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Endometrial cancer risk factors, hormone receptors, and mortality prediction

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Abstract

Background—Endometrial tumors arise from a hormonally-responsive tissue. Defining subtypes by hormone receptors might better inform etiology and prediction of patient outcomes. We evaluated the potential role of tumor estrogen receptor (ER) and progesterone receptor (PR) expression to define endometrial cancer subtypes.

Methods—We measured semi-continuous ER and PR protein expression in tissue specimens from 360 endometrial primary tumors from the Nurses' Health Study. To explore the impact of different definitions of marker positivity, we dichotomized ER and PR expression at different cut points in increments of 5% positive cells. Logistic regression was used to estimate associations between endometrial cancer risk factors, such as body mass index, with dichotomous ER or PR status. Reclassification statistics were used to assess whether adding dichotomous ER or PR status to standard prognostic factors of stage, grade, and histologic type would improve prediction.

Results—Compared to not being obese, obesity increased the odds of having an ER-positive tumor at cut points of 0–20% (maximum OR=2.92, 95% CI 1.34, 6.33) as well as the odds of having a PR-positive tumor at cut points of 70–90% (maximum OR=2.53, 95% CI 1.36, 4.68). Adding dichotomous tumor ER or PR status to the panel of standard predictors did not improve both model discrimination and calibration.

Conclusion—Obesity may be associated with greater endometrial tumor expression of ER and PR. Adding either marker does not appear to improve mortality prediction beyond the standard predictors.

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Impact—Body mass index might explain some of the biological variation among endometrial tumors.

Keywords

Endometrial cancer; body mass index; risk factors; estrogen receptor; progesterone receptor; etiology; prediction; mortality

INTRODUCTION

Cancer is a heterogeneous disease, with multiple molecular subtypes having been recognized at each of several different tumor sites (1–5). Ideally, molecular subtyping of a given tumor site provides insight into disease etiology, prognosis, and response to therapy, and thereby can guide prevention and treatment strategies.

Endometrial tumors are classified primarily by histology (6, 7). While this approach generally works well for prediction of patient outcomes, defining subtypes by molecular markers might better inform etiology and further refine prediction for a disease that is currently considered homogeneous.

Endometrial cancer arises from a tissue that is sensitive to endogenous hormone levels (8–10), growing and differentiating according to the coordinated actions of estrogen and progesterone via their respective receptors. Exposures that either elevate estrogen or lower progesterone levels, such as body mass index (BMI), increase endometrial cancer risk (8, 11, 12). Endometrial tumor expression of hormone receptors could be an important biological feature of the disease that may provide a basis for distinguishing subtypes.

Using an incident case series of endometrial tumors from the Nurses' Health Study (NHS), we evaluated the potential role of tumor expression of estrogen receptor (ER) and progesterone receptor (PR) to define endometrial cancer subtypes. Our analysis aimed to explore how the definition of marker positivity impacts the relationship of marker expression to both risk factor exposures (especially BMI) and outcomes prediction, a crucial public health and clinical consideration. Based on prior research (11–17), we hypothesized that high BMI would be associated with increased endometrial tumor expression of ER and PR, and that marker expression status would substantially improve prediction of endometrial cancer-specific mortality.

MATERIALS AND METHODS

Conceptual Model

We considered tumor marker expression an intermediate between risk factors and patient outcomes (Figure 1). Therefore, evaluating the potential role of a marker to define subtypes should consider relationships in both directions (18). Figure 1 depicts risk factors as influencing patient outcomes through both direct effects and tumor-mediated indirect effects. In practice, some risk factors might have direct effects on patient outcomes while others might not. Thus, risk factors should be distinguished from confounders of tumor-outcomes associations, even though the two sets of variables might overlap substantially.

Relationships between risk factors and marker-defined subtype can be properly conceived as population-level questions. However, relationships between tumor subtype and outcomes are an inherently clinical, individual-level matter where the practical concern is the ability to classify a given individual as high risk or low risk for a specified outcome. Thus, different kinds of analyses can be most informative for the two halves of the investigation (19).

Measures of association are an informative approach for population-level research questions, while prediction modeling is most relevant for questions at the level of the individual (19). Since a strong association between a marker and outcome does not necessarily mean that the marker can accurately classify an individual's risk for that outcome (19), association modeling is appropriate to examine disease etiology, but risk classification methods grounded in prediction modeling are preferred to examine relationships between subtype and outcomes (20, 21). Control of confounding is an important feature of association modeling but not of prediction modeling.

Study Population

Participants in this case-only analysis came from the NHS, a prospective cohort that enrolled 121,700 female registered nurses aged 30–55 in 1976 from 11 states across the United States (22–24). At baseline and biennially thereafter, participants completed self-administered questionnaires to capture detailed information on a variety of lifestyle and reproductive characteristics and to update health-related outcomes, including cancer diagnoses. Follow-up for each questionnaire cycle exceeded 90%.

Case Ascertainment

Participants reporting a cancer diagnosis on any questionnaire after baseline in 1976 and through 2012 were mailed a release form requesting permission to review medical records to confirm diagnoses, additional pathology information such as tumor stage, date of diagnosis, and request permission to access tissue specimens. After medical records were obtained, they were reviewed by an NHS physician to confirm the diagnosis, considering primary endometrial cancer cases to be those with International Classification of Diseases 8 codes starting with 182. Women with any prior cancer diagnosis (except non-melanoma skin cancer), or whose self-reported diagnosis could not be confirmed by medical records, were excluded. Based on medical records information, a pathologist (GLM) updated endometrial cancer case histologic classifications using 2009 standards (25).

