



RESEARCH ARTICLE

Age of Women as a Parameter Affecting CA-125, TSH, and CBC: A Correlation Study

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ABSTRACT

One of the cancer's antigens is the CA125, which is a protein antigen, found at excessively high levels in females characterized with ovarian cancer. It is suggested for ovarian cancer screening of women that are at higher risk to get the disease, despite its limited sensitivity and specificity. This study is conducted to identify possible correlations between CA125 and thyroid stimulating hormone (TSH) levels with parameters of hematological origin among women of different ages. This study included 44 healthy looking females, and 20 individuals as control group most but not all patients were from Erbil. The study revealed that, CA125 and TSH levels were not associated. Furthermore, the elevation of the CA125 levels in the females could be related to other non-cancerous factors such as menstrual cycle, or postmenopausal. Furthermore, WBC parameters and Hb levels were not affected by CA125. The only parameter that was affected by CA125 elevation was RBCs. The research recorded a significant difference of RBC between patient group and control group. Also recorded, no difference to be considered as an indication related to the difference in women age.

Keywords: Cancer antigen 125, thyroid stimulating hormone, white blood cells, red blood cells, pregnant women

INTRODUCTION

Identified women with ovarian cancer are likely to have the Cancer protein antigen CA125 at excessively high levels their blood of Yurkovetsky *et al.*^[1] Sikaris^[2] stated that the serosal epithelial cells produce CA125 naturally. And this product can be found in both malignant and benign serosal fluids. Meanwhile, Bast *et al.*^[3] advocated in a small segment of diseased patients that the ascending of the CA125 levels facilitated the triggering of transvaginal sonography. Further, Yurkovetsky *et al.*^[1] stated that the blood serum of a large segment of healthful females contained levels lower than 35 units/ μ L of CA125. Besides, there were indicators of noncancerous origin contributed to the elevation of CA125 levels.

Other scholars stated, when thyroid hormones extensively exposed they have the tendency to influence ovarian tumors development.^[4] In addition,^[5] in their *vitro* research illustrated that at the physiological levels both hormones 3,5,3'-triiodo-L-thyronine and L-thyroxin, (T3) and (T4), respectively, were capable of the expansion and improvement of the ovarian cancer cells. Accordingly, these cells were grown much slower when exposed to (T3) and (T4) below normal serum concentrations levels. Hence, thyroid functionality evaluation would be important to adjudge whether it is an elevation in the tumor markers or high-protein ascites.^[6]

A positive correlation was found between CA125 and the total white, neutrophil, monocyte and neutrophil-to-lymphocyte ratio (NLR) counts. But conversely, a negative correlation recorded with lymphocytes.^[7] The current study by Ceran *et al.*^[8] demonstrated that the rise in neutrophil and platelet counts, NLR, along with platelet-to-lymphocyte ratio (PLR) correlated to an adverse clinic pathological results subsequent to various cancer types which comprised the epithelial ovarian cancer (EOC). While a previous study mentioned, that Van Derr Zee *et al.* shown whether the ovarian tumors were malignant or benign the elevation in interleukin-6 level in cystic fluids is related to a decline

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in the hemoglobin level and an inclination in platelet count.^[9,10]

Based on Lengye study, the ovary cell transformation occur due to ovarian carcinoma that is consequent to genetic and epigenetic alterations.^[11] Ovarian cancer etiology is still not verified. However, the incessant ovulation theory is one of the models to explain the issue. It states that women have a continual ovulation regardless to age.^[12] Another proponents stated that high contributors to ovary carcinoma were, that is, infertility alongside to menopause age. Yet, determinants particularly hysterectomy, pregnancy, and tubal ligation showed to diminish such risk.^[13,14]

Abdominal size, bloating, urinary symptoms, and pelvic pains are the symptoms that were frequently informed by women prior diagnosing them with ovarian cancer. Such symptoms are likely indicators causing cancer more than benign. Yet, distinguishing cancer symptoms from those associating with benign is difficult. Consequently, results, regardless how sensitive and specific pelvic examinations that were carried out to detect asymptomatic ovarian cancer recorded poor also, not supporting the physical examination in same way as the screening method.^[15]

According to national Academies of Sciences and Medicine women and their designated health care providers repeatedly look upon as such symptoms (ovarian cancers) as non-specific and not referring to critical illness until they are dramatically worsen or developed.^[16] Which concurrent with Rauh-Hain *et al.*^[17] who suggested that 70% of women with ovarian cancer were diagnosed at late stages of the disease hence, these women have a high fatality rate and have a 5 year survival rates with advanced illness ranging between 20% and 30%. In contrast, early diagnosed women as the disease is encompassed within the ovary the cure percentage were 70–90%. More into this, due to an association between the disease stage and survival, early detection provides higher hope to reduce mortality besides long-term disease control.

