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Running Title: Trends in Endometrial Cancer with a Correction for Hysterectomy

Keywords: endometrial cancer, corpus uteri, incidence, hysterectomy, disparity

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Abstract

Background: Incidence rates of endometrial cancer are routinely calculated without removing women who have had a hysterectomy from the denominator which leads to an underestimate. Furthermore, since the number of women who have had a hysterectomy (hysterectomy prevalence) varies by race, the estimate of racial difference in endometrial cancer incidence is incorrect.

Methods: Data from 1992 to 2008 from the SEER Program were used to calculate incidence rates of endometrial cancer (corpus uterus and uterus, NOS) for 67,588 women age 50 and older. Data from the Behavioral Risk Factor Surveillance System were used to estimate hysterectomy prevalence. SEER area populations were reduced by hysterectomy prevalence and corrected incidence rates were calculated.

Results: For women age 50 and older, the corrected incidence rate of endometrial cancer was 136.0 per 100,000 among whites and 115.5 among blacks, a 73% and 90% increase respectively compared to the uncorrected rate. The increase was greater for black women because hysterectomy prevalence was higher among black women (47%) compared to white women (41%). The corrected incidence among black women significantly increased 3.1% per year compared to a 0.8% significant decrease among white women resulting in higher rates among black women toward the end of the study period.

Conclusion: Correcting the incidence rate for hysterectomy prevalence provides more accurate estimates of endometrial cancer risk over time.

Impact: Comparisons of rates of endometrial cancer among racial groups may be misleading in the absence of denominator correction for hysterectomy prevalence.
Introduction

Endometrial cancer is the most common cancer of the female genital tract and the fourth most commonly diagnosed cancer among women in the United States with 47,130 new cases and 8,010 deaths estimated in 2012 (1). The incidence rate for white women has been stable since 1992 but has been increasing among black women (2). Risk factors such as hormone replacement therapy use and obesity (3-7) and tumor characteristics including histologic subtype (8-12) vary by race.

Hysterectomy, the surgical removal of the uterus, is the second most frequently performed major surgical procedure for women of reproductive age in the United States and more than one-third of all women have had a hysterectomy by age 60 (13, 14). From 2000 to 2004, the rate of hysterectomy in the U.S. was highest among women age 40 to 49 and varied by region with the highest rates found in the South and the lowest in the Northeast. Moreover, the proportion of women who have had a hysterectomy (referred to as “hysterectomy prevalence” in this paper), varies by race and is highest among black women (14-18). Women who have had a hysterectomy are no longer at risk of endometrial cancer and failure to remove these women from the population-at-risk leads to an underestimate of endometrial cancer incidence rates (15, 19-24) and an incorrect estimate of the difference in incidence among various population groups. Previous studies in the U.S. have reported endometrial cancer incidence rates corrected for hysterectomy prevalence for a fixed time interval (17, 23, 25); however, corrected trends of endometrial cancer have not been examined recently (26, 27).

This analysis examines trends in endometrial cancer incidence from 1992 to 2008 by histology among white and black women age 50 and older, both with and without correction for hysterectomy prevalence. In addition, corrected and uncorrected incidence rates are presented for white, black, Asian/Pacific Islander (API), and Hispanic women age 50 and older by endometrial cancer subtype.
Materials and Methods

Data Sources

This analysis included white, black, and API women age 50 and older diagnosed from 1992 to 2008 with microscopically-confirmed invasive cancer occurring in the corpus uteru (C54) and uterus NOS (C55) as defined by or converted to the International Classification of Diseases for Oncology, third edition (ICD-O-3) (28). Since approximately 90% of these cancers arise from the endometrium, we used the term endometrial cancer for all cancers of the corpus uteru and uterus NOS. Data were obtained from 12 population-based cancer registries in the Surveillance, Epidemiology, and End Results (SEER) Program (Connecticut, Hawaii, Iowa, New Mexico, Utah, metropolitan Detroit, metropolitan Atlanta, rural Georgia, Seattle-Puget Sound, San Francisco-Oakland, San Jose-Monterey, and Los Angeles) (2, 29). These data cover 14% of the overall population of the U.S. (12% of whites, 12% of blacks, and 35% of APIs). Results are also presented for Hispanic women (22% population coverage), but these results are not mutually exclusive from the results by race. Women of American Indian/Alaska Native, other, and unknown race were excluded because there were not enough cases to analyze by histologic subtype.

