Gynecological cancer and metabolic screening of 1001 elderly Brazilian women

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate gynecological cancer and metabolic screening of Brazilian women aged 65 years or older.

METHODS: This retrospective descriptive study was conducted by including 1,001 Brazilian patients of the gynecological geriatric outpatient office of our institution to evaluate the influence of age on gynecological cancer and metabolic screening parameters at the first clinical visit. All patients were divided into three groups: a) 65 to 69 years; b) 70 to 74 years; c) ≥ 75 years. We considered clinical, laboratorial, and image data as variables of this study. The Chi-square test was used to assess the proportion of differences among the age groups, and Kruskal-Wallis was used for quantitative variables.

RESULTS: The values of BMI and height in the group over 75 years was lower than that of the 65 to 69 years (p = 0.001). Regardless of the age group, high arterial blood pressure levels were found in 85.45% of participants. Also, many patients had glucose intolerance in the blood. The pelvic ultrasonography showed abnormal endometrial echo thickness (> 5 mm) in 6.14% of patients, but with no significant statistical difference between the age groups. A total of 4.04% of patients had ovaries with high volume values (> 6.1 mL). Abnormal mammography (BI-RADS 3 or 4) was observed in 12.21%.

CONCLUSIONS: Our data suggest that a great reduction in BMI and stature is more frequent in the group over 75 years. Also, systemic arterial hypertension and carbohydrate disturbance are frequent morbidities in women over 65 years.

KEYWORDS: Aged. Women. Menopause. Body mass index. Genital neoplasms, Female.

INTRODUCTION

The increase of populational longevity concerning people over 60 years old is a reality all over the world. According to the Brazilian Institute of Geography and Statistics (IBGE), the elderly age group increased proportionally more than any other age group in the 20th century, with life expectancy at birth jumping from 42.7 years in 1930 to 74.8 years in 2014¹. The United Nations World Populations Prospects in 2002², estimates that by 2050, the population over 60 years probably will lead 2 billion individuals. These demographic data and others like climate, race, socioeconomic level, health and physical conditions and are very important,
and more information about the female population aged 65 and over is still necessary.

Over the last few decades, there has been increased interest in studying and learning the general conditions of the aging population, particularly women after menopause, which is a particular period with a reduction in estrogen levels and its consequences on the organism, such as vasomotor symptoms. However, a high number of patients present an excessive increase in body mass index (obesity), systemic arterial hypertension, higher fast glucose level, and diabetes mellitus, among other cardiovascular risks, and gynecological cancer during this period. This phenomenon is well reported.

This period finishes at the age of 65 years. However, data on age influence on gynecological and metabolic parameters of women aged over 65 years are scarce. In fact, some guidelines suggest not continuing with cancer screening, such as cervical cancer, in this population. However, life expectancy is rising in Brazil, so this is an opportune time to understand the real influence of age on the gynecological parameters for cancer screening, such as pap smears (cervical and vaginal cancer), mammography (breast cancer), ultrasound (endometrial cancer), and physical examination (genital cancer) for starting preventive strategies to reduce morbidity associated with cancer. Also, obesity is an independent factor for cancer (breast and endometrial) as well as metabolic disturbance. In a recent study on postmenopausal patients, 53% of participants had multimorbidities, including gynecological disturbance, which may have an impact on the quality of life. Also, the gynecological population of Hospital das Clínicas reflects the five macro-regions of Brazil. Those conditions may be worsening with aging. Therefore, the knowledge of this study may provide new information for elaborating strategies for the care of this specific female population.

The aim of the study was to evaluate the influence of the age on clinical and laboratory gynecological parameters for screening morbidity on a large group of Brazilian women aged 65 years or older at the Gynecology Discipline of the Department of Gynecology and Obstetrics at the Hospital das Clínicas, Faculty of Medicine of the University of São Paulo.

METHODS
Study design and subject selection

This was a descriptive, transversal and retrospective study on women without previous chronic comorbidities, aged 65 years or older, conducted by the Gynecology Discipline, at the Department of Gynecology and Obstetrics of Hospital das Clínicas, Faculty of Medicine, University of São Paulo. The length of the study was from 1983 to 2010. We used patient records that included all clinical history, physical examinations, and laboratorial results for evaluating the gynecological and metabolic screening.

