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LETTER

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A cross-sectional study of 55,415 women validating the effect of age on serum CA125 levels

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Dear Editor,

Ovarian cancer remains the deadliest gynecological malignancy, with a global age-standardized mortality rate of 4.0/100,000 (GLOBOCAN 2022). Ovarian cancer incidence and mortality rates in China have reached 5.7 and 2.6/100,000, respectively, reflecting rising global burdens.[1] Approximately 60% of patients present at advanced stages (III-IV), characterized by peritoneal metastasis and ascites formation, primarily due to non-specific clinical manifestations (abdominal bloating, early satiety) and screening limitations.

Early detection is crucial for improving ovarian cancer prognosis, with 5-year overall survival rates exceeding 90% in stage I versus <30% in advanced stages. Screening heavily relies on serum CA125, large studies have evaluated its efficacy: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial (n=39105) showed no mortality reduction after 6 years of annual CA125/ultrasound, with a 15% false-positive rate leading to unnecessary surgeries.[2] The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study (202562 postmenopausal women) found higher stage I+II detection (39.2%) with multimodal screening but no mortality reduction in either arm (multimodal: p=0.58; ultrasound: p=0.36).[3] These trials highlight CA125 and imaging potential but underscore the urgent need for improved risk-stratification.

CA125, encoded by the Mucin-16(MUC16) gene, is expressed in mesothelial cells and ovarian cancer cells. Serum CA125 levels are influenced by physiological factors including age, menopausal status, and hormonal milieu. Postmenopausal women typically show lower levels than premenopausal women, but reported trends conflict: some studies indicate a 3.6-7.1% annual increase postmenopause,[4] while others describe biphasic patterns with perimenopausal declines. These inconsistencies highlight the need to standardize age-specific reference intervals. CA125 is also elevated in non-malignant conditions like endometriosis, pelvic inflammatory disease, and heart failure. Chronic conditions (e.g., hypertension, diabetes) are significant confounder (OR=1.2-2.5).[4] Hormonal contraception and tubal ligation further modulate baseline levels, increasing variability.[5] These reduce CA125's utility as a standalone biomarker, necessitating integration with clinical and imaging parameters.

This study characterizes age-dependent CA125 trajectories in a large Chinese cohort by establishing 10-year age-group reference intervals and identifying inflection points using joinpoint regression, aiming to improve CA125 interpretation and facilitate personalized screening algorithms—particularly for premenopausal/elderly populations where current thresholds have low accuracy.

STUDY DESIGN

A multicenter cross-sectional study was conducted from January 2016 to December 2021, involving 164,236 women undergoing health screenings at three Chinese health screening centers (referred to as Centre 1, Centre 2, and Centre 3, respectively).

Participants underwent clinical assessment, including pelvic examination and transvaginal or transabdominal ultrasound. The distribution of CA125 levels was assessed across different age groups, and the CA125 levels by age was analyzed in women with normal ultrasonographic findings.

Fasting venous blood samples were collected between 08:00-10:00 hours. Serum CA125 levels were measured using electrochemiluminescence immunoassay (ECLIA) with the CA125 II Reagent Kit (Abbott or Mindray) according to the manufacturer's instructions. Assay coefficients of variation (CV) were <5% for both platforms. The upper limit of normal (ULN) was defined as 35 U/mL according to manufacturer guidelines.

PARTICIPANTS

Women meeting the following criteria were included: (1) aged ≥14 years; (2) Normal pelvic ultrasonography (no adnexal masses); (3) Negative chest X-ray findings; (4) using cutoff values of CA125 <200 U/mL (premenopausal) or <65 U/mL (postmenopausal). Exclusion criteria were: (1) Pregnancy (n=149); (2) Missing CA125 measurements (n=43,088); (3) Abnormal ultrasound and chest Computed Tomography (CT) results (n=17,935); (4) Concomitant malignancies (n=3,584).