Globally, the ovarian cancer is ranked the 7th disease that is commonly diagnosed cancer while, it is classified the 8th among cancer diseases causing death. 239,000 women were diagnosed with this illness in 2012, 152,000 did not survive.^[18] Yet, the disease mortality rates and its frequencies vary from one region to another. And the variance is due to genetic factors and environmental influences.^[19]

Moradi *et al.* stated that Iran is witnessing an inclination in ovarian cancer cases, specifically in the central and northwestern regions. They suggested that this increment is stemming from changes in the patterns of risk factors regarding this disease, that is, changes in the population's lifestyle that caused this escalation.^[20] Meanwhile, it was illustrated that, the risk of confronting severe and death from this disease in the developed countries are higher and nearly the double from those of less developed countries. Yet, the latter countries recorded higher ovarian cancer cases because of the large populations. Comparing the diagnosed cases number per year China recorded 34,575, India 26,834 and the USA 20,874.^[21]

After more than two decades from the discovering CA125, its antigen was recommended for screening women with high risk with ovarian cancer at clinical level regardless

to its sensitivity and specificity limitation.^[22] Current results advise that CA125 possibly be a foretelling indicator of per-invasive ovarian cancer. The CA125 measuring approaches had progressed toward sensitive and reliable double-determinant ELISA assays.^[23] While others findings that, the escalated levels of CA125 serum are not correlated to the size of the tumor of both age groups.^[24]

As a glycosylated membrane protein and a high molecular weight, the CA125 can be identified in the serum which is levitated in over 80% of ovarian cancer patients. Developing CA125 from the coelomic epithelium facilitated the marking of the epithelial. It had marked 90% of advanced and 50% of early ovarian cancer cases but, 20% were marked as low or had no expression. The CA125 is likely to arise its level if any disruptions occurred to the peritoneum epithelial lining. Similarly, pregnancy, leiomyomata, ovarian cysts, endometriosis, appendicitis, and diverticulitis which are all benign conditions the CA125 level were high. Equally, lung, pancreas, colon and uterine cancers showed and escalation in the CA125 levels. Therefore, it is lacking the sensitivity and specificity and thus, it will not be adequate to identify the ovarian cancer at early stages.^[25,26]

Gyftaki *et al.* stated that, the functionality of a normal thyroid is regulated by the thyroid stimulating hormone (TSH) by attaching to the thyroid receptor TSH receptor that is located at its cells surface. They further demonstrated that among other tissues, other than the thyroid, specifically the surface of a normal ovarian epithelium is amply expressed on.^[27]

The encoding thyroid hormone with estrogen receptors (TR) and (ER) were among various nuclear hormone receptor genes that are distributed in ovarian surface epithelial cells (OSE). Equally important, from the epidemiology perspective, evidently correlate the ovarian surface inflammation of the ovary and hyperthyroidism with the ovarian cancer (hormone-dependent).^[28]

Hyperthyroidism is where hormones of the thyroid T3 and T4 excessive concentrations travel through blood stream through the human body reaching the ovarian tissue and consequently causing its inflammation. The receptors in the OSE cells are responsive to thyroid and estrogen hormones. However, direct effects of ovarian epithelial cells inflammation are compelled by the T3. Once the latter hormone attaches to its corresponding OSE receptor the ER α and mRNA expressions are increased then the estrogen receptor action is mirrored resulting in encoding the ER isoforms.^[29] They further suggested that, ovarian cancer is highly correlated with isoforms and likely to be linked with hyperthyroidism.

