# Risk and Protective Factors Associated with Ovarian Cancer among Two Egyptian Cohorts

Sahar A. A. Ahmed[1], Sahar Y. Mohammad[2]

[1]Maternity and Child Health Nursing, Faculty of Nursing, El-Minia University.
e-mail: saharshamandy@yahoo.com
[2]Medical-Surgical Nursing, Faculty of Nursing, Ain Shams University.
e-mail: saharyassien@yahoo.com

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**ABSTRACT**

***Context:*** Ovarian cancer is a global health crisis, as it is one of the devastating diagnoses for the patient and family. A nurse is a key person in the effort of health promotion, screening, and early detection. As well as care through the illness continuum.
***Aim:*** This study aims to determine the risk factors of ovarian cancer among two Egyptian cohorts and determine the possible protective factors of ovarian cancer among two Egyptian cohorts.
***Methods:*** A descriptive exploratory (Case/control) prospective research design was used to achieve the study aim. The study was conducted in two clinical settings: National Cancer Institute (for cases) and El-Minia General Hospital (for controls). The study recruited 80 cases with a confirmed diagnosis of ovarian cancer and 456 healthy controls without ovarian cancer. A structured interview questionnaire was used to collect data regarding the presence of possible risk and protective factors.
***Results:*** The results of the present study revealed a highly statistically significant difference between cases and controls regarding their educational level, family history of ovarian cancer, types of other cancers, hysterectomy, and eating a low-fat diet at $p<0.001$. The study also showed a statistically significant difference regarding age at menopause, the degree of relationship with colorectal cancer relatives, and history of endometriosis at $p<0.05$.
***Conclusion:*** The study signifies the level of education, hysterectomy, late age at menopause, and eating a low-fat diet as protective-factors against ovarian cancer while signifies the positive family history of ovarian cancer and endometriosis as risk factors associated with ovarian cancer. The study recommended trained health care providers to monitor trends in ovarian cancer occurrence, disparities in care and health assurance assistance, provide screening and early detection activities, care, education for healthy women at risk for ovarian cancer.

***Keywords:*** Risk factors, protective factors, ovarian cancer, Egyptian cohort

## 1. Introduction

Ovarian cancer (OC) is one of the most aggressive reproductive cancers among women *(Sumanasekera, Beckmann, Fuller, Castle, & Huff, 2018)*. Ovarian Cancer is a global health crisis and one of the deadly gynecological cancers worldwide *(Matz et al., 2017)*. Despite OC being only 3% of all cancer incidents, the mortality rate of the OC is extremely high, making it the fifth leading cause of cancer–related deaths in women *(Varas, Rice & Illanes 2017; Siegel, Miller & Jemal, 2015; Goff, Balas, & Tenenbaum 2013)*. Globally, developed countries have a higher incidence of OC, and, by continent, the highest rate is seen in Europe, while Africa has the lowest rate *(Lingeman, 1983)*.

Ovarian cancer is accountable for about six percent of all women cancer deaths that exceed combined deaths from cervical and endometrial cancer *(Jemal et al., 2007)*. Unfortunately, the life expectancy of those patients revealed that seventy-six percent of them live for only one year, and about forty-five percent live to five years after diagnosis. Expectedly, early diagnosis can increase the survival rate, but it does not happen. Women always presented at a late stage due to indefinite or no symptoms. Delayed diagnosis hinders early intervention, which consequently adversely affects the long-term survival of those patients *(Coleman & Monk, 2006)*.

The causes of ovarian cancer are not clearly stated; however, a long list of risk factors is thought to be associated with the emergence of ovarian cancer. One or more risk factors could potentiate the occurrence of ovarian cancer, although their presence does not confirm ovarian cancer will occur *(Bohnenkamp, LeBaron, & Yoder, 2007)*. Premenopausal women are at a lower risk of developing ovarian cancer than postmenopausal women. More than fifty percent of ovarian cancer patients detected after the age of sixty-three *(National Comprehensive Cancer Network [NCCN] & American Cancer Society [ACS], 2004)*.

*National Comprehensive Cancer Network and American Cancer Society (2004)* reported an increased ovarian cancer risk in women with first-degree relatives of ovarian cancer (women's mother, sister, daughter), mainly if diagnosed before the age of fifty-five. NCCN & ACS also stated that the inherited BRCA1 and BRCA2 gene mutation are responsible for about ten percent of all ovarian cancer cases. Ovarian cancer risk also increased

[1]*Corresponding author: Sahar Ahmed Alshamandy*

with a genetic mutation associated with colorectal cancer. However, trained genetic counselors can assess the women's genetic risk profiles and screen for specific gene mutations.

*Breek (2005)* added other significant factors that could increase the risk of ovarian cancer, such as earlier age of menarche (before the age of twelve), nulliparity, women who had their first child after the age of thirty, and late menopause (after the age of fifty). A relationship is believed to exist between the number of ovulation times and the women's risk of developing ovarian cancer. Infertility also believed to rises ovarian cancer risks, whether the women used clomiphene citrate or not. The risk is increased in long-term use (three years or more), particularly if pregnancy is not achieved *(NCCN & ACS, 2004)*. Although the mechanism of association is not well recognized *(Berek, 2005)*. A fifty percent decrease in ovarian cancer risk in women who had a child through their lifetime *(Garcia, 2006)*.

Many prophylactic interventions thought they could decrease the ovarian cancer risk. Indeed, they are quite dramatic. Those interventions include tubal ligation, salpingo-oophorectomy, and total hysterectomy *(NCCN & ACS, 2004)*. These interventions may be considered practical choices for high-risk women. Oral contraceptives for five years or more, pregnancy, breastfeeding, ideal bodyweight, and maintaining a well-balanced diet with low fat may also provide a varying degree of protection against ovarian cancer *(Berek, 2005; NCCN & ACS, 2004)*. A previous landmark study *(Gershenson et al., 1996)* demonstrated a relationship between ovarian cancer and high fat intake. The *American Cancer Society (2002)* reported a fifty percent increase in the death rate among ovarian cancer obese women.

