Clinic-based Case-control Study of the Association between Body Mass Index and Endometrial Cancer in Puerto Rican Women

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Background: Obesity is an established risk factor for endometrial cancer (EC). This association, however, has not been studied in Puerto Rico, where overweight and obesity have reached epidemic levels (38% and 26%, respectively).

Methods: A hospital based case-control study was designed to evaluate the association between body mass index (BMI) and EC in women older than 21 years of age. Seventy-four prevalent EC cases diagnosed between January 2004 and August 2007 and a random sample of 88 healthy controls were recruited from gynecology clinics of the Medical Sciences Campus, University of Puerto Rico. Demographic, reproductive, lifestyle, and clinical information was obtained via structured telephone interviews and medical chart review. Unconditional logistic regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: A significant trend was observed between BMI and EC in bivariate analyses (p<0.05). Results showed that overweight (25.0 > BMI < 29.9 kg/m²) (OR=4.4, 95% CI=1.6-12.3) and obese (BMI ≥ 30 kg/m²) (OR=9.9, 95% CI=3.6-26.9) women were more likely to have EC when compared to non-obese women. In multivariate analysis, obese women had a 4-fold greater possibility of EC (OR=4.1; 95% CI: 1.8-8.6) than non-obese women, after adjusting for age, education, employment status, hypertension and diabetes diagnosis, use of oral contraceptives and consumption of poultry.

Conclusion: Consistent with previous studies worldwide, adult obesity was a strong predictor for EC in this sample of Puerto Rican women. Thus, cancer control strategies should promote weight reduction strategies to reduce disease risk in this population. [PR Health Sci J 2010;3:272-278]

Key words: Endometrial cancer, Obesity, Puerto Rico

In 2002, there were 198,783 endometrial cancer cases worldwide, 69% of which were diagnosed in developed regions (1). In Puerto Rico, endometrial cancer is the leading gynecologic cancer, and the third most common type of cancer among women (6.8% of all cancers in 2003), as well as the 8th leading cause of cancer death in this group (3.7% of all cancer deaths) (2-3). From 1999-2003, age-standardized incidence and mortality rates from endometrial cancer in Puerto Rico were 18.5 and 5.1 per 100,000, respectively (4). Symptoms of the disease include abnormal uterine bleeding, vaginal discharge, lower abdominal pain and pelvic cramping, among others (5-6).

Identified risk factors for endometrial cancer include late menopause, unopposed estrogen therapy, nulliparity, physical inactivity, diabetes mellitus and hypertension; most of which are related to western lifestyles (7-9). Body mass index (BMI) has also been shown to increase the risk for endometrial cancer; the evidence for the adverse effects of overall adiposity on the endometrium is convincing (10-11). Obesity has been described as an important risk factor for endometrial cancer, albeit not studied in Puerto Rico, where overweight and obesity have increased in the last decades (12-13) and have reached epidemic levels (38% and 26%, respectively) (14). This increase is consistent with increases in the incidence rates of endometrial cancer observed in Puerto Rico since the 1990’s (period 1992-2003=2.8% per year) (4).
Knowledge of the epidemiology of endometrial cancer in Puerto Rico is limited. Descriptive studies have shown a historical and current lower incidence of the disease among women living in Puerto Rico as compared to those in the United States (US), particularly non-Hispanic whites (NHW) and Puerto Ricans living in the US (4, 15-16). Yet, they share a similar risk of death than NHW (4). Despite these racial/ethnic differences, few studies (17) about factors associated with endometrial cancer have been conducted among Hispanics. Thus far, no epidemiologic study in Puerto Rico has investigated risk factors associated with endometrial cancer in our population. The present case-control study aimed to study whether obesity is associated with endometrial cancer among women in Puerto Rico. We hypothesized that obese women would be more likely to have a diagnosis of endometrial cancer than non-obese women, after adjusting for potential confounders and covariates. Results from our study will provide a venue for advancing epidemiologic knowledge in this field.

