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Prediction models for endometrial cancer for the general population or symptomatic women: A systematic review

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ABSTRACT

Objective: To provide an overview of prediction models for the risk of developing endometrial cancer in women of the general population or for the presence of endometrial cancer in symptomatic women.
Methods: We systematically searched the Embase and Pubmed database until September 2017 for relevant publications. We included studies describing the development, the external validation, or the updating of a multivariable model for predicting endometrial cancer in the general population or symptomatic women.
Results: Out of 2756 references screened, 14 studies were included. We found two prediction models for developing endometrial cancer in the general population (risk models) and one extension. Eight studies described the development of models for symptomatic women (diagnostic models), one comparison of the performance of two diagnostic models and two external validation. Sample size varied from 60 (10 with cancer) to 201,811 (855 with cancer) women. The age of the women was included as a predictor in almost all models. The risk models included epidemiological variables related to the reproductive history of women, hormone use, BMI, and smoking history. The diagnostic models also included clinical predictors, such as endometrial thickness and recurrent bleeding. The concordance statistic (*c*), assessing the discriminative ability, varied from 0.68 to 0.77 in the risk models and from 0.73 to 0.957 in the diagnostic models. Methodological information was often limited, especially on the handling of missing data, and the selection of predictors. One risk model and four diagnostic models were externally validated.
Conclusions: Only a few models have been developed to predict endometrial cancer in asymptomatic or symptomatic women. The usefulness of most models is unclear considering methodological shortcomings and lack of external validation. Future research should focus on external validation and extension with new predictors or biomarkers, such as genetic and epigenetic markers.

1. Introduction

Endometrial cancer is the sixth most common type of cancer in women worldwide and its incidence has been increasing since 1990 (Ferlay et al., 2013). This increase might be related to improvements in detection in the general population and in diagnostics in women with (postmenopausal) bleeding. Further, in many populations the body mass index (BMI) is rising and several studies have shown that adiposity is the strongest risk factor of endometrial cancer (Kyrgiou et al., 2017; Dixon, 2010; Collaboration NCDRF, 2016; Ng et al., 2014). Other risk factors that are associated with endometrial cancer are higher age, hypertension, diabetes, nulliparity, early menarche, late menopause, oestrogen uptake, and genomic alterations (MacMahon, 1974; Hecht and Mutter, 2006). Combining these risk factors in multivariable prediction models may help to identify women in the general population at high risk of developing endometrial cancer. Prediction models can also facilitate early diagnosis in symptomatic women.

Several risk and diagnostics models for endometrial cancer have been developed (Pfeiffer et al., 2013; Wong et al., 2016; Husing et al., 2016; Burbos et al., 2010; Giannella et al., 2014). The models can be used for risk prediction for prevention purposes. Particularly models with modifiable risk factors, such as BMI, hypertension, and oestrogen uptake may facilitate tailored preventive interventions on diet, lifestyle or drug use. This might reduce the incidence of endometrial cancer.

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Once endometrial cancer has developed, diagnostic models can be used for early diagnosis. Postmenopausal bleeding and increasing endometrial thickness are the most common symptoms of endometrial cancer and are often considered in these diagnostic models (Gull et al., 2003). The diagnostic models facilitate early diagnosis, which may result in efficient use of diagnostic resources and improved survival.

Since no overview of these models has been published so far, we aimed to systematically review multivariable models predicting the risk of endometrial cancer in the general population. We also systematically reviewed models for the presence of endometrial cancer in symptomatic women. We describe the model development, the included predictors, the predicted outcome, and any attempts to external validation to assess the quality of the models and determine if these models are ready for use in practice.

2. Methods

2.1. Search strategy

The search strategy that was used in this review was based on previous published searches (Damen et al., 2016; Ingui and Rogers, 2001) and other systematic reviews of prediction models (Smit et al., 2015; Meads et al., 2012; Mushkudiani et al., 2008). Specific terms for endometrial cancer were added to the search strategy. The index terms of papers that were considered relevant were manually searched to check if any search terms were missing from the search strategy. The final strategy (S1) was used in the PubMed and Embase databases in August 2017.

2.2. Inclusion criteria

We included all papers with the main aim of developing, validating or updating a model predicting the risk of endometrial cancer in the general population or presence in symptomatic women. Any multivariable (at least two predictors) prediction model was eligible for inclusion, including prediction scores or prediction tools. Only papers written in the English language were included. There was no restriction on publication date.