Another significant risk factor that may increase ovarian cancer risk is polycystic ovarian syndrome (PCOS). This syndrome is altering the hormonal microenvironment, thus the hormone secretions patterns, resulting in disturbed ovulation cycles and multiple ovarian cysts development. Another risk factor mentioned in earlier research is talcum powder used over the genital area or used on female sanitary pads. Talcum powder might be associated with an increased risk of ovarian cancer. This thought due to old talcum powder preparation contained asbestos, but for over twenty years, it has been asbestos-free *(NCCN & ACS, 2004)*.

The misfortune of ovarian cancer patients is its initial presentation that is often deceptive and misleading. This presentation is often unclear for both patients and health care providers. So, the definite diagnosis is confirmedat an advanced stage. Therapeutic interventions of ovarian cancer comprise a combination of surgery and chemotherapy. These treatment options had many adverse consequences in the long run. Symptom management and nursing care are paramount through the course of this devastating disease. Nurses in a critical position to care for patients and families through education, counseling, caregiving, and support *(Bohnenkamp, LeBaron, & Yoder, 2007)*.

Nurses also are in a key position to increase cancer awareness *(Martin, 2005)*. Health education is the crucial nurses' role in health promotion and disease prevention *(Bohnenkamp, LeBaron, & Yoder, 2007)*. Nurses also can participate in the early detection of ovarian cancer. The nurse can screen for possible risks of various disorders during history taking, particularly women genital cancers *(Bohnenkamp, LeBaron, & Yoder, 2007)*. Moreover, nurses are the health care providers who provide care throughout the trajectory of ovarian cancer for patients and their families. Nurses can tailor the plan of care according to the stage of the disease, considering both physical and emotional aspects and potentiate patient and family coping *(Christy & Nixon, 2004)*. Health education function continues through the stage of treatment. The nurse provides health education regarding treatment side effects and disease progression. Through the ovarian cancerillness continuum, the nurse could provide help for both patient and family from the time of diagnosis until fullrecovery or even death *(Martin, 2005)*.

## 2. Significance of the study

*Gawad (2018)* reported eight years' statistics of the female genital system from (2010-2017). It represented 4.8% of all cancers among both genders, with an absolute number of 3987 cases in 2017. Ovaries cancer represented >2/5$^{th}$ (1629, 41.1%) of all female genital cancer, followed by cervix uteri (1000, 25.3%) and corpus uteri (755, 19.1%). *National Cancer Institute registry, (2018)* declared that among major surgery performed between Jan. 2015 and Dec. 2015, there was 579 female genial cancer surgery, with a rate of 20-35 cases per month for staging for ovarian carcinoma.

The annual incidence of ovarian cancer in Egypt is 5.4/100,000 women. 45% of them are younger than 50 years of age. The annual rate in women between 50-69 years of age is 17.7/100,000. 75% of ovarian cancer patients presented at stage I, 80% responded to surgery and chemotherapy. 80% of patients relapsed within two years, and 80% will die within the further two years *(National Cancer Institute Registry, 2018)*. The geographical distribution showed 5.1/100,000 as a crude rate in lower Egypt between 2009-2011, 3.6/100,000 in middle Egypt in 2009, and 7.1 crude rates in upper Egypt in 2008 *(Gawad, 2018)*. *Ibrahim, Khaled, Mikhail, Baraka, &Kamal (2014)* reported ovarian cancer projected annual caseload in Egypt as 2100 cases in 2013, 2200 cases in 2015, 2400 cases in 2020, 3100 cases in 2025, and 5900 cases in 2050.

Over the past few years, the mortality rate due to ovarian cancer has not improved significantly. This finding might be due to a lack of effective screening for this type of cancer in an early stage of the disease. Many factors could participate in improving the survival rate. Among them are disease stage at diagnosis, women's age, the women's functional status, and general health status. Therefore, this study was conducted to explore the possible risks and protective factors associated with the development of this devastating disease and empower nurses to screen for this

high mortality illness.

## 3. Aim of the study

The present study aims

- To determine the risk factors of ovarian cancer among two Egyptian cohorts.
- To determine the possible protective factors of ovarian cancer among two Egyptian cohorts.

## 4. Subjects & Methods

### *4.1. Research design*

Descriptive exploratory (Case/control) prospective research design.

### *4.2. Research setting*

For cases, they recruited from the National Cancer Institute affiliated with Cairo University. It is the largest comprehensive cancer center in the Middle East and Africa. It is an academic institution, cancer treatment, and research center. NCI total capacity of 350 beds (85% of them provided free of charge services, the other 15% are economical and private sections). NCI is receiving 19,000 newly diagnosed cancer patients each year, plus around 19,600 patients followed from the previous year. It has five operating rooms that received around 25-30 ovarian cancer patients per month. This clinical setting is selected for their previous characters and for the feasibility to collect as much number as the researcher could to obtain ovarian cancer cases with a confirmed diagnosis.

The controls were recruited from the outpatient clinics at El-Minia General Hospital outpatient clinics. It is a central district hospital that served all rural and urban communities affiliated to the El-Minia governorate and nearby governorates. The rationale for selecting this setting is the high utilization of their services by women seeking various maternal and child health services.

### *4.3. Subjects*

The study included a convenient sample of ovarian cancer patients with confirmed diagnosis at any stage of illness at the NCI (80 cases). The controls were recruited from the outpatient clinic at El-Minia General hospital who came for follow-up, child vaccination, family planning, and female relatives accompanying patients (465 controls). Only exclusion criteria among controls are diagnosed with ovarian cancer or had a history of ovarian cancer. All cases and controls were illegible if they were mentally incompetent to give informed consent or comprehend the structured interview questions.