Eligibility criteria

We included patients who were: women aged 65 years old or over, with adequate and complete medical information (medical records of the clinical evaluation, laboratory analysis) to execute and analyze the study variables. Our study included patients invited for gynecological and metabolic screening.

We excluded patients with surgical menopause (ovariectomy or/and hysterectomy), menopause before the age of 40 (premature ovarian insufficiency) and those unable to be examined or who reported previous health problems.

Selection

Initially, 1,325 Brazilian women aged 65 years or older were included in the study. After applying the eligibility criteria, the final number was 1,001 women. Figure 1 summarizes the selection of patients. The main reasons for exclusion were incomplete patient medical data and surgical menopause.

FIGURE 1. PATIENT SELECTION FLOWCHART
To evaluate the influence of age on the gynecological parameters of health, the patients were divided into the three following groups: a) 65 to 69; b) 70 to 74; c) ≥ 75 years old. The Ethics Committee approved this study for Research Project Analysis of HC-FMUSP (#number 0757/08).

Study variables

Dependent variables: 1) gynecological cancer screening: a) breast; b) cervical; c) ovary; d) endometrium; e) colon cancer (hidden blood in feces); 2) metabolic screening: a) BMI (body mass index, kg/m²); b) Systemic blood pressure; c) laboratory evaluation (fasting glucose, cholesterol, total and fractions, triglycerides, thyroid-stimulating hormone (TSH), free thyroid hormone (FT4), urea, creatinine).

Independent variables: formal education, sexual partner, religion, skin color, socioeconomic status, alcohol consumption, frequency of alcohol consumption, frequency of physical exercise, mass index (kg/m²), number of sexual partners over a lifetime. The variable regarding the age of natural menopause was divided into three categories: a) Early menopause (between 40 years and 45 years); b) Adequate menopause (between 45 years and 55 years); c) Late menopause (over 55 years). The rationale of this classification is that women in early menopause have higher metabolic and cardiovascular risk (longer period in hypoestrogenism) and women in late menopause have higher gynecological cancer risk (larger estrogen window).

Physical examination

The methods for Anthropometric measures were: a) stature was measured with a rounding of 0.1 cm, using a standard stadiometer, with the participants standing and without shoes; b) body weight was measured barefoot on a calibrated precision digital scale (Filizola PL 200, Filizola®, São Paulo, Brasil) with precision for the nearest 100 grams. Body mass index (BMI) was determined by calculating the ratio of body mass in kilograms to height in square meters.

The gynecologic examination included an examination of the breasts, abdomen, and pelvic organs. The pelvic examination was performed with the patient lying supine on an office examination table with the knees flexed, and with the feet in supporting stirrups. The vagina and cervix were inspected for lesions. Pap Smears were taken for cervical or vaginal cytology with a spatula, and a sample from the endocervical canal was taken with a brush. The material was fixed immediately after obtaining the sample in order to avoid air-drying artifact.

The bimanual examination was performed with the aid of lubricating jelly. The examiner placed two fingers in the vagina and used the opposite hand to palpate the lower abdomen. In some cases, a single digit was placed in the vagina. The examiner palpated the vagina, cervix, uterus, adnexa, and surrounding structures by elevating structures with the vaginal hand and palpating in a downward fashion with the abdominal hand. The posterior cul-de-sac and utero-sacral ligaments were checked for nodularity and masses.

LABORATORY PARAMETERS

Gynecological cancer screening

Mammography screening: all views from the mammogram pairs were evaluated by the radiologists of Hospital das Clínicas. The BIRADS Classification was used for reducing confusion in breast imaging interpretations. If necessary, breast ultrasound was performed for final diagnosis.

Pap smears: the conventional Pap smear was done. The samples were smeared directly onto a microscope slide after collection and evaluated by a pathologist. The classification was described as class I, II, III, IV, and V.