Hysterectomy prevalence was estimated using data from the Centers for Disease Control and Prevention’s (CDC’s) Behavioral Risk Factor Surveillance System (BRFSS), the only national dataset available to estimate hysterectomy prevalence at the state level (30). The BRFSS is a cross-sectional state-specific telephone survey administered to adults age 18 and older living in households. While BRFSS results are based on self-reports, self-reports of hysterectomy have been found to be reliable (31, 32). BRFSS data were available for SEER states (Connecticut, Hawaii, Iowa, New Mexico, and Utah), but since BRFSS data are not routinely available at the county level, the entire state was used to represent SEER metropolitan areas (Michigan for Detroit, Georgia for Atlanta and rural Georgia, Washington for Seattle Puget-Sound and California for San Francisco-Oakland, San Jose-Monterey, and Los Angeles).
The hysterectomy question was asked each year from 1992 to 1999 and every other year thereafter (2000, 2002, 2004, 2006, 2008). This information along with race and current age was used to estimate annual race- and age-specific hysterectomy prevalence from 1992 to 2008.

Histology

The classification of endometrial cancer subtypes in this analysis was defined by Curtis and colleagues in 2004 (33). Specifically, rates and trends are presented for four subtypes of endometrial cancer: Type I which represents over 80% of all endometrial cancer and is primarily endometrioid adenocarcinoma and adenocarcinoma, NOS (histology codes 8380 and 8140); Type II which is primarily papillary serous cystadenocarcinoma and clear cell adenocarcinoma (codes 8460 and 8310); malignant mixed Mullerian tumors (codes 8950 and 8980); and all other invasive endometrial cancers combined including leiomyosarcomas, endometrial stromal and adenosarcomas (33).

Within Type I endometrial cancer, the proportion of cases belonging to the two most common histology codes changed over the study period; coding of adenocarcinoma, NOS (8140) decreased from a majority of the Type I cases in 1992 to less than 10% in 2008 while the more specific endometrioid adenocarcinoma, NOS (8380) increased from less than 15% of the cases to a majority of the cases by 2008. Since these codes both belong to Type I endometrial cancer, the results over time were not impacted.

Statistical Analysis

Age-adjusted incidence rates uncorrected for prevalence of hysterectomy among women age 50 and older by race were calculated using SEER*Stat software Version 7.07 (34). Rates were age-adjusted by the direct method using a truncated 2000 U.S. standard population with age groups 70 and older combined (50-54, 55-59, ..., 65-69, 70+) to align with estimates from the BRFSS. Rates were shown per
100,000 women and plotted on a log-linear scale (35). Rate ratios were calculated to quantify the changes in the risk of uterine cancer among black, API, and Hispanic women relative to white women. In addition, incidence trends of endometrial cancer were estimated from 1992 to 2008 for 3-year time intervals (1992-1994, 1995-1997, ..., 2007-2008) using Joinpoint Regression Program version 3.5.2 (36, 37). Joinpoint regression is a weighted least-squares regression technique that fits linear segments to log-transformed incidence rates and identifies time points at which statistically significant changes occur. Because of the 3-year time intervals, joinpoint models were fit allowing a maximum of one joinpoint. Trends were summarized by the annual percent change (APC) of the last segment. P-values less than 0.05 were considered statistically significant.

The proportion of women who reported having a hysterectomy was estimated for women age 50 and older by race, 5-year age group and 3-year time interval using the BRFSS data from the states with SEER registries used in this analysis. Estimates for API and Hispanic women were imprecise and highly variable over time due to small unweighted sample sizes of women with hysterectomy. Therefore, only hysterectomy prevalence and corrected endometrial cancer incidence over the entire time period was calculated for these women. Finally, since there was some variation over time in hysterectomy prevalence estimates among white and black women, a linear regression was fit to the log of the prevalence rates over time for each race group. The smoothed estimated hysterectomy prevalence from the linear regression was back-transformed to the original scale and used for correction of the incidence rates.