### *4.4. Tools of the study*

#### 4.4.1. A Structured Interview Questionnaire

It was designed by the researchers to explore risk and protective factors among ovarian cancer patients and healthy controls. The questionnaire encompasses five parts. The first part is designed to reveal the participant's socio-demographic characteristics such as age, marital status, and educational level. The second part included assessing the participant's reproductive history, such as the age of menarche, age of menopause (if reached/NA), parity, and history of multiple births. The third part covered the participants' health history of different cancers such as ovarian, breast, colorectal, and other cancers (i.e., blood, lung, bone, thyroid, cervix, lymphoma).

The fourth part was exploring the participants' medical history and health profile such as the use of oral contraceptives, use of the intrauterine device, history of tubal ligation, hysterectomy, infertility, use of fertility drugs, use of hormonal replacement therapy after menopause, history of endometriosis, history of ovarian cysts, history of polycystic ovary, history of diabetes mellitus, and breastfeeding. The fifth part was encompassing the participant's lifestyle attributes such as height and weight (BMI), use of talc powder on the genital area, smoking, alcohol, eating fresh fruits and vegetables in their diet, eating a low-fat diet, tea consumption, living active life (regular walking or sports activity), and practicing recreation.

### *4.5. Procedures*

The operational design started with the preparatory phase, including an extensive review of the literature to construct the study tool surveying all possible risks and protective factors. A jury of 7 experts is subjected to validating the study tool (three professors of maternal and child health nursing, two professors of obstetrics and gynecology medicine, and two professors in gynecologic oncology). Assessment of the study setting to disclose the number of recurred ovarian cancer patients. Official permission was obtained from the NCI and El-Minia General Hospital.

Ethical consideration is assured by obtaining the participant's informed consent after explaining the aims and benefits of the study. The anonymity of the study tool was assured, and confidentiality of the women's personal information was granted. Then, the pilot study was conducted to test the feasibility of the study process, the clarity, comprehensiveness of the study tool. The pilot study was conducted on 10% of the study sample (8 ovarian cancer patients and 45 healthy females). There were no modifications in the study tool, and the pilot sample was further included in the mainstream sample. The structured questionnaire lasted 20-30 minutes to be completed by the researchers.

The researcher-interviewers obtained the past and present history according to the structured interview questionnaire, obtain anthropometric measurements, calculates the BMI based on the women's height and weight. The fieldwork included an individual interviewing with each participant during their treatment or follow-up visits (for ovarian cancer patients) and during child vaccination, child follow-up, or visiting family planning clinic to complete the structured questionnaire (for controls). Participation was optional, and the participant

could withdraw at any time without reasoning. The data collection process started from January to September 2018.

### 4.6. Data analysis

The data computed using the SPSS program version.

23. Qualitative data presented as a number and percentage, while quantitative data were presented as mean±SD. Chi-square test used to compare cases and controls regarding their qualitative data, and t-test used to compare cases and controls' quantitative data. Logistic regression analysis was used to calculate odds ratios and at a confidence interval of 95%. The case/control ratio was exceeding 1:5 to increase the power of the study; after the case-control ratio of 1:5, no more new findings could be detected.

## 5. Results

Table 1 illustrates comparable groups regarding women's age and marital status with a non-statistically significant difference between both groups. The table also signifies education as a point of difference between both groups. Near half of the controls had a university education or more at p<0.001. One of the noticeable findings was that 61.6% of healthy controls were married compared to 48.8% of cases.

While table 2 shows matching reproductive history between the two groups regarding their age of menarche, parity, and history of twins, age of menopause was a significant factor at p<0.05 as cases were menopaused earlier. Another distinct finding in this table that 42.5% of cases had zero parity, while 41.8% of healthy controls have four or more children.

In the analysis of cases and control's health history of cancers, table 3 signifies the positive family history of ovarian cancer as a risk factor (at p= 0.001) with a four folds increase for cases more than controls (8.8% vs. 2.0%). Also, it reveals the closest the relationship, as all cases, and 88.9% of controls with a positive history of ovarian cancer had a first-degree relative with ovarian cancer. Besides, 88.9% of cases and 70.3% of controls with a positive family history of breast cancer had first-degree relatives with breast cancer. It is also the case with a positive family history of colorectal cancer that 40% of cases and 88.6% of controls had the first-degree relative with colorectal cancer, with a significant difference between the two groups. Another significant factor is the type of cancer among those with a personal history of other cancers that 83.3% of the ovarian cancer patient had a positive history of other cancers (12 cases) vs. 66.7 of controls (108 control) had a positive history of breast cancer.

Table 4 signifies the history of hysterectomy as a protective factor with a highly statistically significant difference between the two groups. Endometriosis also shows as a significant risk factor at (p= 0.2). Surprisingly, use of oral contraceptives, IUDs, history of tubal ligation, infertility, use of ovulation induction, use of hormonal replacement therapy, use of talc powder, ovarian cyst, polycystic ovaries, history of diabetes, and breastfeeding shows no statistically significant difference.

Table 5 reveals no statistically significant difference between cases and control groups regarding numbers of the menstrual cycle in women using Clomid at p-value 0.71.

Body mass index, smoking, alcohol, eating fresh fruits, tea consumption, living an active life, and practicing recreation activities shows no significant difference between both groups, as revealed by table 6. In contrast, a significant difference shows regarding eating a low-fat diet.

Logistic regression analysis for ovarian cancer risk factors emphasized an inverse significance of age at menopause, hysterectomy, and history of endometriosis as a significant risk factor at p <0.001, 0.01 as revealed in table 7.