Another research expressed that *in vitro* the thyroid hormones existing in ovaries cells infected with cancer changed both the genes expression that regulates cell cycle and the apoptosis of cancer cell. This action can be demonstrated by the inclination in the genes expression of which are responsible for the tumor's protein suppression p12 and p16, besides, its significant role in regulating cell cycle.^[30]

Anomalous hematological incidences recorded with ovarian cancer patients when compared with similar benign cases such as: First, hemoglobin Hb and hematocrit Hct levels were substantially low, second, high platelet count, and thirdly lymphocytes values were low.^[31-33]

Van Der Zee *et al.* illustrated that within malignant disease the presence of a conceivable relation between hemoglobin IL-6 levels and platelets. They also stated that, as such patients show negative predicting factors when there is an elevated pre-treatment platelet counts in addition to, low levels of pretreatment hemoglobin. They additionally spotted an association between IL-6 cystic fluid levels with the level of hemoglobin and platelet counts.^[9]

Other scholars suggested similar association in those patients with progressive illness where anemia is probably related to IL-6 levels.^[10] Which agrees with Nomelini *et al.*^[34] identification of the prognostic factors, which are resulting from a probable role of IL-6 tumor derived alongside with irregular rates of hemoglobin and platelet levels.

A late research weighed other ovarian cancer predictive factors for survival. It comprises the ratios of NLR along with PLR. It also added that these ratios highlight the possibility to differentiate whether the ovarian masses are malignant or benign. Yet, because of their values it does not have a total consensus as an ovarian cancer screening tool. Moreover, the research illustrated another survival predictive factor concerning EOC patients whose illness is in early and advanced stages. This factor signifies the absolute neutrophil count to absolute monocyte count ratio (ANC) and (AMC), respectively.^[15]

Aim of the Study

Many women can survive from ovarian cancer if early diagnosis of the disease occurs. CA125 protein test may help to early diagnosis and help others whose life are at risk because of the disease, alongside with high tests' accuracy. Many noncancerous factors can elevate CA125 levels. In this study, we attempted to evaluate how TSH levels affect the CA125 levels among women of different ages, and how does CA125 affect the levels of some hematological parameters.

MATERIALS AND METHODS

All samples 64, 20 control group and 44 non-cancerous patients were collected at "Alfa Lab for Medical Analysis" in Erbil city.

About 6 mL of blood were collected from each, 2 mL were used for hematological performance routine tests including blood film, WBC, Hb., Plt., and DLC.

The remaining 4 mL samples were put aside for clotting in gel tubes and centrifuged for 15 min at 2500 rpm. Then, the serum was used for conducting the test of electrochemiluminescence immunoassay by adding 0.5 mL of serum in a special tube for measuring serum CA-125 and an automated Medonic coulter was used to determine the complete blood count (CBC) to all collected samples.

Statistical Analysis

Since the study in hand is quantitative the augmented data were evaluated, and analyzed statistically, which was organized in tables. Afterward data were analyzed with the version 18 of the Statistical Package for the Social Sciences software. Then the appointed variables were compared following Students

F-test and *t*-test. Later, the *P* value indicates whether a certain variable is significant, if it was either <0.01 or 0.05.

RESULTS

This study included 44 non-cancerous female patients. Their ages ranged from (15 to 59) years, with a mean age of (37.8) year. In addition to, 20 healthy individuals were included as control group.

Table 1 shows and compare the ratio of TSH and CA125 in both control groups and patient group

While [Table 2] demonstrates the results of CBC parameters, alongside with (7) figures were created accordingly, to compare between mean of CA125 with mean of each (CBC) parameter separately. In addition to, a figure illustrating the ratio of CA125 level as the age rises.

Table 1 shows no significant variance in TSH levels between members of both study groups; however, it identified a high substantial variation between CA125 of both groups. While [Figure 1] highlights the correlation between CA125 and TSH ratio in patient and control groups.

[Table 2] shows different CBC parameters, the WBC shown significant variance in patient and control groups. Meanwhile, there was no substantial variation in lymphocyte, monocyte, granulocyte, and hemoglobin, but it identified a high significant difference between RBCs of patient group and control group.

In [Figure 2], there is a difference between WBC ratio in patient group and control group as the CA125 ratio rises.

In [Figure 3], lymphocyte ratio results show no variance in patient group and control group as the CA125 rises.

Figure 4 shows the similarly, monocyte ratio shows no difference in patient group and control group as the CA125 ratio rises.

In [Figure 5], there is difference between granulocyte ratio in patient group and control group as the CA125 ratio rises.

