196a-2 rs11614913                      |
| 261 | Xiaqin Huo               | 2019 | 18              | -                      | 14,440       | -              | Hysterectomy                               |
| 262 | A. Bodurtha Smith        | 2019 | 58              | 292,730                | 528          | 292,202        | HIV                                       |
| 263 | Alireza Sadeghia         | 2019 | 21              | 900,000                | -            | -              | Dietary Fat Intake                         |
| 264 | Kui Zhang                | 2019 | 13              | 40,404                 | 6449         | 33,955         | Fermented dairy foods                      |
| 265 | Zohre Momenimovahed      | 2019 | 20              | -                      | -            | -              | Fertility Drugs                            |
| 266 | Christina Baima          | 2019 | 31              | -                      | 13,111       | -              | Coffee consumption                         |
| 267 | Boris Janssen            | 2019 | 115             | -                      | -            | -              | predicted pathogenic PALB2                 |
| 268 | Yang Liu                 | 2019 | 12              | 1,193,201              | -            | -              | Menopausal Hormone Replacement             |
| 269 | Javaid Iqbal             | 2018 | 2               | 5093                   | 1114         | 3979           | Hormone Levels                             |
| 270 | Sen Li                   | 2019 | 12              | 12,933                 | 5057         | 7876           | Genetic polymorphism of MTHFR C677T       |
| 271 | Guisheng He              | 2019 | 45              | 1,059,975              | 329,035      | 730,940        | TERT rs10069690 polymorphism               |
| 272 | Yizi Wang                | 2019 | 36              | 4,229,061              | -            | -              | Statin use                                 |
| 273 | Jun Yu                   | 2019 | 83              | 21,612                 | -            | -              | SFRP promoter hypermethylation             |
| 274 | Qiao Wen                 | 2019 | 7               | 1,710,080              | -            | -              | Metformin                                  |
| 275 | Suszynska M1             | 2019 | 5               | 3748                   | 1919         | 1829           | EPHX1 polymorphism rs1051740              |
| 276 | Tian Xu1                 | 2019 | 21              | 29,981                 | 13,675       | 16,306         | HOTAIR polymorphisms                       |
| 277 | Jinghua Shi              | 2018 | 13              | 901,287                | -            | -              | Metformin                                  |

Risk of bias assessment

The SIGN checklist was used to assess the methodological quality of systematic reviews (2); it is composed of 12 items containing ‘yes’, ‘no’, ‘can’t’, or ‘not applicable’ options. Generally, the methodological quality of the studies in this checklist was categorized into low quality, acceptable, and high quality, (Fig. 1).

The quality assessment of the eligible studies was undertaken independently by four authors (RR, MM, SL, and KT). Any disagreements were resolved through discussion.
Data synthesis
All statistical analyses were performed using Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX; StataCorp LLC.).

Most of the studies reported measures of the association between each factor and OC using the odds ratio (OR) or risk ratio (RR) with their corresponding CIs. Only one study used a standardized incidence rate ratio (SIR) and standardized mean difference (SMD) as an effect size. Thus, OR or RR and 95% confidence intervals (CIs) were used to present the association between the factors and OC. For conducting the meta-analysis, all related information about measures of association (e.g., Pooled OR, Pooled RR, Standard error, 95% Confidence Interval) were extracted and converted to pooled effect size and its SE for every factor in each study.

Since the reported combined effects from systematic reviews were used in the analysis, so primary studies may have been included in different systematic reviews and meta-analyses in the different years which we were not able to exclude them in the analysis. Heterogeneity was evaluated among the primary studies using the forest plots, Cochran's Q statistic, and I² statistic. A random-effects model using restricted maximum-likelihood was used if heterogeneity was high (I² > 50%); otherwise, a fixed-effects model was applied.

Since the number of first reviews combined for the meta-analysis was less than 10, Egger's regression asymmetry tests were used for assessing the publication bias instead of funnel plots (Egger et al., 1997), where p <0.10 was considered as evidence of bias. The characteristics of the included studies were descriptively summarized using a structured table.

