Analysis of Ovarian Cancer Risk Factors: Systematic Review

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ABSTRACT

Introduction: Ovarian cancer risk factors are health problems that risk women's survival. Health workers and women must recognize the risk factors that can lead to ovarian cancer as early prevention. **Objectives:** This systematic review aimed to analyze various risk factors for ovarian cancer. **Methods:** The systematic review used 4 databases, Proquest, Pubmed, Willey, and Ebsco, with the keywords ovarian cancer AND risk factors AND determinant factors OR predisposition factors AND incident OR prevalence. Inclusion criteria include relevant articles according to the topic, type of quantitative research, no year limit specified, and English. The initial number of searches obtained was 3,507 articles. The PRISMA usage flow and JBI tools 15 articles were reviewed. **Result:** The study's results identified risk factors for ovarian cancer: reproductive factors, lifestyle, family history, benign ovarian tumors, endometriosis, and endometriomas. **Discussion:** Reproductive factors are the factors most associated with the occurrence of ovarian cancer. Reproductive factors covered pain during menstruation, menstrual age, delayed menopause, infertility, use of fertility drugs, parous women, childbearing age, miscarriage, induced abortion, not breastfeeding, and intrauterine contraceptives, use of exogenous hormones, and use of hormone supplements.

Keywords: Risk Factors, Ovarian Neoplasms, Gynecological Disorders, Female Health.

ABSTRAK

Pendahuluan: Faktor risiko kanker ovarium merupakan masalah kesehatan yang berisiko terhadap kelangsungan hidup perempuan. Petugas kesehatan dan perempuan harus mengenal faktor risiko yang dapat menyebabkan terjadinya kanker ovarium sebagai pencegahan secara dini. Tujuan: Tujuan sistematik review untuk menganalisis berbagai faktor risiko kanker ovarium. Metode: Metode systematic review menggunakan 4 database, yaitu Proquest, Pubmed, Willey dan Ebsco, dengan kata kunci ovarian cancer AND risk factors AND determinant factors OR predisposition factors AND incident OR prevalence. Kriteria inklusi meliputi artikel relevan sesuai dengan topik, jenis penelitian kuantitatif, tidak ditentukan batas tahun, pencarian menggunakan Bahasa Inggris. Jumlah awal pencarian didapat 3.507 artikel, hasil seleksi menggunakan alur PRISMA dan menggunakan tools JBI sehingga terdapat final artikel akan di review sebanyak 15 artikel. Hasil: Hasil penelitian mengidentifikasi faktor risiko kanker ovarium, yakni faktor reproduksi, gaya hidup, riwayat keluarga, riwayat penyakit tumor ovarium jinak, endometriosis dan endometrioma. Diskusi: Faktor reproduksi merupakan faktor yang paling banyak berhubungan dengan terjadinya kanker ovarium. Faktor reproduksi tersebut meliputi nyeri pada menstruasi, usia menstruasi, keterlambatan menopause, infertile, penggunaan obat kesuburan, perempuan parous, usia

melahirkan, keguguran, aborsi di induksi, tidak menyusui, penggunaan kontrasepsi intrauterin, penggunaan hormon eksogen dan penggunaan hormon suplemen.

Kata Kunci: Faktor Risiko, Kanker Ovarium, Kelainan Ginekologi, Kesehatan Perempuan

INTRODUCTION

Cancer is one of the diseases that cause death in women (Momenimovahed, 2019). According to the Global Burden of Cancer GLOBOCAN, cancer is the second leading cause of death after heart disease in the United States. Cancer cases worldwide in 2015-2019 caused 52% of women to die, while in Indonesia, it is 5.4% (WHO, 2019). Such conditions cannot be ignored, and efforts are needed from various parties to prevent such incidents. The prevalence of ovarian cancer in Indonesia has continued to increase in the last three years. From 2017, to 2019 at 0.07%, 0.10% and 0.14%, respectively, (Liu et al., 2020). Although the increase was insignificant, ovarian cancer is a silent killer (Prawirohardjo, 2010). So, it is necessary to continue research to determine the efforts needed to reduce this number.

Ovarian cancer is an increasingly worrying sufferer, considering that ovarian cancer is a malignant tumor formed from ovarian tissue and can spread to the pelvis, abdomen, liver, and lungs (Utami, 2016). In addition, this condition is also asymptomatic. There are no complaints and will only cause protests when metastases have occurred (Rosida et al., 2020). It causes the patient to experience a significant change in health status, which impacts the unpreparedness of the patient and his family to face the condition.

Patients with ovarian cancer have several characteristics based on research results. Women with ovarian cancer range from 18 years old to some patients over 40 years old (Cress et al., 2015; Gea et al., 2016; Liu et al., 2020; Rosida et al., 2020); it shows that ovarian cancer is often found in women who are in menopause. In addition, the results showed that most ovarian cancer patients had an average Body Mass Index (BMI) category of 18.5-24.9 kg/m2 (Gea et al., 2016; Rosida et al., 2020). Moreover, most ovarian cancer patients are multiparous (Gea et al., 2016; Indriani et al., 2018;

Rosida et al., 2020). Regarding ovarian cancer, the research results in Indonesia show that most patients are at stage III C (Gea et al., 2016; Rosida et al., 2020). It shows that most ovarian cancer patients are diagnosed at an advanced stage. These various characteristics affect the impact experienced by ovarian cancer patients.