Ultrasound: The participants were placed on the examination table in dorsal decubitus. The evaluation was performed with the HDI-5000 Philips Sono System (Philips Medical Systems, Andover, MA, USA). We followed the parameters: normal uterus volume < 60 cm³, enhanced volume > 60 cm³; endometrial echo thickness: the cut-off of normality was 5 mm. The cut-off of the ovarian volume normality was 3 cm³.

The classic fecal occult blood test was used to check stool samples for hidden blood. Negative exams were defined as normal.

Metabolic screening

The blood was collected for laboratory metabolic analyses: fasting glucose, cholesterol total, fractions and triglycerides, urea, creatinine, thyroid-stimulating hormone (TSH), free thyroid hormone (FT4), testosterone, and androstenedione.

The values for abnormally high levels of fast glucose, LDL-cholesterol, triglycerides, urea, creatinine, testosterone, and androstenedione were >100 mg/dl,
> 130 mg/dl, 150 mg/dl, > 50mg/dl, > 1.30mg/dl, >70 mg/dl, and > 2.8 mg/ml, respectively.

The diagnosis of diabetes mellitus was made when fast glucose was over 125 mg/dl. The low level of HDL-cholesterol was defined at <50 mg/dl. Hypothyroidism was defined when TSH > 4.5 mUI/L and FT4 <0.6 ng/d (if the patients had symptoms).

**Statistical analysis**

The variables were analyzed, and the representation of data was done by using mean and standard deviation. We used the chi-square test to assess the relationship among the categorical proportion variables mentioned above; p-values less than 0.05 were considered statistically significant. The statistical method of Kruskal-Wallis was used for quantitative variables. After that, Dunn’s Multiple Comparison Test was applied for evaluating the differences between the two groups. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, SPSS Inc, Chicago, II, US), version 16.01.

**RESULTS**

**Demographic data**

The age of the 1001 women selected ranged from 65 to 98 years (68.56 ± 4.47 years). The composition of the patients seems to mirror the geographic distribution of the Brazilian population: 23.3%, 14.1%, 27.5%, 17.3%, and 17.8%, respectively, were from the North, Northeast, Midwest, Southeast, and South of Brasil. Also, approximately 90% of the patients were of low-level socioeconomic status, and around 10% were of medium socioeconomic status. All variables were similar among the groups (formal education; sexual partner; religion; skin color; socioeconomic status; alcohol consumption; frequency of alcohol consumption; frequency of physical exercise). The age of natural menopause was similar among groups (Table 1).

**Metabolic screening data**

Table 1 summarizes the BMI, height, and systemic arterial pressure of participants in this study. In the assessment of BMI in different ages, groups were observed that with the increasing of age there is a decrease in BMI, with statistically significant difference (p= 0.001), mainly in the patients with obesity and morbidly obesity over 75 years compared to ones with less 69 years. The height of the patients ranged from 138 cm to 173 cm, with a reduction in stature with a significant statistical difference with the increase of age (p<0.001), mainly in the group over 75 years compared to the one between 65 and 69 years. Regardless of the group, high systemic arterial blood pressure was detected in most women (85.45%), but there was no difference among the age groups (p=0.15).

| TABLE 1. NATURAL MENOPAUSE AND PHYSICAL DATA FROM 1001 BRAZILIAN WOMEN PER AGE GROUP |
|---------------------------------|------------------|------------------|------------------|------------------|
| Age Groups  | 65-69 years (n = 661) | 70-74 years (n = 233) | ≥ 75 years (n = 107) | p |
| Menopause*  |                                |                                |                                | 0.59 |
| Early       | 97 (14.67%)                  | 31 (13.30%)                  | 10 (9.35%)                  | 0.59 |
| Adequate    | 510 (77.16%)                 | 193 (82.83)                  | 91 (85.05%)                 | <0.001|
| Late        | 54 (8.17%)                   | 9 (3.86%)                    | 3 (2.81%)                   | 0.001 |
| Body mass index (kg/m²)*     |                                |                                |                                | 0.001 |
| ≥20         | 24 (3.63%)                   | 8 (3.43%)                    | 9 (8.41%)                   | 0.001 |
| 20-25       | 159 (24.05%)                 | 66 (28.33%)                  | 31 (28.97%)                 | <0.001|
| 26-30       | 241 (36.46%)                 | 106 (45.49%)                 | 48 (44.86%)                 | <0.001|
| 31-35       | 161 (24.36%)                 | 43 (18.45%)                  | 15 (14.02%)                 | 0.15  |
| ≥35         | 76 (11.50%)                  | 10 (4.29%)                   | 4 (3.74%)                   | 0.15  |
| Height **    |                                |                                |                                | <0.001|
| Means (cm)  | 1.54 ± 0.05                  | 1.53 ± 0.06                  | 1.52 ± 0.05                  | <0.001|
| Blood pressure (maximum and/or minimum, mmHg)*  |                                |                                |                                | <0.001|
| Normal (<140 and <90)         | 106 (16.04%)                 | 28 (12.02%)                  | 11 (10.28%)                 | 0.15  |
| High (≥ 140 and/or ≥ 90)       | 555 (83.96%)                 | 205 (87.98%)                 | 96 (89.72%)                 | <0.001|

