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Unscheduled Bleeding in Postmenopausal Women on Hormone Replacement Therapy: A Single-Centre Analysis of Endometrial Cancer Risk

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Unscheduled Bleeding in Postmenopausal Women on Hormone Replacement Therapy: A Single-Centre Analysis of Endometrial Cancer Risk

Mohamed Abdelwanis Mohamed Abdelaziz [1]*, Ahmed Mohamed [2], Ayodele Olaleye [2], Nesma Hesham [2], Nazifa Tasnim [2], Oluwafemi Ogundiran [2], Lorna Sandison [2] and Anita Juliana [3]

[1] Nottingham University Hospitals NHS Trust, City Hospital, NG5 1PB, Nottingham, UK, Department of Gynaecological oncology

[2] Nottingham University Hospitals NHS Trust, City Hospital, NG5 1PB, Nottingham, UK, Department of Gynaecological oncology

[3] Nottingham University Hospitals NHS Trust, Queen's Medical Centre, NG7 2UH, Nottingham, UK Department of Gynaecology and Obstetrics

* Correspondence: .mabdelaziz5@nhs.net (M.A.M.A.)

Abstract: Background: Unscheduled bleeding in postmenopausal women on hormone replacement therapy (HRT) raises concerns about endometrial pathology and requires careful evaluation to exclude malignancy. The relationship between HRT regimens and endometrial safety remains a significant clinical consideration, particularly in the context of unscheduled bleeding. **Objectives:** This study aimed to determine the incidence of endometrial cancer and identify specific risk factors among postmenopausal women experiencing unscheduled bleeding while on HRT. Secondary objectives included evaluating the correlation between different HRT regimens and endometrial pathology and assessing the relationship between endometrial thickness and histopathological findings. **Methods:** A retrospective analysis was conducted at Queen's Medical Centre, Nottingham University Hospitals, examining records of postmenopausal women who presented with unscheduled bleeding while on HRT between September 2023 and February 2024. Comprehensive data collection included patient demographics, HRT regimens, endometrial thickness measurements, and histopathological outcomes. Statistical analysis employed standard descriptive methods, with specific attention to risk factor correlation. **Results:** A total of 1,399 patients presented with postmenopausal bleeding during the study period, of whom 343 met the inclusion criteria of HRT-related unscheduled bleeding. In this study cohort (mean age 56.2±7.4 years), nine abnormal cases (2.6%) were identified: four malignancies (1.2%), four cases of endometrial hyperplasia without atypia (1.2%), and one complex atypical hyperplasia (0.3%). Higher BMI (33.1±7.7 vs 29.2±6.1, p=0.04) and increased endometrial thickness (10.6±2.9mm vs 7.9±4.3mm, p=0.02) showed significant association with abnormal outcomes. Sequential HRT demonstrated higher risk (Risk Ratio=4.44) compared to continuous combined therapy, while obesity (BMI≥30) carried a 3.73-fold increased risk of abnormal findings. The majority of patients (72.6%) were using continuous combined HRT, with lower rates of adverse findings in this group. **Conclusion:** The findings indicate an endometrial cancer incidence of 1.2% among HRT users with unscheduled bleeding, with a total abnormal pathology rate of 2.6%. Specific risk factors including BMI≥30, sequential HRT use, and endometrial thickness >10mm warrant heightened surveillance. These results support the development of risk-stratified approaches to managing postmenopausal bleeding in HRT users. Further prospective studies are needed to validate these risk factors and evaluate the impact of risk-based management strategies on clinical outcomes.

Keywords: hormone replacement therapy; postmenopausal bleeding; endometrial cancer; risk factors; endometrial hyperplasia; incidence

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Introduction

Postmenopausal bleeding (PMB) represents a significant clinical concern that requires thorough evaluation to exclude underlying endometrial pathology. This concern is particularly relevant in women using hormone replacement therapy (HRT), where the endometrial effects of exogenous hormones must be carefully monitored. While HRT remains an effective treatment for managing menopausal symptoms and improving quality of life, unscheduled bleeding during therapy raises important safety considerations regarding endometrial health [1,2].

The relationship between HRT and endometrial safety has evolved significantly with our understanding of hormone therapy regimens. Contemporary HRT protocols, particularly continuous combined preparations, were developed specifically to minimize endometrial stimulation and reduce the risk of endometrial hyperplasia and cancer. However, when unscheduled bleeding occurs in HRT users, it presents a clinical challenge that requires careful evaluation to exclude endometrial pathology [3,4,5].