For each eligible, confirmed endometrial cancer case, a letter was sent to the hospital that performed surgery requesting all available tissue blocks containing representative samples of the endometrial carcinoma as well as original diagnostic Hematoxylin and Eosin (H&E) slides. Participants were not re-contacted at this step unless the hospital requested a further release form that was more recent than that on file with the NHS, or contained specific language.

Of 2,035 NHS participants who were sent a release form, 106 did not have records available and 521 were not eligible for other reasons such as lack of returning a release form or not having surgery. Of the remaining 1,408 participants, 904 had no tissue available due to tissue destruction or hospital refusal, for 21 the hospital did not respond to contacts, and for 11

tissue could not be obtained for other reasons. We obtained primary tumor tissue specimens from 472 cases. Of these, we excluded 102 due to diagnostic confirmation failure, 4 had depleted tissue blocks, 2 had no blocks, 2 had mismatches between tissue slides and blocks, 1 had no cancer, and 1 had a sarcoma. The remaining 360 participants provided tissue adequate to be incorporated into a paraffin tissue microarray (TMA). Receipt of a completed questionnaire was considered as evidence of a desire to participate in the study and was taken as a formal indication of consent. The NHS protocol was approved by the Institutional Review Board of Brigham and Women's Hospital (BWH), Boston, MA, USA.

ER and PR Measurements

Detailed immunohistochemistry (IHC) methods are provided in the Supplemental Materials and Methods file. To visually score nuclear marker staining of tumor cells across all 3 tissue cores per surgical specimen, cellular signal intensity exceeding background noise defined a positive cell. Each marker was scored in semi-continuous fashion as the percentage of positive cells in 5% increments ranging from 0–100%, then averaged across duplicate runs to produce a final marker expression score for the participant. Technical failures due to tissue dropout, high background, or low signal were excluded as non-informative.

Covariates

Endometrial cancer risk factors were assessed in the biennial NHS questionnaires and included BMI (measured as continuous kilograms/meters^2 and then dichotomized at 25 or 30, depending on the model), years of unopposed estrogen hormone therapy (HT) use (continuous), years of estrogen-progesterone combination HT use (continuous), years of other HT use (continuous), years of oral contraceptive use (continuous), whether the participant was a current smoker (yes/no), whether the participant was a former smoker (yes/no), number of pack-years smoked (continuous), diabetes status (yes/no), family history of endometrial cancer (yes/no), parity (continuous), years from menarche to menopause (continuous), and years since menopause (continuous). Risk factor values were those from the last biennial questionnaire prior to cancer diagnosis, except for family history of endometrial cancer, which was asked on the 1996 and 2008 questionnaires, and parity, which was most recently updated on the 1996 questionnaire. Unopposed estrogen and estrogen-progesterone combination HT use were each restricted to orally-ingested pills. Other HT use included progesterone-only pills and any vaginal creams regardless of what hormones the creams contained.

Prognostic factors were those variables most commonly used to make endometrial cancer treatment decisions: tumor stage (I/II or III/IV), tumor grade (well-/moderately-differentiated or poorly-differentiated), and histologic type (endometrioid or non-endometrioid). All confirmed cases of endometrial cancer were staged at initial diagnosis using guidelines applicable at the time ("legacy stage"). Tumors for which tissue was available for this study were restaged by our pathologist (GLM) according to 2009 guidelines of the International Federation of Gynecology and Obstetrics ("2009 stage") (25). Legacy staging was used for descriptive statistics and standardized 2009 staging was used for statistical models.

Two patient outcomes were assessed: time from cancer diagnosis to all-cause mortality and time from diagnosis to endometrial cancer-specific mortality. Deaths were identified using the National Death Index or by report from relatives or the United States Postal Service. For each outcome, survival time ended at death or in January 2012, whichever came first, and was censored at 10 years after diagnosis.

Statistical Analysis

Univariate analyses were performed separately for all endometrial cancer cases, those who provided any tissue specimens, and those whose tissue specimens were adequate to be incorporated into TMAs. All other analyses were restricted to those with TMA specimens and successful ER or PR marker measurements.

To evaluate how the definition of marker-positivity influences associations between marker expression and risk factors as well as with outcomes, for each of ER and PR, we created a series of dichotomous marker status variables based on semi-continuous measurements and using cut points in 5% increments (0%, 5%, 10% and so on). For a cut point of 0%, we defined marker-positive status as expression above 0% and marker-negative as expression of 0% (>0% vs. 0%). For all other cut points, marker-positive status meant expression at or above the cut point and marker-negative meant expression below the cut point (e.g. >=5% vs. <5%).

To evaluate associations between risk factors and hormone receptor expression, we performed unconditional logistic regression with a dependent variable of dichotomous hormone receptor expression status defined by a given cut point and with independent variables of the risk factors listed above. BMI was included as a single dichotomous variable, either at a cut point of 25 or 30, but not both in the same model. For each combination of hormone receptor and dichotomous BMI variable, a series of models was run, with each model using a different cut point to define dichotomous hormone receptor status. To evaluate whether any risk factors were also prognostic, risk-factor models of dichotomous ER or PR status were run that further included stage or all established prognostic factors (stage, grade, and histologic type). As a sensitivity analysis, we ran linear regressions using an outcome of continuous ER or PR expression.