Ovarian cancer can impact sufferers physically, psychologically, sexually, socially, and spiritually. Women with ovarian cancer experience various symptoms, including pain, difficulty sleeping, nausea, vomiting, loss of appetite, and fatigue (Ahmed-Lecheheb & Joly, 2016; Ebell et al., 2016; Rietveld et al., 2019). Various symptoms are felt impact psychology. Women will experience anxiety, depression, and even lose enthusiasm because they are burdened with their illness, affecting their attitude towards the treatment process (Ebell et al., 2016; Inci et al., 2021; Wulandari, 2018). Social and sexual relationships of ovarian cancer patients will also be disrupted, where women with ovarian cancer do not enjoy intimate relationships with their husbands due to decreased desire to have sex and the pain experienced during sexual intercourse (Ahmed-Lecheheb & Joly, 2016; Fischer et al., 2019; Mayer et al., 2019). Women with ovarian cancer can experience various changes to lose hope and enthusiasm for treating the disease. Facing these conditions, ovarian cancer patients need multiple support from their families and health workers related to the disease they are experiencing.

Previous research found a variety of risk factors. Based on various possibilities that can influence the occurrence of ovarian cancer, it can be influenced by menstrual factors, family history, lifestyle, and hormones (Momenimovahed, 2019; Li et al., 2015; Lisnawati, 2013; Shields et al., 2014). Women must know to reduce or avoid factors that trigger ovarian cancer.

Various risk factors have been identified through several research results. It is necessary to have a unique study related to similar research to obtain a specific description of the risk factors associated with ovarian cancer. Therefore, a Systematic Review was conducted to evaluate various risk factor problem articles. In addition, this systematic review is carried out for the researchers' benefit and for health workers responsible for providing services and counseling to women as ovarian cancer sufferers. Thus, this disease can be prevented as early as possible, especially in preventing ovarian cancer risk factors. This research aimed to analyze various risk factors for ovarian cancer.

METHODS
Eligibility Criteria

The inclusion criteria are (1) The researcher limits the publication language to English. (2) This type of research uses cross-sectional, case-control, and cohort studies. (3) Researchers only included research reported thoroughly (full text). Moreover, the literature found no time limit, meaning that all years related to ovarian cancer were taken to analyze the context characteristics that differed from year to year from the study results.

Exclusion Criteria are Review Literature Research, Systematic Review, and Methodological Quality Test Results Less than 70%.

Information Sources

The research design used is a literature review with a systematic approach. Electronic data search through four databases: Proquest, PubMed, Ebsco, and Wiley. The keywords used in the search were: ((ovarian cancer) AND (((risk factors))) AND (determinant factors)) OR (predisposition factors))) AND ((incident) OR (prevalence) ovarian cancer. The keywords in this systematic review used the PICO framework (Table 1).

Table 1. Keyword systematic review Analysis of Ovarian Cancer Risk Factors

PICO Framework	Description	Keywords
Population	Ovarian cancer patient	Ovarian cancer
Intervention	Risk factors	Risk factors AND determinant factors OR predisposition factors
Comparators	There is no comparison of all populations is ovarian cancer.	-
Outcomes	Incident	Incident OR prevalence ovarian cancer.

Searching Strategy

PRISMA article selection stages consist of 4 stages: identification, screening, feasibility test, and article determination (Liberati et al., 2009) (Chart 1). The identification results based on search results with keywords obtained 3,507 articles, and 2 articles were excluded due to duplication. Then screening 3,505 pieces, got 15 parts that fit the inclusion criteria.
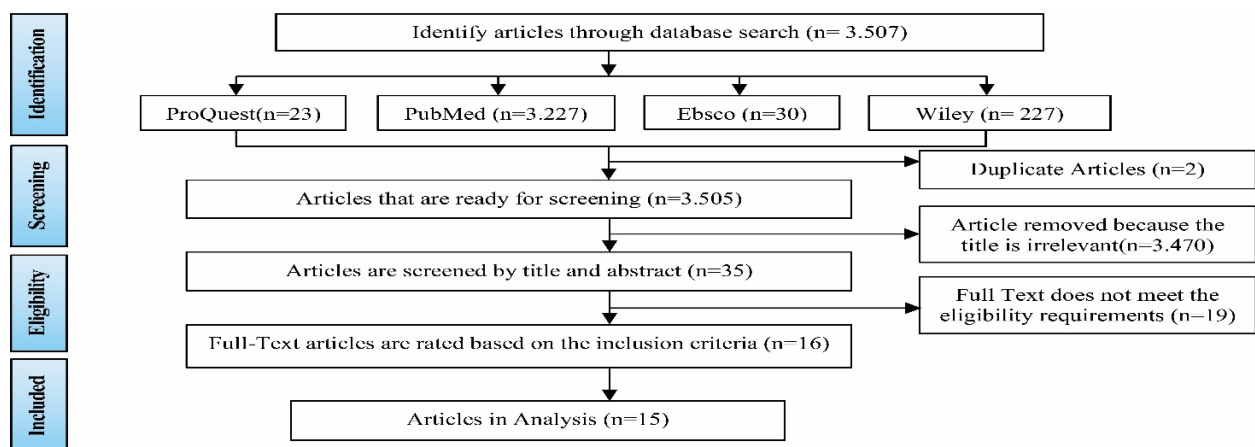
Article Screening

Chart 1. Article Selection Process based on PRISMA (Liberati et al., 2009)

Data Extraction and Critical Appraisal

The feasibility test has done on fifteen reports using the 2020 Joanna Briggs Institute (JBI) critical appraisal tools for cross-sectional, case-control, and cohort studies. The selected articles can be included in a systematic review of the results that meet the predetermined cut-off of 70% and the inclusion criteria. The result is that all articles get a score of more than 70% and can be used for this systematic review (n=15). Then the papers involved were analyzed descriptively.

RESULT

Based on the database search, 3,227 articles were from the Pubmed database, 227 were from Wiley, 23 from Proquest, and 30 from Ebsco. Titles were reviewed to eliminate irrelevant articles and 3,470 duplicates. The researcher then selected 16 articles based on full-text articles according to the criteria. Next, the researcher analyzed the full text of all the articles and identified one article that did not meet the tools based on JBI. The 15 (fifteen) articles have met the criteria.

