

An Accessible Framework for Early Endometrial Cancer Risk Stratification Using Survey and Blood-Based Biomarkers

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ABSTRACT

Endometrial cancer, also known as uterine cancer, develops when cells in the endometrium, the lining of the uterus, grow uncontrollably. The most at-risk demographics for this specific cancer are women older than the age of 55 and post-menopausal women. Even though the cancer has high survival rates when detected in early stages, diagnosis is often delayed due to the invasive nature of current diagnostic procedures such as endometrial biopsy and hysteroscopy. Diagnosis is also hindered by limited awareness of early symptoms, including abnormal vaginal bleeding and pelvic pain.

This study proposes a two-part screening framework designed to identify risks related to endometrial cancer. The first component consists of a structured risk-assessment survey incorporating demographic, clinical, genetic, and lifestyle factors with weightings based on how much they would increase the risk of endometrial cancer. The second component involves analysis of blood-based biomarkers associated with endometrial cancer. Data from both components are integrated using a rule-based algorithm to stratify individual cancer risk.

This framework models a minimally invasive and accessible approach to early risk assessment that could support earlier clinical evaluation of at-risk individuals. While not intended to replace clinical diagnostic procedures, it illustrates how such a framework might help address barriers to initial risk assessment and encourage individuals to seek more conclusive testing.

INTRODUCTION

Endometrial cancer, also referred to as uterine cancer, is the most common gynecologic cancer in the United States. The average age when women are diagnosed is 60, and incidence increases significantly after menopause.¹ Overall, the five-year survival rate for Stage 1 Endometrial Cancer is 96%.² However, the survival rate for “distant” endometrial cancer, defined as late Stage 3 and Stage 4, is 20%.² Earlier identification of high-risk individuals may be associated with diagnosis at earlier stages, which are characterized by higher survival rates and less aggressive treatment options.

March 2026
Vol 5, No 1.

Early detection of endometrial cancer remains challenging. The process of diagnosing endometrial cancer is extremely invasive and uncomfortable for the person. Current diagnostic methods include transvaginal ultrasound, hysteroscopy, and endometrial biopsy, where a piece of tissue is taken from the lining of the uterus.³ At this time, there are no screening tests or exams to find endometrial cancer early in women who are at average endometrial cancer risk and have no symptoms, making it critical to recognize symptoms and be evaluated.⁴

There are disparities when it comes to diagnosis and outcomes as it relates to early detection. Black women have the highest death rate of any demographic and are more likely to be diagnosed at advanced stages than white women, even though their overall incidence is lower.⁵ It seems that this trend is not due to socioeconomic status and can be traced to a mix of social and biological factors.⁶

Given rising incidence rates, increasing rates of obesity, and persistent diagnostic inequities, there is a growing need for accessible, minimally invasive screening approaches that can identify individuals who may benefit from further diagnostic evaluation. This study proposes a combined survey-based and blood-based screening framework designed to function as a preliminary risk stratification tool, with the goal of reducing barriers to initial evaluation and improving equity in endometrial cancer detection.

LITERATURE REVIEW

Endometrial cancer risk is shaped by a combination of biological, demographic, and socioeconomic factors. Age is one of the strongest predictors of disease, with incidence rising sharply after menopause due to prolonged, unopposed estrogen exposure.⁷ The majority of cases occur in postmenopausal individuals, highlighting the role of hormonal imbalance in endometrial cancer.

Racial and ethnic disparities in endometrial cancer have been reported across multiple studies. While white women experience the highest overall incidence, black women are more likely to have aggressive subtypes, advanced cancer, and poorer survival rates.⁸ These disparities are partially explained by differences in access to care and socioeconomic status, but not fully. Genetic factors and barriers to healthcare equity may also contribute to these disparities.⁹

Obesity is one of the most significant modifiable risk factors for endometrial cancer. Being overweight roughly doubles the risk of disease, while obesity nearly triples it.¹⁰ Excess adipose tissue increases estrogen levels by converting androgens into estrogen, especially after menopause.¹¹ Lifestyle habits like eating a high-fat diet and getting little exercise can further disrupt metabolism and hormones, increasing the risk of cancer.¹²

Socioeconomic status also impacts disease progression and prognosis. Individuals from lower-income backgrounds are more likely to experience delays in diagnosis and have later-stage disease, leading to higher mortality rates.¹³ Limited access to gynecologic care and lower awareness of early symptoms can add to existing disparities.

