
Article

Risk Prediction of Second Primary Endometrial Cancer in Obese Women: A Hospital-based Cancer Registry Study

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Abstract: Due to the high effectiveness of cancer screening and therapies, the diagnosis of second primary cancers (SPCs) has increased in women with endometrial cancer (EC). However, there's no previous literature mentioned about adequate evidence to support screening for SPCs in endometrial cancer. This study was aimed to develop effective risk prediction models of second primary endometrial cancer in women with obesity (Body-mass index; BMI > 25) and this study includes datasets of the incidence of SPCs and the other risks of SPCs in 4480 primary cancer survivors by a hospital-based cancer registry database. In our study, we found the obesity played a key role in SPCs. There're 10 independent variables used as predicting variables, which correlated to obesity should be monitored for the early detection of SPCs in endometrial cancer. In conclusion, it is a promising SPCs prediction. The proposed scheme can support the important influence of obesity and clinical data representations in all cases after primary treatments. Our results suggested that obesity is still a crucial risk factor to SPCs in endometrial cancer.

Keywords: second primary cancers (SPCs); endometrial cancer (EC); risk prediction.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy, and its incidence is rising alongside the growing prevalence of obesity.[1]

Endometrial cancer effected women worldwide, and resulted in an estimation of 42 000 deaths from this cancer.[2] The most endometrial cancer happens after the menopause, with a relation of long-term exposure to unopposed estrogens. For average, the overall 5-year survival is around 80%. Overweight (defined as body-mass index [BMI] of at least 25 kg/m²) also plays an important risk factor present in 50% of endometrial cancers. A BMI above 25 kg/m² doubles a woman's risk of endometrial cancer, and a BMI above 30 kg/m² triples the risk.[3,4] Therefore, understanding the key mechanisms driving endometrial carcinogenesis in primary endometrial cancer may affect second primary endometrial cancer diagnoses if aimed at those at greatest risk. An understanding of the correlation between obesity and SPCs is critical in developing such prevention strategies.[1]

In Taiwan Cancer Registry database, there're 9 variables recorded as clinical prognostic factors, (1) Age at Diagnosis, (2) Grade/differentiation, (3) Tumor size, (4) Clinical stage Group, (5) Pathologic Stage Group, (6) Surgical Margins involvements of The Primary Site, (7) Date of first surgical procedure, (8) Sequence of Radiotherapy and Surgery, (9) Sequence of Locoregional Therapy and Systemic Therapy. In this study, we proposed those factors and BMI could be the important predictors in SPCs of endometrial cancers. Therefore, the purpose of the analysis is to identify the most important risk factors from 10 predictors: (Table 1&2).

Table 1. The important variables associated with endometrial cancer.

Rank	Variable Name
1	Clinical stage Group
2	Tumor size
2	Pathologic Stage Group
2	Date of first surgical procedure
5	BMI
6	Age at Diagnosis
7	Sequence of Locoregional Therapy and Systemic Therapy
8	Grade/differentiation
8	Surgical Margins of The Primary Site
10	Sequence of RT and Surgery

We suggest potential prevention strategies and make a case for the need for risk prediction models that identify specific groups of women at a particularly high risk of endometrial cancer for whom risk-reducing interventions are likely to have a significant impact.

Table 2. Subject Demographics of all primary endometrial cancers.

Characteristics	Endometrial cancer (N=1560)		p value
	Without SPCs	With SPCs	
N (%)	1040(66.7%)	520(33.3%)	
Age at Diagnosis			<0.001**
<50 year-old	372(35.7%)	140(26.9%)	
≥50 year-old	668(64.3%)	380(73.1%)	
Grade/Differentiation			0.014*
1,2	705(67.8%)	320(61.5%)	
others	335(32.2%)	200(38.5%)	
Tumor Size			<0.001**
<2cm	262(25.2%)	220(42.3%)	
≥2cm	778(74.8%)	300(57.7%)	
Clinical Stage			<0.001**
<II	838(80.6%)	280(53.8%)	
≥II	202(19.4%)	240(46.2%)	
Pathologic Stage			<0.001**
<II	834(80.2%)	480(92.3%)	
≥II	206(19.8%)	40(7.7%)	
Surgical Margins involvement			0.405
No	947(91.1%)	480(92.3%)	
Yes	93(8.9%)	40(7.7%)	
Surgical procedure			<0.001**
No	40(3.8%)	0(0.0%)	
Yes	1000(96.2%)	520(100.0%)	
Sequence of Radiotherapy/Surgery			0.689
No	611(58.8%)	300(42.9%)	
Yes	429(41.2%)	220(57.1%)	
Sequence of Locoregional/Systemic therapy			<0.001**
No	740(71.2%)	320(57.7%)	
Yes	300(28.8%)	200(42.3%)	
BMI			0.001*
≤ 25	464(44.6%)	280(53.8%)	
>25	576(55.4%)	240(46.2%)	