Results
Twenty-eight thousand sixty-two papers were initially retrieved from the electronic databases, among which 20,104 studies were screened. Two hundred seventy-seven articles met our inclusion criteria, 226 of which included in the meta-analysis (Fig. 2). The eligible articles were those published between 1998 (when meta-analyses in this field first became available) and 2020. All of the studies had utilized a healthy control group against women with OC.

Overall, from the 277 eligible meta-analyses or systematic reviews, 216 putative risk/protective factors of OC were reported.

Due to the number of evaluated factors, all were categorized into 5 main groups: (1) Nutritional factors, (2) Drug use and Medical history, (3) Diseases, (4) Genetic factors, (5) Other factors.

Among all of the studied factors, 109 had one quantitative synthesis report, and 53 did not have any quantitative synthesis of individual findings but reported valuable data in systematic review articles (Table 2 S and Table 3 S).

Meta-analysis results of the outcomes of interest
Meta-analyses were conducted on the 53 associated factors with OC with sufficient data (two or more reports
Most commonly reported genetic factors were MTHFR C677T (OR = 1.077; 95% CI (1.032, 1.124); P-value < 0.001), BSML rs1544410 (OR = 1.078; 95% CI (1.024, 1.153); and P-value = 0.004) and Fokl rs2228570 (OR = 1.123; 95% CI (1.089, 1.157); P-value < 0.001), which were significantly associated with increasing risk of OC (Fig. 3). The results of publication bias assessed using the Egger’s test indicate significant publication bias only for MTHFR C677T factor (P-value = 0.017).

Among the other factors, coffee intake (OR = 1.106; 95% CI (1.009, 1.211); P-value = 0.030), hormone therapy (RR = 1.057; 95% CI (1.030, 1.040); P-value < 0.001), hysterectomy (OR = 0.863; 95% CI (0.745, 0.999); P-value = 0.049), and breast feeding (OR = 0.719; 95% CI (0.679, 0.762); P-value < 0.001) were mostly reported in studies. Final results of all conducted meta-analysis are presented in Table 2.

The risk of bias was assessed using the SIGN checklist. Among 277 included studies, 24.19%, 39.35%, and 36.46% had “low quality”, “acceptable” and “high quality”, respectively.

**Discussion**

This study focuses on OC risk factors and protective measures. The factors can be classified into nutritional, drug use and medical history, diseases, and genetic. As regards nutritional factors, intake of coffee, egg, and fat can significantly enhance the risk of OC. Estrogen and estrogen-progesterone therapies (generally, hormone therapy) are also associated with the elevated risk of OC. Several diseases (e.g., diabetes, endometriosis, and polycystic ovarian syndrome), as well as some genetic polymorphisms (e.g., BRCA2 N372H rs144848, BSML rs1544410, Fokl rs2228570, MTHFR C677T, P16INK4a, ERCC2 rs13181, MMP-12 rs2276109, and VDR rs11568820), can significantly increase the incidence of OC. Other factors, like obesity, overweight, smoking, and the use of perineal talc, are also accompanied by an increased risk of OC.
Coffee is rich in several anti-oxidant and anti-carcinogenic bioactive compounds (e.g., phenolic acids, cafestol, and kahweol, respectively) [6]. This beverage has shown an inverse correlation with liver and endometrial cancer risk [4]. Furthermore, coffee and caffeine have an inverse relationship with sex hormones (testosterone and estradiol) [2]. High levels of these hormones have exhibited direct association with enhanced breast and ovarian cancer [8, 9]. Coffee contains acrylamide, which has been shown to increase the risk of breast and ovarian cancer as well [10]. The meta-analysis in the present study indicates a positive correlation between coffee drinking and OC risk.

Eggs are rich in cholesterol and choline, thus providing quite high protein per energy content, all of which are linked to the risk of breast, ovarian, and prostate cancers. Nonetheless, the majority of these studies on the mentioned cancers have not explored egg consumption as a primary exposure of interest, restricting a robust assessment of the hypothesized correlations. Since eggs have been considered as a source of protein and fat, its intake association with the OC risk has been primarily explored to examine the impact of protein or fat [11]. In this meta-analysis, egg consumption has been shown to be significantly and positively correlated with OC.

