Article is available online at http://www.webio.hu/por/2007/13/4/0360

ARTICLE

Factors Influencing Serum Concentration of CA125 and CA15-3 in Iranian Healthy Postmenopausal Women

Alamtaj Samsami DEHAGHANI,[1] Alireza Fotouhi GHIAM,[2] Marjan HOSSEINI,[1] Sareh MANSOURI,[1] Abbas GHADERI[2,3]

[1]Department of Obstetrics and Gynecology, [2]Institute for Cancer Research, [3]Department of Immunology, Shiraz University of Medical Sciences, Shiraz, Iran

Screening for breast and ovarian cancers are required due to the late stage at diagnosis and poor survival. Serum CA125 and CA15-3 are important cancer-detecting agents in patients with ovarian and breast cancers, respectively. Elevation of CA125 and CA15-3 level correlates with malignant and non-malignant conditions. Moreover, a series of individual characteristics affect the serum level of these markers. The objective of the present study was to evaluate CA125 and CA15-3 levels in cancer-free postmenopausal women to investigate the impacts of patient parameters on the serum level of these markers. 203 subjects were studied prospectively. Serum CA125 and CA15-3 assessment was done subsequent to the direct interview. The associations between marker levels and presenting features were examined. CA125 and CA15-3 levels were elevated in 35 (17.2%) and 12 (5.9%) of persons, respectively. A higher CA125 level was associated with advanced age ($p = 0.046$), while a lower level was correlated with hormone replacement therapy (HRT) and having smoking habits ($p = 0.000$ and $p = 0.01$, respectively). CA15-3 level was remarkably lower amongst oral contraceptive (OCP) users ($p = 0.03$). Serum marker levels were not significantly related to menarche age, age at menopause, height, weight, BMI and parity. Serum CA125 is imperative indicator for malignancies of the ovary; however, personal and medical factors influence its serum level. A fair interpretation of results must be due to an accurate attention to the individual characteristics. (Pathology Oncology Research Vol 13, No 4, 360–364)

Key words: breast health, menopause, cancer

Introduction

Menopause as a physiological event begins 12 months after the cessation of the menstrual period.[1,2] Fifty years of age is considered as the best estimation for menses-based description of menopause, though its timing might differ due to genetic and environmental factors.[3] Aging per se plays a substantial role in the decline of ovarian production, thereby deteriorated hormonal status influences middle-aged women by numerous physical, emotional and social changes.[4]

After menopause, women loose the protective role of the reproductive period which results in an increase of cancer rate. That is why recent studies focus on the areas of cancer prevention and treatment in postmenopausal women, particularly of the breast and ovary.[1]

Despite a variety of preventive measures, breast cancer, the leading cause of cancer in females, still shows an upward trend in incidence by aging phenomenon and by the advent of menopause.[5] Ovarian cancer, the most lethal gynecological malignancy, mostly afflicts postmenopausal women over the age of 60 years.[6,7] Therefore, according to the goals of Healthy People 2010, engaging the proper strategies for early screening of breast and ovarian cancer is top priority.[7,8]

Human CA125 (carbohydrate antigen-125), encoded by the MUC16 gene, is a giant mucin-like glycoprotein present on the tumor cells.[9] Since the past four years, CA-125

Received: Jan 2, 2007; *accepted:* Oct 13, 2007

Correspondence: Prof. Abbas GHADERI, Shiraz Institute for Cancer Research (ICR), Shiraz University of Medical Sciences, Shiraz, Iran. PO BOX: 71345-1798. Tel: (+) 98 711 230 3687, fax: (+) 98 711 230 4952, e-mail: ghaderia@sums.ac.ir

has shown the highest diagnostic accuracy to be a great assistance to detect ovarian cancers.[6,10]

CA15-3 (human MUC1) was discovered in the early 1980s by monoclonal antibody technology.[11] CA15-3, a high-molecular-mass mucin-like glycoprotein, is expressed at the luminal surface of most secretary epithelia.[12] Of the tumor markers examined in breast cancer, it is the best and the most extensively used one as its expression greatly increases in most breast carcinomas.[13]

Cancer screening protocols generally have been restricted by unspecific serum elevation of tumor markers in various malignant and non-malignant conditions, and by a wide fluctuation in normal women.[11] Thus, better understanding of the normal behavior of tumor markers in cancer-free women is required to launch an optimal screening program.[14]

The aims of the present study were to characterize the serum level of two tumor markers, CA125 and CA15-3, in an Iranian population of healthy postmenopausal women, as well as to highlight its association with individual characteristics.