**Materials and Methods**

**Study design and study population**

A clinic-based case-control study of endometrial cancer was conducted in two gynecology clinics of the Medical Sciences Campus, University of Puerto Rico. Seventy-four prevalent endometrial cancer cases diagnosed between January 2004 and August 2007, and a random sample of 88 healthy controls were recruited. Cases were identified from a review of endometrial cancer cases treated at the hospital, while controls were randomly selected from a list of patients (21 years and older), seeking medical services at the same clinics. Selection procedure was performed using frequency matching of cases and controls by age (± 5 years). To be eligible, cases must have had a histological confirmation, no previous cancer diagnosis and a valid telephone number. Potential controls must have had an intact uterus, no previous cancer diagnosis, a valid telephone number, and no current pregnancy.

In more detail, from January 2004 to August 2007, 178 potential cases were identified; 14 were deceased, 17 could not be reached at the phone number provided and 57 changed their telephone numbers or had telephones out of service. Telephone interviews were performed for 74 out of 80 eligible and contacted cases, for a response rate of 92.5 percent among those contacted. A total of 195 potential controls were identified; 43 were not eligible, 17 could not be reached by the phone number provided and 66 changed telephone numbers or had telephones out of service. A total of 92 eligible controls were contacted for possible participation, 4 persons declined to be interviewed, and 88 were enrolled in the study. The response rate for contacted eligible controls was 95.7 %. Thus, the final study sample included 74 cases and 88 controls. The study protocol was approved by the Institutional Review Board of the Medical Sciences Campus, University of Puerto Rico.

**Data collection**

After oral consent was obtained, a structured telephone interview was conducted to obtain information on demographic (age, education, marital status, and employment status), reproductive (number of pregnancies, menopausal status, oral contraceptive use, and hormone therapy use), clinical (self-reported information on height and weight, diabetes mellitus, hypertension and cancer history among first degree relatives) and lifestyle characteristics (alcohol consumption, smoking behavior, diet, and physical activity) of cases and controls. Time of reference for cases and controls was defined as a year prior to diagnosis and a year prior to interview, respectively. Medical charts were also reviewed to collect additional information on weight and height. The chart review also provided pathology information on histology, stage and grade of the tumor for endometrial cancer cases. The International Federation for Obstetrics and Gynecology (FIGO) surgical staging criteria were used to assign the stage of the tumors (18). Information regarding treatment received was also collected.

**Study variables**

Demographic characteristics included age in years (≤ 50, 51-60 and > 60), education level (high school or less, college or above), and marital status (unmarried, married/cohabitating, and separated/divorced/widowed). Age was also evaluated as a continuous variable. Reproductive variables included self-reported number of pregnancies (0-1, 2-3, ≥ 4), lifetime use of oral contraceptives and hormone therapy (yes, no), age at menarche, menopausal status (premenopause, postmenopause) and age at menopause. Menopause was defined as cessation of the menstrual cycle for 12 months or longer, excluding those periods caused by pregnancy or breastfeeding.

Pathological characteristics of cases included histological type of the tumor (endometriod, serous, mixed, clear cell), grade (1, 2, 3, not otherwise specified [NOS]), stage (I, II, III, IV) and treatment (surgery, chemotherapy, radiotherapy, combined treatment). Medical history included self-reported history of physician diagnosed diabetes and hypertension (yes, no), as well as having had a first degree relative with cancer (yes, no). Information on self-reported weight and height was used to calculate BMI as weight in kilograms divided by the square of the height in meters (kg/m2) and categorized as under/normal weight (BMI≤24.9 kg/m2), overweight (25.0 ≥ BMI < 29.9 kg/m2) and obese (BMI ≥30.0 kg/m2).

Among lifestyle characteristics, persons who had consumed at least 100 cigarettes in their lifetime were considered smokers (yes, no). A person who had consumed at least one cocktail or any alcoholic beverage in a month during the last year was considered a regular alcohol consumer (yes, no). Physical activity was based on six questions about physical activity during the previous year. Participants were asked to indicate their frequency of vigorous, moderate, and light physical activity during a typical week in the last year that lasted at least 10 minutes. Vigorous...
activity was defined as physical activity that caused increases in breathing, heart rate, or sweating such as: heavy lifting, digging, aerobics or fast bicycling. Moderate activity was defined as activities that take moderate physical effort and cause breathing to be somewhat harder than normal such as: carrying light loads, bicycling at a regular pace; walking was excluded. Light physical activity or walking was defined as walking to travel from place to place, and any other walking that participants might do solely for recreation, sport, exercise or leisure. Of each type of physical activity, duration was asked and assigned mean metabolic equivalent (MET) values [multiples of MET (kcal kg \(^{-1}\) h \(^{-1}\))] based on the Physical Activity Compendium (19).