In [Figure 6], there is difference between RBC ratio in patient group and control group as CA125 ratio rises.

[Figure 7] shows that there is non-significant difference between Hb ratio in patient group and control group as CA125 ratio rises.

Figure 8 shows, CA125 ratio as the age rises, where there is no difference to be considered as indication related to the difference in the age of women, despite the high peaks in age (34–37) years and (50) years. Thus, the age of women does not give any sign to be mentioned.

DISCUSSION

This study is aiming to discover possible correlations linking TSH level and CA125 with hematological parameters among women of different ages. In the present study, no association was found between TSH and CA125 levels. As the CA125 levels elevated no significant change were recognized in TSH levels. Nine patients with high CA125 levels above

Table 1: TSH and CA125 ratio of patient group and control group

Parameters	No.	ALL patients		No.	C.G		T-test P value	P
		Mean±SE			Mean±SE			
TSH (mIU/mL)	44	2.20±0.17		20	2.00±0.25		0.526	N.S
CA-125 (U/mL)	44	27.68±4.79		20	14.43±0.84		0.009	H.S**

P: Probability, *P<0.05: Significant, P≥0.05: Non-significant, **P<0.01: Highly significant

Table 2: CBC parameters of patient group and control group

Hematological parameters	No.	All patients		No.	C.G		T-test P value	P
		Mean±SE			Mean±SE			
WBC (×10 ⁹ /L)	44	8.19±0.33		20	6.79±0.39		0.010	S*
Lymphocyte (×10 ⁹ /L)	44	2.55±0.13		20	2.95±0.23		0.158	N.S
Monocyte (×10 ⁹ /L)	44	0.46±0.02		20	0.45±0.05		0.884	N.S
Granulocyte (×10 ⁹ /L)	44	5.16±0.22		20	4.63±0.34		0.213	N.S
Hb (×10 ⁹ /L)	44	12.06±0.26		20	12.59±0.30		0.203	N.S
RBC (×10 ⁹ /L)	44	4.48±0.06		20	5.03±0.14		0.002	H.S**

P: Probability, *P<0.05: Significant, P≥0.05: Non-significant, **P<0.01: Highly significant

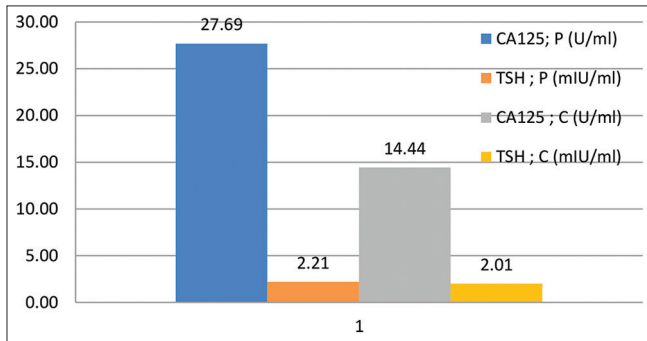


Figure 1: Correlation between CA125 and TSH ratio in patient group and control group

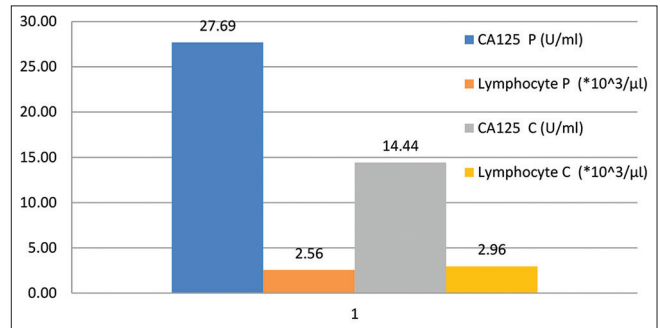


Figure 3: Correlation between CA125 and lymphocyte ratio in patient group and control group