Materials and Methods

Subjects

A series of 203 consecutive Iranian female subjects, passing no less than a year after their menopause commencement, were enrolled in this cross-sectional study over a one-year period, from 2003 to 2004. The subjects were women referring to outpatient clinics affiliating to Shiraz University of Medical Sciences, for routine checkup. They were all asymptomatic healthy women with no evidence of any gynecological or non-gynecological disease, or any malignancy or autoimmune disease based on complete physical examination. Any subjects with suspicious evidence of malignancy or autoimmune disease, and those with pertinent personal or familial history in first- or second-degree relatives were excluded. Furthermore, the cases were required to have no record of oophorectomy or hysterectomy.

After taking an informed consent, the subjects' information was gathered via a direct interview filling out a questionnaire. Then, 5 ml blood was obtained for measuring the serum concentration of CA125 and CA15-3 using an indirect ELISA assay. CA125 and CA15-3 were measured as recommended by the manufacturer (IBL, Germany); cutoff levels of 35 units/ml and 30 units/ml were chosen as an upper normal limit for CA125 and CA15-3 concentration, respectively, as it was previously reported.[15]

Owing to the assumed fluctuation of these markers with different personal factors such as age, age at menarche, age at menopause, body mass index (BMI), history of hormone replacement therapy (HRT), previous oral contraceptive (OCP) use and smoking habit, the related information was composed. We considered the history of HRT use as positive whenever the subject had used any hormonal agent for at least one year. OCP use was considered positive when a minimal prior history of a 1-year period of consumption was mentioned by the study participant. Smoking was considered in the case of cigarette consumption of 10/day or more over the course of two years.

All but one of the cases had a positive history of marriage, and in terms of career situation, they did not have any specific vocational distribution.

Statistical analysis

Data were analyzed using SPSS software (version 11.5.0; SPSS Inc., Chicago, IL, USA). Pearson's chi-square test and Fisher's exact probability test were used to compare the differences between groups considering factors affecting the serum concentration of the tumor markers. The mean serum level of the markers was compared using *t*-test and one-way ANOVA (Duncan test). P value < 0.05 was deemed to be significant.

Results

Demographic characteristics

In total, 203 postmenopausal women were investigated. The mean age of the studied individuals was 59.9 years (SD = 9.5 years), ranging from 43 to 85 years. The mean age at menopause was 48.8 ± 4 years, ranging from 35 to 60 years, while mean age of menarche was calculated to be 13.2 years (SD = 1.6 years), ranging from 9 to 18 years.

Based on their body mass index (BMI), the subjects were categorized into two groups, below 30 kg/m^2 and over or equal to 30 kg/m^2. The former consisted of 169 (83.3%) of subjects, and the latter had 34 (16.7%) members.

Of the subjects, 3 (1.5%) persons were nulliparous women, while 200 (98.5%) had a history of at least one pregnancy. They all had experienced the first pregnancy below the age of thirty. Twenty (9.9%) of individuals were HRT consumers, while 183 (90.1%) were not. Other characteristic data are shown in *Table 1*.

Serum level of CA125 and CA15-3

The mean levels of CA125 and CA15-3 in examined sera were shown to be 29.23 ± 49.35 units/ml (ranging from 0.0 to 314 units/ml) and 15.49 ± 8.53 (1 to 62) units/ml, respectively. In terms of CA125 serum concentration, 36 (17.7%) of subjects revealed levels exceeding 35 units/ml versus 168 (82.8%) who had normal values. Serum concentration of CA15-3 was higher than normal limits (≥30 units/ml) in 12 (5.9%) of study participants, while the rest, 191 (94.1%), fell into the normal range (<30 units/ml).