As one of the most controversial nutritional factors, dietary fat can enhance the development of hormone-related cancers (e.g., breast, endometrial, and OCs). However, the reports on this field are discrepant. High-fat diets may stimulate over-secretion of ovarian estrogen, leading to tumor-promoting mechanisms through mitogenic impacts on ERα-positive or negative tumor cells [12].

Epidemiologic reports indicate an association between estrogen exposure duration and OC induction and biology [13]. Recent research has expressed that besides inhibiting estrogen-driven growth in the uterus, progesterone can protect the ovaries against neoplastic transformation [14]. Despite the available poor knowledge of the etiology of OC, the role of estrogen and progesterin seems biologically plausible. Based on a theory, high levels of menopausal gonadotropins due to estradiol expression may elevate OC risk. In other words, HRT can decrease the risk of OC by reducing the levels of menopausal gonadotropins. However, due to small HRT-related decrease, the mentioned advantages could be overruled by the estrogen-induced proliferation of ovarian cells. Moreover, the epithelial surface of both normal and malignant ovaries expresses estrogen receptors [15]. Furthermore, progesterin is responsible for the declined risk associated with oral contraceptive
| Variables                      | Measure of Association | Odds Ratio (95% CI) | P-value | I² %  | No. of study in analysis |
|-------------------------------|------------------------|---------------------|---------|------|-------------------------|
| **Nutritional factors**       |                        |                     |         |      |                          |
| Alcohol use                   | RR                     | 1.015 (0.974 – 1.052) | 0.485   | 0.01 | 3                       |
| Coffee intake                 | OR                     | 1.106 (1.009 – 1.211) | 0.030   | 0.00 | 4                       |
| Egg intake                    | RR                     | 1.036 (0.967 – 1.109) | 0.317   | 0.00 | 3                       |
| Fat intake                    | RR                     | 1.147 (1.045 – 1.250) | <0.001  | 17.73 | 2                       |
| Fiber intake                  | OR                     | 1.188 (1.090 – 1.296) | <0.001  | 0.00 | 3                       |
| Milk intake                   | RR                     | 0.760 (0.714 – 0.810) | <0.001  | 0.00 | 3                       |
| Tea intake                    | OR                     | 1.016 (0.664 – 1.554) | 0.941   | 0.08 | 2                       |
| Vegetables intake             | RR                     | 0.856 (0.779 – 0.959) | 0.005   | 0.00 | 2                       |
| **Drug use and Medical history** |                        |                     |         |      |                          |
| Aspirin                       | OR                     | 0.894 (0.854 – 0.935) | <0.001  | 0.00 | 3                       |
| Metformin                     | RR                     | 0.718 (0.602 – 0.855) | <0.001  | 0.00 | 3                       |
| NSAIDs                        | RR                     | 0.898 (0.819 – 0.984) | 0.020   | 0.00 | 3                       |
| Oral contraceptive           | OR                     | 0.655 (0.515 – 0.833) | <0.001  | 78.23 | 2                       |
| Statin                        | RR                     | 0.849 (0.749 – 0.962) | 0.010   | 0.00 | 2                       |
| Hormone therapy (estrogen)    | RR                     | 1.305 (1.210 – 1.407) | <0.001  | 0.00 | 2                       |
| Hormone therapy (Overall)     | RR                     | 1.057 (1.030 – 1.400) | <0.001  | 94.44 | 4                       |
| Hormone therapy (estrogen-pro-| OR                     | 1.190 (1.043 – 1.357) | 0.009   | 82.24 | 2                       |
| gestin)                       |                        |                     |         |      |                          |
| Hysterectomy                  | OR                     | 0.863 (0.745 – 0.999) | 0.049   | 67.12 | 4                       |
| Tubal ligation                | OR                     | 0.693 (0.657 – 0.731) | <0.001  | 0.00 | 2                       |
| **Diseases**                  |                        |                     |         |      |                          |
| Diabetes                      | RR                     | 1.24 (1.32 – 1.35)   | <0.001  | 0.00 | 3                       |