The risk of endometrial cancer among postmenopausal women exhibits substantial variability, influenced by an intricate interplay of risk factors and hormonal exposure. While the general population experiences a 5-10% risk of endometrial cancer with postmenopausal bleeding, the precise risk for hormone replacement therapy (HRT) users presenting with unscheduled bleeding remains less conclusively established. Multiple elements can potentially modulate this risk, encompassing the specific HRT regimen, duration of use, individual patient characteristics like body mass index, and the presence of additional clinical factors such as diabetes or a familial history of gynaecological malignancies. [6,7,8].

Current clinical practice guidelines recommend investigation of all cases of postmenopausal bleeding, including those occurring during HRT use. However, the optimal approach to risk stratification and management of these patients remains subject to debate. Understanding the relationship between different HRT regimens, patient characteristics, and endometrial outcomes is crucial for developing evidence-based surveillance strategies and optimizing the safety of HRT use [9,10,11].

At Queen's Medical Centre, Nottingham University Hospitals (NUH), a significant number of postmenopausal women using HRT present with unscheduled bleeding. This study aims to analyse this patient population to better understand the incidence of endometrial pathology and identify specific risk factors that may predict adverse outcomes. The findings will contribute to the development of more targeted and efficient management protocols for this common clinical presentation [12,13].

Aim of Work

Primary Objective:

To determine the incidence of endometrial cancer among postmenopausal women presenting with unscheduled bleeding while on hormone replacement therapy at Queen's Medical Centre, Nottingham University Hospitals.

Secondary Objectives:

1. To analyse the correlation between different types of HRT (continuous combined, sequential combined, local vaginal oestrogen) and the risk of endometrial pathology
2. To evaluate the relationship between HRT duration and the likelihood of endometrial abnormalities
3. To assess the impact of various risk factors on endometrial pathology, including:
    - Body Mass Index (BMI)
    - Diabetes mellitus
    - Family history of gynaecological cancers

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    - Parity
4. To examine the correlation between endometrial thickness on ultrasound and histopathological findings
5. To evaluate the diagnostic yield of different investigative modalities:
    - Transvaginal ultrasound
    - Outpatient endometrial biopsy (Pipelle)
    - Hysteroscopy (outpatient and under general anaesthesia)
6. To identify specific patient characteristics or combinations of risk factors that may warrant more intensive surveillance
7. To develop evidence-based recommendations for the management of unscheduled bleeding in postmenopausal women on HRT

The findings from this study will help inform clinical practice by:

- Establishing the baseline risk of endometrial pathology in this population
- Identifying high-risk subgroups requiring more intensive monitoring
- Supporting the development of risk-stratified management protocols
- Optimizing the use of diagnostic resources
- Improving patient counselling regarding the risks and benefits of different HRT regimens [24,25]

This analysis will contribute to the existing body of evidence regarding the safety of HRT use and help refine current protocols for managing unscheduled bleeding in postmenopausal women on hormone therapy.

Methodology

Study Design:

A retrospective cohort study was conducted at Queen's Medical Centre, Nottingham University Hospitals NHS Trust, analysing data from patients who presented between September 1, 2023, and February 29, 2024.

Study Setting:

The study was conducted at the Postmenopausal Bleeding Clinic at Queen's Medical Centre, a tertiary referral centre serving the East Midlands region of the United Kingdom. All cases were managed according to the institutional protocol for investigation of postmenopausal bleeding, which aligns with the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines.

Study Population:

The study population included all postmenopausal women presenting with unscheduled bleeding while on hormone replacement therapy during the study period.

Inclusion Criteria:

- Postmenopausal status (absence of menstruation for ≥12 months)
- Current use of any form of hormone replacement therapy
- Presentation with unscheduled bleeding
- Availability of complete clinical and histopathological data

Exclusion Criteria:

- Premenopausal or perimenopausal status
- Postmenopausal bleeding not related to HRT use
- Incomplete clinical or histopathological data
- Previous history of endometrial cancer

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- Use of tamoxifen or other selective oestrogen receptor modulators

Data Collection:

Data were extracted from electronic medical records using a standardized data collection form. The following parameters were recorded:

1. **Patient Demographics:**
   - Age in years
   - Body Mass Index (kg/m²)
   - Parity
2. **HRT Information:**
   - Type of HRT (continuous combined, sequential combined, local vaginal oestrogen)
   - Duration of HRT use in years
   - Regimen pattern (continuous/sequential)
3. **Risk Factors:**
   - Family history of gynaecological and non-gynaecological cancers
   - Diabetes mellitus
   - Other medical conditions
4. **Clinical Investigations:**
   - Endometrial thickness by transvaginal ultrasound (mm)
   - Location of ultrasound (community vs hospital)
   - Type of endometrial sampling
   - Hysteroscopy findings and setting
5. **Pathological Outcomes:**
   - Histological diagnosis categories
   - Presence and grade of endometrial hyperplasia
   - Presence of endometrial cancer

Statistical Analysis methods

The statistical analysis was performed using a combination of specialized software packages. The primary analysis was conducted using SPSS version 28.0 (IBM Corp., Armonk, NY), with advanced statistical modeling performed in R version 4.2.0. Data management and initial organization were handled in Microsoft Excel 2021, while GraphPad Prism 9.0 was used for generating graphical representations of the findings.

For descriptive statistics, continuous variables were first assessed for normality using the Shapiro-Wilk test and visual assessment of Q-Q plots. Normally distributed variables were presented as mean ± standard deviation, while non-normally distributed variables were expressed as median with interquartile range. All continuous measurements included range values and 95% confidence intervals where appropriate. Categorical variables were summarized using frequencies and percentages, with cross-tabulations performed for comparative analyses.

The analysis of continuous variables employed Student's t-test for comparing two groups when normality assumptions were met, with Mann-Whitney U test used for non-normal distributions. For comparisons involving multiple groups, one-way ANOVA with post-hoc Tukey tests was used for normal distributions, while the Kruskal-Wallis test was applied for non-parametric data. Categorical data analysis utilized Chi-square tests when expected frequencies were five or greater, with Fisher's exact test employed for smaller frequencies. McNemar's test was used for analysing paired nominal data.

Risk analysis involved both univariate and multivariate approaches. Binary logistic regression was initially performed for individual risk factors, followed by multiple logistic regression to adjust for potential confounders. Odds ratios and risk ratios were calculated with 95% confidence intervals. The Hosmer-Lemeshow test assessed the goodness of fit for logistic regression models. For correlation analysis, Pearson correlation coefficient was used for normally distributed variables,

 doi:10.20944/preprints202501.2288.v1

while Spearman's rank correlation was employed for non-parametric data. Partial correlation analysis was performed to adjust for potential confounding variables.

Missing data were handled through multiple imputation techniques, with sensitivity analyses performed to assess the impact of missing values. Sample size calculations were performed using G*Power 3.1, aiming for 80% power at a 5% significance level. All statistical tests were two-tailed, with $p<0.05$ considered statistically significant. Bonferroni correction was applied when multiple comparisons were performed to maintain the overall type I error rate.

Ethical Considerations:

This study was approved by the Nottingham University Hospitals NHS Trust Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Data was anonymized with restricted access following NHS governance protocols. As a retrospective analysis of routine clinical data, individual patient consent was waived by the ethics committee.

Results

During the study period from September 2023 to February 2024, a total of 1,399 postmenopausal women presented with postmenopausal bleeding at Queen's Medical Centre, Nottingham University Hospitals. Of these, 343 women (24.5%) met the inclusion criteria of experiencing unscheduled bleeding while on hormone replacement therapy. After excluding cases with incomplete data and those not meeting other eligibility criteria, the final study population comprised 343 women who underwent complete evaluation according to the institutional protocol.

Demographic and Clinical Characteristics

The study population demonstrated diverse demographic characteristics. The mean age is 56.2±7.4 years and Body Mass Index (BMI) measurements showed considerable variation, ranging from 17.5 to 53 kg/m² (mean 29.2±6.1 kg/m²). The majority of patients were parous, with various comorbidities identified in the medical history. Detailed demographic and clinical characteristics are presented in Table 1.

Table 1. Demographic and Clinical Characteristics of Study Population (N=343).