*Chi-square test, p<0.001 when ≥75 year-group was compared to the 65-69 year- group; *Kruskal-wallis followed by Dunn test (comparison between the 65-69 year and over 75 years groups).
The laboratory data are summarized in Table 2. There is no difference among groups in relation to the following variables: fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, VDLR-cholesterol, triglycerides, TSH, free T4, total testosterone, and androsterone blood levels. The total testosterone level has high only on 2 patients (values: 111ng/dL and 79ng/dL), and androstenedione levels were high on one patient (127ng/dL). High values of TSH (mUI/ml) and low values of free T4 (ng/dl) were detected in women with clinical symptoms of thyroid dysfunction. Creatinine and urea blood levels of patients over 75 years was significantly superior to the 65-69 years group, respectively, p=0.009 and p=0.085.

**GYNECOLOGICAL CANCER SCREENING**

**Gynecological examination**

The percentage of patients with normal gynecologic examination, breast, abdomen, external genital organs, vagina and internal genital organs, was, respectively, 82.57%, 95.67%, 32.33%, 26.33%, and 33.45%. Most women had abnormal characteristics with atrophic external and internal genital organs. Also, 17.43% of women with abnormal breast examination presented nodules or papillary discharge. There was no difference among the age groups.

**Colon and cervical screening**

The positive and negative results of fecal occult blood in 313 women were respectively 17.57% and 82.43%. There was no difference among age groups. Vaginal and cervical oncological cytology results of 818 patients were: a) category I - n=350 (42.79%); b) category II – n=464 (56.72%); c) category III – 4 (0.49 %); there was no detection of category IV or V in our study. There was no difference among age groups.

**OVARIAN AND ENDOMETRIAL CANCER SCREENING**

**Pelvic sonography data**

Pelvic ultrasonography was performed in 546 women and showed 94.14% and 5.86%, respectively, normal and abnormal values in general. Normal and high volume uterus were detected respectively in 83.47% and 16.53% of the women. In the comparison between the groups, low values of volume were detected in patients over 75 years old compared to the other groups (p=0.03). Endometrial echo thickness was normal in 93.86% of participants (<5mm) and abnormal in 6.14% (> 5.1 mm). The statistical analysis did not detect significant differences among the groups. Ovarian volume was assessed in 173 women; 95.96% and 4.04%, respectively, presented normal and abnormal volume. The ultrasound did not detect the ovarian image in 374 patients. There was no difference between age groups. The abnormal values of ultrasonography were forwarded to a cancer center for final diagnosis.

**Mammography data**

The mammography evaluation was done using the BI-RADS method in 852 women: 87.80% and 12.21% of patients presented, respectively, BI-RADS 1/2 and BI-RADS 3/4. The patients with suspected breast
cancer image were forwarded to the mastology sector for final diagnosis.

**DISCUSSION**

The elderly demographic has increased in most countries of the world, and one of the main objectives of public health programs is to know the conditions of health and lifestyle that can be controlled in the population to improve the quality of life of elderly individuals. Geriatric women have been studied by many researchers, and this retrospective study conducted at the gynecological geriatric outpatient office at Hospital das Clínicas, College of Medicine University of São Paulo by gynecologists had the opportunity to evaluate 1001 elderly women (aged from 65 to 98 years old) from different Brazilian regions. In general, the data analyzed presented similar features in postmenopausal women (age<65 years)\textsuperscript{5-7}. Apparently, health conditions (metabolic and gynecological cancer screening) of geriatric women are not worse than those during the postmenopausal period. Also, our data suggest that the great reduction in BMI and stature is more frequent in the group over 75 years.