| Endometriosis                 | OR                     | 1.433 (1.294 – 1.586) | <0.001  | 3.05 | 2                       |
| Poly cystic ovarian syndrome  | OR                     | 1.580 (1.081 – 2.310) | 0.018   | 29.48 | 2                       |
| **Genetic factors**           |                        |                     |         |      |                          |
| Asn680Ser                     | OR                     | 1.120 (0.594 – 2.110) | 0.726   | 86.32 | 2                       |
| BRC2A2 N372H (rs144848)       | OR                     | 1.079 (1.018 – 1.143) | 0.010   | 44.61 | 4                       |
| Variables          | Measure of Association | Odds Ratio (95% CI) | P-value | I² % | No. of study in analysis |
|--------------------|------------------------|---------------------|---------|------|-------------------------|
| BSML rs1544410     | OR                     | 1.078 (1.024 – 1.153) | 0.004   | 0.00 | 8                       |
| ESR2 rs3020450     | OR                     | 0.818 (0.719 – 1.040) | 0.151   | 61.20 | 2                       |
| Fokl rs2228570     | OR                     | 1.123 (1.089 – 1.157) | <0.001  | 0.00 | 8                       |
| GSTM1              | OR                     | 1.015 (0.928 – 1.111) | 0.741   | 0.00 | 2                       |
| MTHFR A1298C       | OR                     | 0.997 (0.943 – 1.054) | 0.907   | 0.00 | 3                       |
| MTHFR C677T        | OR                     | 1.077 (1.032 – 1.124) | <0.001  | 45.55 | 9                       |
| NFkB1              | OR                     | 1.680 (1.08 – 2.62)  | 0.020   | 69.07 | 2                       |
| P16INK4a           | OR                     | 2.657 (1.173 – 6.014) | 0.019   | 51.28 | 2                       |
| RAD51 135G-C       | OR                     | 0.996 (0.922 – 1.075) | 0.910   | 0.00 | 4                       |
| ERCC1 rs11615      | OR                     | 0.987 (0.756 – 1.287) | 0.920   | 0.00 | 2                       |
| ERCC2 rs13181      | OR                     | 1.42 (1.15 – 1.76)   | 0.001   | 0.00 | 2                       |
| VGEFGF rs699947    | OR                     | 0.983 (0.644 – 1.502) | 0.938   | 78.04 | 2                       |
| VDR rs731236       | OR                     | 0.996 (0.882 – 1.125) | 0.842   | 56.81 | 6                       |
| FASL rs763110      | OR                     | 0.640 (0.520 – 0.788) | <0.001  | <0.01 | 2                       |
| VEGFA rs833061     | OR                     | 0.834 (0.324 – 2.149) | 0.707   | 76.02 | 2                       |
| RAD51 rs1801320    | OR                     | 0.656 (0.349 – 1.232) | 0.189   | 41.43 | 3                       |
| FAS/APO-1 rs2234767| OR                     | 1.001 (0.956 – 1.068) | 0.982   | 0.00 | 3                       |
| MMP-12 rs2276109   | OR                     | 1.588 (0.694 – 3.630) | 0.273   | 88.80 | 2                       |
| VEGF rs3025039     | OR                     | 0.869 (0.719 – 1.04)  | 0.144   | 0.00 | 2                       |
| VDR rs7975232      | OR                     | 0.990 (0.901 – 1.088) | 0.842   | 0.00 | 5                       |
| VDR rs11568820     | OR                     | 1.164 (1.087 – 1.248) | <0.001  | 0.00 | 4                       |
| XRCC2r rs3218536   | OR                     | 0.887 (0.750 – 1.050) | 0.163   | 51.57 | 3                       |
| **Other factors**  |                        |                     |         |      |                         |
| Acrylamide         | RR                     | 0.994 (0.930 – 1.063) | 0.865   | 0.00 | 2                       |
| Obesity            | RR                     | 1.274 (1.194 – 1.36)  | <0.001  | 0.00 | 2                       |
| Overweight         | OR                     | 1.079 (1.041 – 1.119) | <0.001  | 24.04 | 3                       |
| Height             | RR                     | 1.071 (1.041 – 1.102) | <0.001  | 0.00 | 3                       |
| Weight             | RR                     | 1.128 (1.064 – 1.196) | <0.001  | 87.71 | 3                       |
| Smoking            | RR                     | 1.311 (0.847 – 2.029) | 0.225   | 98.13 | 3                       |
use. Pregnancy can also offer a biologic basis for weak correlations with HRT formulations, including progestins [16]. The current work indicates a significant positive association between hormone therapy (estrogen, estrogen-progestin, and overall) and OC.

