Review Article

The Effect of Maternal Age at First Pregnancy on the Risk of Gynaecological Cancers – A Literature Review and Retrospective Analysis

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Abstract

Background: What impact does the age of first pregnancy has on the incidence of gynecological cancers? The major objective of our study was to test the hypothesis that the earlier the age of first pregnancy, the lesser the risk of gynecological cancers among women in Jiangsu Province, Nanjing, China.

Method: We collected cases of gynecologic cancer patients diagnosed between 2015 and 2018 to evaluate the impact that the age of first pregnancy might have on the incidence of gynecological cancers. Participants' data were collected from the Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research registry. Gynecologic cancer cases were subdivided into uterine, ovarian and cervical cancers. Patients' obstetric history and age of first pregnancy were recorded. As a control group, women who have not been pregnant but suffered from gynecological cancer within the same period were selected. No animals/human tissue were used in this study, and thus no ethical committee was set up for approval.

Result: Based on the statistical findings of this study, it can be concluded that the age of first pregnancy has an impact on the risk of gynecological cancers.

Conclusion: This analysis provides an evaluation of the age of first pregnancy and its relative effect on the incidence of gynecologic cancer. If the age of first pregnancy has an impact on the incidence of gynecological cancer, this can be used accordingly to reduce the risk. It is to be noted that age of first pregnancy, is not to be confused with age of first delivery. The first pregnancy might have been concluded by a delivery or by an abortion (procured and spontaneous). Like any other study, this study had its own shortcomings as well. One of the major short coming of this study was that the number of pregnancies couldn't be used as an indicative parameter because of the 'One Child Policy' prevailing in China.

Abbreviations: HPV: Human Papilloma Virus Infection; IVF: In-vitro Fertilization; DES: Diethylstilboestrol; IUD: Intrauterine Device; PCOS: Polycystic Ovarian Syndrome; OR: Odds Ratio; CI: Confidence Interval.

Keywords: Pregnancy; Age of first pregnancy; Gynecological Cancer; Ovarian Cancer; Uterine Cancer; Cervical Cancer

Background

Cancer incidence and mortality have been increasing in China, making cancer the leading cause of death since 2010 and a major public health problem in the country. However, with modern advancements in the diagnosis and treatment (radical and conservative), women attained with gynecological cancer can now expect a longer survival following such a diagnosis. Thus, there

exists a rapidly increasing population of survivors of gynecological cancer patients. Emphasis is therefore being laid on the quality of their survivorship and to minimize the side effects of successful cancer treatment. The possible impact on fertility is one of the consequences of cancer treatment which is of greatest importance, mostly to younger women. The adverse effects of cancer treatment on fertility in both men and women have been recognized for many years, and the importance and establishment of fertility preservation as part of current medical practice is recognized in international guidelines. What is less clear, however, is the effect that the age of first pregnancy might have on the incidence of gynecological cancers. With increasing need of acquiring higher education and professional qualifications, the age of getting married is being postponed and so is the age at which women get pregnant for the first time. This study is aiming to find out if the timing of first pregnancy has an effect on the risk of gynecological cancers.

Discussion

Cancer Statistics Worldwide

With an increasing number of cases worldwide, cancer is posing to be a global burden. It can be forecasted that cancer will be the leading cause of death and the single most important barrier to increasing life expectancy in every country of the world in the 21st century

Combining both males and females, the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer death) is lung cancer. Among males, lung cancer is the most common cancer and is also the leading cause of cancer death. Among females, breast cancer ranks first for both incidence and mortality. Cervical cancer ranks as the fourth most common diagnosed and cause of cancer death [1]. As for gynecological cancers, the three main types are Cervical, Uterine and Ovarian cancers.

Cancer Statistics in China

The 5 leading causes of cancer death among both men and women are cancers of the lung and bronchus, stomach, liver, esophagus, and colorectum, accounting for about three quarters of all cancer deaths [2].