In a review study by Palacios\textsuperscript{4,6,7-10,16} et al and others\textsuperscript{5-7}, age is one factor that increases the risk of cancer and metabolic disturbance. However, obesity, genetic inheritance, and other diseases, such as polycystic ovarian syndrome and diabetes mellitus may play an important role in the development of metabolic disturbances and cancer\textsuperscript{4,6,7-10,16}. The detection of BMI reduction in women over 75 years may be valuable information regarding the health condition, but another possibility is that obesity may increase the morbidity and mortality in other age groups (< 75 years), which may be why the percentage of obese women was low over 75 years. This is important data to create new strategies of public and private health programs targeted at individuals younger than 75 years. Perhaps, it could increase the life expectancy in the female population\textsuperscript{4,7,10-12,15}.

Excess weight is considered a problem for the health and quality of life. It is important to emphasize that most of these factors can be prevented with recommendations for a better lifestyle, including regular physical and intellectual activity, correct nutritional approaches, and others\textsuperscript{5,6,12,16}. Excess weight and arterial hypertension in climacteric and postmenopausal women are considered major risks for cardiovascular diseases and metabolic syndrome, and preventive care is recommended for this group of women to reduce morbidity and mortality\textsuperscript{5-7,9,17-19}. Also, it partially explains why high levels of systemic arterial blood pressure are also detected in women over 65 years. In addition, this disease needs a unique health care program for this specific population to prevent and reduce morbidity and mortality\textsuperscript{5,18-21}.

The atrophy of the genital system is frequently found in most patients after menopause. It is related to a hypoestrogenism state\textsuperscript{5,6,9,16,22}. However, breast papillary discharge is not common after menopause\textsuperscript{5,6,9,16,22}. We found this in approximately 17% of cases. One possibility for this change is the atrophy of mammary ducts\textsuperscript{5,6,22}. However, those women need to maintain an evaluation for warding off other conditions or diseases.

Regardless of the age, the metabolic results of patients did not show great concerns regarding the lipid profile. However, carbohydrate metabolism is a problem due to insulin resistance and glucose intolerance in many women over 65 years\textsuperscript{5,6,9,21,23}. This seems to be more of an individual problem than an age influence\textsuperscript{5,6,9,21,23}. Also, this glucose profile may be no worse than that reported by postmenopausal women\textsuperscript{5,6}. Androgen production is similar among the age groups, and it reflects the ovarian and, mainly, adrenal production. Previous studies by our group found that 5-10 years after menopause the ovaries are no longer relevant for sex steroid synthesis\textsuperscript{24}. Therefore, androgen levels can be used to evaluate adrenal metabolism.