**Table (1): Comparison between two groups regarding Socio-demographic data.**

| Socio-demographic characteristics | Cases (N=80) | | Control (N= 456) | | test | P-value |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | |
| **Women age** | 43.89±14.41 | | 42.43±14.64 | | t=0.82 | 0.41 |
| | N | % | N | % | | |
| **Marital status** | | | | | | |
| Married | 39 | 48.8 | 281 | 61.6 | $X^2$=4.81 | 0.19 |
| Single | 28 | 35.0 | 116 | 25.4 | | |
| Widow | 7 | 8.8 | 30 | 6.6 | | |
| Divorced | 6 | 7.5 | 29 | 6.4 | | |
| **Education** | | | | | | |
| Cannot read &write | 13 | 16.3 | 18 | 3.9 | $X^2$=30.59 | <0.001 |
| Primary | 23 | 28.7 | 107 | 23.5 | | |
| Secondary | 30 | 37.5 | 138 | 30.3 | | |
| University or more | 14 | 17.5 | 193 | 42.3 | | |

**Table (2): Comparison between two groups regarding reproductive history.**

| Reproductive history | Cases (N=80) | | Control (N= 456) | | test | P-value |
|---|---|---|---|---|---|---|
| | Mean±SD | | Mean±SD | | | |
| **Age of menarche** | 12.61±1.68 | | 12.80±2.70 | | t=0.61 | 0.54 |
| **Age of menopause** | 43.38±6.87 | | 46.25±8.80 | | t=2.08 | 0.04 |
| | **N** | **%** | **N** | **%** | | |
| **Parity** | | | | | | |
| Zero | 34 | 42.5 | 147 | 32.2 | | |
| 1-3 | 16 | 20.0 | 118 | 25.9 | $X^2$=3.35 | 0.18 |
| Four or more | 30 | 37.5 | 191 | 41.8 | | |
| **History of twins** | | | | | | |
| No | 76 | 95.0 | 420 | 92.1 | $X^2$=0.83 | 0.36 |
| Yes | 4 | 5.0 | 36 | 7.9 | | |

**Table (3): Comparison between two groups regarding the history of cancers.**

| Reproductive history | Cases (N=80) | | Control (N= 456) | | $X^2$ | P-value |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | | |
| **Family history of ovarian cancer** | | | | | | |
| No | 73 | 91.3 | 447 | 98.0 | 10.79 | 0.001 |
| Yes | 7 | 8.8 | 9 | 2.0 | | |
| If yes | | | | | | |
| First degree | 7 | 100 | 8 | 88.9 | 0.83 | 1.00 |
| Second degree | 0 | 0.0 | 1 | 11.1 | Fisher exact | |
| **Family history of breast cancer** | | | | | | |
| No | 71 | 88.8 | 365 | 80.0 | 3.40 | 0.07 |
| Yes | 9 | 11.3 | 91 | 20.0 | | |
| If yes | | | | | | |
| First degree | 8 | 88.9 | 64 | 70.3 | 1.40 | 0.24 |
| Second degree | 1 | 11.1 | 27 | 29.7 | | |
| **Family history of colorectal cancer** | | | | | | |
| No | 75 | 93.8 | 421 | 92.3 | 0.20 | 0.66 |
| Yes | 5 | 6.3 | 35 | 7.7 | | |
| If yes | | | | | | |
| First degree | 2 | 40 | 31 | 88.6 | 5.94 | 0.04 |
| Second degree | 3 | 60 | 4 | 11.4 | Fisher exact | |
| **Personal history of other cancers** | | | | | | |
| No | 68 | 85.0 | 348 | 76.3 | 2.95 | 0.09 |
| Yes | 12 | 15.0 | 108 | 23.7 | | |
| If yes | | | | | | |
| Breast | 1 | 8.3 | 72 | 66.7 | | |
| Colon | 1 | 8.3 | 8 | 7.4 | 18.53 | <0.001 |
| Rectal | 0 | 0.0 | 4 | 3.7 | Fisher exact | |
| Others (blood, lung, bone, thyroid, cervix, lymphoma) | 10 | 83.3 | 24 | 22.2 | | |

**Table (4): Comparison between two groups regarding medical history and health profile.**

| Medical history and health profile | Cases (N=80) | | Control (N= 456) | | $X^2$ | P-value |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **Use oral contraceptive** | | | | | | |
| No | 43 | 53.8 | 257 | 56.4 | 0.19 | 0.67 |
| Yes | 37 | 46.3 | 199 | 43.6 | | |
| **Use IUDS** | | | | | | |
| No | 70 | 87.5 | 385 | 84.4 | 0.50 | 0.48 |
| Yes | 10 | 12.5 | 71 | 15.6 | | |
| **History of tubal ligation** | | | | | | |
| No | 71 | 88.8 | 417 | 91.4 | 0.61 | 0.44 |
| Yes | 9 | 11.3 | 39 | 8.6 | | |
| **Hysterectomy** | | | | | | |
| No | 41 | 51.2 | 449 | 98.5 | 193.39 | <0.001 |
| Yes | 39 | 48.8 | 7 | 1.5 | | |
| **Infertility** | | | | | | |
| No | 75 | 93.8 | 440 | 96.5 | 1.36 | 0.24 |
| Yes | 5 | 6.3 | 16 | 3.5 | | |
| **Use of ovulation induction (Clomid)** | | | | | | |
| No | 70 | 87.5 | 400 | 87.7 | 0.003 | 0.96 |
| Yes | 10 | 12.5 | 56 | 12.3 | | |
| **Use of hormonal replacement therapy*** | | | | | | |
| No | 47 | 97.9 | 143 | 92.9 | 1.68 | 0.20 |
| Yes | 1 | 2.1 | 11 | 7.1 | | |
| **History of endometriosis** | | | | | | |
| No | 75 | 93.8 | 448 | 98.2 | 5.81 | 0.02 |
| Yes | 5 | 6.3 | 8 | 1.8 | | |
| **History of ovarian cyst** | | | | | | |
| No | 75 | 93.8 | 441 | 96.7 | 1.66 | 0.20 |
| Yes | 5 | 6.3 | 15 | 3.3 | | |
| **History of polycystic ovaries** | | | | | | |
| No | 79 | 98.8 | 445 | 97.6 | 0.42 | 0.52 |
| Yes | 1 | 1.3 | 11 | 2.4 | | |
| **History of DM** | | | | | | |
| No | 57 | 71.3 | 328 | 71.9 | 0.02 | 0.90 |
| Yes | 23 | 28.7 | 128 | 28.1 | | |
| **History of breastfeeding** | | | | | | |
| No | 47 | 58.8 | 264 | 57.9 | 0.02 | 0.89 |
| Yes | 33 | 41.3 | 192 | 42.1 | | |