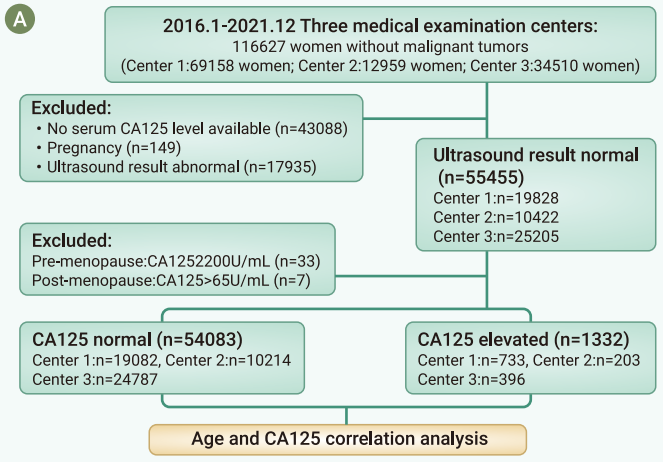
A total of 55,415 women were eligible for analysis (Figure 1A). Reliable epidemiological estimates for menopause suggest a median age of natural menopause between 48 and 52 years among women in developed nations.[6] In this study, menopausal status was defined as ≥50 years old based on the median menopause age in Chinese populations, in line with our previous studies.[7]

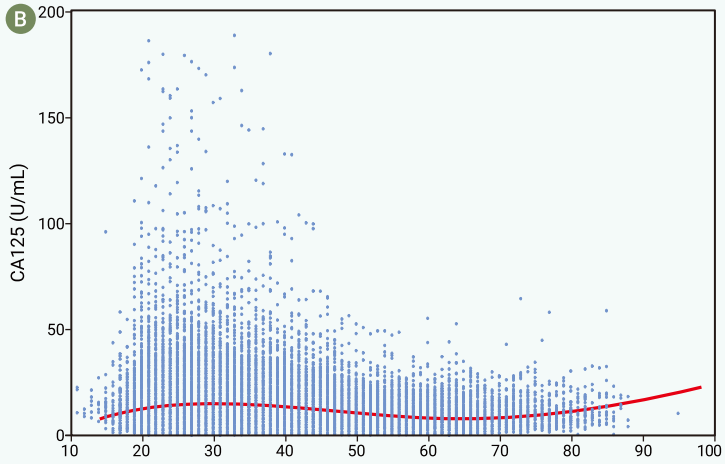
STATISTICAL ANALYSIS

Analyses used SPSS 26.0 (IBM), GraphPad Prism 9, and Joinpoint Regression 4.9.1.0. CA125 distributions were evaluated by age groups (<30, 30-39, 40-49, 50-59, ≥60 years), expressed as medians with interquartile ranges (IQR). CA125 values were logarithmically transformed to approximate normality, and an independent samples t-test was used to compare differences between subgroups. Joinpoint regression identified age-related inflection points (max 3 joinpoints, $\alpha = 0.05$). Percentile smoothing curves (R 4.3.1) visualized age-dependent trends. All tests were two-tailed (significance: $P<0.05$).

DESCRIPTIVE ANALYSES

A total of 55,415 women (mean age: 40.94±13.5 years) were analyzed, including 1332 (2.4%) with elevated CA125 (≥35 U/mL). The median CA125 level of pre-menopausal women was 11.9 U/mL, while that of post-menopausal women was 7.6 U/mL. Scatter plots demonstrated a triphasic age-dependent pattern (Figure 1B): the 30–39 years group had the highest median level at 12.1 U/mL (IQR: 10.4), which significantly declined to 7.4 U/mL (IQR: 6.4) in the 50–59 years group, followed by a moderate resurgence to 7.7 U/mL (IQR: 6.5) among postmenopausal women aged ≥60





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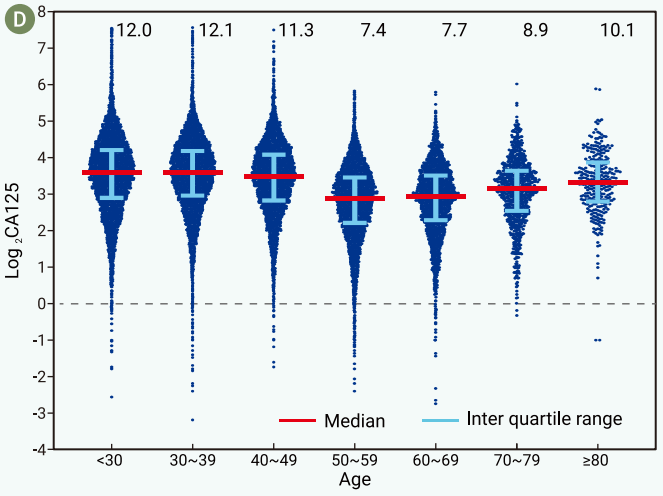
Age	Number	Median	IQR	Average	SD	95%RI
<30	12384	12.0	10.9	14.7	12.4	33.17
30~39	18560	12.1	10.4	14.3	10.7	30.96
40~49	8255	11.3	9.8	13.3	9.9	29.49
50~59	10846	7.4	6.4	8.4	5.5	18.39
60~69	3920	7.7	6.5	8.8	5.5	19.42
70~79	1140	8.9	6.6	10.0	6.0	21.43
≥80	310	10.1	7.5	11.6	7.1	23.73
Total	55415	10.4	9.6	12.6	10.2	28.8