Table 2. Results of Article Assessment Using *The JBI Critical Appraisal Tool*

Citation	Criteria											Result
	1	2	3	4	5	6	7	8	9	10	11	
Hughes, 2003	✓	✓	✓	✓			✓	✓				75%
Qin, 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100%
Asante, 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100%
Guleria, 2019	✓	✓	✓			✓	✓	✓	✓	✓	✓	81,8%
Licaj, 2012	✓	✓	✓			✓	✓	✓	✓	✓	✓	81,8%
Lundberg, 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	90.9%
Cuong Le, 2012	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100%
Zhuxua, 2020	✓	✓	✓	✓				✓	✓	✓		70%
Babic, 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100%
Pięta, 2012	✓	✓	✓	✓	✓	✓	✓	✓				100%
Bethea, 2017	✓	✓	✓	✓	✓	✓	✓	✓				100%
Lee, 2013	✓	✓	✓	✓	✓			✓	✓	✓		80%
Mori, 1988	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100%
Burghaus, 2015		✓	✓	✓	✓	✓		✓	✓	✓		80%
Xing He, 2017	✓	✓	✓	✓			✓	✓				75%

The study results follow the criteria for this systematic review. There are 15 articles in table 3.

Table 3. Summary of Article Search Results for Systematic Review

No	*Authors and years*	*Objective Study*	*Research Methods*	*Place*	*Findings*
1	Hughes et al., 2003	Determining the prevalence of familial breast cancer and ovarian cancer in patients in primary care	***Subject***: 540 women less than 81 years old ***Design:*** Crossectional	Boston, United States	- As many as 65% of respondents do not have a family history of cancer, and nonly51 (9.4%) have a history of cancer. - Of the 51 respondents with a family history of cancer, 62% are at risk.
2	Qin, 2017	Evaluating the three dietary indices HEI-2005, Hey-2010, and AHEI-2010 concerning ovarian cancer among African American women	***Subject***: 415 African-American women with ovarian cancer cases and 629 controls. ***Design:*** Case-control Study	United States	- adherence to an overall healthy diet may reduce the risk of ovarian cancer in African-American women

Table 3. Summary of Article Search Results for Systematic Review (*Continued*)

No	*Authors and years*	*Objective Study*	*Research Methods*	*Place*	*Findings*
3	Asante et al., 2013	Assessing the effect of fertility drugs on the risk of ovarian tumors	*Subject*: 1,028 women with ovarian tumors and 872 controls *Design:* Case-control Study	United States	- Among infertile women using fertility drugs, 24% were in the control group and 17% in the case group - Infertile women who took fertility drugs did not increase the risk of ovarian tumors compared to infertile women who did not use fertility drugs (OR=0.64 (95% CI, 0.37, 1.11)) - The result is that there is no significant relationship between the use of fertility drugs and the risk of ovarian tumors
4	Guleria et al., 2020	Identify all cases of epithelial ovarian cancer	*Subject*: 1,582,221 women diagnosed with benign tumors *Design:* Cohort study	Denmark	Benign ovarian tumors may be associated with an increased long-term risk for mucinous ovarian cancer.
5	Licaj et al., 2016	estimated the impact of smoking on epithelial ovarian cancer (EOC)	*Subject*: 154,234 women aged 34-70 years *Design:* Cohort Study	Norwegia	Significantly increased risk of mucinous tumors for smokers compared to non-smokers
6	Lundberg et al., 2019	Investigating whether assisted reproductive technology (ART) treatment or a diagnosis of infertility is associated with the risk of ovarian cancer or borderline ovarian tumor (BOT) in parous women.	*Subject*: 1,340,097 women with their first live birth *Design:* Cohort Study	Swedia	Women on ART have a higher risk of developing ovarian cancer and BOT. At least part of the risk appears to be due to underlying infertility, not the treatment itself, as the increased risk is more negligible compared to other infertile women.
7	Le et al., 2012	Analyzing reproductive factors with ovarian cancer risk	*Subject*: 262 ovarian cancer patients and 755 controls *Design:* Case-control	Vietnam	The risk of ovarian cancer is significantly lower in parous women than in nulliparous women. The use of intrauterine contraceptives can reduce the risk. In contrast, induced abortion and late menopause were significantly associated with increased cancer risk.
8	Zhuxua, 2020	Examined the association between hereditary sex and epithelial ovarian cancer (EOC).	*Subject*: sex of offspring between 664 incident EOC cases and 1531 controls *Design:* Case-control	United States	Giving birth to a boy may be associated with a reduced risk of EOC compared to giving birth to a girl
9	Babic et al., 2014	investigated the association between menstrual pain and ovarian cancer risk.	*Subject*: 2,028 epithelial cancer cases and 2091 control cases *Design:* Case-control	United States	The risk of ovarian cancer was increased in women with moderate pain (OR = 1.22, 95% CI: 1.05–1.42) and severe pain (OR = 1.34, 95% CI: 1.09–1.65) compared with women without pain or mild pain during menstruation. This association was differentiated by histologic subtype, with significant associations for severe pain with endometrioid (OR = 1.64, 95% CI: 1.15-2.34) and clear tumor cells (OR = 1.91, 95% CI: 1 ,11–3.28).