** (48 cases & 145 control only who use HRT)*

**Table (5): Comparison between two groups regarding the number of menstrual cycles for those using Clomid.**

| Number of menstrual cycles | Case | | Control | | z* | P-value |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | | |
| **if use Clomid no. of the menstrual cycle** | 8 | 17 | 3 | 9 | 0.37 | 0.71 |

**Mann Whitney U test*

**Table (6): Comparison between two groups regarding lifestyle attributes.**

| Medical history and health profile | Cases (N=80) | | Control (N= 456) | | t-test | P-value |
|---|---|---|---|---|---|---|
| | Mean±SD | | Mean±SD | | | |
| **BMI** | 31.04±8.60 | | 31.41±7.62 | | 0.40 | 0.69 |
| | **N** | **%** | **N** | **%** | **$X^2$** | |
| **Use of talc powder** | | | | | | |
| No | 70 | 87.5 | 362 | 79.4 | 2.87 | 0.09 |
| Yes | 10 | 12.5 | 94 | 20.6 | | |
| **Smoking** | | | | | | |
| Non-smoker | 75 | 93.8 | 438 | 96.1 | 2.86 Fisher Exact | 0.11 |
| Current smoker | 1 | 1.3 | 11 | 2.4 | | |
| Ex-smoker | 4 | 5.0 | 7 | 1.5 | | |
| **Alcohol use** | | | | | | |
| No | 80 | 100 | 444 | 97.4 | 2.15 | 0.14 |
| Yes | 0 | 0.0 | 12 | 2.6 | | |
| **Eating fresh fruits and vegetables** | | | | | | |
| No | 26 | 32.5 | 167 | 36.6 | 0.50 | 0.48 |
| Yes | 54 | 67.5 | 289 | 63.4 | | |
| **Eating low fat** | | | | | | |
| No | 53 | 66.3 | 212 | 46.5 | 10.63 | 0.001 |
| Yes | 27 | 33.8 | 244 | 53.5 | | |
| **Tea consumption** | | | | | | |
| No | 33 | 41.3 | 171 | 37.5 | 0.41 | 0.52 |
| Yes | 47 | 58.8 | 285 | 62.5 | | |
| **Living active life** | | | | | | |
| No | 61 | 76.3 | 385 | 84.4 | 3.26 | 0.07 |
| Yes | 19 | 23.8 | 71 | 15.6 | | |
| **Practice recreation activity** | | | | | | |
| No | 18 | 22.5 | 145 | 31.8 | 2.78 | 0.10 |
| Yes | 62 | 77.5 | 311 | 68.2 | | |

**Table 7: Logistic regression analysis for risk factors of ovarian cancer**

| | B | Sig. | Odds ratio | 95% CI for odds ratio | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Age of menopause** | -0.058 | <0.001 | 0.944 | 0.925 | 0.962 |
| **Hysterectomy** | 4.724 | <0.001 | 112.644 | 33.731 | 376.169 |
| **Family history of ovarian cancer** | 0.156 | 0.923 | 1.169 | 0.050 | 27.321 |
| **History of endometriosis** | 2.467 | 0.010 | 11.789 | 1.802 | 77.114 |
| **Eating low fat** | -0.617 | 0.253 | 0.539 | 0.187 | 1.554 |

## 6. Discussion

Ovarian cancer is considered one of the major clinical challenges in gynecologic oncology as most of the patients are asymptomatic until the disease has metastasized. About two-thirds of ovarian cancer patients are diagnosed in an advanced stage *(Holschneider & Berek, 2000)*. Ovarian cancer is a devastating disease for both patients and their families. Ovarian cancer patients have diverse needs regarding their physical, psychological, and spiritual coping. The nurses are in a unique position to help the patients through these needs. The nurse could provide tailored holistic care to ovarian cancer patients through the health-illness continuum *(Bohnenkamp, LeBaron, & Yoder, 2007a)*. So, this study aimed to determine the risk factors of ovarian cancer among two Egyptian cohorts and determine the possible protective factors of ovarian cancer among two Egyptian cohorts.

The present study results reveal two comparable women groups regarding their age, marital status, age at menarche, parity, history of twins, and body mass index (BMI). The study signifies education as a point of difference between both groups as the highest percentage of controls had a university education and more plus a fewer percentage who cannot read and write. This result may rationalize that a higher educational level may be associated with high awareness of the risk and protective factors linked to female genital cancer as a whole and particularly ovarian cancer. This finding was also declared by a study conducted by *Alberg et al. (2016)*. The study reported an inverse association between educational level and ovarian cancer.

Contrary to this finding a previous study done by *Tavani, Negri, Franccesch, Parazzini, and La Vecchia, (1993)*. The study reported an elevated relative risk (RR, 1.6) of ovarian cancer found among women who had twelve or more years of education. Similar findings were reported by *Gazibara, Filipovic, Kesic, Kisic-Tepavcevic, and Pekmezovic (2013)*. They reported no statistically significant differences in educational level and years of schooling between patients with OC and women in the control group.