Table 1. **Factors affecting serum level of CA125 and CA15-3**

Factor	*Number of cases*	*CA125 units/ml mean (range)*	*CA15-3 units/ml mean (range)*
Age (years)			
40-55	79 (38.9%)	22.17 (0-306)	15.10 (1-62)
56-70	93 (45.8)	26.08 (0-314)	16.10 (4-42)
>70	31 (15.3%)	56.54 (6-290) [p1]	14.64 (1-41)
Age at menarche (years)			
<12	28 (13.8%)	30.9 (0-180)	14.07 (5-33)
12-14	131 (64.5%)	28.6 (1-314)	16 (1-62)
>14	44 (21.7%)	30.27 (1-290)	14.93 (5-41)
Age at menopause (years)			
<40	4 (2.0%)	17.5 (6-40)	10.5 (8-13)
40-50	156 (76.8%)	30.5 (1-314)	15.5 (1-62)
>50	43 (21.2%)	25.9 (0-220)	15.8 (5-33)
BMI (kg/m^2)			
<30	169 (83.3%)	29.28 (0-314)	15.13 (1-52)
≥30	34 (16.7%)	29.21 (4-290)	17.26 (1-62)
Parity			
childless	3 (1.5%)	66.00 (14-144)	12.67 (10-18)
have child	200 (98.5%)	28.72 (0-314)	15.53 (1-62)
OCP			
user	76 (37.4%)	26.21 (1-306)	14.79 (1-42)
non-user	127 (62.6%)	31.10 (0-314)	15.9 (1-62)
HRT			
user	20 (9.9%)	13.83 (1-54)	15 (7-24)
non-user	183 (90.1%)	30.77 (0-314) [p2]	15.53 (1-62)
Smoking			
smoker	26 (12.8%)	19.19 (4-64)	14.46 (5-31)
non-smoker	177 (87.2%)	30.75 (0-314) [p3]	15.64 (1-62)

p1 = 0.003, p2 = 0.000, p3 = 0.01

The serum concentration of CA125 revealed significant correlation with age (χ^2 test, $p = 0.046$), i.e. the number of subjects with abnormal serum CA125 was significantly higher in those aged over 70. Ten out of 79 in the age group of 40-55 years, 15 out of 93 in age group of 56–70 years and 10 out of 31 in those over 70 showed serum levels higher than normal limits. An increase in mean serum level of CA125 with age was observed in study participants (one-way ANOVA, Duncan test, $p = 0.003$; *Table 1*).

The number of subjects with normal level of CA15-3 was significantly greater in OCP consumers compared to non-consumers (Fisher's exact test, $p = 0.03$); only one out of 76 OCP users had a CA15-3 level above the upper normal limit versus 11 out of 127 in non-OCP users. A significant decrease in mean serum concentration of CA125 was observed in HRT user subjects comparing to non-user ones (t-test, $p = 0.000$). Of interest, the mean serum level of CA125 revealed a decrease in smokers in comparison to non-smokers (t-test, $p = 0.01$; *Table 1*). Other recorded personal factors had no significant association with serum level of CA125 or CA15-3.

Discussion

Menopause coinciding aging phenomenon makes women prone to a series of diseases, of which the malignancies of the breast and ovary are of great importance. An improvement in clinical outcome will be achieved if the malignancies become detected at an early-stage.[10] Therefore, developing proper screening procedures is a major concern.

Using tumor markers, substances produced either by the body in response to cancer or by the tumor tissue itself, as first step screening tool is quite beneficial because this method is not only easy to perform and cost-effective but also safe and well accepted by the patients.[16]

Current non-invasive modalities for the early detection of ovarian cancer are comprised of rectovaginal examination, transvaginal sonography (TVS) and CA125 blood test.[6,15] Serum assessment of CA125 in combination with adjunct tumor markers and engaging TVS are newly emerged strategies to reach optimal screening programs.[17]

Although CA125 lacks the sufficient specificity because of elevated levels in certain malignant and non-malignant

conditions,[15] it is still respected as a valuable serological screening test because TVS, despite its high sensitivity, is too expensive to be used as first-line screening. The importance of CA125 is more evident in developing countries where most women are not able to afford the expenditure of other screening strategies.