Diabetes mellitus (DM) is also positively and significantly associated with the risk of OC. Although the carcinogenic influence of DM on the ovary has not been completely understood, some mechanisms have been introduced to describe it partially. Hyperinsulinemia (often associated with insulin resistance) is commonly observed in type 2 DM patients. Chronic hyperinsulinemia has an association with tumor promotion due to the oncogenic potentials of insulin by stimulating cellular signaling cascade or incrementing growth factor-related cell proliferation [17]. Moreover, increased levels of insulin are associated with high bioactivity of insulin growth factor-1 (IGF-1) [18]. Considering the anti-apoptosis and mitogenic influences of IGF-1 on normal and cancerous human cells, type 2 DM can promote tumor development [19]. Besides, hyperglycemia has been recognized as one of the major health consequences of DM. Based on numerous animal and clinical studies, hyperglycemia is related to oxidative stress [20]. Oxidative stress refers to an imbalance between the reactive oxygen species (ROS) production and antioxidant defense mechanisms. ROS can damage the biomolecules of the cells, including those involved in cell proliferation and repair [21].

Based on the results, the risk of developing OC is 43% in women with endometriosis. The endometriosis mechanisms in epithelial OC can be divided into 3 types. The first one is estrogen-dependent. Ness et al. introduce endometriosis as a precursor for epithelial OC, which is easily developed in the low-progesterone and high-estrogen conditions [22]. The second involves the genetic mutation in endometriotic tissues, like hepatocyte nuclear factor-1β (HNF-1β) [23] and ARID1A [24]. Furthermore, chronic inflammations, heme, or free iron-induced oxidative stress in endometriotic tissues also exhibit an association with epithelial OC [25].

The risk of OC shows a 60% increase in women suffering from polycystic ovary syndrome (PCOS). PCOS has various risk factors, including obesity, diabetes, inflammation, metabolic syndrome, and aging. However, it is not clear whether the elevated risk of endometrial cancer is due to separate risk factors (e.g., diabetes, obesity) or PCOS itself. PCOS has its own metabolic characteristics, including hyperinsulinism, hyperglycemia, insulin resistance, and hyperandrogenism, enhancing cancer risk. Moreover, such a relationship between PCOS and endometrial cancer could be due to common inherited genetic variants. Other factors, such as parity (nulliparous versus multi), age at first pregnancy, and use/length of hormone therapy (HRT, OCP), could confound the results.

Some genetic factors may enhance the risk of developing OC. In the present study, Asn680Ser, BRCA2 N372H rs144848, BSML rs1544410, FokI rs2228570, GSTM1, MTHFR C677T, NFKB1, P16INK4a, ERCC2 rs13181, MMP-12 rs2276109, and VDR rs11568820 have been found to increase the risk of OC significantly. Among the mentioned polymorphisms, P16INK4a has the strongest impact on the risk of OC (2.6-fold increase), followed by NFKB1 and MMP-12. rs2276109.

Some studies have mentioned the crucial role of p16INK4a inactivation as the result of aberrant hypermethylation in the lung, liver, stomach, breast, and uterus carcinogeneses [26, 27]. In a meta-analysis on 6 eligible research encompassing 261 patients, Hu et al. show a correlation between p16INK4a promoter hypermethylation and elevated risk of endometrial carcinoma [27]. A meta-analysis by Xiao et al. also report the significant association of aberrant methylation of p16INK4a promoter with OC [28]. This could be regarded as a potential molecular marker for monitoring the diseases and providing new insights into OC therapies.

NFKB1 can significantly inhibit cell apoptosis through regulation of the level of survival genes, such as BCL-2 homolog A1, PAI-2, and IAP family. Moreover, studies have indicated the role of the NFKB1 signaling pathway in cellular proliferation by IL-5 enhancement, MAPK
phosphorylation, and cyclin D1 expression modulation [29].