Genetic predisposition accounts for a subset of endometrial cancer cases. Lynch syndrome, caused by mutations in mismatch repair genes including MLH1, MSH2, MSH6, and PMS2, significantly increases lifetime cancer risk.¹⁴ Non-hereditary endometrial cancers often involve mutations in genes such as PTEN, TP53, PIK3CA, ARID1A, KRAS, CTNNB1, and ESR1. These genes normally help control cell growth and regulate how cells respond to hormones.¹⁵

Because symptoms alone do not reliably identify endometrial cancer at an early stage, blood-based biomarkers have emerged as promising tools for non-invasive screening. Although CA-125 and HE4 are frequently elevated in endometrial cancer, their use as independent indicators can result in both false-positive and false-negative findings.¹⁶ Changes in red blood cell distribution width (RDW) markers are linked to endometrial cancer because the disease often causes prolonged abnormal uterine bleeding.¹⁷ Additionally, abnormal DNA methylation patterns, particularly examples of tumor suppressor genes that are hypermethylated, have shown strong ties to endometrial cancer.¹⁸ These findings support an integrated screening approach combining demographic risk factors with biological markers.

METHODOLOGY

Study Design

This study uses computational simulations to develop and test a preliminary screening framework for endometrial cancer. No human participants or real patient data were used. Instead, simulated datasets were created to examine how the model assigns risk and to evaluate its overall behavior, the process of risk stratification, and the clarity of predictions. The simulation inputs, including probability distributions and risk thresholds, were based on published epidemiological studies and clinically established biomarker cutoffs.¹⁹

A simulated cohort of 500 hypothetical individuals was used to reflect realistic population variation while keeping the analysis manageable. This sample size was large enough to show how risk scores were distributed and how different data types interacted, without overfitting the model. The framework was structured to prioritize identifying potentially higher-risk individuals rather than minimizing false positives, consistent with its role as a preliminary screening tool rather than a diagnostic test.

In building the simulated dataset, survey responses were generated using probability ranges informed by published prevalence data cited in the Literature Review. Biomarker values were assigned independently according to clinically established threshold levels (such as HE4 and CA-125 cutoffs) rather than being statistically linked to survey variables. The weighting structure applied to survey and biomarker inputs was informed by prior research but implemented heuristically for illustrative purposes and was not empirically optimized. No actual cancer diagnoses or clinical outcomes were simulated. The purpose of the simulation was to observe how the scoring framework behaves under plausible input conditions, not to evaluate real-world diagnostic accuracy.

Survey-Based Risk Assessment

The first part of the framework is a structured survey that collects information on demographic, clinical, genetic, and lifestyle factors linked to endometrial cancer risk. It includes 14 questions, with a total possible score of 100 points. Each factor is assigned a point value intended to reflect its relative influence on risk, based on patterns reported in clinical studies.

Rather than deriving weights through formal statistical modeling, the scoring system was designed to be transparent and rule-based. Points were assigned to reflect the relative importance of risk factors described in prior studies while maintaining a clear additive structure. These weights illustrate relative influence within the simulation and are not intended to provide precise risk estimates or probability calculations.

Key survey variables include menopausal status, body mass index (BMI), race, abnormal vaginal bleeding, and pelvic pain. Additional factors include infertility or nulliparity, family history of endometrial cancer, diagnosis of Lynch syndrome, prior breast or ovarian cancer, and history of complex or atypical endometrial hyperplasia. Hormonal exposures such as tamoxifen use and unopposed estrogen therapy were included because of their known effects on the uterine lining. Lifestyle factors, including physical activity and dietary fat intake, were also considered, as they can indirectly influence metabolic and hormonal risk.²⁰

Race is included as a demographic risk indicator reflecting documented disparities in incidence and outcomes, not as a biological determinant of disease. Its inclusion is intended to capture population-level risk patterns described in the literature rather than to imply inherent biological differences.

By assigning higher point values to factors more strongly associated with disease risk, the survey generates a structured risk profile that is easy to interpret and suitable for integration with biomarker data. The full survey instrument and scoring rubric are provided in Appendix A.