To investigate relationships between tumor ER or PR expression and patient outcomes, we used Cox proportional hazards modeling (26) of time from diagnosis to all-cause mortality or to endometrial cancer-specific mortality. For association modeling, we ran series of Cox models with independent variables of risk factors (BMI dichotomized at 30) and dichotomous ER or PR expression defined by a given cut point. For prediction modeling, we ran Cox models with independent variables of established prognostic factors (stage, grade, histologic type), then further Cox models with independent variables of established prognostic factors and dichotomous ER or PR expression defined by a particular cut point. Probabilities for cancer-specific mortality for individual participants based on prediction models with and without a hormone receptor variable were compared to each other to assess mortality risk reclassification. Cox models using continuous marker expression were run as a sensitivity analysis.

The predictive Cox models were used to construct risk stratification tables (21, 27), with one table per dichotomous hormone receptor expression variable. To evaluate prediction models, several measures of discrimination—area under the receiver operating characteristic (ROC) curve for censored outcomes (c-index), Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI)—as well as a measure of calibration (reclassification calibration statistic) were calculated (28, 29). Statistically-significant reclassification calibration statistics indicated poor fit. For model discrimination, larger values meant better discrimination according to all three measures.

Risk stratification and reclassification analyses were performed using SAS macros available through the BWH Division of Preventive Medicine Risk Prediction Modeling website (http://ncook.bwh.harvard.edu/). Mortality risk category cut points of 5% and 10% were used because patient obesity is often incorporated into treatment decisions, particularly regarding surgery, and among our cases with ER or PR measurements, the 10-year risk of endometrial cancer-specific death was 3.6% among the obese and 9.5% among the non-obese.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Models were not adjusted for multiple comparisons because the variables in a cut point analysis do not change, only the coding of variables (30, 31).

RESULTS

Participant characteristics for all cases, cases who provided any tissue specimens, and cases included in TMAs are presented in Table 1. For those with TMA specimens, ER and PR expression distributions are presented in the supplement (Table S1). Cases who provided tissue were generally similar to all cases, with the main differences being that those who provided tissue were a little older due to more years since menopause, were less frequently current smokers, and more frequently diabetic. Cases were diagnosed throughout the 40-year history of the NHS, but most of those for whom we obtained tissue specimens were diagnosed in the past 20 years.

Compared to being non-obese (BMI<30) and adjusted for all other risk factors, obesity (BMI>=30) was associated with greater odds of ER-positive status at ER cut points ranging from 0–20% (Table 2). Among these estimates, the greatest magnitude of effect was observed at a cut point of 10% (odds ratio [OR]=2.92, 95% confidence interval [CI] 1.34, 6.33) and the best precision at 20% (OR=2.40, 95% CI 1.22, 4.74). Although each model included all risk factors, no risk factor other than BMI was associated with tumor ER status in any of the models. BMI dichotomized at 25 (greater than normal weight versus normal weight) was not associated with tumor ER status (Table 2).

Compared to non-obesity, obesity was associated with greater odds of PR-positive status at PR cut points ranging from 70–90% (Table 3). Among these estimates, the greatest magnitude of effect was observed at a cut point of 90% (OR=2.53, 95% CI 1.36, 4.68) and the best precision at 70% (OR=2.03, 95% CI 1.25, 3.30). No other risk factor was associated with PR status. When dichotomizing BMI at 25, estimates of the association of BMI with

PR status were generally similar to those for BMI dichotomized at 30, but attenuated across PR cut points of 70–90% (Table 3).

The Supplemental Results file presents further analyses including associations between BMI and hormone receptor status when adjusted for risk factors plus tumor stage or all prognostic factors, and separate comparison of obese or overweight participants to a consistent reference group of normal weight participants (Tables S2–S6). After addition of all prognostic factors to etiologic models, associations between BMI and ER were consistently eliminated (Table S2) while associations between BMI and PR persisted in some, but not all, cases, (Tables S4 and S5).

Regarding patient outcomes, out of 360 patients included in the TMAs, 56 (16%) died from any cause within 10 years of diagnosis. Among the 56 deaths, 25 (7% of 360) were attributed specifically to endometrial cancer. In association Cox models (i.e. adjusted for risk factors as confounders), ER-positive status was associated with better endometrial cancer-specific survival at ER cut points ranging from 0–75%, with the greatest magnitude of effect at a cut point of 45% (hazard ratio [HR]=0.19, 95% CI 0.08, 0.45) and best precision at 50% (HR=0.20, 95% CI 0.09, 0.47) (Table 4). PR-positive status was associated with better cancer-specific survival at most PR cut points of at least 20%, with the greatest magnitude at a cut point of 80% (HR=0.08, 95% CI 0.01, 0.61) and best precision at 20% (HR=0.33, 95% CI 0.15, 0.77) (Table 4). Both ER and PR marker-positive status generally correlated with better overall survival, but the estimates were rarely statistically significant (Table 4). Aside from hormone receptor status, the only other risk factor associations with survival were greater years from menarche to menopause and years since menopause each being associated with worse survival (estimates not shown).

To assess how the addition of dichotomous marker status to the panel of established prognostic factors impacted mortality prediction, Table 5 presents results for cut points that converged successfully; corresponding risk stratification tables are in Supplemental Results (Tables S7–S11). The c-index for a model of established prognostic factors but no marker was 74.5%. Addition of a hormone receptor variable to the panel of established prognostic factors increased the c-index, with addition of ER to the panel of predictors increasing the c-index to a greater extent than the addition of PR (Table 5). In terms of reclassification measures of discrimination, ER performed better by NRI and PR performed better by IDI, but improvements in discrimination appeared smaller by these metrics than by the c-index. Dichotomous PR led to better calibration than ER.