To estimate age-adjusted incidence rates and trends for women at risk of endometrial cancer, the SEER populations were reduced by the corresponding hysterectomy prevalence for each race, 5-year age group and 3-year time interval (19, 20, 38). The corrected age-adjusted incidence rates for each race and year group were calculated as follows:
\[
\sum_{i=50-54}^{70+} \left[ \frac{C_i}{L_i} \times \frac{1}{1-P_i} \times 100,000 \times \left( \frac{stdpop_i}{\sum_{j=50-54}^{70+} stdpop_j} \right) \right]
\]

where \( C \) is the number of cases for a given race and year group, \( L \) is the population for a given race and year group, \( P \) is the estimated hysterectomy prevalence for a given race and year group, and \( stdpop \) is the 2000 US standard population for a given age group. The standard error of the corrected incidence rate was calculated from the above equation considering the estimated hysterectomy prevalence as a constant. The populations used to calculate the incidence rates by age and year for white and black women combined were reduced by the race-, age-, and year-specific hysterectomy prevalence and then summed over race to provide the total population by age and year.

Since the standard errors of the estimated hysterectomy prevalence rates from the BRFSS were large for some age and year groups among white and black women, we performed a sensitivity analysis of the trend estimates by race for all histology types combined. In order to approximate the 95% confidence interval for the prevalence, the smoothed hysterectomy prevalence estimates were increased and then decreased by 10% for whites and 25% for blacks and the APC of incidence was estimated again. Because hysterectomy prevalence estimates over the entire time period were stable, a sensitivity analysis was not performed for these estimates.

**Results**

**Hysterectomy Prevalence**

Among women age 50 and older, the prevalence of hysterectomy from 1992 to 2008 was highest among black women (47%), lowest among API women (29%), and intermediate among white and Hispanic women (41% and 36%, respectively). Black women had higher hysterectomy prevalence than whites in all age groups. API women had lower hysterectomy prevalence than whites in younger
age groups but similar prevalence among women age 70+. All estimates of hysterectomy prevalence from the BRFSS and the smoothed estimates used for correction are presented in Appendix A by age, race, and year.

Hysterectomy prevalence decreased over time among white women and remained fairly stable among black women (Figure 1). Specifically, the prevalence among white women decreased from 42% in 1992 to 1994 to 36% in 2007 to 2008 but remained at 46% to 47% among black women. Although hysterectomy prevalence for all black women age 50 and older combined was stable, prevalence increased over time among women age 60 and older but decreased among women age 50 to 59 (Appendix A).

Corrected and Uncorrected Endometrial Cancer Incidence Rates and Trends

The corrected age-adjusted incidence rates of endometrial cancer from 1992 to 2008 were highest among white women (136.0 per 100,000), followed by black (115.5), Hispanic (82.3), and were lowest among API women (67.4) (Table 1). As expected, the corrected rates were higher than the uncorrected for each race group (73%, 90%, 61%, and 42% increases, respectively). Compared to white women, the rate ratio for black women increased from 0.77 (23% lower risk) before correction to 0.85 (15% lower risk) after correction. In contrast, the rate ratio for API women compared to white women decreased from 0.60 (40% lower risk) before correction to 0.50 (50% lower risk) after correction. Since hysterectomy prevalence was not constant over time, the corrected trends were not parallel to the uncorrected trends among blacks and whites (Figure 2). Specifically, from 1992 to 2008 among white women, the corrected incidence significantly decreased 0.8% per year compared with a 0.5% annual decrease using uncorrected incidence. The corrected incidence among black women significantly increased 3.1% per year, which was almost twice the 1.8% increase based on uncorrected incidence rates. From 1992 to 2008 the uncorrected incidence rates among white women were higher than among
black women. After correction, however, the incidence rates for black women surpassed those among white women from 2004 to 2008. After collapsing to 3-year groups, no changes were identified in the corrected or uncorrected incidence trends. Joinpoint may have been able to detect more complex underlying trends if it had been feasible to use single year data.