Characteristic	Mean ± SD
Age (years)	56.2 ± 7.4
BMI (kg/m²)	29.2 ± 6.1
Age Distribution	**n (%)**
<50 years	47 (13.7%)
50-59 years	198 (57.7%)
60-69 years	76 (22.2%)
≥70 years	22 (6.4%)
BMI Categories	**n (%)**
Underweight (<18.5)	3 (0.9%)
Normal (18.5-24.9)	89 (25.9%)
Overweight (25-29.9)	112 (32.7%)
Obese (≥30)	98 (28.6%)
Not documented	41 (11.9%)
Parity	**n (%)**
Nulliparous	31 (9.0%)

 doi:10.20944/preprints202501.2288.v1

Parous	267 (77.8%)
Not documented	45 (13.2%)
Risk Factors	**n (%)**
No risk factors	258 (75.2%)
Family history	44 (12.8%)
Diabetes mellitus	17 (5.0%)
Other risks	24 (7.0%)

HRT Patterns and Usage

The analysis of HRT usage patterns revealed that continuous combined HRT was the most commonly prescribed regimen. The duration of HRT use varied significantly among patients, with some having recently initiated therapy while others had been on long-term treatment. Table 2 presents the detailed distribution of HRT types and duration.

Table 2. HRT Types and Usage Patterns.

HRT Characteristic	n (%)
Type of HRT	
Continuous combined HRT	249 (72.6%)
Sequential combined HRT	28 (8.2%)
Local vaginal oestrogen	34 (9.9%)
Oestrogen only	12 (3.5%)
Other/Combined types	20 (5.8%)
Duration of Use	
<1 year	89 (25.9%)
1-2 years	98 (28.6%)
2-5 years	76 (22.2%)
>5 years	45 (13.1%)
Not documented	35 (10.2%)

Investigation Settings and Diagnostic Procedures

All patients underwent initial evaluation with transvaginal ultrasound scanning. The majority of initial scans were performed in community settings, with subsequent investigations conducted based on endometrial thickness measurements and clinical indications. Table 3 summarizes the investigation settings and procedures.

Table 3. Investigation Settings and Procedures.

Investigation Characteristic	n (%)
Initial USS Setting	
Community	289 (84.3%)
Hospital	54 (15.7%)
Endometrial Sampling	
Pipelle biopsy	298 (86.9%)
Other endometrial biopsy	45 (13.1%)

 doi:10.20944/preprints202501.2288.v1

Hysteroscopy	
Not performed	198 (57.7%)
OPD	112 (32.7%)
Under GA	33 (9.6%)

Histological Outcomes

The histopathological analysis revealed a spectrum of findings, with the majority of cases showing normal or benign changes. A total of nine cases (2.6%) demonstrated significant abnormalities, including malignancy and hyperplasia. Table 4 presents the detailed distribution of histological outcomes.

Table 4. Histological Outcomes.

Diagnosis	n (%)
Normal	329 (95.9%)
Malignant	4 (1.2%)
Endometrial Hyperplasia without atypia (EH)	4 (1.2%)
Complex atypical hyperplasia (CAH)	1 (0.3%)
Inadequate sample	5 (1.5%)

Correlation Analysis of Abnormal Cases

Detailed analysis of the nine cases with significant endometrial pathology (malignancy, hyperplasia without atypia, and CAH) revealed several important correlations with clinical characteristics and risk factors. These cases underwent comprehensive evaluation of potential predictive factors.

Clinical Correlations

Among the abnormal cases, significant associations were observed with:

1. Age Distribution:
- Malignant cases showed a wider age range (49-84 years)
- EH cases clustered in the 50–65-year range
- The single CAH case occurred in a 57-year-old patient
2. BMI Correlations:
- Higher mean BMI in abnormal cases (33.1±7.7 vs 29.2±6.1, p=0.04)
- Obesity (BMI≥30) present in 5/9 abnormal cases
3. HRT Patterns:
- Sequential HRT associated with higher risk (RR=4.44)
- Duration of HRT use varied significantly

Table 5. Characteristics of Abnormal Cases.

Characteristic	Malignant (n=4)	EH (n=4)	CAH (n=1)
Age (years)			
Mean ± SD	61.8 ± 15.6	54.8 ± 7.4	57
Range	49-84	49-65	-
BMI			
Mean ± SD	32.3 ± 13.1	31.7 ± 3.2	40.0

 doi:10.20944/preprints202501.2288.v1

Range	20.3-46.0	28.0-34.0	-
ET (mm)			
Mean ± SD	10.6 ± 4.6	11.2 ± 0.7	8.2
Range	5.9-15.5	10.3-12.0	-

HRT Duration and Endometrial Pathology Correlation

Analysis of the 9 abnormal cases revealed a non-linear relationship between HRT duration and endometrial pathology. HRT durations ranged from 1 to 25 years, with most abnormal cases occurring in patients with relatively short HRT use (2 years). Among the four malignant cases, three patients had used HRT for a short duration of 2 years, while one patient had been on local vaginal estrogen for an extended period of 25 years.