Blood-Based Biomarker Analysis

The second part of the framework evaluates blood-based biomarkers linked to endometrial cancer. These biomarkers include CA-125, human epididymis protein 4 (HE4), red blood cell count, red blood cell distribution width (RDW), and DNA methylation of tumor suppressor genes. Biomarkers were selected based on how easily they can be measured in routine blood tests and how often they have been associated with endometrial cancer in previous studies.²¹ Similar to the survey component, biomarker point values were assigned to reflect their relative importance in the model rather than to generate precise statistical risk estimates. The scoring was designed to represent biological contribution using a transparent, rule-based approach, not to produce mathematically optimized predictions.

CA-125 and HE4 levels were evaluated using standard clinical thresholds, with higher levels increasing the risk score. Blood measurements were included to reflect anemia caused by chronic abnormal uterine

bleeding, a common symptom of endometrial cancer. RDW values outside the normal range were assigned higher point values to account for their association with cancer-related anemia.²²

DNA methylation was measured in tumor suppressor genes CDH13, HSPA2, MLH1, SOCS2, and RASSF12. Detection of hypermethylation in three or more of these genes was considered indicative of higher cancer risk, in line with previous studies on epigenetic markers in endometrial cancer and Lynch syndrome-related tumors.²³

Algorithm Integration and Risk Stratification

Survey-based and biomarker-based scores were computed independently and then integrated using a rule-based scoring algorithm. Conservative thresholds were applied to prioritize identifying potentially higher-risk individuals within the simulated framework. Total risk scores were categorized as low (<50), moderate (50-79), or high (≥ 80) risk.

The algorithm is intended to assist clinical evaluation by assigning individuals to risk categories that may warrant further clinical assessment. It was designed to be transparent and easy to understand so that both clinicians and patients can clearly interpret how risk levels are determined.

Because this framework was evaluated using simulated data rather than patient outcomes, the results should be interpreted as illustrative of model behavior and structure, not as evidence of clinical diagnostic accuracy.

RESULTS

To evaluate the utility of the proposed screening framework, a simulated dataset of 500 hypothetical individuals was created. The simulation used published epidemiological data and established clinical biomarker thresholds. The results are meant to show how the model assigns risk and behaves overall, rather than to represent true diagnostic performance.

Survey-Based Risk Score Distribution

Survey-based risk scores showed central clustering with a gradual rightward taper, reflecting the distribution of high-weight clinical and lifestyle risk factors within the simulated cohort (Figure 1). Most individuals clustered within a moderate-risk range, suggesting that the survey does not disproportionately classify people as high risk. This pattern illustrates how the survey component generates differentiated risk scores across demographic, clinical, and lifestyle factors within the simulated cohort.

Blood-Based Biomarker Score Distribution

The blood-based biomarker score distribution is right-skewed and clustered around specific values, reflecting the threshold-based and point-based design of the biomarker scoring system. Most individuals received low biomarker scores, while a smaller subset accumulated higher scores due to multiple elevated biomarkers (Figure 2), reflecting differences in underlying biology. This result is consistent with prior research showing that biomarkers alone may not be specific enough when used on their own, supporting the value of combining biological measures with survey-based data.

Combined Risk Stratification

Survey and biomarker scores were combined into a total risk score for each individual. Risk levels were defined as low (<50), moderate (50–79), and high (≥ 80). In the simulated cohort of 500 individuals, 282 were categorized as low risk, 190 as moderate risk, and 28 as high risk (Figure 3). This pattern reflects the model's design as a preliminary risk stratification framework, illustrating how individuals might be categorized for further evaluation within the simulated cohort.

As an internal consistency assessment, individuals meeting an assumed high-likelihood (AHL) profile were examined relative to assigned risk categories. The high-likelihood profile was defined as abnormal vaginal bleeding combined with elevated tumor biomarkers (HE4 or CA-125) and the presence of three or more hypermethylated genes. Nineteen individuals met this predefined definition within the simulated dataset. All 19 of these cases were categorized as either moderate or high risk, corresponding to a 100% capture rate within the simulated framework. This analysis reflects behavior within the simulated environment and does not represent clinical validation.