Table 3. Summary of Article Search Results for Systematic Review (*Continued*)

No	*Authors and years*	*Objective Study*	*Research Methods*	*Place*	*Findings*
10	Pięta et al., 2012	Analyzing the influence of reproductive factors on the risk of ovarian cancer.	*Subject*: Healthy women without a diagnosis of ovarian cancer lesions and women diagnosed with ovarian cancer. The number of respondents is 1,346 women. *Design:* Crossectional	Poland	- Among women who started menstruating at 11 years, the risk of ovarian cancer was 1.6 higher than among those whose first menstruation occurred at 13. Likewise, for women who menstruate at the age above - 55, the risk of developing ovarian cancer is 1.4 times higher. - The age at which a woman gives birth to her first live baby - also necessary. In the women who gave birth over 35 years, the risk increased and remained - at level OR = 1.7; 95% CI 0.66-4.5, compared with those who delivered their first baby under 25. - If pregnant - ended with a miscarriage, the risk of contracting ovarian cancer decreased, and was at the level of OR = 0.8; 95% CI - 0.53-1.28, compared with women who have never been pregnant. - Among patients who do not breastfeed their babies, - the risk of ovarian cancer was 1.7 times higher than those who breastfed.
11	Bethea et al., 2017	assessing reproductive and exogenous hormonal factors with ovarian cancer among black women.	*Subject*: 115 black women *Design:* Prospective Cohort Study	Amerika	Overall, the findings show a relationship between reproductive factors and exogenous hormones on the risk of ovarian cancer among black and white women. The results on estrogen-specific and estrogen-specific supplementation with progestin supplements add to the evidence from white women, suggesting that hormone supplements may increase the risk of ovarian cancer.
12	Lee, 2013	To investigate the association between consumption of preserved foods and the risk of epithelial ovarian cancer in southern Chinese women.	*Subject*: 500 epithelial ovarian cancer patients and 500 controls, with a mean age of 59 years *Design:* Case-control	South china	- The ovarian cancer patients consumed more preserved foods (median 15.5, interquartile range) (IQR 18.2 g/day) than the control group (median 13.8, IQR 20.5 g/day). P<0.001 - There is a significant relationship between the intake of preserved vegetables and meat that is twice positively associated with epithelial ovarian cancer in southern Chinese women.
13	Mori & Miyake, 1988	Identifying diet and other factors associated with ovarian cancer in elderly women	*Subject*: 56 elderly with ovarian cancer case group 56 people in control *Design:* Case-control	Japan	- There is a significant relationship between daily meat consumption and the incidence of ovarian cancer (OR=3.11, P<0.01) - Daily fish consumption was positively related to ovarian cancer (OR=2.54, P<0.05) - There is no significant relationship between the consumption of milk, coffee, alcohol, and cigarettes on the incidence of ovarian cancer.

Table 3. Summary of Article Search Results for Systematic Review (*Continued*)

No	*Authors and years*	*Objective Study*	*Research Methods*	*Place*	*Findings*
14	Burghaus et al., 2015	Investigating the medical history of endometriosis may be a risk factor for ovarian or endometrial cancer.	*Subject*: 289 people in the case group and 1016 in the control group *Design:* case-control study	United States	- endometriosis can be a predictor factor in cases of ovarian cancer (OR=2.63, 95% Cl, 1.28 to 5.41 - Age and BMI are risk factors for ovarian cancer
15	He et al., 2017	Investigating risk factors for ovarian cancer in women with endometriomas	*Subject*: 1038 women over 45 years old *Design:* Cross-Sectional	China	- Patients who were older when diagnosed with OEM had a higher risk of developing EAOC by 1.7% (13/751) at 45–49 years, 5.6% (12/215) at 50–54 years, and 10.0% (5/50) at 55–59 years (P < 0.001).

The research results for articles in the table above regarding risk factors for ovarian cancer in developed and developing countries obtained 15 articles. Based on the search, most of the articles reviewed were conducted in Europe. It can be seen from the research countries, namely, 7 articles in the United States, while the others have 1 article each, namely in Denmark, Norway, Sweden, and Poland. The other 4 articles are in Asia, with 1 research article in Vietnam, 1 in Japan, and 2 in China. However, no relevant research has been found in Indonesia.

The articles were obtained from the journal Ebsco (4 articles), the Willey database (1 article), Pubmed (7 articles), and Proquest (3 articles). The research articles that involved the most respondents were research conducted (Guleria et al., 2020) in Norway with 1,582,221 female respondents with a diagnosis of benign tumors, and at least 56 respondents in the study (Mori & Miyake, 1988) in Japan, with 56 elderly respondents with ovarian cancer.

The results of the review of risk factors for ovarian cancer in several countries, it have been belonging to the category of developed countries and several countries belonging to developing countries as a whole obtained several factors, including pain in menstruation, menstrual age, delayed menopause, infertility, use of fertility drugs. In addition, parous women, childbearing age, miscarriage, induced abortion, non-breastfeeding, intrauterine contraceptives,

exogenous hormones, and hormone supplements. Furthermore, it obtained ways of food processing, types of food consumed (consumption of excess meat and fish), healthy diet patterns, and smoking habits. In addition, having a family history of cancer and gender of heredity. It also includes women with benign ovarian tumors, then a medical history of endometriosis, and women with endometriomas. Then these factors are classified into 4 (four) groups: reproductive factors, lifestyle, family history, history of benign ovarian tumors, endometriosis, and endometrioma.

Reproductive factors include menstrual pain, menstrual age, delayed menopause, infertility, use of fertility drugs, parous women, age at delivery, miscarriage, induced abortion, not breastfeeding, use of intrauterine contraceptives, use of exogenous hormones, and use of hormone supplements. It affects and is related to reproductive organs, systems, and functions. Reproduction is part of the system, function, and process of reproductive organs. (Prayitno, 2014).

Furthermore, the lifestyle factors include food processing, food consumption (excessive consumption of meat and fish), healthy diet patterns, and smoking habits. Lifestyle is a person's behavior pattern applied in everyday life (Kotler, 2012). It includes smoking, physical activity, and vegetable and fruit consumption. Then it is generally associated with health (E.M. Simonsick, 2016). A high frequency of physical activity, not

consuming alcohol, and not smoking are included in good health status (Velten, 2014).