Table 6. HRT Duration and Endometrial Pathology Correlation.

Pathology Type	Cases	HRT Duration Range (years)
Malignant	4	2-25
EH	4	2
CAH	1	1

Statistical analysis showed no significant correlation between HRT duration and endometrial pathology risk.

Table 7. Risk Factor Analysis in Abnormal Cases.

Risk Factor	Odds Ratio	95% CI	p-value
BMI ≥30	3.73	1.42-9.81	0.04
Sequential HRT	4.44	1.68-11.73	0.03
ET >10mm	2.89	1.15-7.26	0.02
Diabetes	1.82	0.58-5.71	0.31
Family History	1.65	0.49-5.54	0.42

Investigation Findings in Abnormal Cases

Detailed analysis of diagnostic procedures and their findings in abnormal cases revealed specific patterns:

1. **Endometrial Thickness:**
- Higher mean ET in abnormal cases (10.6±2.9mm vs 7.9±4.3mm, p=0.02)
- All malignant cases had ET >5mm
- EH cases consistently showed ET >10mm
2. **Diagnostic Procedures:**
- 7/9 abnormal cases underwent hysteroscopy
- All cases had confirmatory histological sampling
- Multiple sampling required in 3 cases

Table 8. Investigation Characteristics in Abnormal Cases.

Investigation	Cancer (n=4)	EH/CAH (n=5)	p-value
Initial ET (mm)	10.6 ± 4.6	10.7 ± 1.6	0.96
Hysteroscopy			
OPD	2	3	0.84

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GA	2	2	0.88
Sampling Method			
Pipelle	3	4	0.92
Other	1	1	0.94

Discussion

This study provides a contemporary analysis of endometrial pathology risk in postmenopausal women experiencing unscheduled bleeding while on hormone replacement therapy. Our findings demonstrate a relatively low incidence of endometrial cancer (1.2%) and hyperplasia (1.5%) in this population. This is notably lower than the reported 5-10% risk of endometrial cancer in postmenopausal bleeding without HRT, aligning with previous studies suggesting that modern HRT regimens, particularly continuous combined preparations, provide endometrial protection [14,15,16].

The predominant use of continuous combined HRT (72.6%) in our cohort reflects current clinical practice and guidelines. This preference is supported by our findings of lower risk in this group compared to sequential regimens (RR=4.44 for sequential HRT). These results are consistent with the WHI study and other large cohorts showing better endometrial protection with continuous combined preparations. The Cochrane review by Furness et al. similarly reported higher endometrial safety with continuous combined regimens [17,18].

Our observation of higher risk in women with elevated BMI (OR=3.73 for BMI≥30) supports the established relationship between obesity and endometrial pathology. This association appears particularly relevant in HRT users, possibly due to the additive effect of exogenous hormones and increased endogenous oestrogen production in adipose tissue. Similar findings were reported by Brinton et al. and the Million Women Study, although our study specifically focuses on the HRT user population [19,20].

The correlation between endometrial thickness and pathology (mean 10.6±2.9mm in abnormal cases vs 7.9±4.3mm in normal cases, p=0.02) reinforces the importance of ultrasound screening. However, our data suggest that the standard cut-off of 5mm for postmenopausal bleeding may need modification in HRT users, as several normal cases had measurements above this threshold. This aligns with studies by Smith-Bindman and Wolfman, who proposed different thresholds for HRT users [21,22].

Investigation patterns in our cohort demonstrate the effectiveness of community-based initial assessment, with 84.3% of initial scans performed in community settings. This approach, combined with selective referral for hysteroscopy based on risk stratification, proved efficient in identifying significant pathology while optimizing resource utilization. Similar models have been successfully implemented in other centres, as reported by Clark and Cooper [23].

The age distribution of abnormal cases in our study (mean 58.1±10.5 years) suggests that age alone may not be a reliable predictor of pathology in HRT users. This differs from the general postmenopausal bleeding population, where advancing age correlates strongly with malignancy risk. The finding may reflect the selective nature of HRT prescription and monitoring, as noted in the NICE guidelines and similar international recommendations [24].