Relationship Between Survey and Biomarker Scores

The survey-based and biomarker-based risk scores showed limited correlation, indicating that each captures different aspects of endometrial cancer risk. As shown in Figure 4, some individuals with moderate survey scores had high biomarker scores, indicating that using only one risk-assessment method could miss higher-risk cases.

DISCUSSION

The results of this study illustrate how combining survey-based risk assessment with blood-based biomarker analysis can stratify individuals within a simulated population. Survey scores reflected demographic, symptom-based, and lifestyle risk factors, while biomarker scores captured underlying

March 2026

Vol 4, No 1.

biological changes. Using both together illustrates how individuals who do not present with overt symptoms may still exhibit elevated biological indicators within the simulated framework.

Importantly, survey and biomarker risk scores were weakly correlated, showing that each measures different aspects of endometrial cancer risk as shown in Figure 4. This result supports the conceptual rationale for a combined risk-stratification framework and is consistent with prior research showing the limits of using biomarkers alone.

The risk thresholds clearly separated individuals into low-, moderate-, and high-risk groups (Figure 3). A defined subset of individuals were classified as high risk, reflecting the framework's conservative design. If evaluated in clinical settings after appropriate validation, this framework could inform future exploration of structured referral workflows.

From a public health standpoint, the framework illustrates how structured, non-invasive risk assessment can be conceptually aligned with accessibility in mind. Using minimally invasive tools illustrates how future risk-stratification frameworks might be structured to prioritize accessibility for individuals who face delays in diagnosis due to socioeconomic factors or limited access to gynecologic care. By combining demographic and social risk factors with biological markers, the model reflects the many factors that contribute to disparities in endometrial cancer risk.

Several limitations must be acknowledged. All results come from simulated data and are intended to show how the model works, not to provide real diagnostic accuracy. Because no real patient outcomes were modeled, the internal consistency assessment does not represent sensitivity, specificity, or predictive value.

The scoring structure is informed by published research but remains heuristic. Points were assigned to reflect the relative importance of risk factors within a transparent rule-based model rather than to generate precise quantitative risk estimates. Demographic variables were included to reflect documented population-level disparities and must be interpreted carefully to avoid unintended bias. Additionally, biomarker abnormalities such as CA-125, HE4, and RDW can be elevated for reasons other than cancer, which means some healthy individuals could be incorrectly flagged as higher risk. Testing the framework with actual patient data is necessary before it can be applied in real-world settings.

Future research should test this framework in real clinical populations, refine biomarker thresholds, and consider ethical issues around using algorithms for screening. Incorporating the model into primary care and providing patient education could help improve early detection and reduce disparities in endometrial cancer risk.

CONCLUSION

This study presents a simulation-based, rule-driven framework for early endometrial cancer risk stratification that integrates survey-based and blood-based inputs. By combining demographic, clinical,

March 2026

Vol 4, No 1.

lifestyle, and molecular factors, the model assigns individuals to defined risk categories intended to support consideration of further clinical evaluation.

The findings illustrate how a transparent, additive scoring system can organize diverse risk signals within a structured framework. Although the model is not diagnostic and requires empirical validation using patient data, it provides a conceptual foundation for future research on accessible and integrated approaches to endometrial cancer risk assessment.

ETHICAL CONSIDERATIONS

Although this study relies solely on simulated data and does not involve human participants, ethical considerations remain important. Any screening or risk-stratification model can create unintended consequences if used or interpreted without appropriate clinical context.

One ethical concern is false-positive classification. Several biomarkers included in the model, such as CA-125, HE4, RDW, and low RBC count, can be elevated in non-cancerous conditions. As a result, some individuals could be categorized as moderate or high risk despite not having cancer. Without physician oversight, such classifications may cause anxiety, unnecessary testing, or additional financial burden. For this reason, the proposed framework is explicitly positioned as a preliminary risk-stratification tool rather than a diagnostic instrument.

Over-referral is another important consideration. If threshold values are applied too broadly, healthcare systems could experience increased demand for diagnostic procedures, potentially placing strain on medical resources. Any practical implementation would therefore require careful adjustment of thresholds to balance early detection goals with responsible resource use.

Algorithmic bias also requires careful attention. The inclusion of demographic variables such as race is intended to reflect documented disparities in incidence and outcomes, not to suggest that these differences are biologically driven. Algorithmic use of demographic factors must be approached cautiously to avoid reinforcing existing structural inequities. Ongoing evaluation, transparency in scoring logic, and clinical oversight are important safeguards.