As expected, the incidence rate was highest for Type I endometrial cancer (Table 1). Specifically, the corrected incidence of Type I endometrial cancer was highest among white women, similar among black and Hispanic women, and lowest among API women (114.2, 69.0, 63.8, and 54.1, respectively). The corrected incidence trend from 1992 to 2008 showed a significant decline among white women (1.2% per year) but a significant increase among black women (2.3% per year) (Figure 3). In contrast, the corrected incidence rates for the other three subtypes of endometrial cancer (Type II, malignant mixed Mullerian tumors, and all others combined) were higher among black women compared with white women. In addition, the trend for corrected rates of Type II endometrial cancer were non-significantly increasing among white women (1.5% per year) and significantly increasing among black women (5.1% per year). Both corrected and uncorrected incidence rates for malignant mixed Mullerian tumors were increasing among white and black women. Specifically, among black women, the corrected incidence rate of malignant mixed Mullerian tumors significantly increased 3.8% a year compared with a non-significant 2.4% annual increase based on uncorrected rates. The corrected incidence trend among white women for malignant mixed Mullerian tumors (1.6%) changed minimally compared to the uncorrected (1.5%).

A sensitivity analysis showed that for all endometrial cancer types combined a 10% change in hysterectomy prevalence among white women resulted in an APC ranging from an annual decrease of 0.8 to 0.9% (95% CIs: -1.2 to -0.4 and -1.3 to -0.5, respectively). Among black women, a 25% change in hysterectomy prevalence resulted in an increase in APC ranging from 2.5 to 4.3% (95% CIs: 1.4 to 3.6 and 2.4 to 6.1, respectively). The APCs were fairly robust to these changes in hysterectomy prevalence;
statistical significance was retained and 95% confidence intervals of the APCs overlapped the original APC estimates.

Discussion

A primary goal of this analysis was to assess the effect of using a more accurate population-at-risk, i.e., women with an intact uterus, on the relative magnitude of race-specific incidence rates of endometrial cancer. When using a denominator that included all women (the uncorrected rates), the incidence trend of endometrial cancer was higher among white women than black women during the entire study period, 1992 to 2008. After correction, incidence for black women surpassed that for white women from 2004 to 2008. The removal of individuals from a denominator without changing the numerator will always increase the resulting rate. However, in the case of endometrial cancer, the correction had the largest impact on black women because of their higher hysterectomy prevalence. During the entire study period, the overall uncorrected rate of endometrial cancer was highest among white women followed by black, Hispanic, and API women. Correction did not change the rank order of the overall rates but reduced the relative difference between black and white women especially toward the end of the study period. Furthermore because the baseline hysterectomy prevalence was higher among black women and changed over time, trends in endometrial cancer among black women were especially affected. The difference in hysterectomy prevalence between black and white women has been previously observed but is not yet fully understood (39, 40).

The differences in hysterectomy prevalence also impacted the results by histologic subtype. Both with and without a correction for hysterectomy prevalence, the incidence rate of Type I endometrial cancer was highest among white women. Consistent with previous studies, the rates of Type II, malignant mixed Mullerian tumors and other types of endometrial cancer were highest among
black women (41, 42). Specifically, compared to white women, the rate ratios for black women were about two times higher for these subtypes. Trends for Types I and II endometrial cancer based on corrected rates increased sharply among black women, but declined or showed non-statistically significant increases among white women. Malignant mixed Mullerian tumors based on corrected rates increased among both black and white women. Estimates of hysterectomy prevalence were too unstable to present corrected trends by histologic subtype for API and Hispanic women; however, recent population-based analyses report an increase in incidence among these women (2, 43) and variation by subtypes (41) without correction for hysterectomy prevalence.