** p value<0.001; * p value <0.05

2. Materials and Methods

A hospital-based cohort of 4,480 diagnosed endometrial cancer patients was identified from the database of Taiwan Cancer Registry from 2009 to 2016. The risk of endometrial cancer in Age/Grade-Differential/Clinical or pathological Stages/Therapies was

compared with analysis between obesity and non-obesity groups. By using these different decision tree models, prediction factors combinations for conditions of interest were identified. Moreover, a comprehensive clinical prevention approach is associated to all factors.

This study aimed to utilize data mining methods involving Support Vector Machine (SVM), Linear Discriminant Analysis (LDA), Logistic regression(LGR), C4.5, CART, Random forest (RF), and C5.0 to predict second primary endometrial cancer in obese women by different variables (Table 3). The classification accuracy of the seven methods was evaluated using receiver operating characteristic curve analysis to estimate the area under the curve (AUC) (Table 4). Accuracy, sensitivity and specificity were considered in this study (Figure 1). Support Vector Machine (SVM) classifiers operate by separating the two classes using a linear decision boundary called the hyperplane. The hyperplane is placed at a location that maximizes the distance between the hyperplane and instances. [5,6] Linear Discriminant Analysis (LDA) is a well-known generic method used for dimensionality reduction and classification. [7,8] Logistic regression(LGR) is the most widely used modeling approach for binary outcomes in epidemiology and medicine. The model is a part of the family of generalized linear models that explicitly models the relationship between the explanatory variable X and response variable Y. [9,10] C4.5 is also a decision tree algorithm which selects the decision tree's attributes on each node based on the concept of information entropy. It adopts a greedy approach in which the decision trees are constructed in a top-down recursive divide and conquer manner. [11,12] Random forest (RF) is an ensemble learning method. It generates many classification trees by selecting subsets of the given dataset and selecting subsets of predictor variables randomly, finally aggregating the results of all models to obtain a random forest.[13] The C5.0 decision tree is a classification approach which generates the tree in top-down scheme based on the information using a recursive process.[14] CART is a decision tree system which uses a binary recursive procedure to partition the data in homogenous subsets based on Gini index.[15,16]

In this study, CART can drive an ideal prediction model in obese woman (BMI > 25) (Figure 2).

Table 3. The important variables and coding in this study.

Variable	Name	Definition of normal test data
X1	Age at Diagnosis	<50/≥50
X2	Grade/differentiation	≤2/>2
X3	Tumor size	<2cm/≥2cm
X4	Clinical stage Group	<II /≥II
X5	Pathologic Stage Group	<II /≥II
X6	Surgical Margins of The Primary Site	No/Yes
X7	Date of first surgical procedure	No/Yes
X8	Sequence of RT and Surgery	No/Yes
X9	Sequence of Locoregional Therapy and Systemic Therapy(Chemotherapy)	No/Yes
X10	BMI	≤25/>25
Y	SPC	No/Yes

Table 4. Classification results of the seven methods.

