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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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Abstract ***Background:*** The oestrogen receptor beta (ERβ) 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 ERβ in colorectal cancer (CRC) progression remains unclear.
Aim: To investigate the role of ERβ 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-ERβ antibody. The staining intensity was evaluated using immunohistochemistry. The association of ERβ 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 ERβ, 182 (58%) had low expression and 132 (42%) had high expression. The Cox multivariate analysis indicated that patients with high ERβ 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 ERβ expression was significantly correlated with shorter breastfeeding time and longer use of hormone

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replacement therapy. No association was found between ERβ expression and lifestyle indicators.
Conclusion: Elevated ERβ expression is independently associated with a better prognosis and hormone status but not lifestyle indicators in female CRC patients.

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 cancer-related 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 (ERα) and oestrogen receptor beta (ERβ), both of which are members of the nuclear receptor family [1,16]. ERβ 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 ERβ expression and CRC survival, with consistent results showing that high nuclear ERβ 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 ERβ 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 ERβ 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 ERβ 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 ERβ expression relative to 120 patients with high ERβ 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 ERβ 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