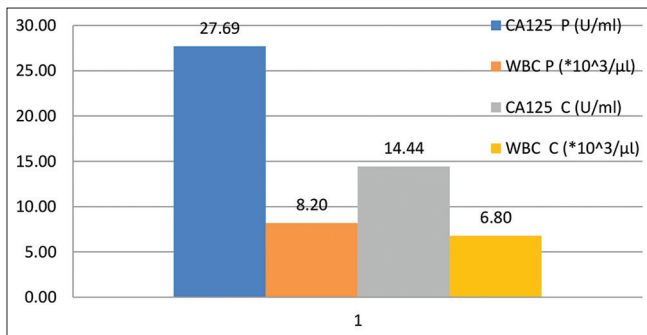


Figure 2: Correlation between CA125 and WBC ratio in patient group and control group

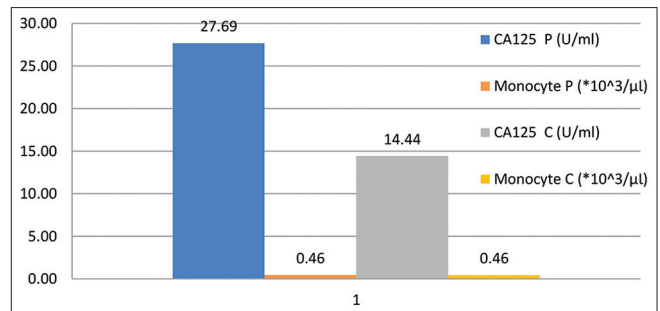


Figure 4: Correlation between CA125 and monocyte ratio in patient group and control group

the normal were found, but their TSH levels were still at normal range as other (35) patients. Meanwhile, the failure of ovulation is considered owing to severe hypothyroidism, whereas, menstrual anomalies stem from hypothyroidism and hyperthyroidism.^[35] Rae *et al.* suggested, ovaries sensitivity to estrogen and its inflammatory state be affected due to the status of the thyroid hormone, which consequently raise a gynecological health and disease impact.^[28]

According to Kang *et al.* advocated the absence of possible relationship in the history of hyperthyroidism and hypothyroidism with ovarian cancer.^[36] However, current hyperthyroidism history was linked with the increment of 5-year mortality among ovarian cancer patients. Yet, a mildly decreased mortality risk was associated with hypothyroidism.^[4] While other scholars stated that, although, hyperthyroidism, and OC association apparently persist only at an epidemiological level. Yet, the demonstration of the association mechanism has not been prevailed.^[37]

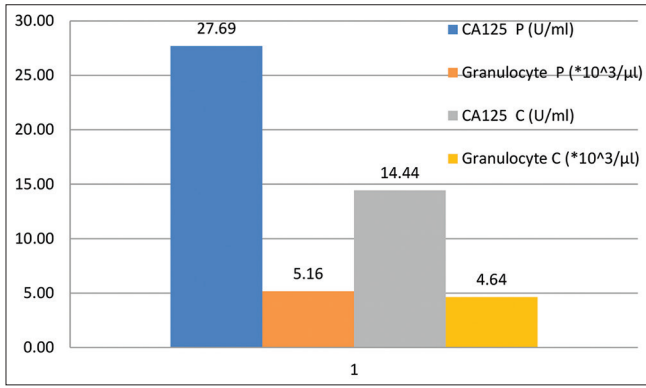


Figure 5: Correlation between CA125 and Granulocyte ratio in patient group and control group

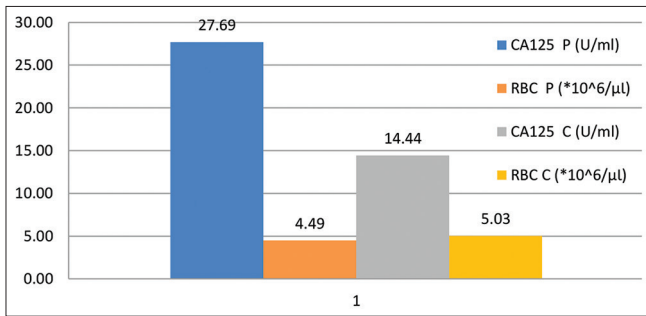


Figure 6: Correlation between CA125 and RBC ratio in patient group and control group