One of the striking findings in this study is that near two-thirds of healthy control subjects were married compared to less than half of cases that could not reach the significant level. Similar findings were reported by a previous study conducted on 49,777 patients with Epithelial Ovarian Cancer (EOC) by *Mahdi et al. (2013)*. The study reported a percentage of 51.2% married women among their studied controls. Contrary to findings reported by a study published in 2017 conducted retrospectively on 10,905 eligible EOC patients. The study revealed that 5,919 (54.28%) were married, 1268 (11.63%) were divorced or separated, 1733(15.89%) were widowed, and in 1985 (18.20%) never married, with a significant difference in all subgroups. This study denoted to marital status plays an important role in women's physical and mental health *(Wang, Li, Su, &Liu, 2017)*.

The current study revealed that age at menopause was a significant factor as cases were menopaused earlier, with a statistically significant difference between cases and controls. This finding is supported by *Schildkraut et al. (2001)*. The study was conducted on 1411 women with epithelial ovarian cancer and 6,380 control. They observed a weak association between ovarian cancer and age at natural menopause. There was little evidence to suggest that early menopause is related to ovarian cancer among women with early-onset disease. Also, for women with cancer, menopause may begin earlier *(American Society of Clinical Oncology, 2019)*.

This finding is not consistent with a previous study done by *Pięta, Chmaj- Wierzchowska, and Tomasz-Opala, (2012)* on 1346 women. The study stated that early age at menarche and late age at last menstrual period might be responsible for the occurrence of even 16% of cases of ovarian cancer in the population. *Pięta et al. (2012)* added that among females who began menstruating by the age of eleven, the relative risk of ovarian cancer might increase to 1.6 higher than among those in whom the first period occurred at the age of over 13. In a meta-analysis study of 27 observational studies, the findings concluded that menarche age was inversely associated with the risk of ovarian cancer *(Gong, Wu, Vogtmann, Lin, & Wang, 2013)*. This finding is inconsistent with the current study finding as the age of menarche was not a factor associated with ovarian cancer as the two groups had nearly similar age at menarche (12.61for cases vs. 12.80 for controls).

Despite a non-statistically significant difference between the cases and controls regarding their parity, the current study revealed an imperative verdict that more than two-fifths of cases had zero parity, with more than two-fifths of controls and four or more children. This finding is supported by *Riman, Nilsson, and Persson (2004)* findings that reported nulliparity or low parity among consistent ovarian cancer risk factors. The incidence of ovarian cancer is also higher among nulliparous women and those who rarely become pregnant *(Pięta et al., 2012)*. This finding is also evident by the current study results, as 6.3 of the cases were infertile compared to 3.3% of the controls. The relative risk for women who had never given birth was 1.3, and it has been estimated that this factor is responsible for 5% of cases of ovarian cancer. Four or more childbirths probably decrease ovarian cancer risk (*Ulman-Włodziarz, Nowosielski, Romanik, Pozowski, & Jurek, 2011; Markowska, 2002; Anastiasiadis et al., 2000)*. Risk is reduced by about 40% for the first birth and 14% for each new birth *(Whittemore, Harris, & Itnyre, 1992)*.

Two leading hypotheses may explain these findings. The first hypothesis is incessant ovulation‖ that the rupture and subsequent rapid proliferation of the ovarian surface epithelium with ovulation may lead to the malignant transformation of the ovarian epithelium *(Fathalla, 1971; Fleming et al., 2006)*. Pregnancy and oral contraceptive use should reduce ovarian cancer risk by reducing the number of ovulation cycles. An alternative hypothesis suggests that exposure to high progestin levels either through pregnancy or exogenous hormones reduces ovarian cancer risk *(Lukanova & Kaaks, 2005)*. Experimental studies in animals or human cell lines have shown that administration of progestins up-regulates the expression of the p53 tumor suppressor gene *(Murdoch & Van Kirk, 2002)* and induces apoptosis. These data suggest that apoptosis resulting from high progesterone levels during pregnancy or exogenous hormones could "clear" transformed cells in the ovarian epithelium *(Moorman et al., 2013)*.

In the analysis of cases and controls' history of cancers, the current study results signify the positive family history of ovarian cancer as a risk factor, with a four folds increase for cases more than controls. The current study also emphasizes the closest relationship, the high incidence of cancer, as all cases and most of the controls with a positive history of ovarian cancer had a first degree relative with ovarian cancer. It is also the case for those with a positive family history of breast cancer as most of the cases, and about three-fourths of controls had first-degree relatives who have breast cancer. Two-fifths of cases and four-fifths of controls with a positive history of colorectal cancer had a first-degree relative with colorectal cancer, with a significant difference between the two groups. The current study also revealed that among those with a personal history of other cancers, more than four-fifths of cases had a personal history of other cancers (blood, lung, bone, thyroid, cervix, and lymphoma), more than two-thirds of the controls had breast cancer, and more than one fifth had a history of other cancers. This verdict may reflect the possibility of genetic predisposition in families.

This finding is supported by *Kerber and Slattery, (1995)* study that reported a fourfold increase in ovarian cancer risk among women had first degree relative with ovarian cancer and a two-fold increase among those with second degree relative with ovarian cancer. The risk of ovarian cancer may reach seventy percent among females with a first-degree relative who had a history of breast cancer *(Tung et al., 2004*). Forty percent of all cases of ovarian cancer with a positive family history are due to mutation in BRCA1 and BRCA2 susceptibility genes *(Alsop et al., 2012)*. The present study results evidence this

sighting as all ovarian cancer patients in the case group had a first-degree relative to another ovarian cancer patient. *Norquist, et al. (2016)* reported similar findings. The study informed that about twenty percent of ovarian cancer cases were thought to be due to inherited mutation of BRCA1, and BRCA2, predominantly high-grade cancer tumors. Providentially, not all women with this inherited mutation develop cancer *(Ramus et al., 2015)*. This finding supports the finding of the present study that more than eighty percent of both groups have a negative history of breast cancer.