E

Age subgroup	Difference of means±SEM	95% CI	P value
30~39 vs. <30	0.004±0.012	-0.019 to 0.027	0.722
40~49 vs. 30~39	-0.113 ± 0.013	-0.139 to -0.087	<0.001
50~59 vs. 40~49	-0.630 ± 0.014	-0.660 to -0.604	<0.001
60~69 vs. 50~59	0.062 ± 0.018	0.026 to 0.098	<0.001
70~79 vs. 60~69	0.226 ± 0.032	0.163 to 0.289	<0.001
≥80 vs. 70~79	0.232 ± 0.057	0.121 to 0.344	<0.001



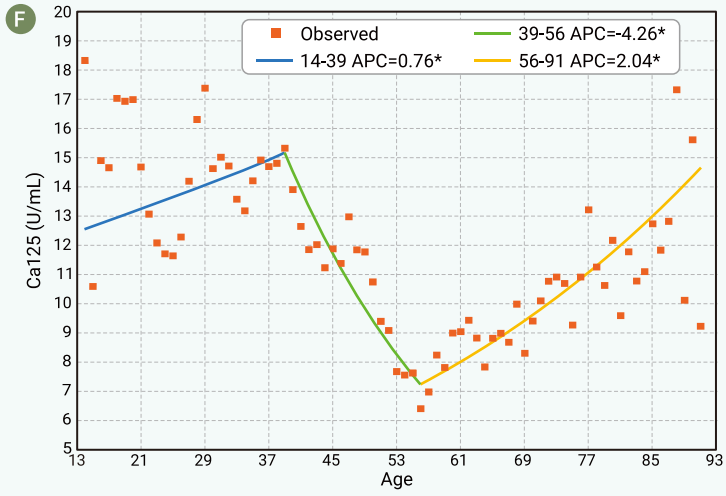


Figure 1. Analysis of distribution, variation, and trends in CA125 levels across age groups among 55,415 Women (A) Enrollment flowchart (n=55,415) across 3 centers. Center 1: Health Management Center of the First Affiliated Hospital of University of Science and Technology of China (USTC); Center 2: Health Management Center South Region Branch of the First Affiliated Hospital of USTC; Center 3: Ruici medical examination center. (B-C) The scatter plots and the table presenting the distribution of age and CA125 levels. (D) Scatter plots of CA125 by age group. The median CA125 (U/mL) were labeled at the top, red/blue bars = mean/SD. (E) Log-transformed CA125 variation between age subgroups. (F) Joinpoint regression presented the specific trends and turning points of CA125 level, Final Selected Model:2 Joinpoints. *Indicates that the Annual Percent Change (APC) significant (α=0.05). SD: Standard deviation; IQR: Inter quartile range; RI: Reference intervals; SEM: Standard error of the mean; CI: Confidence interval; Age groups: <30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80 years.

years. The 95th percentile reference intervals were: premenopausal groups <30 (33.2 U/mL), 30-39 (31.0 U/mL), 40-49 (29.5 U/mL); postmenopausal groups 50-59 (18.4 U/mL), 60-69 (19.4 U/mL), 70-79(21.4 U/mL), ≥80(23.7 U/mL) (Figure 1C).

MAIN ANALYSIS

For further analysis, the 55,415 women with normal CA125 levels were stratified by 10-year age intervals. The median CA125 levels for each age group were plotted on scatter diagrams (Figure 1D). Significant differences were observed between all adjacent age groups except <30 vs 30-39 years (p=0.722). The largest reduction occurred between 40-49 and 50-59 years [-0.630 U/mL (95%CI: -0.660 to -0.604), p<0.001]. In postmenopausal groups, the ≥60 years group showed stepwise increases compared to 50-59 years group, with the ≥80 years group reaching 10.1 U/mL (Figure 1E).

Furthermore, Joinpoint regression identified two significant inflection points (Figure 1F): a significant annual increase of +0.8% until 39 years (p=0.023), followed by a significant annual decline of -4.3% between 39-56 years (p<0.001) and a secondary increase of +2.0% per year after 56 years (p<0.001). Combined with nonlinear curve fitting, it confirmed a biphasic decline during perimenopause (39-56 years) and gradual resurgence post-56 years (Figure 1B).