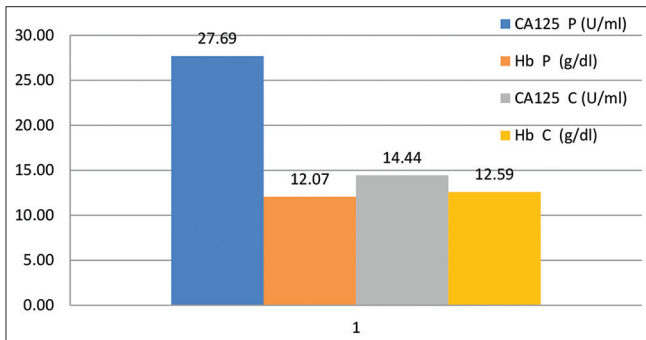


Figure 7: Correlation between CA125 and Hb ratio in patient group and control group

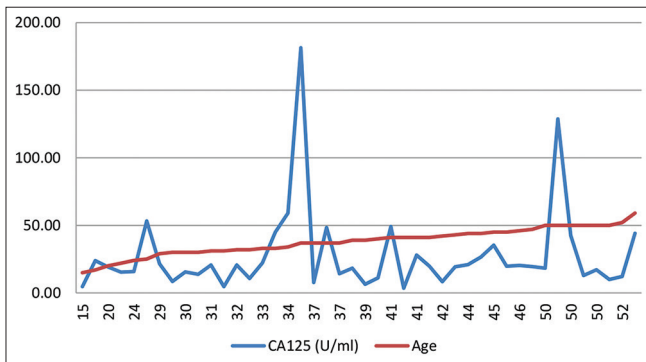


Figure 8: Correlation between CA125 and age

Bishara *et al.* reported that even when a fractional count of lymphocyte to WBCs total is significantly associated with mortality. While an elevated count of monocyte showed a substantial recurrence association. However, a raised count of eosinophil was a mortality and recurrence predictor among the ovarian cancer women. Equally, Bekmezci and Gunenc^[38] reported that, in older women both pre-operative NLR alongside to CA125 are to be a conceivable prognostic malignant adnexal mass indicator.^[39] Yildirim *et al.* demonstrated that in patients of ovarian cancer, NLR, and PLR values are significantly high when compared to patients of benign ovarian tumor.^[40] Furthermore, no change was observed in granulocyte, monocyte, and lymphocyte values as the CA125 was elevated.^[41]

Obermair *et al.* illustrated that the inversed Hb concentrations were associated to the disease stage along with the chronic inflammatory status severity. While, Föhréc *et al.*^[42] suggested that red cell distribution width (RDW) was linked with the stage of the ovarian cancer, if the stage is advanced or high, equally the RDW is high.^[43] Similarly, it was positively correlated with CA125 levels. Where, an elevated RDW in peripheral blood smears probably to correlate with iron, Vitamin B12, or folic acid, and Hb deficiencies; hemolysis or the transfusion of the blood is a reason of elevating the RDW.^[44] In the present work, there was no significant change of Hb levels, as the CA25 levels elevated among non-cancerous women. But a lower RBC count of patients was recognized.

Lehtovirta *et al.* and Juma and Ubeid demonstrated that, the CA125 test should not be conducted directly, before, or during menstrual cycle, as the CA125 physiological elevation levels possibly to provide false and positive results. In the present study, patients with high CA125 were found, with normal levels of each parameter WBC, Hb, and TSH, but without respect to their menstrual cycle.

As it was revealed by the previous studies, that hyperthyroidism and mortality rate are correlated to patients of ovarian cancer. In addition, high RDW signifies the disease advanced stage. Whereas, CA125 was inadequate biomarker for diagnosing early ovarian cancer.^[45,46]

As the age rises, many factors will have effect on human health. In this regard many determinants impact the CA125 level especially in females who passed menopause and ovarian cancer disease free. These factors are: Age, hysterectomy, obesity, race/ethnicity, and the smoking background.^[47] The serum of carbohydrate antigen CA125 serves an indicator to the inclination risk of ovarian cancer. It is also obesity indicator which is considered a significant element to the metabolic syndrome.^[48] It is worthy to mention that, the level of serum CA125 showed a significant inclination in patients of chronic heart failure.^[49,50]

CONCLUSION

The study revealed that there was no association regarding CA125 serum and the levels of TSH. However, the elevated CA125 levels in healthy females could be related to other non-cancerous factors such as menstrual cycle, or postmenopausal.

Furthermore, WBC parameters and Hb levels were not affected by CA125. The only parameters that were affected with CA125 elevation were RBC. The study results show that there was no association between CA125 and women age.

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