In addition, family history factors include having a family history of cancer and gender of heredity. Gene factors can influence the occurrence of cancer. Genes are genetic information that is passed down from one generation to the next. Women with a family history of cancer, including ovarian cancer, are compared to women who do not have a family history of cancer (Rasjidi, 2013).

The next grouping is women with a history of benign ovarian tumors, endometriosis, and endometriomas. It includes women with ovarian tumors, medical history of endometriosis, and endometriomas. History of the disease can be a trigger for ovarian cancer (Bobak, 2005).

DISCUSSION
Reproductive Factor

The results from 15 articles reviewed found 6 articles that include reproductive factors. It includes menstrual pain, menstrual age, delayed menopause, infertility, use of fertility drugs, parous women, age at birth, miscarriage, induced abortion, not breastfeeding, use of intrauterine contraception, use of exogenous hormones and the use of hormone supplements (Asante et al., 2013; Babic et al., 2014; Bethea et al., 2017; Le et al., 2012; Lundberg et al., 2019; Pięta et al., 2012).

The risk of ovarian cancer can be detected with early symptoms, especially when women are menstruating. Women who experience pain during menstruation indicate that women are at higher risk of developing ovarian cancer than those who do not experience pain during menstruation. The pain level also shows a high and low risk of contracting ovarian cancer. If she experiences severe pain during menstruation, the woman is at increased risk of developing ovarian cancer and vice versa. If she encounters a lower level of pain, the risk is lower. It follows the results of a review of research (Babic et al., 2014), which shows that the risk of ovarian cancer will increase in women who experience

moderate and severe pain during menstruation compared to women who experience mild pain. This relation is distinguished based on histological subtypes, with influential groups for severe pain in the endometrioid and clear tumor cells.

Feeling discomfort in the lower abdomen and pain during menstruation caused by the epithelial surface of the ovary that is damaged and repaired repeatedly in the menstrual cycle can increase the probability of spontaneous mutations that can lead to malignancy (Berek, 2012). If women and not have an early examination experience this, it can lead to the risk of ovarian cancer. Next, Pięta et al. (2012) show that those who experience menstruation at the age of 11 will experience a 1.6 higher risk of ovarian cancer compared to women who experience menstruation at the age of 13 years. Similarly, women who ended their period at the age of 55 years had a 1.4 higher risk of ovarian cancer. In addition, the research conducted by Le et al. (2012) found that delayed menopause can significantly increase the risk of ovarian cancer. The cause of ovarian cancer can grow, such as the menstrual cycle coming before the age of 12 and menopause after 50 (Ratnawati, 2018). It is necessary to watch out for menstruation before the age of 12 and if menopause occurs over 50.

This review also identifies the relationship between reproduction and the incidence of ovarian cancer in women in both developed and developing countries. Lundberg et al. (2019) showed that women on ART had a higher risk of developing ovarian cancer and BOT. Ovarian cancer risk factors are caused by infertility, not ART treatment; it is proven that the increased risk of ovarian cancer caused by ART treatment is more minor than infertility. Likewise, the results of research by Asante et al. (2013) in the United States among infertile women using fertility drugs were 24% in the control group and 17% in the case group. Infertile women who use fertility drugs do not increase the risk of ovarian tumors compared to infertile women who do not, resulting in no

significant relationship between the use of fertility drugs and the risk of ovarian tumors.

Fertility drugs are clomiphene citrate; it has given orally. Moreover, gonadotropin drugs have given by injection, such as follicle-stimulating hormone (FSH). A combination of FSH and Luteinizing Hormone (LH) will induce ovulation. Or multiple ovulations. Using these fertility drugs will increase the relative risk of ovarian cancer. Clomiphene citrate for more than 12 cycles will increase the relative risk (Aziz et al., 2006). In general, the use of drugs, fertilizers, and fertility inhibitors, can affect the risk of ovarian cancer.

Similarly, Le et al. (2012) found a significantly lower risk of ovarian cancer in parous women than nullipara women. However, Pięta et al. (2012) show that the age of a woman when giving birth to her first child is essential to note. In the women group who gave birth at the age of over 35 years, the risk of ovarian cancer increased compared to the group of women who gave birth to their first baby under the age of 25. If the pregnancy ends in miscarriage, then the risk of contracting ovarian cancer will decrease compared to women who have never been pregnant. On the other hand, Le et al. (2012) research states that induced abortion can significantly increase the risk of ovarian cancer.

Furthermore, Pięta et al. (2012) suggested that among patients who do not breastfeed their babies, the risk of ovarian cancer is 1.7 times higher compared to patients who breastfeed. In addition, women with high parity had a lower risk of developing ovarian cancer, compared to nullipara, with a relative risk of 0.7. In women who have had four or more pregnancies at term, the development of ovarian cancer is reduced by 40% compared with nulliparous women (Aziz et al., 2006).

The research result by Le et al. (2012) showed that intrauterine contraceptives could reduce cancer risk. Meanwhile, in the research by Bethea et al. (2017) In America, findings suggest an association between reproductive factors and the use of exogenous hormones and the risk of ovarian cancer between black and white women. The results on estrogen-specific and estrogen-specific supplementation with progestin supplements add to the evidence from white women, suggesting that hormone supplements may increase the risk of ovarian cancer. Some health experts believe that the factors often done by women knowingly can cause ovarian cancer include using IUD contraception and taking estrogen hormone therapy long-term (Ratnawati, 2018). Thus, intrauterine contraceptives and hormonal use in the long term can continuously increase the risk of ovarian cancer.

Lifestyle Factor

The results from 15 articles reviewed found 4 articles related to lifestyle factors include food processing, types of food consumed (consumption of excess meat and fish), healthy diet patterns, and smoking habits (Lee et al., 2013; Licaj et al., 2016; Mori & Miyake, 1988; Qin, 2017).