For women, 6 of the 10 most common cancers had a significant upward trend in age standardized incidence rates (cancers of the colorectum, lung, breast, cervix, uterine corpus, and thyroid; P < .05). As with men, a downward trend was seen for cancers of the stomach, esophagus, and liver [2].

Types of Gynecological Cancers [3]

Based on the organ or part of the body where they first develop, gynecological cancers are named accordingly.

- Ovarian cancer : Affecting the ovaries.
- Uterine cancer : Begins in the main body of the uterus.
- Endometrial cancer is cancer that arises from the lining of the uterus (called the endometrium). It is the most common type of cancer of the uterus.
- Cervical cancer : Begins in the cervix
- Vaginal cancer : Begins in the vagina.
- Vulval cancer : Begins in the vulva.

Other types of gynecological cancers include fallopian tube cancer and gestational trophoblastic disease (a pregnancy-related cancer).

In this study, we will concentrate mostly on the three main types of gynecological cancers, which are cervical, uterine and ovarian cancers.

Despite the fact that the exact causes of many gynecological cancers are not fully understood, there are many factors believed to be agents that can precipitate the onset of gynecological cancers. One of them is the reproductive history. These risk factors include:

- Increasing age
- Having a strong family history
- Identified gene mutations
- Reproductive history, such as child-bearing
- Exposure to hormones – produced by the body or taken as medication
- Exposure to Diethylstilbestrol (DES) in the womb
- Viral infection such as Human Papillomavirus (HPV) infection
- Lifestyle factors such as smoking and those leading to excess body weight.

Researches carried out have proven the following facts with regard to pregnancy and the risk of gynecologic cancers:

- Full-term pregnancy tends to reduce the risks of ovarian [4,5] and endometrial [6] cancers and with each additional full-term pregnancy, the incidence of these malignancies declines.
- Pregnancy also has an important impact on Gestational Trophoblastic Tumor.
- Hormonal level changes during pregnancy may contribute to the alteration in risk of these tumors after pregnancy [7].

The effect of reproductive factors on the risk of ovarian cancer

Ovarian cancer is the third most common malignancy and the second most common cause of cancer death worldwide among gynecologic cancers [8]. Previous studies and researches show that increasing age, family history of ovarian cancer, nulliparity and exposure to radiation and asbestos are risk factors for ovarian cancer, whereas the use of oral contraceptives, parity and tubal ligation decrease ovarian cancer risk [9]. In women with multiple pregnancies, it has been established that there is a consequent reduction in the risk of ovarian cancer with each additional pregnancy [10]. It is actually considered that the main mechanism of how pregnancy may lower the risk of ovarian cancer is by:

- lowering the lifetime number of ovulatory cycles [11]
- lowering gonadotropin secretion and subsequent estrogen stimulation of the ovarian surface epithelium [12], and/or
- induces clearance of premalignant cells from the ovaries [13].

Hormone-related factors have also been associated with ovarian cancer, the major aspects being parity and oral contraceptive use [14]. However, it is still not clear whether the hormonal treatment for infertility is a risk factor for ovarian cancer. A 2013 systematic review found, overall, that there was no strong evidence to prove an increased risk of invasive ovarian cancer for women treated with fertility drugs [15]. In another study, women who underwent IVF was shown to have an increased risk of ovarian borderline malignant tumors [16].

The effect of reproductive factors on the risk of uterine cancer

Uterine cancer or endometrial cancer is another common type of gynecological cancer. It comprises of adenocarcinoma (80%) and sarcoma. The exact etiology of uterine cancer is still unclear, however, it is believed that it can be due to a change in the lining of the uterus, whereby the cells grow at an uncontrollable pace and apoptosis is impaired. Thus, resulting in the formation of a tumor [17].