Our data confirm significantly lower postmenopausal CA125 (median: 7.6 U/mL vs. premenopausal 11.9 U/mL), consistent with previous studies. Unlike reported linear reductions, we observed a sinuous decline, suggesting distinct hormonal regulation in Asians.[4] The early inflection point (39 years) precedes the global median menopause age (48.8 years),[6] indicating estrogen withdrawal may modulate endometrial CA125 expression. The perimenopausal decline likely results from reduced MUC16 expression post-ovulation and endometrial glands secretory differentiation. This reduction is hypothesized to reflect menopausal gland atrophy, exacerbated by estrogen-withdrawal-induced endometrial thinning.

CA125 resurgence after age 56 diverges from reported continuous post-

menopausal declines. It is potentially driven by chronic inflammation, immunosenescence, and hormone replacement therapy (HRT). Age-related increases in inflammatory mediators could elevate CA125. Elevated CA125 levels correlates with conditions such as heart failure, coronary artery disease (CAD), elevated C-reactive protein (CRP), and interleukin-6 overexpression in postmenopausal women.[8] Immunosenescence (pro-inflammatory state) may explain the post-59 rise. HRT also contributes: hysterectomized postmenopausal women on HRT showed higher CA125 (12.3 U/mL) vs. non-HRT (11.9 U/mL).[5]

PROSPECTIVE

These findings support age-stratified CA125 thresholds to optimize ovarian cancer screening. The established 95% reference intervals (e.g., 18.4 U/mL for aged 50–59 years vs. traditional 35 U/mL) could reduce false positives in perimenopausal and elderly populations. The Ovarian-Adnexal Reporting and Data System (O-RADS) risk stratification system for ultrasound (US) and Magnetic Resonance Imaging (MRI) demonstrates high sensitivity (91-100%) and moderate specificity (46-93%) for malignant tumors.[9] Thus, combining CA125 with O-RADS is recommended, especially for persistent CA125 elevation. A cost-effective strategy would be to maintain traditional thresholds for women <30 years and incorporate inflammatory markers (e.g., CRP) for those aged 60 and above to minimize misdiagnosis.

While establishing CA125 range across age groups, further studies are needed to define physiological fluctuations. CA125 exhibits cyclic endometrial changes (menstrual peaking),[10] requiring hormonal impacts research. In elderly women, age-related comorbidities confound CA125, increasing false-positives. While our retrospective design precludes direct clinical application, these intervals may inform future guideline refinements; for instance, integrating age-stratified thresholds (e.g., 18.4 U/mL for 50-59y) into O-RADS with inflammatory markers like CRP to potentially reduce false positives in multi-morbid populations. Such strategies require prospective validation. Therefore, a comprehensive algorithm combining imaging, chronic medical history, inflammatory markers, and tumor biomarkers is essential for improving tumor screening accuracy. Additionally, analysis of 149 excluded pregnant women showed elevated CA125 versus non-pregnant women (medians: 28.2 U/mL <30y, 24.4 U/mL 30-39y, 19.1 U/mL 40-49y), though with considerable inter-individual variation.

While our study characterizes age-specific trends, unmeasured confounders (e.g., genetics/lifestyle) may influence CA125 levels despite adjustments. Furthermore, the cross-sectional design precludes analysis of intra-individual trajectories over time—a limitation requiring longitudinal validation of the 39y/56y inflection points. Finally, generalizability beyond Asian cohorts necessitates verification in diverse populations.

In conclusion, our study demonstrates an age-dependent fluctuation pattern.CA125 levels increase before 39 years, followed by a decrease, and then increase after 56 years. This work contributes to personalized ovarian cancer screening by defining age-specific CA125 trajectories, addressing the long-standing limitations of traditional thresholds, and providing a framework for integrating molecular and imaging modalities.

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AUTHOR CONTRIBUTIONS

C.Z.: Conceptualization, Formal analysis, Writing - Original Draft; X.L.: Methodology, Software, Writing - Original Draft; H.X.: Writing-Review & Editing; C.P.: Data Curation, Resources; Y.P.: Data Curation, Resources; B.Y.: Resources; Y.L.: Resources; Y.W.: Data Curation; L.C.: Writing-Review & Editing; B.L.: Validation, Project administration; Y.Z.: Conceptualization, Supervision. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Ethical approval was obtained from the Institutional Review Board of our hospital (IRB No. 2023KY077), with informed consent waived due to anonymized data usage.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.