Most etiologic and outcomes sensitivity analyses using continuous versions of BMI, ER, and PR showed no association (not shown). Continuous PR was associated with continuous BMI and BMI dichotomized at 30 (not shown). Greater continuous expression of each hormone receptor was associated with better endometrial cancer-specific survival (not shown). However, associations involving continuous hormone receptor expression were always weaker than the several strongest associations involving different dichotomizations of hormone receptor expression.

DISCUSSION

Overall, our results suggest that ER and PR status measured by IHC might usefully distinguish subtypes of endometrial tumors in terms of different etiologic processes. Compared to non-obese women, those who were obese had greater odds of high tumor ER and PR expression across a range of cut points defining dichotomous marker status. Although there was some evidence that any weight above normal (overweight or obese) could be associated with high PR expression, in general it appeared that obesity was more strongly associated with greater hormone receptor expression than was simply being overweight (Tables 2 and 3; Supplemental Tables S3 and S6).

Excess weight could be responsible for about 40% of endometrial cancer incidence in affluent societies (32). Past research suggested that some endometrial tumors might arise due to carcinogenic effects on endometrial tissue of exposure to high levels of estrogen in the absence of progesterone, and excess weight might promote these carcinogenic effects by affecting endogenous hormone metabolism (12). Our results provide evidence that endometrial tumor expression of ER and PR could be associated with obesity. This suggests that there might be at least two different pathways to endometrial carcinogenesis, although our data cannot inform what the mechanistic differences might be.

The potential value of the hormone receptors as predictors of endometrial cancer-specific mortality was uncertain. Past studies concluded that endometrial tumor hormone receptor expression correlated with patient outcomes (16, 17), but the analysis techniques in those studies have known limitations for purposes of prediction (19, 20). In our study, dichotomous ER and PR status were each associated with endometrial cancer-specific survival at multiple cut points (Table 4). Most relevant to clinical settings, we evaluated whether adding the markers to the panel of established prognostic factors (stage, grade, histologic type) would improve patient mortality prediction in terms of reclassifying individual risks compared to prediction based only on established prognostic factors (Table 5). The meaning of these results was unclear because different prediction statistics yielded qualitative differences: adding a marker (especially ER) to the panel improved model discrimination as measured by the c-index, but in the reclassification analysis, adding a marker never yielded clear improvements in both model discrimination and calibration. This might be clarified by assessing hormone receptor prediction of response to therapy rather than prediction of mortality, but information on treatment response was not available in our dataset.

Critically, for either marker, no single definition of high versus low expression was objectively best in the sense that it optimized all statistical measures across the disease trajectory. Rather, evaluating multiple cut points for a given marker revealed a series of trade-offs. This is an important point for research and translation because it informs the choice of how to define marker-positive status, and thereby how to define the disease state (subtypes).

To illustrate for ER, we found associations between BMI dichotomized at 30 and dichotomous ER status at cut points ranging from 0% to 20% positive cells (Table 2).

Among these ER cut points, the greatest magnitude of effect was at 10% (OR=2.92, 95% CI 1.34, 6.33) but the best precision was at 20% (OR=2.40, 95% CI 1.22, 4.74). The cut point with the best precision of all was at 75% (OR=0.94, 95% CI 0.58, 1.52). When turning to association modeling of dichotomous ER and time to endometrial cancer-specific mortality (Table 4), the cut point with the greatest magnitude of effect (cut point 45%; HR=0.19) was different than the cut point with the greatest magnitude of effect for the association between BMI and ER (10%). Further trade-offs between cut points were apparent in terms of the proportion of individuals defined as marker-positive (Tables 2 and 3), prediction model discrimination and calibration (Table 5), and different measures of prediction discrimination (c-index, NRI, IDI) (Table 5).

Our study had several strengths. First, to our knowledge this is the first attempt to assess whether and how to define endometrial cancer subtypes in terms of tumor expression of hormone receptors. Second, while previous IHC studies of cancer subtyping markers have considered the role of more than one threshold to define marker-positivity (5, 33, 34), to our knowledge the cut point analyses in this study were the first attempt to investigate all possibilities. This approach allowed the widest-possible assessment of how tumor marker expression relates to risk factors and outcomes. For example, we showed that obesity was associated with increased odds of having an ER-positive tumor (rather than ER-negative) when ER was dichotomized in the range of 0–20% positive cells, but similar associations for PR were observed at a different set of cut points (70–90%). Using cut points from only a portion of the full range would have led to missing one of these sets of associations. Presenting the detailed results of a cut point analysis, as shown in our tables, allows for assessment of the trade-offs between different definitions of marker positivity and provides insight into the implications of any choice for research and translation.

Third, our risk stratification tables and related reclassification statistics measured the ability of tumor ER or PR status to classify an individual’s risk for a future event of interest, in this case death from endometrial cancer (21). Given known limitations of measures of association (19) and ROC curves (20) as prediction techniques, the reclassification framework provided an outcomes prediction analysis that more closely reflected clinical decision-making than those other methods.