The lifestyle of women in various developed and developing countries has undergone many changes due to demands where the role of women is currently equal to that of men. It takes much time and changes habits, including consuming food. According to (Lee et al., 2013), intake of preserved vegetables and meat was positively associated with epithelial ovarian cancer in women in Southern China. It is in line with (Mori & Miyake, 1988), where is a significant relationship between daily meat consumption and the incidence of ovarian cancer P<0.01), and daily fish consumption is positively related to ovarian cancer P<0.05). While consumption of milk, coffee, alcohol, and cigarettes have no significant relationship with the incidence of ovarian cancer.

Further research in the United States shows that adherence to an overall healthy diet may reduce the risk of ovarian cancer in African-American women, particularly among postmenopausal women (Qin, 2017). It shows that the nutrients from the food consumed have an

essential role in the growth and development of cancer, especially the high animal fat content in the diet. Consume cereals, nuts, vegetables, and fruit, especially those high in lutein. In addition, preserved food contains sodium nitrate, which forms a carcinogenic component, so this food is harmful to health and can trigger cancer (Subagja, 2014).

In another study by (Licaj et al., 2016) in Norway, the results showed a significant increase between smokers and non-smokers, where the smokers had a higher risk of developing mucinous tumors than non-smokers. Cigarettes contain chemicals that are harmful to the body. Cigarettes contain various substances that are very lethal, including nicotine, CO (carbon monoxide), carcinogens, and irritants. Carcinogens are substances that can trigger cancer (Subagja, 2014). In addition, cigarettes are made of a substance called nicotine. Nicotine is a toxic substance that can directly stimulate cancer cell formation. As a result, using these materials can reduce the local immune status and cause infection by carcinogenic viruses. Avoiding smoking can prevent the presence of CIN (cervical intraepithelial neoplasia) or malignant growth of epithelial cells and minimize the risk of ovarian cancer. Avoiding this cigarette is done by not smoking (active smokers) and avoiding exposure to cigarette smoke (passive smoking) (Aziz et al., 2006). If this is still done, the risk of someone contracting ovarian cancer will be even more significant. It will be increasingly difficult for those with ovarian cancer to cure.

Family History Factors

The results from 15 articles reviewed found 2 articles discuss related to the family history factor include having a family history of cancer and the sex of the offspring (Hughes et al., 2003; Zhuxuan, 2020).

Hereditary factors significantly influence a person related to the risk of contracting the disease and the risk factors for ovarian cancer. As stated by (Hughes et al., 2003), in Boston, the incidence of

cancer according to family history shows that as many as 65% of respondents do not have a family history of cancer, and only 51 respondents have an incidence rate (9.4%). They have a family history of cancer; of 51 respondents with a family history of cancer, 62% are at risk for cancer. Also, the research found that giving birth to a boy was associated with a reduced risk of EOC compared to giving birth to a girl (Zhuxuan, 2020).

One meta-analysis study in 1998 found an increased and different relative risk in family members with a history of ovarian cancer. Mothers of patients with ovarian cancer have a relative risk of 1.1, sisters have an equal chance of 3.8, and children with ovarian cancer have a relative risk of 6. Between 5-10% of ovarian cancers are considered hereditary. This group of ovarian cancers is included in the hereditary breast and ovarian cancer (HBOC) syndrome (Aziz et al., 2006).

Ovarian cancer that is genetically inherited is associated with mutations in the BRCA-1 and BRCA-2 genes, where mutations in the BRCA-1 gene are more commonly happen. The presence of BRCA gene mutations is associated with the risk of ovarian cancer by 27-44% compared to the risk of ovarian cancer in the average population, which is 1.4%. Mutations cause gene instability and make cells more likely to transform into a malignancy. This mutation is inherited through an autosomal dominant gene (Berek, 2005). Genetic history shows that women born to breast and ovarian cancer families are at higher risk of developing ovarian cancer.

Factors History of Ovarian Tumor Disease, Endometriosis, and Endometrioma

The results from 15 articles reviewed found 3 articles discuss related to women's history of ovarian tumors, endometriosis, and endometriomas. It included women with ovarian tumors, medical history of endometriosis, and also women with endometriomas (Burghaus et al., 2015; Guleria et al., 2020; He et al., 2017).

Women with tumors, endometriosis and endometriomas need to be careful because they trigger ovarian cancer. Research (Guleria et al., 2020) in Denmark showed that identified benign ovarian tumors could develop into mucinous ovarian cancer in the long term. Similarly, (Burghaus et al., 2015) in the United States showed that Endometriosis could be a predictor factor in cases of ovarian cancer. Age and BMI are risk factors for ovarian cancer. Likewise, (He et al., 2017) in China showed that patients who were older when diagnosed with OEM had a higher risk of developing EAOC by 1.7% at 45–49 years, 5.6% at age 50–54 years, and 10.0% at age 55–59 years (P < 0.001).

Every woman can experience endometriosis, but certain risk factors in some women have a higher risk of developing endometriosis. Including age, most often shared between 30 to 40 years, genetics, nulliparity, and medical history have experienced conditions that prevent menstrual blood expulsion—infection in the pelvis or anatomical abnormalities of the uterus. In addition, endometriosis, ovarian cysts, inflammation, scar tissue, tissue adhesions, and complications in the bowel and bladder can increase the risk of ovarian cancer (Bobak, 2005). Women who suffer from tumors, endometriosis, and endometriomas, should be routinely controlled and check themselves to health services to avoid ovarian cancer.

CONCLUSION

A systematic review found four risk factors: reproductive factors, lifestyle, family history, and disease history. These risk factors can be prevented by conducting early screening for ovarian cancer. Nurses in the health sector can provide health services and education as early as possible to prevent ovarian cancer risk factors in women from reduce the number of ovarian cancer cases. The limitations of this systematic review study, during the literature collection and review process, namely: Research on ovarian cancer and theories related to ovarian cancer are still limited.