The investigation of occult blood in feces was positive in more than 17% of participants of our study. It is a health concern because this exam is used for screening gastrointestinal tract diseases\textsuperscript{5,9}. This test has both merits and weaknesses. Testing does uncover subclinical colorectal cancer, often at a relatively early stage, but whether this actually improves the prognosis remains to be proven. Benign polyps are also detected, which is a limitation of this exam. The test sensitivity for malignancy varies from good to moderate, but it is poor for polyps. Specificity is usually around 97%-98%, yet the predictive value of a positive test for cancer is only about 10%\textsuperscript{25}. However, it is cheaper and less complex than a colonoscopy\textsuperscript{25}. Colorectal cancer represents the third most common malignancy in high-income countries, where it also ranks third in leading causes of cancer deaths\textsuperscript{26}. Although it is not a gynecological cancer, we included this exam due to its prevalence and importance for public health.
Women diagnosed with early-stage ovarian cancer may have a better prognosis. Accordingly, it is imperative to detect and diagnose the disease as early as possible in its development. Unfortunately, there are no biomarkers or ultrasound exams with good accuracy for screening this cancer in early stage\textsuperscript{27}. Therefore, the ovarian volume can be used as a way to identify patients with risk of this type of cancer through a physical examination or pelvic ultrasonography\textsuperscript{27}. Regardless of age, we found this change in a small number of patients in our study. However, it is a great concern to the high morbidity and mortality of this disease\textsuperscript{27}. Endometrial cancer is more frequent than ovarian, but the most important marker is abnormal uterine bleeding\textsuperscript{28}, which goes directly to the other sector of our outpatient system in Hospital das Clínicas. It is a limitation of our ultrasonographic results, which found around 6\% of our patients had endometrial echo over 5.1 mm. This exam in asymptomatic women will result in unnecessary additional biopsies because of false-positive test results, such as polyps or other affections\textsuperscript{28}. However, being overweight or obese, adult weight gain, and diabetes are associated with an increased risk of endometrial cancer\textsuperscript{28}. Regardless of age, we found a high number of patients with carbohydrate metabolism disturbance. It is a public health concern that requires special care by public programs to reduce this affection on women over 65 years. Also, those diseases or affections interfere with the quality of life\textsuperscript{9,11,29}.

The mammography showed 12.21\% of patients had abnormal BIRADS classification. This is important because gynecological cancer causes high rates of mortality and morbidity among young and old women\textsuperscript{1,18,30,31}. Our study is limited because the final cancer diagnosis is performed in the breast section of our institution to be sure that this high rate of abnormal BIRADS correspondent to a true disease. However, it is a alert due to the risk of breast cancer related to a high score of BIRADS\textsuperscript{1,18,30,31}.

**CONCLUSION**

The fact that the female population over 65 years has increased longevity makes this study interesting because we found a metabolic and gynecological cancer profile of those patients. Our data may help public programs for diagnosis, treatment, and advice for a better lifestyle to reduce morbidity and mortality with this specific population. Finally, our data suggest that a great reduction in BMI and stature is more frequent in the group over 75 years. Also, systemic arterial hypertension and carbohydrate disturbances are frequent morbidities in women over 65 years.

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RESUMO

**OBJETIVO:** O objetivo deste trabalho foi estudar retrospectivamente alguns dados clínicos, laboratoriais e imagens de um grupo de idosas brasileiras.

**MÉTODO:** Estudo observacional retrospectivo realizado com inclusão de 1.001 mulheres brasileiras atendidas no ambulatório de ginecologia de nossa instituição. Foram analisados: a idade dos pacientes na primeira consulta clínica e a idade na menopausa natural; alguns achados clínicos durante um exame ginecológico; resultados de análises laboratoriais. Considerou-se a relação dessas variáveis com o grupo da idade das mulheres. O teste do qui-quadrado foi utilizado para avaliar os dados e para algumas variáveis, Kruskal-Wallis ou Anova.

**RESULTADOS:** A avaliação do IMC e da estatura nas diferentes faixas etárias das mulheres mostrou que, com o aumento da idade, há diminuição do IMC e da estatura (p=0.001). Nível anormal de pressão arterial estava presente em 85,45\%. De acordo com o grupo de idade, as medidas laboratoriais foram avaliadas pelo método estatístico Kruskal-Wallis, e a Anova mostrou diferença estatisticamente significante apenas no valor da creatinina, com pequeno aumento com a idade. A ultrasonografia pélvica foi alterada com espessura endometrial normal (>5 mm) em 29 (6,14\%), mas sem diferença estatística significativa com os grupos de idade, e os ovários mostraram sete (4,04\%) com volume anormal (>6,1). Mamografia anormal (BIRads 3 ou 4) foi observada em 104 pacientes (12,21\%).

**CONCLUSÕES:** O estudo conclui que, com o aumento da idade, há redução do IMC e da estatura. A hipertensão é morbidade frequente. Os dados laboratoriais e a avaliação de imagens deste estudo são importantes para aumentar o conjunto de informações sobre mulheres idosas e talvez para melhorar a assistência à saúde.

**PALAVRAS-CHAVE:** Idoso. Mulheres. Menopausa. Índice de Massa Corporal. Neoplasias dos genitais femininos.
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