Methods	Accuracy	Sensitivity	Specificity	AUC
SVM	0.875	0.8919	0.8692	0.8767
LDA	0.7014	0.9459	0.6168	0.7835
LGR	0.7431	0.8649	0.7009	0.8047
C4.5	0.8819	0.9065	0.8108	0.914
CART	0.8403	0.8108	0.8505	0.9153
RF	0.7778	0.9459	0.7196	0.8881
C5.0	0.7153	0.9459	0.6355	0.851

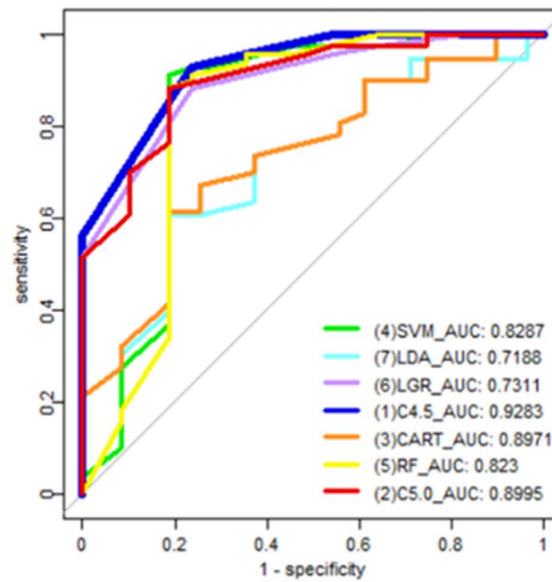


Figure 1. ROC curves of the seven methods.

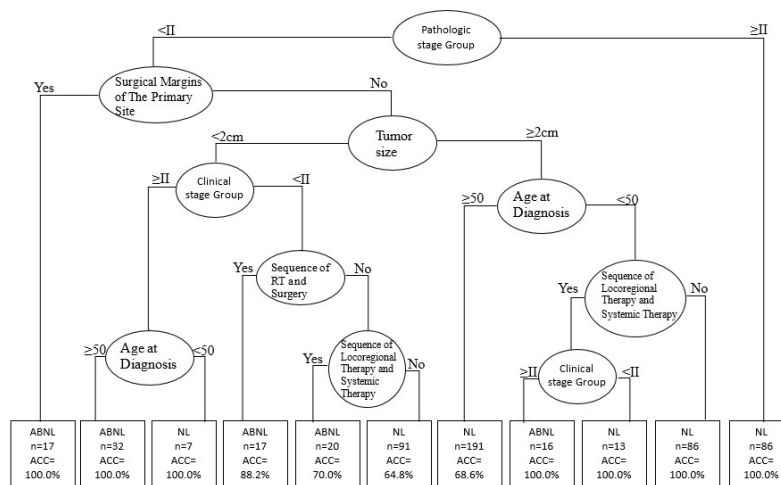


Figure 5. Classification Tree Depicting the SPC of endometrial cancer Predictors of CART. (BMI>25)

Figure 2. Classification tree depicting the SPCs of endometrial cancer predictors of CART (BMI>25)

3. Results

During the study period, 530 patients were diagnosed with SPCs in endometrial cancers.

All subjects were divided into 13 subgroups, from the root node to leaf nodes, through different branches. As previously explained, clinical stage variable has a great influence on the interpretation of the SPCs and was, therefore, identified as the root node of the classified decision tree.

The first-rule decision tree was obtained from the following determining factors: pathologic stage (<II) + surgical margins involvement (Yes), and the accuracy obtained was 1 across 17 samples. The second-rule decision tree was obtained from the following determining factors: pathologic stage (<II) + surgical margins involvement (No) + tumor size (<2cm) + clinical stage (≥II) + age at diagnosis (≥50), and the accuracy obtained was 1 across 32 samples. The fourth-rule decision tree was obtained from the following determining factors: pathologic stage (<II) + surgical margins involvement (No) + tumor size (<2cm) + clinical stage (<II) + sequence of radiotherapy/Surgery (Yes), and the accuracy obtained was 0.882 across 17 samples. The fifth-rule decision tree was obtained from the following determining factors: pathologic stage (<II) + surgical margins involvement (No) + tumor size (<2cm) + clinical stage (<II) + sequence of radiotherapy/surgery (No) + sequence of locoregional/systemic therapy(Yes), and the accuracy obtained was 0.7 across 20 samples. The eighth-rule decision tree was obtained from the following determining factors: pathologic stage (<II) + surgical margins involvement (No) + tumor size (≥2cm) + age at diagnosis (<50) + sequence of locoregional/systemic therapy (Yes) + clinical stage (≥II), and the accuracy obtained was 1 across 16 samples.