Indeed, our results showed how the performance of a potential predictor can vary depending on the prediction methods used. For example, ER dichotomized at any of several cut points appeared to perform well as a predictor of cancer-specific mortality when assessed by association hazard ratios (Table 4) and c-indices (Table 5). In contrast, reclassification analysis suggested that the extent to which a marker might reclassify individuals’ risks for cancer-specific mortality could be negligible (Table 5). Our integration of cut-point and reclassification analyses in Table 5 indicated the varying impact of adding tumor ER or PR status to the panel of clinical predictors by definition of marker positivity, providing further information to consider in selecting cut points of marker expression.

Regarding study limitations, first, although the correlation between IHC measurements obtained by manual and digital scoring can be excellent (35), digital image analysis provides certain advantages that we could not avail ourselves of. While our manually-scored marker

expression data were approximately continuous, truly continuous IHC data can only be obtained from digital image analysis. Continuous data maximize the number of cut points that can be analyzed. Furthermore, digital image analysis provides cell counts for each tissue core analyzed, whereas manual scoring generally does not. Obtaining cell counts per core permits calculation of a weighted average expression score (weighted by core cell count) across multiple cores for an individual. A weighted average score might be more representative of marker expression throughout the tumor than an unweighted average of cores and might also show greater interobserver agreement (33).

Second, while our results suggest that whether an individual is obese might influence the ER or PR expression level of an incident endometrial tumor, our case-only study design did not permit evaluation of whether obesity influences the risk of developing different kinds of endometrial tumors in terms of their level of ER or PR expression (36). Examining the latter question requires comparing cancer cases to non-cases. The case-only design did, however, allow us to evaluate whether BMI is prognostic for endometrial cancer outcomes by adjusting models for tumor characteristics that serve as standard predictors.

Third, only 18% of endometrial cancer cases confirmed in the NHS were included in the TMAs. However, as the overall cases and TMA cases had similar demographic, exposure, and tumor characteristics (Table 1), it is reasonable to think that the observed results are similar to what would have been observed if we had obtained tumor tissue on all cases.

Fourth, with 11 out of 360 (3%) TMA cases having non-endometrioid tumors (Table 1), we were not able to perform meaningful analyses stratified by tumor histologic type: power was insufficient for non-endometrioid tumors and any analyses restricted to endometrioid tumors would produce results virtually identical to those for the full sample.

In sum, we found some evidence that obesity may be associated with greater hormone receptor expression in endometrial tumors compared to those who are not obese. The value of using ER or PR to improve the accuracy of clinical prediction of endometrial cancer-specific mortality requires further investigation. Broadly, our analysis showed that extensive trade-offs between various statistical quantities must be considered in choosing cut points to define marker positivity. Nevertheless, this kind of analysis can inform the nuanced thinking that lies at the heart of personalized medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
ER	Estrogen Receptor
HR	Hazzard Ratio
H&E	Hematoxylin and Eosin
HT	Hormone Therapy
IHC	ImmunoHistoChemistry
IDI	Integrated Discrimination Improvement
NRI	Net Reclassification Improvement
NHS	Nurses' Health Study
OR	Odds ratio
PR	Progesterone Receptor
ROC	Receiver Operating Characteristics
TMA	Tissue Micro Array

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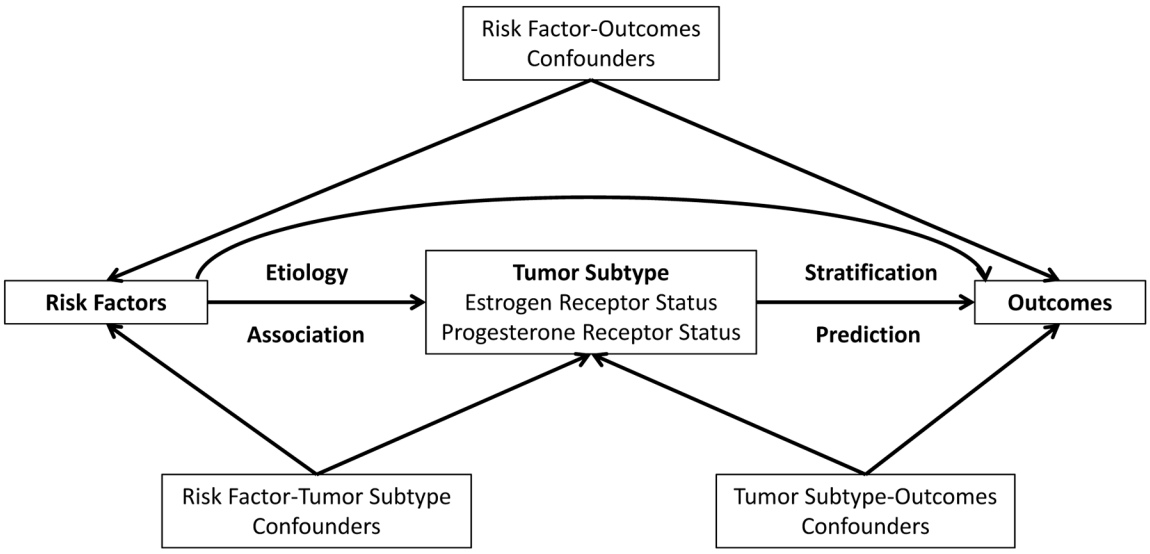

Figure 1.