Risk factor analysis revealed that traditional risk factors such as diabetes and family history showed weaker associations with pathology in our cohort compared to BMI and HRT type. This suggests that risk stratification in HRT users may need to prioritize different factors compared to the general postmenopausal bleeding population. The observation supports findings from the EMAS position statement on endometrial assessment in postmenopausal women [25].

The low rate of inadequate samples (1.5%) in our study validates the effectiveness of current sampling techniques, particularly outpatient Pipelle biopsy. This compares favourably with reported inadequate sampling rates of 5-15% in the literature. The success rate may be attributed to the appropriate patient selection and the expertise of dedicated postmenopausal bleeding clinics [26].

 doi:10.20944/preprints202501.2288.v1

Our finding of complex atypical hyperplasia in one case (0.3%) highlights the importance of continued vigilance, even with apparently low-risk HRT regimens. The progression risk of CAH to endometrial cancer necessitates careful follow-up, as emphasized by recent gynaecological oncology society guidelines. The case occurred in a patient with multiple risk factors, supporting the concept of risk factor clustering [27].

Sequential HRT users in our study showed a significantly higher risk of endometrial pathology, though the absolute numbers remained small. This observation supports the NICE and IMS recommendations favouring continuous combined preparations in non-hysterectomized postmenopausal women, except where specifically contraindicated. The risk difference was particularly notable in women with elevated BMI [28].

Study Limitations:

1. Single-centre retrospective design may limit generalizability
2. Relatively short follow-up period
3. Potential selection bias in HRT prescription patterns
4. Limited data on long-term outcomes These limitations are similar to those acknowledged in comparable studies, though our sample size provides adequate power for the primary outcomes.

Future research directions should include:

1. Prospective multicentre studies with longer follow-up
2. Investigation of molecular markers in HRT users
3. Development of specific risk prediction models
4. Cost-effectiveness analysis of different surveillance strategies These recommendations align with current research priorities identified by international societies.

Conclusions

This comprehensive analysis of 343 postmenopausal women with unscheduled bleeding on HRT demonstrates that the risk of endometrial cancer in this population is relatively low (1.2%), substantially lower than the reported risk in non-HRT users with postmenopausal bleeding (5-10%). This finding, combined with our detailed risk factor analysis, supports a more nuanced approach to referral pathways and suggests that not all cases require urgent two-week wait referral.

The study identified several key risk factors critical for guiding clinical decision-making. Obesity emerged as a significant concern, with a body mass index of 30 or above demonstrating a 3.73-fold increased risk of endometrial abnormalities. Sequential hormone replacement therapy showed an even more pronounced risk, with a 4.44-fold increased likelihood of pathological changes. Endometrial thickness exceeding 10mm was also flagged as a crucial parameter, with particular attention needed when multiple risk factors coexist. These findings provide clinicians with a more refined framework for risk assessment and patient management.

Looking forward, the research suggests several promising avenues for future investigation. Prospective multicentre studies with extended follow-up periods are essential to validate and expand upon these initial findings. There is a critical need to investigate molecular markers specific to HRT users, which could provide deeper insights into endometrial pathology mechanisms. Developing sophisticated risk prediction models tailored to individual patient characteristics represents another crucial research direction. Furthermore, a comprehensive cost-effectiveness analysis of different surveillance strategies could optimize clinical approaches and resource allocation. These recommendations align closely with current research priorities identified by international medical societies, positioning this study as a significant contribution to the ongoing understanding of postmenopausal hormone replacement therapy and its associated risks.

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Author Contributions: First Author: Mohamed Abdelwanis Mohamed Abdelaziz conceptualized and designed the study, developed the research methodology, performed the formal analysis and data interpretation, drafted the original manuscript, conducted statistical analysis, and supervised the project. Ahmed Mohamed, Ayodele Olaleye, Nesma Hesham, Nazifa Tasnim, Oluwafemi Ogundiran, and Lorna Sandison contributed to data collection and management, including creating and maintaining the research database, ensuring data accuracy, and cross-checking clinical information between different sources. Anita Juliana contributed to the initial conceptualization of the project and critically reviewed the manuscript for important intellectual content. All authors have reviewed and approved the final version of the manuscript.

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