Regarding breast cancer screening programs, breast self-examination and screening mammography have been engaged more commonly than serum markers like CA15-3.[18]

Since the marker levels are a direct reflection of the activity of the tumor, it is essential to know the factors affecting the serum levels in cancer-free women to accurately interpret the screening results and select the high-risk women for the next diagnostic procedure.[14]

Our study results are in accordance with those of Pauler et al and Lopez et al where the CA125 level showed a positive correlation with age, but in contrast to results of Takami et al and Hornstein et al where it shomed a in negative correlation,[19-22] or others showing no significant correlation.[23,24]

Consistent with another study,[25] we observed no correlation between age at menarche or age at menopause and serum concentration of the tumor markers.

Some publications indicate that the serum levels of CA125 and CA15-3 are independent of parity.[26] In our study, although the mean serum level of CA125 seemed significantly higher in nulliparous cases, the number of these cases was not enongh to permit statistical analysis.

We could not detect any association between serum level of CA125 and history of OCP use in accordance with previously published data,[26] but a high CA15-3 level was seen more often in cases with no history of OCP consumption.

The effect of HRT use on the serum level of tumor markers is still under debate. While some studies have shown a rise in concentration of CA125 and CA15-3 subsequent to long-term usage of HRT,[19,27] others have considered no role for HRT[14] or reported a statistically significant decrease in CA125 and CA15-3 levels.[23,26] Our results are in agreement with those of the latter group, showing a remarkable decrease in the serum level of CA125 in HRT users.

In contrast to Hornstein et al reporting no association between smoking status and CA125, the mean serum level of CA125 was significantly lower among smokers.[22]

Regarding CA125 as a predictor of ovarian cancer and our study findings indicating that CA125 serum level exceeds the upper normal limit in a noticeable number of subjects (17.2%), especially in those with higher age, we suggest that only postmenopausal women with abnormal CA125 serum level be referred for TVS. Also, as CA125 level showed an increase with age, a consecutive screening is recommended. However, it can be assumed that the mean level of serum CA125 may be higher in the Iranian population, an area which needs further investigations on a larger population to be fairly confirmed. Due to our study results, to draw an accurate interpretation of serum level of CA125 and CA15-3 individual characteristics should be considered.

Acknowledgements

This work was financially supported by a grant from Shiraz University of Medical Sciences (grant no. 82-1911) and in part by Shiraz Institute for Cancer Research.