REFERENCES

Ahmed-Lecheheb, D., & Joly, F. (2016). Ovarian cancer survivors' quality of life: a systematic review. *Journal of Cancer Survivorship*, *10*(5), 789–801. https://doi.org/10.1007/s11764-016-0525-8.

Asante, A., Leonard, P. H., Weaver, A. L., Goode, E. L., Jensen, J. R., Stewart, E. A., & Coddington, C. C. (2013). Fertility drug use and the risk of ovarian tumors in infertile women: a case-control study. *Fertility and Sterility*, *99*(7), 2031–2036. https://doi.org/10.1016/j.fertnstert.2013.02.010.

Aziz, M. F., Andrijono, & Saifuddin, A. B. (2006). *Buku Acuan Nasional Onkologi Ginekologi* (M. F. Aziz, Andrijono, & A. B. Saifuddin (eds.); 1st ed.). Yayasan Bina Pustaka Sarwono Prawirohardjo.

Babic, A., Cramer, D. W., Titus, L. J., Tworoger, S. S., & Terry, K. L. (2014). Menstrual pain and epithelial ovarian cancer risk. *Cancer Causes and Control*, *25*(12), 1725–1731. https://doi.org/10.1007/s10552-014-0463-6.

Berek, J. S. (2012). *Berek & Novak's Gynecology* (Fifteenth). Lippincott Williams & Wilkins.

Bethea, T. N., Palmer, J. R., Adams-Campbell, L. L., & Rosenberg, L. (2017). A prospective study of reproductive factors and exogenous hormone use about ovarian cancer risk among Black women. *Cancer Causes and Control*, *28*(5), 385–391. https://doi.org/10.1007/s10552-016-0840-4.

Bobak. (2005). Buku Ajar Keperawatan Maternitas. Jakarta: EGC.

Burghaus, S., Häberle, L., Schrauder, M. G., Heusinger, K., Thiel, F. C., Hein, A., Wachter, D., Strehl, J., Hartmann, A., Ekici, A. B., Renner, S. P., Beckmann, M. W., & Fasching, P. A. (2015). Endometriosis as a risk factor for ovarian or endometrial cancer - results of a

hospital-based case-control study. *BMC Cancer*, *15*, 751. https://doi.org/10.1186/s12885-015-1821-9.

Cress, R. D., Chen, Y. S., Morris, C. R., Petersen, M., & Leiserowitz, G. S. (2015). Characteristics of Long-Term Survivors of Epithelial Ovarian Cancer. *Obstetrics and Gynecology*, *126*(3), 491–497. https://doi.org/10.1097/AOG.0000000000000981.

Ebell, M. H., Culp, M. B., & Radke, T. J. (2016). A Systematic Review of Symptoms for the Diagnosis of Ovarian Cancer. *American Journal of Preventive Medicine*, *50*(3), 384–394. https://doi.org/10.1016/j.amepre.2015.09.023.

E.M. Simonsick, H.C.S. Meier, N.C. Shaffer, S.A.Studenski, L. Ferrucci.2016.Basal body temperature as a biomarker of healthy aging (Dordr), 38 (5–6) (2016), pp. 445-454,10.1007/s11357-016-9952-8 39.

Fischer, O. J., Marguerie, M., & Brotto, L. A. (2019). Sexual Function, Quality of Life, and Experiences of Women with Ovarian Cancer: A Mixed-Methods Study. *Sexual Medicine*, *7*(4), 530–539. https://doi.org/10.1016/j.esxm.2019.07.005.

Gea, I. T., Loho, M. F., & Wagey, F. W. (2016). Gambaran jenis kanker ovarium di RSUP Prof. Dr. R. D. Kandou Manado. *Journal E-Clinic*, *4*(2), 2–6.

Guleria, S., Jensen, A., Toender, A., & Kjaer, S. K. (2020). Risk of epithelial ovarian cancer among women with benign ovarian tumors: a follow-up study. *Cancer Causes and Control*, *31*(1), 25–31. https://doi.org/10.1007/s10552-019-01245-4.

Hamid Prasetya Subagja. (2014). *Kanker- Kanker Ganas Pembunuh Wanita* (Hira (ed.)).

He, Z.-X., Shi, H.-H., Fan, Q.-B., Zhu, L., Leng, J.-H., Sun, D.-W., Li, Z.-F., Shen, K., Wang, S., & Lang, J.-H. (2017). Predictive factors of ovarian carcinoma for women with ovarian endometrioma aged 45 years and older in China. *Journal of Ovarian Research*, *10*(1), 45. https://doi.org/10.1186/s13048-017-0343-2.

Hughes, K. S., Roche, C., Campbell, C. T., Siegel, N., Salisbury, L., Chekos, A., Katz, M. S., & Edell, E. (2003). Prevalence of a family history of breast and ovarian cancer in a single primary care practice using a self-administered questionnaire. *The Breast Journal*, *9*(1), 19–25. https://doi.org/10.1046/j.1524-4741.2003.09105.x.

Inci, M. G., Richter, R., Heise, K., Dukatz, R., Woopen, H., & Sehouli, J. (2021). Patient-reported outcomes (Pros) and health-related quality of life (hr-qol) in patients with ovarian cancer: What is different for healthy women? *Cancers*, *13*(4), 1–11. https://doi.org/10.3390/cancers13040631.

Indriani, R., Amarullah Ritonga, M., & Suardi, D. (2018). Evaluasi tindakan operatif pada kanker serviks, endometrium, dan ovarium di RSUP Dr. Hasan Sadikin Bandung tahun 2015-2016. *Indonesian Journal of Obstetrics & Gynecology Science*, *1*(2), 79–86. https://doi.org/10.24198/obgynia.v1n2.49.

Kotler, P. (2012). *Kotler on marketing*. Simon and Schuster.