Finally, misuse outside clinical supervision presents an additional risk. A risk-stratification framework should not be viewed as a substitute for professional medical evaluation. Clear communication about the tool's purpose and limitations would be critical to prevent overreliance or misinterpretation.

Because this framework is conceptual and simulation-based, these ethical considerations remain theoretical at this stage. Nonetheless, acknowledging these risks is essential before considering future efforts.

FIGURES

Figure 1. Distribution of survey-based risk scores across a simulated population of 500 individuals. Scores demonstrate central clustering with a gradual rightward taper, reflecting the distribution and weighting of demographic, clinical, and lifestyle risk factors within the simulated cohort.



Figure 2. Distribution of blood-based biomarker risk scores. The distribution is right-skewed and clustered around specific values, reflecting the threshold-based and point-based design of the biomarker scoring system. Most individuals received low biomarker scores, while a smaller subset accumulated higher scores due to multiple elevated biomarkers.

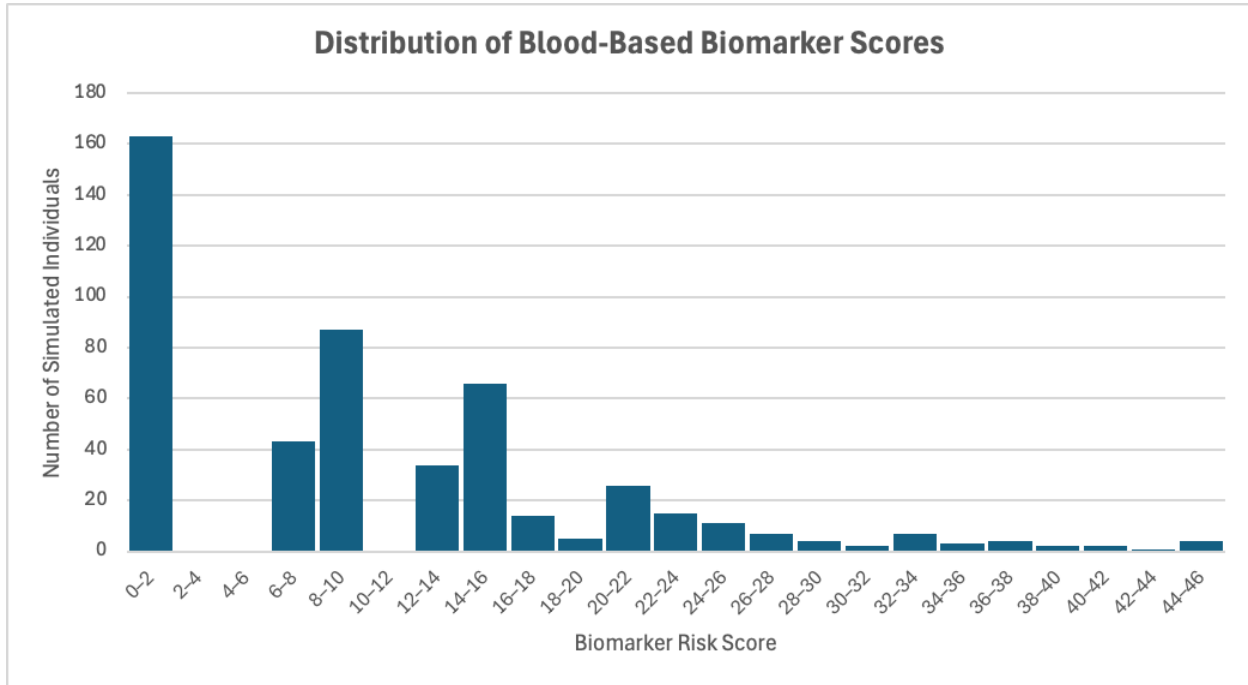


Figure 3. Total risk score distribution with predefined risk thresholds. Vertical lines indicate the boundaries for low (<50), moderate (50–79), and high (≥ 80) risk categories. In the simulated cohort, 282 individuals were classified as low risk, 190 as moderate risk, and 28 as high risk, illustrating stratification across the full risk spectrum.