With this information, we categorized individuals as less active (< 600 MET/min per week), active (600-1,499 MET/min per week) and very active (≥ 1,500 MET/min per week). Nutritional information included dietary consumption of fruits, fruit juice, vegetables, fried food, eggs, red meats, poultry, dairy products (0-1, 2-3, ≥ 4 times a week), and consumption of vitamins and supplements such as multivitamins, vitamin C, and calcium (<3 or ≥ 3 times a week).

Statistical analysis

Central tendency and dispersion summary statistics were used to describe the epidemiologic profile of participants. Contingency tables were used to determine the magnitude of the association between endometrial cancer and covariates. To assess these comparisons t-tests, Mann-Whitney’s test, and chi-square statistics for contingency tables were conducted to determine associations between endometrial cancer and covariates. All tests were considered two-sided. Tests for trend were performed using the Chi-square test for linearity. We estimated the odds of endometrial cancer associated with obesity and other risk factors by calculating odds ratios and 95% confidence intervals derived from unconditional logistic regression modeling, while adjusting for covariates. Potential confounders included risk factors reported in the literature and factors associated to endometrial cancer in bivariate analysis (p<0.05). Factors that altered obesity and endometrial cancer odds estimates by 5 percent were considered as confounders and adjusted for in the multivariate model. A multivariate unconditional logistic regression model was used to estimate the association between endometrial cancer and BMI, while adjusting for potential confounding variables. The likelihood ratio test was used to evaluate interaction between variables before adjusting for potential confounders. Statistical analyses were conducted using SPSS 13.0 (20).

Results

Pathological characteristics of cases

A higher proportion of endometrial cancer cases (n=69) had endometrioid type tumors (93.2%). Regarding the tumor grade, 64.9% were classified as grade 1 (n=48), 21.6% as grade 2 (n= 16), 10.8% as grade 3 (n=8), and 2.7% as NOS (n=2). Most cases had a Stage I classification (70.3%) at the time of diagnosis, while 21.6% were classified as Stage II, 5.4% in Stage III, and 2.7% in Stage IV. A total of 67.6% of all cancer cases received a hysterectomy as their first course of cancer-directed therapy. Hysterectomy plus radiotherapy was the second (17.6%) most common treatment received by endometrial cancer cases (Table 1).

Table 1. Pathologic characteristics of the tumor of cases, San Juan, Puerto Rico: 2004-2007 (n=74).

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>69</td>
<td>93.24</td>
</tr>
<tr>
<td>Other*</td>
<td>5</td>
<td>6.76</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>64.86</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>21.62</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>10.81</td>
</tr>
<tr>
<td>NOS†</td>
<td>2</td>
<td>2.70</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>52</td>
<td>70.27</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
<td>21.62</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>5.41</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2.70</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>50</td>
<td>67.57</td>
</tr>
<tr>
<td>Surgery + Radiotherapy</td>
<td>13</td>
<td>17.57</td>
</tr>
<tr>
<td>Other‡</td>
<td>11</td>
<td>14.86</td>
</tr>
</tbody>
</table>

*2 patients had serous, 2 patients mixed, and 1 patient clear cell histology
†Not otherwise specified
‡3 patients received surgery and chemotherapy; 1 patient chemotherapy; and 1 patient chemotherapy and radiotherapy