Mutations in BRCA1 and BRCA2 are not merely the inherited gene mutation. The studies revealed a mutation in other genes such as BRIPI, MSH6, and RAD15C that could affect ovarian cancer risk to a varying degree. *(Ramus et al., 2015)*. Studies to explore these new gene mutations and their probable risk of developing ovarian cancer may participate in cancer prevention efforts *(American Cancer Society, 2018)*. *American Cancer Society (2009); Walsh et al. (2011)* confirmed a thirty percent increase in ovarian cancer development among women with positive family history than those with negative family history. The risk is increased by five times if cancer occurs before the age of forty.

The relation between colorectal cancer and ovarian cancer may be explained in the light of *Bonadona et al. (2011)* study that Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome) that is a rare inherited disease found to linked to an increased risk for several types of cancer, including colorectal and ovarian cancer. About an eight percent increase in the incidence of ovarian cancer by age 70 in women with Lynch syndrome. This result was not evident in the present study, as most of our cases and controls had a negative history of colorectal cancer.

The present study could signify the history of hysterectomy as a protective factor with a highly statistically significant difference between the two groups. Endometriosis also showed as a significant risk factor. The finding is consistent with *Loft, Lidegaard, and Tabor (1997)* in a study that included 22,135 women undergoing a hysterectomy for benign indication. They compared with all Danish women who had not undergone hysterectomy. The result concluded that the risk of ovarian cancer increased among women without hysterectomy than those who had a hysterectomy. The protection seems to decrease with increasing age. *Dixon-Suen et al. (2019)* reported similar findings in their study on 83,7942 female adults in Australia. The study reported a risk reduction in ovarian cancer after hysterectomy. Based on this finding, the benefit of hysterectomy could consider when a decision is made for the surgical management of endometriosis or fibroid.

Several studies support the current study finding in the presence of an association between endometriosis and specific ovarian cancer subtypes (endometrioid, low grade serous, and clear cell), but it is unclear whether the relationship is causal or a result of shared risk factors *(Wentzensen et al., 2016; Guo, Zilberberg, & Hummelshoj, 2012; Nezhat, Pejovic, Reis, & Guo, 2014; Pearce et al., 2012)*.

Surprisingly, use of oral contraceptives, IUDs, history of tubal ligation, infertility, use of ovulation induction, use of hormonal replacement therapy, ovarian cyst, polycystic ovaries, history of diabetes, and breastfeeding shows no statistically significant difference between ovarian cancer cases and controls.

Several studied contradict the current study findings. The previous studies declared an association between the use of oral contraceptives and a significant reduction in the incidence of ovarian cancer. The benefit was raised with a longer duration of use. A risk reduction of 35.6% was found among women who use an oral contraceptive for five to nine years *(Beral, Doll, Hermon, Peto, & Reeves, 2008)*. The protective influence continues for at least ten years after stoppage with diminished strength *(Beral et al., 2008; Tworoger, Fairfield, Colditz, Rosner, & Hankinson, 2007)*. Previous studies explained that the earlier contraceptive user in the 1960s had a more significant protective benefit, maybe due to the high content of estrogen in the contraceptive formula *(Whittemore, Harris, & Itnyre, 1992)*. Another study reported similar findings *Beral et al. (2008); Shafrir et al. (2017); Riman, Nilsson, and Persson, (2004)*.

Previous studies also stated the association between tubal ligation and risk reduction of ovarian cancer. *Cibula, Widschwendter, Majek, and Dusek (2011)* reported a thirty percent reduction. *Falconer, Yin, Gronberg, and Altman (2015)* evidence this association when they reported a sixty percent reduced risk among women undergoing salpingectomy. Moreover, *Finch et al. (2014)* also reported an eighty percent reduction in ovarian cancer risk among women who undergone salpingo-oophorectomy. In clinical practice, salpingectomy might be recommended in high-risk women who completed their childbearing during pelvic surgery or hysterectomy as an alternative to fallopian tube ligation.

Some other studies established a moderate reduction in ovarian cancer risk among women who breastfed, particularly for those who breastfeed for a longer duration *(Wentzensen et al., 2016; Gaitskell, 2017; Danforth et al., 2007; Li et al., 2014; Luan et al., 2013).* Another discussed factor in the literature is the menopausal hormone, either estrogen alone or combined with progesterone. *Beral et al. (2015)* reported a twenty percent decrease in ovarian cancer risk among those who never used hormone replacement therapy than ever-users. *American Cancer Society (2018)* reported a forty percent increased risk of ovarian cancer among current or former users within five years. Even a short duration of use can increase the risk of ovarian cancer. This risk remains elevated for a minimum of ten years after the stoppage.

The association between the use of fertility drugs and ovarian cancer, in the long run, has been investigated by *Diergaarde and Kurta (2014), Trabert et al. (2013), Rizzuto, Behrens, and Smith (2013).* These studies showed little evidence of association. One explanation provided is the increasing age of females seeking fertility treatment as

they enter the risky age of ovarian cancer in addition to the rarity of the disease (*Trabert et al., 2013)*. This contradiction between the previous studies and the current study regarding the health history of cases and control groups may be referred to as our small sample size compared to the mentioned studies' samples.