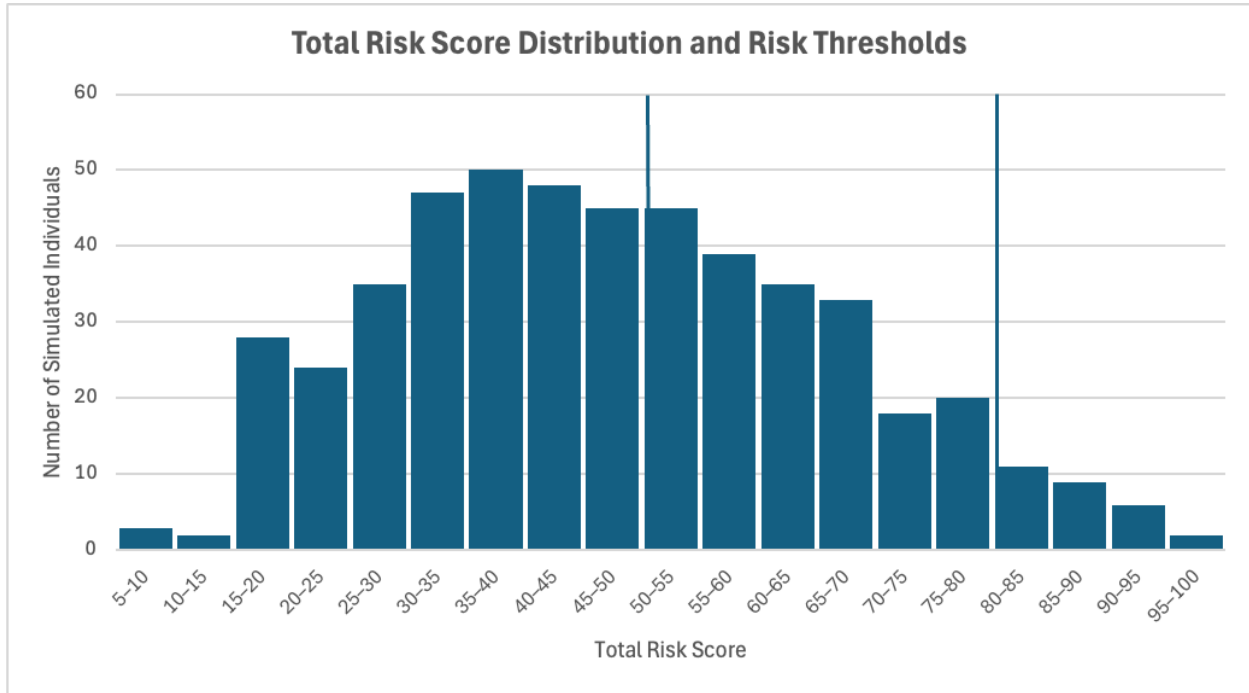
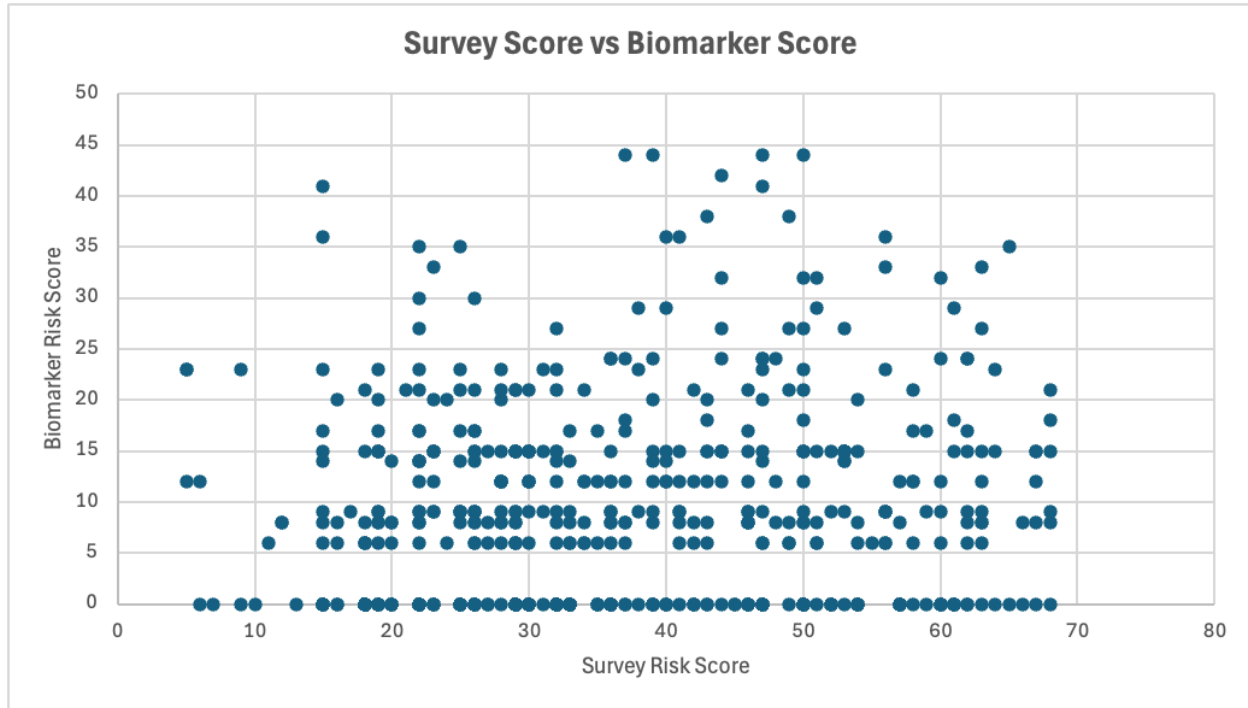