Bivariate analysis

Table 2 compares the demographic, lifestyle and reproductive characteristics of cases and controls. Mean age was slightly higher in cases (56.3 ± 12.1 years) as compared to controls (51.3 ± 11.6 years). According to the Mann Whitney non-parametric test for medians, cases had a significantly higher median age (59.0 years) than controls (52.5 years) (p=0.007). A higher proportion of cases than controls were 60 years of age or older (40.5% vs. 19.3%, respectively), and had less than high-school education (62.2% vs. 14.8%, respectively). In addition, a lower proportion of cases (27.0%) as compared to controls (69.3%) was employed (p<0.05) at time of reference. There were no significant differences between cases and controls with regard to marital status, number of pregnancies, menopausal status, age at menarche, age at menopause, familiar history of cancer, physical activity or smoking. However, a higher proportion of cases than controls had a previous diagnosis of diabetes mellitus (26.0% cases vs 11.4% controls) and hypertension (48.6% cases vs 25.0% controls), while a lower proportion of cases than controls ever used oral contraceptives (32.3% vs. 55.7%, respectively) and hormone therapy (6.9% cases vs 29.6% controls).
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controls). Among lifestyle practices, a lower proportion of cases (19.2%) used alcohol regularly as compared to controls (38.6%), and a lower proportion of cases were very active physically (34.7%) as compared controls (48.9%) (p<0.05).

In terms of dietary habits, a lower proportion of cases ate vegetables (29.2% cases vs 51.1% controls), poultry (41.7% cases vs 53.4% controls) and dairy products (56.9% cases vs 86.2% controls) four times a week or more, whereas a higher proportion ate fried foods as compared to controls (20.8% vs 9.1%, respectively). A lower proportion of cases than controls consumed multivitamins (34.7% cases vs 53.4% controls) and calcium (24.3% cases vs 45.5% controls) three or more times a week. No differences were observed in the consumption of fruit juice, fruits, eggs, meat, and vitamin C (p>0.05) (data not shown).

Table 3 compares the anthropometric characteristics of cases and controls. There were no statistical significant differences in height between cases and controls (p>.05). Median weight was significantly higher in cases compared to controls (173.0 lbs cases vs 150.0 lbs controls) (p <0.01). Median BMI was significantly higher among endometrial cancer cases (31.7 kg/m^2) than among controls (26.5 kg/m^2)(p < 0.01). In addition, a significant trend was observed between BMI and endometrial cancer in bivariate analyses (p<0.05). Overweight (25.0>BMI ≤29.9 kg/m^2) (OR=4.4, 95% CI=1.6-12.3) and obese (BMI ≥ 30 kg/m^2) (OR=9.9, 95% CI=3.6-26.9) women were more likely to have endometrial cancer as compared to controls.

Multivariate analysis

Given the small number of cases (n=6) with an underweight/normal BMI, the primary risk factor under study was dichotomized as being obese (BMI ≥ 30 kg/m^2) or not being obese (BMI< 30 kg/m^2) on all multivariate analyses. Of all factors studied, age,
education, employment status, poultry consumption, oral contraceptive use, diabetes and hypertension diagnoses were found to confound the association of obesity with endometrial cancer. Therefore, these factors were adjusted for in the unconditional multiple logistic regression model. No significant interaction terms were observed in the model (p-value=0.11).

Results from the unconditional multiple logistic model showed that women with a BMI ≥ 30 kg/m² had four-fold greater possibility of having a diagnosis of endometrial cancer (OR=4.1; 95% CI: 2.8-22.7). The highest OR of endometrial cancer was found among these women (95% CI: 1.8-9.9). The OR for non-obese women (BMI < 30 kg/m²) was 1.00 (95% CI: 0.5-2.2). These findings are consistent with other studies conducted in Mexico, Sweden, China, Japan, the United States, and Italy (22-24, 17, 25-29).

In China, Hong et al. found that women with a BMI > 25.7 kg/m² had three-fold greater risk of having endometrial cancer, compared to non-obese women. This association was observed after adjusting for age, educational level, employment status, diagnosis of diabetes mellitus and hypertension, oral contraceptive use, and poultry consumption.