Therefore, the decision tree can be divided into abnormal (ABNL)(SPC) or normal (NL)(Non-SPC) situations. The accuracy ranged from 68.5% to 100%.(Figure 2) There're 5 rules related to prediction models of SPCs in endometrial cancer in obese woman (Table 5).

For obese woman (BMI>25), age (≥50 year-old, p=0.019), tumor size (≥2 cm, p<0.001), clinical and pathological stage (<II, p<0.001), surgery (Yes, p=0.014), and sequence of radiotherapy/surgery (No, p<0.001) had higher risk of SPCs in endometrial cancer (Table 6).

Table 5. The Summarized rules of condition variables. (BMI>25).

Rules No.	Combinations of condition variables	SPCs /Observed (n)	Accuracy
1	Pathologic stage (<II) + Surgical Margins involvement (Yes)	17/20	100.0%
2	Pathologic stage (<II) + Surgical Margins involvement (No) + Tumor size(<2cm) + Clinical stage (≥II) + Age at Diagnosis (≥50)	32/40	100.0%
4	Pathologic stage (<II) + Surgical Margins involvement (No) + Tumor size(<2cm) + Clinical stage (<II)+ Sequence of Radiotherapy (Yes)	17/24	88.2%
5	Pathologic stage (<II) + Surgical Margins involvement (No) + Tumor size(<2cm) + Clinical stage (<II) + Sequence of Radiotherapy (No) + Sequence of Locoregional/Systemic Therapy(Yes)	20/28	70.0%
8	Pathologic stage (<II) + Surgical Margins involvement (No) + Tumor size(≥2cm) + Age at Diagnosis (<50) + Sequence of Locoregional/Systemic Therapy(Yes) + Clinical stage (≥II)	16/20	100.0%

Table 6. The subject demographics of independent predictors of SPCs in endometrial cancer.

Characteristics	BMI≤25			BMI>25		
	Without SPCs	With SPCs	p value	Without SPCs	With SPCs	p value
N (%)	560(66.7%)	280(33.3%)		480(66.7%)	240(33.3%)	
Age at Diagnosis			0.117			0.019*
<50 year-old	190(33.9%)	200(71.4%)		161(33.5%)	60(25.0%)	
≥50 year-old	370(66.1%)	80(28.6%)		319(66.5%)	180(75.0%)	
Grade/Differentiation			0.004			0.698
1,2	377(67.3%)	160(57.1%)		313(65.2%)	160(66.7%)	
others	183(32.7%)	120(42.9%)		167(34.8%)	80(33.3%)	
Tumor Size			0.144			<0.001**
<2cm	172(30.7%)	100(35.7%)		102(21.3%)	120(50.0%)	
≥2cm	388(69.3%)	180(64.3%)		378(78.7%)	120(50.0%)	
Clinical Stage			<0.001			<0.001**
<II	463(82.7%)	120(42.9%)		385 (80.2%)	160(66.7%)	
≥II	97(17.3%)	160(57.1%)		95(19.8%)	80(33.3%)	
Pathologic Stage			0.032			<0.001**
<II	446(79.6%)	240(85.7%)		384(80.0%)	240(100.0%)	
≥II	114(20.4%)	40(14.3%)		96(20.0%)	0(0.0%)	
Surgical Margins involved			0.648			0.170
No	515(92.0%)	260(92.9%)		424(88.3%)	220(91.7%)	
Yes	45(8.0%)	20(7.1%)		56(11.7%)	20(8.3%)	
Surgical procedures			0.002			0.014*
No	19(3.4%)	0(0.0%)		12(2.5%)	0(0.0%)	
Yes	541(96.6%)	280(100.0%)		468(97.5%)	240(100.0%)	
Radiotherapy/Surgery			<0.001			<0.001**
No	332(3.4%)	120(42.9%)		249(51.9%)	180(75.0%)	
Yes	228(96.6%)	160(57.1%)		231(48.1%)	60(25.0%)	
Locoregional/Systemic Therapy			<0.001			0.867
No	402(71.8%)	160(57.1%)		317(66.0%)	160(66.7%)	
Yes	158(28.2%)	120(42.9%)		163(34.0%)	80(33.3%)	