Regarding lifestyle attributes, the current study revealed that body mass index, use of talc powder, smoking, alcohol, eating fresh fruits, tea consumption, living an active life, and stress management show no significant difference between both groups. In contrast, a significant difference shows regarding eating a low-fat diet. *The International Agency for Research on Cancer (2010)* demonstrated a limited association between body weight and ovarian cancer. Some studies reported a moderate risk increase in epithelial ovarian cancer among women with higher body weight. This finding is particularly obvious among those who did not use hormonal replacement therapy after menopause *(Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012; Lauby-Secretan et al., 2016). Beral et al. (2015); Dixon et al. (2016)* verified an increase of about ten percent for each 5kg/$m^2$ extra body mass index among women who had not used hormones. This finding contradicted the findings of this study as the relationship between body weight, the hormone used, and ovarian cancer was not examined in this study. Also, a prominent finding in this study that both groups were borderline overweight.

Another contradiction to the current study findings is reported by *Beral (2012)* that there is an association between smoking and certain types of ovarian cancer. The study reported an increase in the risk of mucinous ovarian cancer by about eighty percent and a decrease in the risk of endometrioid and clear cell carcinoma among smokers. This result is particularly observed for borderline malignant tumors. This relationship was not examined in this study, as histopathological differentiation was beyond this study's aim.

Several studies investigated the association between ovarian cancer risk and various foodstuff and dietary patterns with varying results *(World Cancer Research Fund / American Institute for Cancer Research, 2014; Crane, Khulpateea, Alberts, Basin-Engquist, Thomson, 2014).* A thirty percent increase in the risk of epithelial ovarian cancer is reported among physically inactive women *(Cannioto et al., 2016)*, and likewise, sedentary behavior appears to increase risk *(Patel et al., 2015; Shen et al., 2014; Xiao, Yang, Wentzensen, Hollenbeck, & Matthews, 2013; Zhang, Xie, Lee, & Binns, 2004; Hildebrand, Gapstur, Gaudet, Campbell, & Patel, 2015)*.

Many studies denoted the significance of talc powder as a risk factor for ovarian cancer. *International Agency for Research on Cancer (2010)* reported little evidence of an association between the use of talc powder over the perineal area and increased risk of ovarian cancer. One of the large prospective studies found a marginally increased risk of invasive serous carcinoma among perineal talc-powder users (*Gertig et al., 2000)*. Other studies reported no association *(Houghton et al., 2014)*. Many factors hinder the study of this association as the difficulty in defining and measuring women's exposure to body powder with or without talc and the disease's rarity. The current study results may not reveal this finding as most of our patients did not widely use talc powder in the Egyptian culture.

In emphasis of the current study results, a logic regression analysis confirmed an inverse significance of age at menopause, hysterectomy, and history of endometriosis as a significant risk factor. Summing up, the *American Cancer Society (2018)* published an augmentation of relative risk and protective factors among people with particular exposure to the risks compared to people without that exposure. Among the relative risk (RR) factors were a personal family history of ovarian cancer, first-degree relative (RR, 3.4); second-degree relative (RR, 2.1) *(Kerber & Slattery, 1995)*, family history of breast cancer (1.7) *(Tung et al., 2004)*. Genetic predisposition, BRCA1 mutation carrier (RR, 11.8), and BRCA2 mutation carrier (RR, 5.3) *(Kurian et al., 2017)*. Other factors are specified, smoking (RR, 1.8) *(Beral et al., 2012),* Menopausal hormone therapy (RR, 1.2) *(Beral et al., 2015),* excess body weight (additional 5 kg/$m^2$ BMI) (RR, 1.1) and adult height (per 5 cm above 155cm) (RR, 1.1) *(Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012)*. Factors that might decrease risk, tubal ligation (RR, 0.7) *Cibula et al. (2011)*, pregnancy (first birth) (RR, 0.6) *Whittemore, Harris, and Itnyre, (1992)*, oral contraceptives, 1-4 years (RR, 0.8), 5-9 years (RR, 0.6), 10-14 years (RR,0.6) *(Beral et al., 2008).*

Summarizing the current study, it was clear that higher education, marriage, late menarche, late menopause, high parity, oral contraceptives, hysterectomy, tubal ligation, breastfeeding, ideal body weight, active living, and eating low-fat foods might be protective factors against ovarian cancer. The study also revealed the possibility of increased risks among those with a positive history of ovarian or other cancer, particularly breast and colorectal cancers, with a close relationship (first-degree relative), endometriosis, users of hormonal replacement therapy, use of fertility drugs, high body mass index, use of talc powder,smoking, and sedentary lifestyle.

## 7. Conclusion

In conclusion, the present study evidenced two comparable women groups regarding their age, marital status, age at menarche, parity, history of twins, and body mass index (BMI). The study signifies the level of education, hysterectomy, late age at menopause, and eating a low-fat diet is a protective factor against ovarian cancer, signifying earlier age at menopause, a positive family history of ovarian cancer, and endometriosis as risk factors associated with ovarian cancer.

The study also pointed out other factors that could be considered marriage, late menarche, late menopause, use of oral contraceptives, breastfeeding, infertility, use of fertility drugs, and a close relationship with cancer patients of various types, sedentary lifestyle, and

practicing recreation.

## 8. Recommendations

- Trained health care providers should be recruited to monitor trends in ovarian cancer occurrence, disparities in care and health assurance assistance, provide screening and early detection activities, care, education for healthy women who are at risk for ovarian cancer at their place of work, and through media.
- Establish of helpline and websites that can offer comprehensive, accurate information about ovarian cancer, including in-depth information on risks and protective factors, early signs, treatments, and side effects, and respond to inquiries from women about ovarian and other female genital cancers at their convenience.
- Conducts researches to better understand ovarian cancer risk factors, prevention, treatment, and survivorship.
- Disseminates screening recommendations based on a comprehensive evaluation of evidence on maternal, family planning clinics, obstetrics, and gynecology outpatients and other areas of women gatherings. Women with this family history are referred for genetic counseling and evaluation.
- Allocate funds for individual investigators in medical schools, universities, research institutes, and hospitals and encourage them to research female genital cancer, primarily ovarian cancer.

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