Le, D. C., Kubo, T., Fujino, Y., Sokal, D. C., Vach, T. H., Pham, T. M., & Matsuda, S. (2012). Reproductive factors about ovarian cancer: A case-control study in Northern Vietnam. *Contraception*, *86*(5), 494–499. https://doi.org/10.1016/j.contraception.2012.02.019.

Lee, A. H., Su, D., Pasalich, M., & Binns, C. W. (2013). Preserved foods are associated with an increased risk of ovarian cancer. *Gynecologic Oncology*, *129*(3), 570–573. https://doi.org/10.1016/j.ygyno.2013.03.016.

Li et al. (2015). Passive Smoking and Ovarian Cancer Risk among Non-Smoking Women: A Licaj, I., Lukic, M., Jareid, M., Lund, E., Braaten, T., & Gram, I. T. (2016). Epithelial ovarian cancer subtypes attributable to smoking in the Norwegian Women and Cancer Study, 2012. *Cancer Medicine*, *5*(4), 720–727. https://doi.org/10.1002/cam4.590.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies Evaluating Health Care Interventions : Explanation and Elaboration. *Plos Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000100.

Licaj, I., Lukic, M., Jareid, M., Lund, E., Braaten, T., & Gram, I. T. (2016). Epithelial ovarian cancer subtypes were attributable to smoking in the Norwegian Women and Cancer Study, 2012. *Cancer Medicine*, *5*(4), 720–727. https://doi.org/10.1002/cam4.590.

Liu, Y. L., Filippova, O. T., Zhou, Q., Iasonos, A., Chi, D. S., Zivanovic, O., Sonoda, Y., Gardner, G. J., Broach, V. A., Cearbhaill, R. E. O., Konner, J. A., Aghajanian, C., Roche, K. L., & Tew, W. P. (2020). Characteristics and survival of ovarian cancer patients treated with neoadjuvant chemotherapy but not undergoing interval debulking surgery. *Journal of Gynecologic Oncology*, *31*(1), 1–12.

Lisnawati. (2013). Gambaran Faktor-Faktor Risiko Penderita Kanker Ovarium di RSUD. http://repositori.uin-alauddin.ac.id/.

Lundberg, F. E., Johansson, A. L. V, Rodriguez-Wallberg, K., Gemzell-Danielsson, K., & Iliadou, A. N. (2019). Assisted reproductive technology and risk of ovarian cancer and borderline tumors in parous women: a population-based cohort study. *European Journal of Epidemiology*, *34*(11), 1093–1101. https://doi.org/10.1007/s10654-019-00540-3.

Mayer, S., Iborra, S., Grimm, D., Steinsiek, L., Mahner, S., Bossart, M., Woelber, L., Voss, P. J., Gitsch, G., & Hasenburg, A. (2019). Sexual activity and quality of life in patients after breast and ovarian cancer treatment. *Archives of Gynecology and Obstetrics*, *299*(1), 191–201. https://doi.org/10.1007/s00404-018-4922-2.

Mori, M., & Miyake, H. (1988). Dietary and other risk factors of ovarian cancer among elderly women. *Japanese Journal of Cancer Research : Gann*, *79*(9), 997–1004. https://doi.org/10.1111/j.1349-7006.1988.tb00066.x.

Momenimovahed. (2019). Ovarian cancer in the world: Epidemiology and risk factors. International Journal of Women's Health, 11, 287–299. https://doi.org/10.2147/IJWH.S197604.

Pięta, B., Chmaj-Wierzchowska, K., & Opala, T. (2012). Past obstetric history and risk of ovarian cancer. *Annals of Agricultural and Environmental Medicine : AAEM*, *19*(3), 385–388.

Prayitno, S. (2014). Kesehatan Organ Reproduksi Wanita. Jakarta Selatan: Serambi Semesta Distribusi.

Ratnawati, A. (2018). *Sistem Reproduksi*. Pustaka Baru Press.

Rasjidi, I. (2013). Buku Ajar Onkologi Klinik. *Jakarta: EGC*.

Rietveld, M. J. A., Husson, O., Vos, M. C. (Caroline., van de Poll-Franse, L. V., Ottevanger, P. B. (Nelleke., & Ezendam, N. P. M. (2019). The presence of gastrointestinal symptoms in ovarian cancer patients during survivorship is a cross-sectional study from the PROFILES registry. *Supportive Care in Cancer*, *27*(6), 2285–2293. https://doi.org/10.1007/s00520-018-4510-9.

Rosida, S., Sanif, R., Novaliani, A., & Theodorus. (2020). Efektivitas kemoterapi kombinasi paklitaksel – karboplatin berdasarkan kadar vascular endothelial growth factor A (VEGF-A) serum pada kanker ovarium tipe epitel. *Jurnal Kedokteran Dan Kesehatan*, *7*(2), 91–98.

Shields et al. (2014). A Case-Control Study of Risk Factors for Invasive Cervical Cancer among U.S. Women Exposed to Oncogenic Types of Human Papillomavirus. Cancer Epidemiol Biomarker, 13(10), pp. 1574–1582.

Utami. (2016). *Efektifitas latihan Progressive Muscle Relaxation (PMR) terhadap mual.* Jurnal Keperawatan Jiwa, Volume 4 No 2, Hal 83 - 90, November 2016.

Velten, J., Lavallee, K.L., Scholten, S., *et al.* Lifestyle choices and mental health: a representative population survey. *BMC Psychol* 2, 58 (2014). https://doi.org/10.1186/ s40359014-0055-y.

World Health Organization. (2019). Indonesia Source GLOBOCAN 2018. International Agency for Research on Cancer, 256, 1–2. http://gco.iarc.fr/.

Wulandari, M. R. S. (2018). Kecemasan dan kualitas pada penderita kanker ovarium. *Caring*, *2*(2), 1–7.