Conceptual model of relationships between risk factors, endometrial tumor hormone receptor expression, outcomes, and analytic considerations

Table 1

Characteristics of endometrial cancer cases from the Nurses' Health Study

	All Cases (n=2,035)		Received Any Tumor Tissue (n=472)		In Tissue Microarrays (n=360)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	63.5	8.9	68.2	7.6	69.0	7.3
Years from Menarche to Menopause	38.3	4.5	38.9	4.3	38.9	4.1
Years Since Menopause	12.8	9.0	17.1	8.7	17.7	8.5
E-only HT Use of ever users (years)[a]	5.5	5.0	4.8	4.7	5.1	4.9
E+P HT Use of ever users (years)[a]	5.3	4.3	5.9	5.0	6.2	5.0
Other HT Use of ever users (years)[b]	5.4	12.0	5.1	7.3	5.1	8.1
OC Use of ever users (years)	4.3	8.0	3.5	3.6	3.6	3.7
Pack-Years Smoking	11.5	18.2	11.0	17.3	11.6	17.7
Parity among parous	3.0	1.4	2.9	1.4	3.0	1.4
	N	**%**	**N**	**%**	**N**	**%**
Year of Diagnosis						
1976–1985	324	16	2	0	0	0
1986–1995	642	32	51	11	34	9
1996–2005	757	37	249	53	190	53
2006–2013	311	15	170	36	136	38
Race						
White	1,995	98	467	99	356	99
African-American	22	1	3	1	2	1
Native American	4	0	0	0	0	0
Asian	14	1	2	0	2	1
Hispanic Ethnicity	9	0	1	0	0	0
Body Mass Index (kg/m^2)						
Normal Weight (<25)	627	34	132	30	97	29
Overweight (25<=BMI<30)	562	30	137	31	109	32
Obese (>=30)	654	35	176	40	134	39
E-only HT never users	1,512	74	371	79	281	78
E+P HT never users	1,515	74	310	66	238	66

	All Cases (n=2,035)		Received Any Tumor Tissue (n=472)		In Tissue Microarrays (n=360)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Other HT never users	1,384	68	288	61	224	62
OC never users	1,279	63	273	58	208	58
Nulliparous	158	8	40	9	28	8
Smoking Status						
Never Smoker	1,013	50	228	48	170	47
Former Smoker	821	40	227	48	177	49
Current Smoker	201	10	17	4	13	4
Diabetic	199	10	59	13	48	13
Family History of Endometrial Cancer	158	8	28	6	22	6
Tumor Stage						
I	1,706	88	405	87	313	87
II	65	3	20	4	18	5
III	39	2	7	2	5	1
IV	139	7	36	8	23	6
Tumor Histologic Type						
Endometrioid	1,902	94	457	97	349	97
Non-Endometrioid	113	6	15	3	11	3
Tumor Grade						
Well-Differentiated	988	53	234	51	178	51
Moderately-Differentiated	594	32	140	31	109	31
Poorly-Differentiated	291	16	85	19	65	18

Variables are as of time of endometrial cancer diagnosis.

[a] Orally-ingested pills only.

[b] Includes E-only, E+P, and progesterone-only vaginal creams, as well as progesterone-only orally-ingested pills E-only=Unopposed Estrogen, E+P=Estrogen+Progesterone, HT=Hormone Therapy, OC=Oral Contraceptive

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Table 2

Association between body mass index at diagnosis and endometrial tumor dichotomous ER status (n=346)

		BMI Coding (kg/m^2)[a]			
	# (%)	>=25 vs. <25		>=30 vs. <30	
ER Cut Point	ER+	OR	95% CI	OR	95% CI
0%	303 (88%)	1.29	0.60, 2.75	2.83	1.26, 6.37
5%	299 (86%)	1.45	0.70, 2.99	2.84	1.31, 6.17
10%	298 (86%)	1.36	0.66, 2.80	2.92	1.34, 6.33
15%	294 (85%)	1.23	0.61, 2.48	2.69	1.30, 5.58
20%	286 (83%)	0.92	0.47, 1.82	2.40	1.22, 4.74
25%	276 (80%)	0.96	0.51, 1.80	1.78	0.96, 3.31
30%	267 (77%)	0.93	0.51, 1.70	1.54	0.86, 2.75
35%	264 (76%)	0.85	0.46, 1.56	1.44	0.81, 2.58
40%	258 (75%)	0.91	0.51, 1.63	1.35	0.78, 2.36
45%	250 (72%)	0.79	0.44, 1.41	1.17	0.68, 1.99
50%	245 (71%)	0.79	0.45, 1.40	1.10	0.65, 1.87
55%	237 (68%)	0.98	0.57, 1.69	1.22	0.73, 2.04
60%	228 (66%)	0.93	0.54, 1.60	1.15	0.69, 1.90
65%	218 (63%)	0.96	0.57, 1.62	1.08	0.66, 1.76
70%	201 (58%)	1.00	0.60, 1.68	1.06	0.65, 1.72
75%	176 (51%)	0.98	0.58, 1.63	0.94	0.58, 1.52
80%	149 (43%)	1.14	0.68, 1.93	1.00	0.61, 1.63
85%	124 (36%)	1.23	0.72, 2.11	1.08	0.65, 1.79
90%	103 (30%)	1.36	0.76, 2.42	1.31	0.77, 2.23
95%	59 (17%)	1.51	0.74, 3.10	1.63	0.87, 3.04

(%) ER+ = number (percentage) of patients (out of 346) with ER expression at or above the cut point, except for a cut point of 0% where ER+ is only those above the cut point. ER expression measured as semi-continuous percent positive cells (0–100%), then dichotomized to ER+ and ER− groups.