2.3. Screening process and data extraction

Two authors performed the screening process and data extraction. One author (MA) reviewed the titles and abstracts of all papers that were identified during the search, after which a random sample of 10% was checked by another author (KV). Both authors independently screened the full text of the remaining papers for eligibility. Disagreements were solved by discussion between the authors or consulting a senior author (YV).

The data extraction sheet was based on the CHARMS checklist. The data extraction sheet was pilot tested on two articles to ensure consistency between both authors. Subsequently, both authors performed the data extraction on all included papers. Specific attention was paid to four main topics (study design and methods, outcome and predictors, model development, model performance and model validation) of the CHARMS checklist, as these topics mainly influence the validity of the models.

Study design and methods: We identified the study design (e.g. case-control, cohort, case-cohort), source of data (e.g. hospital based or national registries) and size of the study population. In addition, the inclusion criteria for each study were assessed.

Outcome and predictors: We assessed the measurement and definition of both the outcome and predictors, and the handling of predictors (e.g. predictors were kept continuous or were dichotomized).

Model development: We assessed the following topics: handling of predictors, number of events per variable (EPV), number and handling of missing data (e.g. single imputation, multiple imputation), methods for selection of predictors in the multivariable model (e.g. univariate analyses or subject matter knowledge) and during multivariable modelling (backward or forward selection), modelling method (e.g. logistic regression, cox proportional hazards), shrinkage (e.g. penalized shrinkage or lasso) and model presentation (e.g. regression formula, score chart, nomogram or risk score).

Model performance and validation: Aspects concerning model performance and validation that were assessed were discrimination, calibration, internal validation (e.g. split-sample approach, cross-validation, bootstrapping) and external validation (e.g. geographical or temporal validation). Furthermore, the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values of the diagnostic models were included in this topic, if reported.

3. Results

We identified 2756 papers during the initial search. These records were screened on title and abstract after which 23 records were included for full text screening. The low sensitivity of the search (less than 1% of the initial search result was included for full text screening) is in line with other searches, as a consequence of the lack of adequate search terms for prediction models. After full text screening, 9 papers were eligible for inclusion. In addition, 5 extra papers were identified by hand search, leading to the inclusion of 14 papers in this review (Fig. 1). Two papers developed prediction models for the general population (risk models), eight papers developed prediction models for symptomatic women (diagnostic models), one paper internally evaluated a model, two papers described the external validation of previous developed models and one paper described the extension of an existing prediction model.

3.1. Prediction models for endometrial cancer in the general population (risk models)

3.1.1. Study designs and population

The two studies that developed risk models used data from population based cohorts; one study used the European EPIC cohort (Husing et al., 2016) and one study used a cohort from the United States (Pfeiffer et al., 2013) (US) (Table 1). The data was collected using a

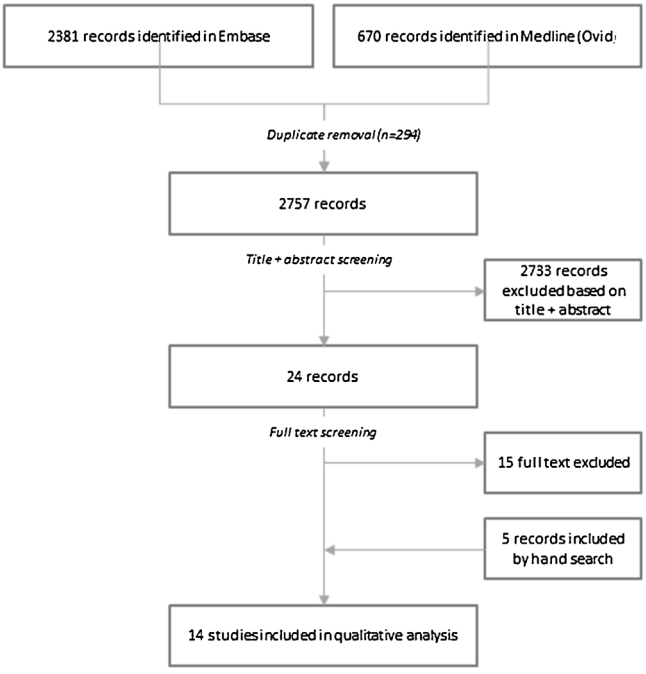

Fig. 1. Flow diagram of study selection process.

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