Figure 4. Relationship between survey-based and biomarker-based risk scores. The limited correlation between the two components demonstrates that survey variables and biomarkers capture distinct dimensions of risk.



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March 2026

Vol 4, No 1.

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March 2026

Vol 4, No 1.

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APPENDIX A: SURVEY INSTRUMENT AND SCORING RUBRIC

The survey instrument consists of 14 questions with a maximum total score of 100 points. Variables are weighted based on published research and their importance for assessing risk.

Demographic and Clinical Factors

- **Body Mass Index (BMI):** <25 (0 points), 25-29.9 (10 points), >30 (13 points)
- **Menopausal status:** Postmenopausal (10 points)
- **Race:** Black (6 points), White (5 points)
- **Abnormal vaginal bleeding:** 14 points
- **Abnormal pelvic pain:** 14 points
- **Infertility or nulliparity:** 1 point
- **Family history of endometrial cancer:** 4 points
- **History of complex or atypical endometrial hyperplasia:** 3 points
- **Lynch syndrome diagnosis:** 4 points
- **Prior breast or ovarian cancer:** 5 points

Hormonal and Lifestyle Factors

- **Tamoxifen use:** 2 points
- **Estrogen therapy without progesterone:** 4 points
- **Physical inactivity (<150 minutes/week):** 4-5 points
- **High-fat or nutritionally unbalanced diet:** 7 points

APPENDIX B: BLOOD-BASED BIOMARKER SCORING

Blood-based biomarkers are scored independently based on predefined thresholds, with points adjusted to match how changes in the biomarker affect cancer risk.

<u>Biomarker</u>	<u>Threshold</u>	<u>Points</u>	<u>Rationale</u>
HE4	>150 pmol/L	Up to 15	Elevated in gynecologic malignancies
CA-125	>35 U/mL	9	Associated with endometrial and ovarian cancer

<u>Biomarker</u>	<u>Threshold</u>	<u>Points</u>	<u>Rationale</u>
DNA methylation	≥ 3 hypermethylated genes	12	Tumor suppressor gene silencing
RDW	Outside normal range	8	Indicative of anemia
RBC count	< 4 million/ μL	6	Associated with abnormal uterine bleeding

DNA methylation analysis focuses on hypermethylation of CDH13, HSPA2, MLH1, SOCS2, and RASSF12. Detection of three or more hypermethylated genes is considered indicative of higher cancer risk.

APPENDIX C: ALGORITHM LOGIC SUMMARY

Survey scores and biomarker scores are computed independently and combined to produce a total risk score. Risk categories are assigned as follows:

- **Low risk:** < 50
- **Moderate risk:** 50-79
- **High risk:** ≥ 80