[a]Each estimate is the BMI result from a separate model with a dependent variable of dichotomous tumor ER status (ER+ vs. ER−) defined by the respective cut point, and with independent variables of BMI (either [>=30 vs. <30] or [>=25 vs. <25] but not both), years of E-Only HT Use (continuous), years of E+P HT Use (continuous), years of Other HT Use (continuous), years of oral contraceptive use (continuous), current smoker (yes/no), former smoker (yes/no), pack-years of cigarettes smoked (continuous), diabetes (yes/no), family history of endometrial cancer (yes/no), parity (continuous), years from menarche to menopause (continuous), years since menopause (continuous). HT results from the same sets of models are presented in Supplemental Tables S2 and S4.

ER=Estrogen Receptor, E-Only=Unopposed Estrogen, E+P=Estrogen plus Progesterone, HT=Hormone Therapy, BMI=Body Mass Index

Table 3

Association between body mass index at diagnosis and endometrial tumor dichotomous PR status (n=342)

		BMI Coding (kg/m^2)[a]			
	# (%)	>=25 vs. <25		>=30 vs. <30	
PR Cut Point	PR+	OR	95% CI	OR	95% CI
0%	278 (81%)	1.40	0.75, 2.62	1.25	0.66, 2.33
5%	268 (78%)	1.55	0.86, 2.80	1.32	0.73, 2.39
10%	262 (77%)	1.59	0.89, 2.83	1.28	0.72, 2.28
15%	260 (76%)	1.52	0.85, 2.69	1.37	0.77, 2.44
20%	253 (74%)	1.59	0.91, 2.80	1.32	0.76, 2.31
25%	244 (71%)	1.65	0.95, 2.86	1.52	0.89, 2.61
30%	232 (68%)	1.39	0.81, 2.38	1.52	0.90, 2.57
35%	226 (66%)	1.46	0.86, 2.48	1.67	1.00, 2.81
40%	221 (65%)	1.42	0.84, 2.40	1.55	0.93, 2.59
45%	215 (63%)	1.36	0.80, 2.29	1.49	0.90, 2.46
50%	207 (61%)	1.35	0.80, 2.27	1.44	0.88, 2.35
55%	194 (57%)	1.22	0.73, 2.04	1.34	0.83, 2.18
60%	181 (53%)	1.15	0.69, 1.91	1.42	0.88, 2.29
65%	169 (49%)	1.13	0.68, 1.89	1.59	0.99, 2.57
70%	156 (46%)	1.33	0.79, 2.24	2.03	1.25, 3.30
75%	134 (39%)	1.76	1.02, 3.03	2.10	1.29, 3.43
80%	111 (32%)	1.70	0.96, 3.01	1.92	1.15, 3.20
85%	92 (27%)	2.13	1.14, 3.98	2.26	1.32, 3.89
90%	65 (19%)	2.40	1.12, 5.18	2.53	1.36, 4.68
95%	49 (14%)	2.50	1.04, 6.00	1.82	0.92, 3.57

(%) PR+ = number (percentage) of patients (out of 342) with PR expression at or above the cut point, except for a cut point of 0% where PR+ is only those above the cut point. PR expression measured as semi-continuous percent positive cells (0–100%), then dichotomized to PR+ and PR− groups.

[a]Each estimate is the BMI result from a separate model with a dependent variable of dichotomous tumor PR status (PR+ vs. PR−) defined by the respective cut point, and with independent variables of BMI (either [>=30 vs. <30] or [>=25 vs. <25] but not both), years of E-Only HT Use (continuous), years of E+P HT Use (continuous), years of Other HT Use (continuous), years of oral contraceptive use (continuous), current smoker (yes/no), former smoker (yes/no), pack-years of cigarettes smoked (continuous), diabetes (yes/no), family history of endometrial cancer (yes/no), parity (continuous), years from menarche to menopause (continuous), years since menopause (continuous). HT results from the same sets of models are presented in Supplemental Tables S6 and S8.

PR=Progesterone Receptor, E-Only=Unopposed Estrogen, E+P=Estrogen plus Progesterone, HT=Hormone Therapy, BMI=Body Mass Index

Table 4

Association between endometrial tumor dichotomous ER or PR status and patient survival