** p value<0.001; * p value <0.05

4. Discussion

Recent advancements in diagnostic and therapeutic methods have increased the overall survival of patients with cancers. As cancer survival rates increased, the incidence of second primary cancers has gradually increased at the same time. However, this phenomenon is due to multiple factors such as genetic or environmental factors, and developments of new anti-cancer drugs. In the present study, SPCs in endometrial cancers was observed in 11.6% of 4480 patients who had been ever diagnosed as primary endometrial cancer. Obesity (BMI ≥ 30 kg/m²) is the strongest risk factor for primary EC. For every 5 kg/m² increase in BMI, there is a 60% increased risk of EC, with a BMI above 25 kg/m² doubling the risk and a BMI above 30 kg/m² tripling the risk.[17] However, obesity could not be a crucial risk factor in second primary endometrial cancers.[18]

Currently, there is no resolution in early screening for endometrial cancer; screening is unable to decreasing mortality from endometrial cancers. It will mainly detect women with low-risk tumors.[19] In literature reviews, increasing age and long-term exposure to unopposed estrogens are strong risk factors for endometrial cancer. Metabolic syndrome (obesity, diabetes) was also a well-known risk factor. It alters concentrations of insulin-like growth factor and its binding proteins.[20] Estrogen-receptor transcriptional activity can be induced by signaling by insulin-like growth factor 1 even in the absence of estradiol, which increases the incidence of endometrial cancer.[21-24] In our study, obesity seems to be an independent risk factor to prognostic factors of primary endometrial cancer. It also plays a key role in the incidence of second primary endometrial cancer.[25]

The use of preoperative radiotherapy has been abandoned because it interferes with surgical staging and there is no benefit over postoperative radiotherapy.[1] The aim of adjuvant radiotherapy is for the pelvic lymph-node regions that might contain microscopic metastasis, as well as the central pelvic region and the upper vagina. There is a consensus that patients with lesions of surgical stage IA or IB and grade 1 or grade 2 (low risk) can be treated without postoperative radiotherapy.[26] Isolated pelvic and vaginal recurrences of low-risk endometrial cancers can successfully be treated at the time of recurrence without radiotherapy. Therefore, radiotherapy usually used in advanced endometrial cancer. In our study, postoperative radiotherapy is an increasing risk factor in non-obesity group but a decreasing risk factor in obesity group.

Endometrial cancer is a surgically staged disease. The most important therapy for endometrial cancer is surgery. The surgical staging will provide the prognostic information for the survivors. In our study, most patients (99.31%) had received surgical interventions for their endometrial cancer. All second primary endometrial cancer came from these patients. In our study, for the obesity group, early endometrial cancer (stage <II) case who had received surgery without radiotherapy and systemic therapy has a higher risk for second primary endometrial cancer at her elder age (≥ 50).

In the past, we used data mining classification techniques for building predictive model for early chronic kidney disease successfully.[27] In this study, we applied 13 prognostic factors to determine SPCs risk factors in obese women using data mining algorithms successfully.

5. Conclusions

Age (>50), BMI (>25), grade/differentiation, cancer stage, grade, and adjuvant therapies were used as the prognostic factors of endometrial cancer. In our study, we found these factors could be used to be predicting factors to secondary primary endometrial cancer. Obesity is an independent risk factor for secondary primary endometrial cancer.

For obese women, there's a higher risk for endometrial cancer. In this study, the decision tree can be divided into abnormal (SPC) or normal (Non-SPC) situations in obese women of primary endometrial cancer, with the accuracy ranged from 68.5% to 100%. In obese women, we also identified that age at diagnosis, tumor size, clinical and pathological stages, surgery, and the sequence of radiotherapy had important impacts on the predictivity of the models, while other predictors, such as grad/differentiation, surgical margin involvement and locoreginal/systemic therapy, were less important.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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