Multiple factors are thought to affect the formation of uterine cancer, both by increasing or decreasing the risks of its formation. These factors include [18]:

- Obesity
- Hormone levels changes, e.g. taking estrogen after menopause, birth control pills, the number of menstrual cycles (over a lifetime), pregnancy, certain
- ovarian tumors, and Polycystic Ovarian Syndrome (PCOS)
- Use of an Intrauterine Device (IUD)
- Age (as age increases, the risk for uterine cancer increases as well)

- Diet and exercise
- Type 2 diabetes
- Family history (having close relatives with endometrial or colorectal cancer)
- Having had breast or ovarian cancer in the past
- Having had endometrial hyperplasia in the past
- Treatment with radiation therapy to the pelvis to treat another cancer

Here again, pregnancy is indicated as having an effect on the risk of formation of uterine cancer. During pregnancy, hormonal changes in a way whereby there is more progesterone. As a result, it is believed that multiple pregnancies help protect against endometrial cancer, and women who have never been pregnant have a higher risk, especially if they were also infertile [18-24].

Several studies have shown an opposite association between older age at last birth and endometrial cancer risk. In a study published in Cancer Causes Control Journal, it was noted that compared to uniparous women, childless women were at a higher risk of endometrial cancer (Odds Ratio [OR] = 1.38, 95% Confidence Interval [CI] = 1.25-1.52). This association was stronger in younger (< 50 years) than in older (50+ years) women. At all ages of first birth, a delivery was associated with a reduced risk of endometrial cancer that slowly diminished with time. Among parous women, the risk decreased by almost 20% for each additional live birth (OR = 0.81, CI = 0.78-0.84). In an analysis limited to women with two or more births that compared the independent effects of age at first and at last birth, only older age at last birth was associated with a lowered risk of endometrial cancer. The risk decreased at a rate of about 15% per five-year delay of last birth. Based on these findings, it was concluded that birth might not only affect risk through hormonal influences, but possibly also through mechanical shedding of cells that have undergone malignant transformation [25].

In western Washington State, another study was carried out to test the hypotheses that younger age of first pregnancy decreases the risk of endometrial carcinoma. The results show that older age at first birth was associated with a reduced risk of endometrial cancer after adjustment for number of births and age at last birth (test for trend P = 0.004). The odds ratio comparing women at least 35 years of age at their first birth with those younger than 20 years was 0.34 (95% confidence interval = 0.14–0.84). Age at last birth was not associated with risk after adjustment for number of births and age at first birth (test for trend P = 0.830). Overall, a history of incomplete pregnancies was not associated with endometrial cancer risk to any appreciable degree. In this study, it was concluded that older age at first birth was more strongly associated with endometrial cancer risk than was older age at last birth [26].

As regards to the use of fertility drugs or in-vitro fertilization, it cannot be concluded that they have a definite effect on the risk of formation of endometrial cancer. However, it does not appear to increase the risk of endometrial cancer either [27].

The effect of reproductive factors on the risk of cervical cancer

Cervical cancer has the highest incidence in both numbers of new cases and in number of deaths among those three mentioned gynaecologic cancers (GLOBOCAN 2018). As for the other types of cancers, the risks factors for cervical cancer are multiple, but they are all outweighed by Human Papilloma Virus infection (HPV). Besides HPV infection, the other risks factors include [28]:

- Smoking
- Having a weakened immune system
- Chlamydia infection
- A diet low in fruits and vegetables
- Being overweight
- Long-term use of oral contraceptives (birth control pills)
- Intrauterine Device (IUD) use
- Having multiple full-term pregnancies
- Being younger than 17 at your first full-term pregnancy
- Economic status
- Diethylstilbestrol (DES), and
- Having a family history of cervical cancer

It is estimated that women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. However, this has not well been proven yet, and the mechanism remains unexplained. Also, studies show that hormonal changes during pregnancy can cause an increase risk by making women more susceptible to HPV infection and thus cancer growth [28].

Another thought explaining the HPV infection and cancer growth in pregnant women is that pregnant women might have weaker immune systems, promoting HPV growth [28].