Numerous meta-analyses have addressed the relationship between NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk, although their findings are not entirely consistent. For instance, Yang et al. [30] and Duan et al. [31] express that the polymorphism in NFκB1 -94ins/del ATTG promoter can increase the overall cancer risk. These results do not agree with those reported by Zou et al. [32]. Such contradictions can be assigned to the bias as the result of a limited sample size.

MMP-12 is involved in the pro-tumorigenesis process through inhibiting cancer cell apoptosis and promoting cancer cell invasion and migration [33]. As SNP of MMP-12-82 A>G can influence the MMP-12 expression and enhance the cancer risk, the correlation between MMP-12 promoter gene polymorphism and the cancer risk has been extensively addressed in recent years.

Obesity, overweight, smoking, and the use of perineal talc could be mentioned as other factors associated with OC risk. The biological mechanisms underlying the relation of overweight and obesity with OC are not clarified and consistent. Based on a study by Kuper et al. [34], progesterone and leptin could be possible endocrine mediators of the weight effect on OC risk. Such an impact could be assigned to elevated insulin levels, androgens, and free IGF-I due to obesity [35].

Regarding disassociation of BMI with OC risk among postmenopausal women, Reeves et al. [36] express that association of BMI with OC risk is under the mediation of hormones, as its impact on OC risk remarkably differs in premenopausal and postmenopausal subjects. BMI shows an inverse association with sex hormone-binding globulin and progesterone, while it is positively correlated with free testosterone in premenopausal women [37]. The mentioned hormone factors seem to be independently or cooperatively involved in the carcinogenic process.

Concerning biological mechanisms, the direct correlation of smoking with mucinous tumors can be assigned to the similarity of this neoplasm with cervical adenocarcinoma and colorectal cancers [38], both of which have exhibited direct association with tobacco exposure. Similarly, endometriosis and clear cell cancers have some biological similarities with endometrial cancer, which is inversely related to tobacco smoking due to the possible anti-estrogenic influence of smoking. The tobacco smoking could exert strong impacts in the early stages of (ovarian) carcinogenesis. Thus, the more powerful tobacco-associated risk for mucinous could be explained by the fact that for the mucinous histotype, there is a continuum from benign to borderline and invasive disease, while serious OCs are often high grade and not originated from the borderline tumors [39]. Furthermore, the smoking-induced mutation in the somatic KRAS gene is more common in mucinous rather than serous borderline ovarian tumors [40], and also in borderline tumors than invasive cancer [41].

The ovarian carcinogenesis mechanism of perineal talc use has remained unclear. Based on a hypothesis, however, as an external stimulus, talc can ascend from the vagina to the uterine tubes and trigger a chronic inflammatory response, further promoting the OC development. Cellular injuries, oxidative stresses, and local elevation of inflammatory mediators (e.g., cytokines and prostaglandins) could be mutagenic, thus encouraging carcinogenesis [42]. Supporting this hypothesis, hysterectomy or bilateral tubal ligation, which may dramatically decline the ovarian exposure to inflammatory mediators, is related to a decreased OC risk [43–45].

Conclusions
Numerous studies have addressed the effective factors of OC; however, these works have resulted in contradicting outcomes. The current study explores all previous meta-analyses and systematic reviews to provide a valuable summary of the OC protective and risk factors, among which nutritional and genetic factors play a more profound role. Although the genetic factors cannot be changed due to their inheritance, nutritional ones could be well regulated to prevent OC.

Supplementary Information
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Statement of significance
Nutritional and genetic factors play a more profound role in ovarian cancer risk. Coffee intake, hormone therapy are risk factors while hysterectomy and breast feeding have protective role.

Authors’ contributions
All authors have read and approved the manuscript. LJ and MN conceptualized and designed the study and critically revised the manuscript for important intellectual content. MM, RR, SL, and KT acquired data. LJ and KT analyzed data, interpreted the study results, and critically revised the manuscript for important intellectual content. AM drafted the manuscript and critically revised the manuscript for important intellectual content.

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Availability of data and materials
The data for supporting the research findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This project was registered and approved by the Iran University of Medical Sciences Ethics committee (Code: IR.IUMS.REC.1396.32585).

Consent for publication
Not applicable.

Competing interests
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