Several limitations for interpreting the findings of this study should be considered. First, the BRFSS is limited to those with working telephones and the median response rate for the nine states in our study has been declining from 67.0% in 1992 (range: 57.4 to 80.7%) to 54.6% in 2008 (range: 38.3 to 64.9%) (44). Lower response rates to the BRFSS have been associated with the underrepresentation of racial and ethnic minorities (45). Second, the BRFSS data were only available for the entire state and so hysterectomy prevalence could not be estimated for specific metropolitan areas. This may lead to a misrepresentation of the hysterectomy prevalence in the metropolitan SEER areas if the hysterectomy prevalence in the SEER catchment area is different from the entire state. Third, since some race, age, year strata had small sample sizes, the standard errors for estimating the prevalence of hysterectomy from the BRFSS were large, but the sensitivity analysis showed the results to be fairly invariable to changes in hysterectomy prevalence. Finally, since the estimates of hysterectomy prevalence were considered fixed when computing the variance of the corrected incidence rates, the variance used to fit the joinpoint models was underestimated.

To validate our findings, we compared the BRFSS hysterectomy prevalence estimates with other published reports. Surveillance reports for the U.S. provide estimates of rates of hysterectomy based on the National Hospital Discharge Survey (NHDS)(13, 14, 18, 46). The hysterectomy surveillance report
from 1994 to 1999, the most recent report to publish results by race, found incidence rates of hyste-rectomy to be higher among black women than among white women age 35-39 and 40-44. The report also found uterine leiomyoma (fibroids) to be the most frequent diagnosis associated with hysterec-tomy and that the rate of leiomyoma was highest among black women (4.2 per 1000) compared with white women (1.8 per 1000) and women of other races (2.6 per 1000) (14). Results based on 90,000 women from the Women’s Health Initiative Observational Study from 1994 to 1998 found that the proportion of women who had a hysterectomy was about 40% among whites, 45% among Hispanics, 53% among blacks, and 34% among APIs age 50 to 79 (16). In addition, our estimates were similar to those in previous studies that estimated hysterectomy prevalence among SEER states by race using data from the BRFSS (20, 23).

We also compared the BRFSS hysterectomy prevalence estimates with those from two other population-based surveys from the CDC’s National Center for Health Statistics: the National Health and Nutrition Examination Survey (NHANES) and the National Health Interview Survey (NHIS) (47, 48). Of these surveys, the NHIS is the most directly comparable to the current study although state-level estimates are not available as they are in BRFSS. National hysterectomy prevalence estimates were obtained for white, black, API, and Hispanic women age 50 and older from NHIS for the survey years 1993, 1994, 1999, 2000, 2005, and 2008 (Appendix B). The NHIS is administered via personal household interviews to a nationally representative random probability sample of noninstitutionalized, civilian U.S. adults (48). The annual response rate of NHIS is close to 90 percent of the eligible households in the sample. The hysterectomy prevalence estimates for the whole study period, 1992 to 2008 for the BRFSS and 1993 to 2008 for the NHIS are very similar for white women (40.8% and 39.5%, respectively). The same estimate for black women is 12% higher in the BRFSS data compared to the national NHIS data (46.8% and 41.8%, respectively). The hysterectomy prevalence estimates are higher among black women than white women in both surveys. The results over time show a similar pattern even though
the absolute levels of hysterectomy prevalence are higher in the BRFSS. Hysterectomy prevalence peaks in the middle of the study period and is followed by a decline in the most recent period. After reviewing other sources of information on hysterectomy prevalence, the available evidence indicates that hysterectomy prevalence is higher among black women than white women. The magnitude of the difference is unclear.

Finally, the decision on which measure of endometrial cancer to present, uncorrected or corrected, depends on the question of interest. If the measure is risk of developing endometrial cancer among women with a uterus, it would be important to use the corrected denominator. It would also be important to use the corrected denominator when assessing health disparities since hysterectomy prevalence varies by race. As indicated by previous research, the issue is complex for measurements such as lifetime risk of developing endometrial cancer (49).

While there are limitations to the estimation of hysterectomy prevalence, especially for smaller populations of women, the results of this study demonstrate the utility of the method for producing more accurate incidence rates of endometrial cancer by race over time. Without a correction for the population-at-risk (i.e. women with an intact uterus), incidence rates are underestimated. More importantly, when hysterectomy prevalence changes over time and differentially among population subgroups, comparisons of trends can be misleading without correction.