It has also been shown that women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older. However, even this fact remains unexplained so far [28].

Current Study

Statistically, Chinese women have a lower risk of endometrial cancer as compared to their counterparts in the United States and other western countries [29].

The major objective of our study was to test the hypotheses that the age of pregnancy has an effect on the risk of gynecological cancer among women in Nanjing, Jiangsu Province, China. The Department of Gynaecologic Oncology Surgery, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, The Fourth Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, provided us a unique opportunity to study this hypothesis.

All patients were diagnosed and treated between 2015 and 2018 inclusive. Based on the registered records of the above named institution, 14959 (fourteen thousand nine hundred and fifty-nine) patients attended the Department of Gynecologic Oncology Unit. Out of them, 4483 (four thousand four hundred and eighty-three) were cervical cancer, 1198 (one thousand one hundred and ninety-eight) were ovarian cancer cases and 808 (eight hundred and eight) were uterine cancer. These data also confirm and matches the findings of GLOBOCAN 2018, that cervical cancer remains of the higher incidence as previously stated. Furthermore, 2614 (two thousand six hundred and fourteen) were other gynecological tumors and 5856 were either non-malignant lesions or other benign cases, but received treatment in this hospital. These data have been illustrated in a tabulated form hereunder Table 1.

Total attendance	14959
Cervical Cancer	4483
Ovarian cancer	1198
Uterine cancer	808
Other Gynecological Tumors	2614
Non-malignant or other benign cases	5856

Table 1: Number of cases recorded between 2015–2018 at the Department of Gynaecologic Oncology Surgery, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, P.R. China.
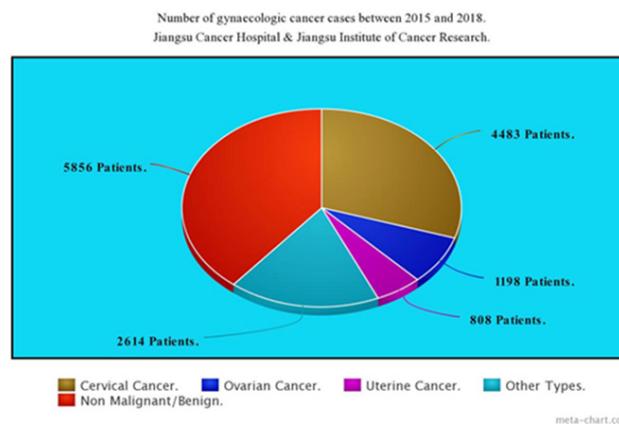
Out of these patients 12028 (80.40%) have been pregnant and 1693 (11.32%) have never been pregnant. Those who have

never been pregnant were chosen as the control for the study. 1238 (8.28%) patients had no reproductive history and were rejected from the study. The table below shows a tabulated form of results gathered from the registry Table 2.

AGE OF FIRST PREGNAN-CY/ YEARS	<20	21-25	26-30	>30
NUMBER OF CASES.	1366 (11.36%)	5373 (44.67%)	4007 (33.31%)	1282 (10.66%)

Table 2: Number of cases recorded at different age groups of first pregnancy.

Out of the 1693 patients who have never been pregnant, 384 patients were of age 20 years or less at time of diagnosis, 714 were

between 21 – 25 years, 468 were between 26 – 30 years and 127 were more than 30 years Table 3 and Table 4.