	ER (ER+ vs. ER−) (n=338)				PR (PR+ vs. PR-) (n=334)			
	Overall Survival		Cancer-Specific Survival		Overall Survival		Cancer-Specific Survival	
Marker Cut Point	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
0%	0.62	0.29, 1.30	0.32	0.13, 0.83	0.68	0.35, 1.31	0.51	0.20, 1.29
5%	0.69	0.33, 1.41	0.32	0.13, 0.79	0.89	0.47, 1.69	0.65	0.26, 1.62
10%	0.61	0.30, 1.22	0.27	0.11, 0.65	0.70	0.38, 1.27	0.46	0.20, 1.09
15%	0.60	0.31, 1.17	0.29	0.12, 0.69	0.64	0.36, 1.15	0.43	0.19, 1.00
20%	0.55	0.30, 1.03	0.29	0.12, 0.69	0.59	0.34, 1.05	0.33	0.15, 0.77
25%	0.55	0.30, 1.00	0.23	0.10, 0.54	0.57	0.33, 0.99	0.32	0.14, 0.73
30%	0.55	0.31, 0.97	0.23	0.10, 0.51	0.63	0.36, 1.09	0.32	0.14, 0.73
35%	0.56	0.32, 1.00	0.24	0.11, 0.54	0.65	0.38, 1.13	0.36	0.16, 0.84
40%	0.55	0.31, 0.96	0.21	0.09, 0.48	0.72	0.41, 1.24	0.41	0.18, 0.95
45%	0.55	0.31, 0.96	0.19	0.08, 0.45	0.78	0.45, 1.35	0.43	0.19, 1.01
50%	0.59	0.34, 1.02	0.20	0.09, 0.47	0.72	0.42, 1.26	0.40	0.17, 0.94
55%	0.63	0.36, 1.08	0.23	0.10, 0.54	0.72	0.42, 1.25	0.45	0.19, 1.05
60%	0.64	0.37, 1.10	0.26	0.11, 0.60	0.62	0.36, 1.08	0.29	0.11, 0.74
65%	0.70	0.41, 1.21	0.32	0.14, 0.74	0.57	0.33, 1.01	0.24	0.09, 0.67
70%	0.62	0.36, 1.07	0.32	0.13, 0.76	0.57	0.32, 1.01	0.20	0.07, 0.61
75%	0.59	0.34, 1.03	0.40	0.17, 0.95	0.64	0.36, 1.15	0.14	0.03, 0.60
80%	0.68	0.39, 1.19	0.57	0.24, 1.35	0.59	0.32, 1.09	0.08	0.01, 0.61
85%	0.69	0.38, 1.23	0.50	0.20, 1.28	0.52	0.26, 1.04	0.11	0.02, 0.83
90%	0.72	0.38, 1.37	0.49	0.16, 1.47	0.40	0.16, 1.00	--[a]	--
95%	0.84	0.40, 1.76	0.97	0.32, 2.93	0.39	0.14, 1.05	--[a]	--

ER and PR expression each measured as semi-continuous percent positive cells (0–100%), then dichotomized to Marker+ and Marker− groups. Marker+ status meant expression at or above the cut point, except for a cut point of 0% where Marker+ is only those above the cut point. During the observation period, among those with ER data there were 56 overall deaths and 25 deaths due to endometrial cancer. Among those with PR data, there were 55 overall deaths and 24 deaths due to endometrial cancer. Each estimate is the ER or PR estimate (as appropriate) from a Cox model with survival as the dependent variable and independent variable of dichotomous tumor PR status (PR+ vs. PR−) defined by the respective cut point, adjusted for BMI (>=30 vs. <30), years of E-Only HT Use (continuous), years of E+P HT Use (continuous), years of Other HT Use (continuous), years of oral contraceptive use (continuous), current smoker (yes/no), former smoker (yes/no), pack-years of cigarettes smoked (continuous), diabetes (yes/no), family history of endometrial cancer (yes/no), parity (continuous), years from menarche to menopause (continuous), years since menopause (continuous). Survival time was defined as time from diagnosis to all-cause mortality or endometrial-cancer specific mortality (as appropriate), administrative censoring at 10 years after diagnosis, or January 2012, whichever came first.

[a] Not estimable

ER=Estrogen Receptor, PR=Progesterone Receptor, E-Only=Unopposed Estrogen, E+P=Estrogen plus Progesterone, HT=Hormone Therapy, BMI=Body Mass Index, HR=Hazard Ratio

Table 5

Endometrial cancer-specific mortality risk prediction after adding dichotomous ER or PR expression at select cut points to standard predictors

	Dichotomous Hormone Receptor Variable Added to Standard Predictors				
	ER Cut Point (n=338)			PR Cut Point (n=334)	
	30%	40%	50%	10%	80%
C-Index[a]	84.6%	84.5%	84.1%	76.5%	79.7%
Reclassification Metric[b]					
Number (%) moved to higher risk category	36 (11%)	43 (13%)	52 (15%)	12 (4%)	167 (50%)
Number (%) moved to lower risk category	14 (4%)	13 (4%)	13 (4%)	9 (3%)	6 (2%)
Total number (%) reclassified	50 (15%)	56 (17%)	65 (19%)	21 (6%)	173 (52%)
Reclassification Calibration Statistic (p-value)	11.04 (0.0009)	8.36 (0.004)	7.58 (0.006)	0.12 (1)	0.28 (0.6)
Net Reclassification Improvement	5.6%	4.0%	1.2%	0.6%	−23.0%
Integrated Discrimination Improvement	−1.5%	−2.0%	−0.9%	3.0%	1.6%

ER and PR each measured on a semi-quantitative percent positive cells scale of 0–100%, then dichotomized at the respective cut point into Marker+ and Marker− groups. Marker+ was defined as expression above the cut point for a cut point of 0% and as expression at or above the cut point for all other cut points. Marker− was defined as expression of 0% at a cut point of 0% and as expression below the cut point for all other cut points.

[a]Each c-index value in the table is for a Cox model estimating 10-year risk of endometrial cancer-specific death based on standard clinical predictors (tumor stage, tumor grade, and histologic type) plus the respective dichotomous marker status variable. C-index for a model of standard predictors only was 74.5%.

[b]Reclassification metrics compare a Cox model estimating 10-year risk of endometrial cancer-specific death based on standard predictors (tumor stage, tumor grade, and histologic type) to a Cox model based on standard predictors plus dichotomous marker status defined by the respective cut point. Mortality risk categories were 0–5%, 5–10%, and >10%.

ER=Estrogen Receptor, PR=Progesterone Receptor