References

1. *Taechakraichana N, Jaisamrarn U, Panyakhamlerd K, Chaikittisilpa S, Limpaphayom KK:* Climacteric: concept, consequence and care. J Med Assoc Thai 85:S1-15, 2002.
2. *Rymer J, Morris EP*: Extracts from "Clinical evidence": Menopausal symptoms. BMJ 321: 1516-1519, 2000.
3. *van Asselt KM, Kok HS, Putter H, Wijmenga C, Peeters PH, van der Schouw YT, Grobbee DE, te Velde ER, Mosselman S, Pearson PL:* Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative trait loci influencing variation in human menopausal age. Am J Hum Genet 74: 444-453, 2004.
4. *Jamjan L, Jerayingmongkol P:* Self-image of people in their fifties. Nurs Health Sci 4:A4, 2002.
5. *Pike MC, Pearce CL, Wu AH:* Prevention of cancers of the breast, endometrium and ovary. Oncogene 23: 6379-6391, 2004.
6. *Jacobs IJ, Menon U:* Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics 3: 355-366, 2004.
7. *Crump C, McIntosh MW, Urban N, Anderson G, Karlan BY:* Ovarian cancer tumor marker behavior in asymptomatic healthy women: implications for screening. Cancer Epidemiol Biomarkers Prev 9: 1107-1111, 2000.
8. Public Health Service. Healthy people 2010: National health promotion and disease prevention objectives – full report with commentary. Washington, DC: U.S. Department of Health and Human Services, 2000.
9. *Maeda T, Inoue M, Koshiba S, Yabuki T, Aoki M, Nunokawa E, et al:* Solution structure of the SEA domain from the murine homologue of ovarian cancer antigen CA125 (MUC16). J Biol Chem 279: 13174-13182, 2004.
10. *Bast RC Jr:* Status of tumor markers in ovarian cancer screening. J Clin Oncol 21: 200-205, 2003.
11. *Zidan J, Hussein O, Basher W, Zohar S:* Serum CA125: a tumor marker for monitoring response to treatment and follow-up in patients with non-Hodgkin's lymphoma. Oncologist 9: 417-421, 2004.
12. *Taylor-Papadimitriou J, Burchell JM, Plunkett T, Graham R, Correa I, Miles D, Smith M:* MUC1 and the immunobiology of cancer. J Mammary Gland Biol Neoplasia 7: 209-221, 2002.
13. *Clinton SR, Beason KL, Bryant S, Johnson JT, Jackson M, Wilson C, Holifield K, Vincent C, Hall M:* A comparative study of four serological tumor markers for the detection of breast cancer. Biomed Sci Instrum 39: 408-414, 2003.
14. *Seregni E, Botti C, Bajetta E, Ferrari L, Martinetti A, Nerini-Molteni S, Bombardieri E:* Hormonal regulation of MUC1 expression. Int J Biol Markers 14: 29-35, 1999.
15. *O' Rourke J, Mahon SM:* A comprehensive look at the early detection of ovarian cancer. Clin J Oncol Nurs 7: 41-47, 2003.

16. *Kayaba H:* Tumor markers: essential diagnostic tools for radiologists. Nippon Igaku Hoshasen Gakkai Zasshi 63: 133-139, 2003.
17. *Lu KH, Patterson AP, Wang L, Marquez RT, Atkinson EN, Baggerly KA, et al:* Selection of potential markers for epithelial ovarian cancer with gene expression arrays and recursive descent partition analysis. Clin Cancer Res 10: 3291-3300, 2004.
18. *Green BB, Taplin SH:* Breast cancer screening controversies. J Am Board Fam Pract 16: 233-241, 2003.
19. *Pauler DK, Menon U, McIntosh M, Symecko HL, Skates SJ, Jacobs IJ:* Factors influencing serum CA125II levels in healthy postmenopausal women. Cancer Epidemiol Biomarkers Prev 10: 489-493, 2001.
20. *Lopez LA, Del Villar V, Ulla M, Fernandez F, Fernandez LA, Santos I, Rabadan L, Gutierrez M:* Prevalence of abnormal levels of serum tumour markers in elderly people. Age Ageing 25: 45-50, 1996.
21. *Takami M, Sakamoto H, Ohtani K, Takami T, Satoh K:* An evaluation of CA125 levels in 291 normal postmenopausal and 20 endometrial adenocarcinoma-bearing women before and after surgery. Cancer Lett 121: 69-72, 1997.
22. *Hornstein MD, Goodman HM, Thomas PP, Knapp RC, Harlow BL:* Use of a second-generation CA125 assay in gynecologic patients. Gynecol Obstet Invest 42: 196-200, 1996.
23. *Cengiz B, Atabekoglu C, Cetinkaya E, Cengiz SD:* Effect of hormone replacement therapy on serum levels of tumor markers in healthy postmenopausal women. Maturitas 46: 301-306, 2003.
24. *Menzin AW, Kobrin S, Pollak E, Goodman DB, Rubin SC:* The effect of renal function on serum levels of CA125.Gynecol Oncol 58: 375-377, 1995.
25. *Brekelmans CT:* Risk factors and risk reduction of breast and ovarian cancer. Curr Opin Obstet Gynecol 15: 63-68, 2003.
26. *Grover S, Quinn MA, Weideman P, Koh H:* Factors influencing serum CA 125 levels in normal women. Obstet Gynecol 79: 511-514, 1992.
27. *Johnson KC, Hu J, Mao Y:* Passive and active smoking and breast cancer risk in Canada. Cancer Causes Control 11: 211-221, 2000.