One of the few studies in Hispanics, conducted among Mexicans, showed that a BMI > 30 kg/m² increased endometrial cancer risk 3.3 times (OR=3.3, 95% CI: 2.4-4.2) (30). In Hawaii, Goodman et al., found that women with BMI > 21.0 kg/m² had 4.3 odds of having endometrial cancer compared to non-obese women. This association was observed after adjusting for age, educational level, employment status, diagnosis of diabetes mellitus and hypertension, oral contraceptive use, and poultry consumption.

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Discussion

To our knowledge, this is the first analytical epidemiologic study of endometrial cancer in Puerto Rico and one of few (17) to be conducted on a homogenous population of Hispanic origin. Given the high burden of this gynecologic malignancy among Puerto Rican women and Hispanics in general, results of our study are important to develop endometrial cancer prevention and control strategies for Hispanic populations. Even though the association between BMI and endometrial cancer is well established and has been studied in different countries worldwide, studies in this area are limited among Hispanics and non-existent for Puerto Ricans. Moreover, there is no information of the magnitude of this association in the Island, which may be useful in creating public policy and campaigns to promote obesity prevention (21). Our study is innovative as it is the first evidence of an association between obesity and endometrial cancer in Puerto Rico. A significant trend was observed in bivariate analysis, where the odds of endometrial cancer increased by BMI categories. In addition, a covariate adjusted association was observed between obesity and endometrial cancer. Specifically, obese women had four-fold greater possibility of having endometrial cancer, compared to non-obese women. This association was observed after adjusting for age, educational level, employment status, diagnosis of diabetes mellitus and hypertension, oral contraceptive use, and poultry consumption.

Our findings are consistent with other studies conducted in Mexico, Sweden, China, Japan, the United States, and Italy (22-24, 17, 25-29). In China, Hong et al. found that women with a BMI > 25.7 kg/m² had three-fold greater (OR=3.3, 95% CI: 2.4-4.2) possibility of having endometrial cancer, when compared to women with a BMI ≤ 21.0 kg/m². Similarly, in the United States, Thretham et al. reported that having a BMI > 29.1 kg/m² increased endometrial cancer risk 3.3 times (OR=3.3, 95% CI: 2.4-4.2) (30). In Hawaii, Goodman et al., found that women with BMI > 27.3 kg/m² had 4.3 odds of having endometrial cancer compared to women with BMI < 21.0 kg/m². One of the few studies in Hispanics, conducted among Mexicans, showed that a BMI > 30 kg/m² increased endometrial cancer risk 2.3 times the odds of having endometrial cancer (95% CI: 1.1-4.5) and by eight-fold the odds of endometrial cancer in women diagnosed with diabetes and obesity (95% CI: 2.8-22.7).

As suggested by previous investigations, our study supports the hypothesis that obesity is a strong predictor of endometrial cancer. It has been hypothesized that this association is due to the excess endogenous estrogen found in adipose tissue (31-32). There are various mechanisms that could be potentially involved in the development of endometrial cancer among obese women. It has been proposed that obese women tend to have higher
levels of circulating estrogen through an increased conversion of circulating androgens into estrone (6). In pre-menopausal women, obesity can cause insulin resistance, anovulatory menstrual cycles, and progesterone deficiency (33-34, 7). In post-menopausal women, the mechanism for endometrial cancer can be explained through the peripheral conversion of androgens to estrogens caused by an increase in peripheral fat stored. This hormonal alteration stimulates the proliferation of endometrial cells by inhibiting apoptosis, thus promoting angiogenesis (33).

Given increasing trends of overweight and obesity among Puerto Rican women (14), our results might help explain increasing trends of endometrial cancer in Puerto Rico (4).

An unexpected finding of our study was that contrary to evidence in other populations (35-37), reproductive characteristics were not found to be associated to endometrial cancer in bivariate analysis. This finding could suggest that in Puerto Rico, reproductive risk factors do not play such an important role in endometrial cancer risk, as occurs in other populations. Meanwhile, although self-reported diabetes mellitus and hypertension were significantly associated to endometrial cancer, other known risk factors for endometrial cancer (35-36, 38-39), such as infertility and family history of endometrial cancer, were not associated with endometrial cancer in bivariate analysis. This finding suggests that in Puerto Rico, important risk factors for this malignancy aremodifiable, such as obesity, or that the sample size of our study was not suitable to study these associations. Future studies should evaluate the impact of these covariates on endometrial cancer risk in Puerto Rico.

