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## Original Research

# Association of the oestrogen receptor beta with hormone status and prognosis in a cohort of female patients with colorectal cancer



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Received 20 April 2017; received in revised form 9 June 2017; accepted 11 June 2017 Available online 29 July 2017

#### **KEYWORDS**

Oestrogen receptor beta; Colorectal cancer; Cancer prognosis; Overall survival; Disease-free survival **Abstract** *Background:* The oestrogen receptor beta  $(ER\beta)$  is the predominant oestrogen receptor in the normal colon mucosa and has been reported to exert anti-proliferative and pro-apoptotic effects. However, the role of  $ER\beta$  in colorectal cancer (CRC) progression remains unclear.

**Aim:** To investigate the role of ER $\beta$  and its association with hormone status and lifestyle indicators in a female cohort of patients with CRC.

*Methods:* Tissue microarrays of primary CRC tumour samples from 320 female patients were conducted with a monoclonal anti-ER $\beta$  antibody. The staining intensity was evaluated using immunohistochemistry. The association of ER $\beta$  expression with overall survival, disease-free survival, hormone status and lifestyle was evaluated, and effect estimators with 95% confidence intervals (CIs) were reported.

**Results:** Among the 314 samples with successfully detected ER $\beta$ , 182 (58%) had low expression and 132 (42%) had high expression. The Cox multivariate analysis indicated that patients with high ER $\beta$  expression had a decreased risk of overall mortality by 50% (hazard ratio [HR], 0.50; CI, 0.30–0.83) and of cancer recurrence by 76% (HR, 0.24; CI, 0.11–0.52) after adjusting for age, tumour-node-metastasis stage and tumour intravascular invasion. Furthermore, high ER $\beta$  expression was significantly correlated with shorter breastfeeding time and longer use of hormone

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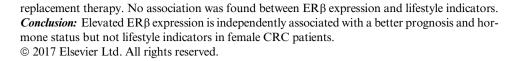
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#### 1. Introduction

Oestrogens regulate various physiological processes such as reproduction, development, cell growth and differentiation [1]. Abnormalities in oestrogen signalling lead to different types of pathological conditions, including metabolic diseases and cancer [1,2]. Colorectal cancer (CRC) is the third most common cause of cancerrelated death worldwide [3]. Gender has been shown to influence CRC localisation and survival. Proximal (right-sided) colon cancer is more common among women, while distal (left-sided) colon cancer and rectal cancer are more common among men [4,5]. Some studies have reported better overall survival (OS) in women after CRC surgery [6,7], but other studies indicated no gender differences [8,9]. Younger women have better survival than younger men, whereas an opposite gender pattern has been shown among older patients [10-12]. Furthermore, the use of oral contraceptives and hormone replacement therapy (HRT) has been reported to play a protective role in the prevention of CRC [13–15]. All these data indicate the prognostic relevance of hormone status and oestrogens in CRC.

Oestrogens act via two main receptors—oestrogen receptor alpha (ER $\alpha$ ) and oestrogen receptor beta (ER $\beta$ ), both of which are members of the nuclear receptor family [1,16]. ER $\beta$  is the predominant oestrogen receptor in the normal colon mucosa, and its loss in CRC has been associated with advanced stages of cancer and poorly differentiated tumours [17–19]. Previous studies suggested an association between ER $\beta$  expression and CRC survival, with consistent results showing that high nuclear ER $\beta$  expression leads to a better prognosis [20,21]. However, these studies did not stratify the population based on gender.

Therefore, we sought to investigate whether  $ER\beta$  expression was independently associated with OS and disease-free survival (DFS) in a cohort of female patients with CRC. Furthermore, we investigated the association between  $ER\beta$  expression and tumour characteristics, hormone status and lifestyle indicators.

#### 2. Materials and methods

#### 2.1. Study design and study population

Female patients those who were diagnosed and treated for primary CRC, who were physically and mentally able to participate, who could effectively communicate in Swedish and were residents within the study region were eligible. All participants gave written informed consent. This study was approved by the Ethical Committee at Lund University.

This investigation involves 333 tumour samples from female patients who underwent surgery for CRC between 1st January 2008 and 30th June 2012 and were randomly chosen from five cities in southern Sweden. No stratification or matching was performed. These 333 samples were incorporated into tissue microarray (TMA) blocks and were histopathologically re-evaluated on haematoxylin and eosin stained slides. A total of 13 samples were excluded from the current study (Fig. 1).

To determine the association between ER $\beta$  expression and DFS, patients with distant metastases at the time of diagnosis and patients with unknown state or date of recurrence were excluded from the analysis (Fig. 1).

The study had a sufficient power of 80% with a type I error probability of 5% to detect a true hazard ratio (HR) of 1.6 for 180 patients with low ER $\beta$  expression relative to 120 patients with high ER $\beta$  expression. The power of the study was calculated using the approach of Schoenfeld and Richter (1982) and assumed a recruitment period of 5 years, an additional follow-up period of 4 years and a median survival time for patients with low ER $\beta$  expression of 5 years.

#### 2.2. Data collection and follow-up

A standardised questionnaire regarding the hormone status was sent out approximately 1 year after the operation to all study participants. The questionnaire had information about menopausal status, menarche, pregnancies and breastfeeding, the use and types of hormone contraception and the use and types of HRT. As of 2010, the questionnaire was updated with information regarding lifestyle indicators such smoking status, alcohol consumption, physical activity and body mass index (BMI). For all the tumour samples retrieved, the pathology records and medical charts were also collected. Data on the patients' vital status and date of death were extracted from population registries. Information regarding cancer recurrence was obtained from patients approximately 3-4 years after the operation. Cases of cancer recurrence were verified through medical records.

#### 2.3. Study end-points

OS and DFS were the primary outcomes for this investigation. Follow-up time was calculated as the time

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