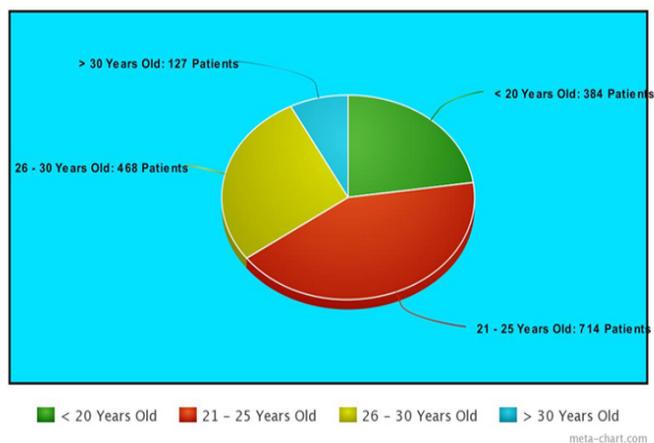| AGE OF PATIENT AT TIME OF DI-AGNOSIS/ YEARS	<20	21-25	26-30	>30
NUMBER OF CASES	384	714	468	127
	22.68%	42.17%	27.64%	7.51%

Table 3: Number of cases recorded at different age groups for patients who have never been pregnant.

GROUP	< 20 Years Old	21 - 25 Years Old	26 - 30 Years Old	> 30 Years Old
CONTROL (Patients who have never been pregnant).	384	714	468	127
TEST.	1366	5373	4007	1282
ODDS RATIO (OR).	0.436	1.106	1.307	1.471
95% CI (low-up).	0.384 - 0.497	0.997 - 1.228	1.166 - 1.467	1.215 - 1.793
X^2	170.04	3.648	21.458	15.712
P	0.0000	0.056	0.00000	0. 0000

Table 4: Statistical interpretation.

Results

A total of 14959 patients were identified. After the initial assessment and considering the inclusion and exclusion criteria, we were left with 12028 patients who have been pregnant and meet all the criteria to be considered as eligible subjects for the study. As a control group for the study, patients who suffered from gynecological cancers but never pregnant were taken, that accounted for 1693. With an

Odds Ratio [OR] of 0.436, 95% Confidence Interval [CI] of 0.38 - 0.49, and X2 170.04, we concluded that compared to non-pregnant women, those who were pregnant before 20 years of age were at a lower risk of developing gynecological cancers

Conclusion

Advancing age is the most important risk factor for cancer overall, and for many individual cancer types. According to the most recent statistical data from NCI's Surveillance, Epidemiology, and End Results program, the median age of a cancer diagnosis is 66 years. This means that half of cancer cases occur in people below this age and half in people above this age. One-quarter of new cancer cases are diagnosed in people aged 65 to 74.

A similar pattern is seen for many common cancer types. For example, the median age at diagnosis is 61 years for breast cancer, 68 years for colorectal cancer, 70 years for lung cancer, and 66 years for prostate cancer. However, it is to be noted that the disease can occur at any age.

When it comes to gynecological cancers, it has been seen that each gynaecologic cancer is unique, with different signs and symptoms, different risk factors, and different prevention strategies. All women are at risk for gynaecologic cancers, and risk increases with age. When gynaecologic cancers are found early, treatment is most effective. One of those risk factors that we investigated upon was the age of first pregnancy.

Our study provides an understanding to the effect that the maternal age of first pregnancy might have on the incidence of developing gynecologic cancer. If the study can be implemented on a global basis and compared to other influential markers, it can be used accordingly to reduce the risk. One of the major shortcomings of this study was that the number of pregnancies couldn't be used as an indicative parameter because of the 'One Child Policy' prevailing in China.

Based on our findings and statistical interpretations, we concluded that as age of first pregnancy increases, the risk of developing a gynecological cancer increases as well. As a result, it can be inferred that the age of first pregnancy does have an impact on the risk of gynecological cancer, in such a way that the earlier the age of first pregnancy, the lower the risk of developing a gynecological cancer.

Author's Contribution

All the authors have equally contributed in this manuscript.

Dr. Nitish Beharee and Dr. Zujun Shi, being the first author and co-author respectively have contributed in drafting this manuscript.

Yaping Cui helped in collecting and compiling data from the medical records department.

Dr. Xianzhong Cheng helped in the creation of graphs and tables.

Dr. Jinhua Wang, corresponding author, supervised the manuscript, carried out the proof reading and final approval of the manuscript.

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