While this study is strengthened by a high response rate among contacted individuals (92.5% for cases and 95.7% for controls), not all eligible individuals could be contacted because of missing contact information and/or deceased status. Among other study limitations, our study was based on self-reported information on weight and height, which were used to calculate BMI. Nonetheless, it is important to mention that self-reported weight had a high correlation with the weight recorded in the medical chart (for cases: r=0.95; p<0.01 and for controls: r=0.90; p=0.01). Another limitation was that controls were different to cases in socio-demographic characteristics, which can be an indication of selection bias. The final multiple logistic regression model took into account such differences by adjusting for these variables. In addition, as inherent in case-control study designs, we cannot exclude the possibility of recall bias given that this study collected data on past diet, physical activity and hormone use practices, and that controls might have had a greater difficulty recalling past history than cases.

Despite the previous limitations, this epidemiologic study establishes for the first time that obesity is a risk factor for endometrial cancer in Puerto Rican women and contributes not only to the better understanding of the disease among Hispanics, but to a better understanding of the impact of overweight and obesity on endometrial cancer risk in this population. Even though case-control studies are not capable of establishing cause and effect relationships, the consistency of this association with previous studies, the strength of the association, and the biological plausibility support a causal relationship between obesity and endometrial cancer in this population (40). Future studies should focus on establishing other risk factors for endometrial cancer risk in Puerto Rico. Given the high burden of overweight and obesity in Puerto Rican women (14), it should be a priority to create educative campaigns to avoid obesity and promote healthier lifestyles in order to prevent endometrial cancer among this population. Education should be focused towards young women, especially for those overweight and obese as this carcinoma can have adverse effects during the reproductive stage, and may potentially negatively impact their ability to conceive. Likewise, it is important to educate women regarding endometrial cancer symptoms and create awareness of the importance of approaching their physician in the event that these symptoms arise.

Resumen

La obesidad es un factor de riesgo para el cáncer de endometrio. Sin embargo, esta asociación no ha sido estudiada en Puerto Rico, donde la prevalencia de sobre peso y obesidad han alcanzado niveles epidémicos (38% y 26%, respectivamente). Para evaluar la asociación entre el índice de masa corporal (IMC) y el cáncer de endometrio en mujeres mayores de 21 años, se diseñó un estudio caso control hospitalario. Se reclutaron 74 casos prevalentes de cáncer de endometrio diagnosticados entre enero del 2004 a agosto del 2007 y 88 controles saludables aleatorios de las clínicas de Obstetricia y Ginecología del Recinto de Ciencias Médicas, Universidad de Puerto Rico. Se realizó una entrevista telefónica para obtener información demográfica, reproductiva, estilos de vida e información médica. Para estimar la desigualdad relativa (OR) se utilizaron modelos de regresión logística incondicional e intervalos de confianza (IC) al 95%. En los análisis bivariantes se observó una tendencia significativa entre el IMC y el cáncer de endometrio (p<0.05). El sobrepeso (25.0 > IMC ≤ 29.9 kg/m²) (OR=4.4, IC95%:1.8-8.6) y la obesidad (IMC > 30.0 kg/m²) (OR=9.9; IC95%:3.6-26.9) se asociaron significativamente al cáncer de endometrio. En el análisis multivariado se encontró que las mujeres obesas tienen cuatro veces (OR=4.1; IC95%:1.8-8.6) mayor posibilidad de tener un diagnóstico de cáncer de endometrio en comparación a las mujeres no obesas, después de controlar por el efecto de la edad, educación, estado de empleo, diagnósticos de diabetes e hipertensión, uso de contraceptivos orales y consumo de aves. De manera consistente con estudios realizados a nivel mundial, la obesidad en la adultez fue un predictor fuerte para el cáncer de endometrio en esta muestra de mujeres puertorriqueñas. Por ende, se deben establecer estrategias que promuevan la reducción de peso en las mujeres en PR, con el objetivo de disminuir la incidencia de cáncer de endometrio en esta población.
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