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Authors' Contributions

Conception and design: PM Jamison, AM Noone, LAG Ries, BK Edwards

Development of methodology: PM Jamison, AM Noone, LAG Ries, BK Edwards

Acquisition of data: PM Jamison, AM Noone

Analysis and interpretation of data: PM Jamison, AM Noone, LAG Ries, NC Lee, BK Edwards

Writing, review and/or revision of the manuscript: PM Jamison, AM Noone, LAG Ries, NC Lee, BK Edwards

Administrative, technical, or material support: PM Jamison, AM Noone

Study supervision: PM Jamison
Reference List


Figure Legends

**Figure 1**: Estimated Hysterectomy Prevalence over Time among White and Black Women Age 50+\(^a\). Error bars represent the 95% confidence interval.

\(^a\)Source: Behavioral Risk Factor Surveillance System (BRFSS) public use file

**Figure 2**: Age-adjusted Endometrial Cancer Incidence Rates by Race, Corrected and Uncorrected for Hysterectomy Prevalence among Women age 50+, SEER from 1992-2008.\(^a\) The annual percent change (APC) is shown next to the regression line and the asterisk indicates APC is statistically significant, \(p < 0.05\).

\(^a\)Source: Incidence data from Surveillance, Epidemiology, and End Results (SEER) 13 areas covering about 14% of the U.S. population (Connecticut, Hawaii, Iowa, New Mexico, Utah, metropolitan Detroit, metropolitan Atlanta, rural Georgia, Seattle-Puget Sound, San Francisco-Oakland, San Jose-Monterey, and Los Angeles)

Hysterectomy prevalence data from Behavioral Risk Factor Surveillance System (BRFSS) public use file

**Figure 3**: Age-adjusted Endometrial Cancer Incidence Rates among Black and White Women by Sub-type, Corrected and Uncorrected for Hysterectomy Prevalence among Women age 50+, SEER from 1992 to 2008.\(^a\). The annual percent change (APC) is shown next to the regression line and the asterisk indicates APC is statistically significant, \(p < 0.05\).

A: Type I endometrial cancer, B: Type II endometrial cancer, C: Malignant mixed Mullerian tumors, D: Other histologic types

\(^a\)Source: Incidence data from Surveillance, Epidemiology, and End Results (SEER) 13 areas covering about 14% of the U.S. population (Connecticut, Hawaii, Iowa, New Mexico, Utah, metropolitan Detroit, metropolitan Atlanta, rural Georgia, Seattle-Puget Sound, San Francisco-Oakland, San Jose-Monterey, and Los Angeles)
Figure 1

Hysterectomy prevalence over time for White and Black populations from 1992 to 2008.
Figure 3

Age-adjusted incidence rate

Corrected
- White
- Black

Uncorrected
- White
- Black

Year of diagnosis


200  150  100  50  0

-1.2*  2.3*  1.1  -0.8*

3.5  1.5*

5.1*  5.1*

2.4  1.5*

2.9  1.8

1.6*  0.6

1.4  0.9

1.1


Year of diagnosis


Year of diagnosis


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Table 1: Age-adjusted Endometrial Cancer Incidence Rates by Race and Subtype, Corrected and Uncorrected for Hysterectomy Prevalence among Women 50+, SEER 1992-2008

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<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>348</td>
<td>3.6</td>
<td>0.88</td>
<td>5.8</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: API=Asian/Pacific Islander

*aICD-O-3 histology codes for Type I: 8050, 8140-8141, 8143, 8210-8211, 8260-8263, 8323, 8340, 8380-8381, 8440, 8470-8471, 8480-8481, 8490, 8550, 8560, 8570, 8571-8573
Type II: 8310, 8441, 8460-8462
Malignant mixed Mullerian: 8950-8951, 8980-8981
Other: All other invasive endometrial cancers

*bSource: Incidence data from Surveillance, Epidemiology, and End Results (SEER)
13 areas covering about 14% of the U.S. population (Connecticut, Hawaii, Iowa, New Mexico, Utah, metropolitan Detroit, metropolitan Atlanta, rural Georgia, Seattle-Puget Sound, San Francisco-Oakland, San Jose-Monterey, and Los Angeles)
Hysterectomy prevalence data from Behavioral Risk Factor Surveillance System (BRFSS) public use file

Hispanic is not mutually exclusive from white, black, and API

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