Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
Cancer Letters 219 (2005) 183–190
CANCER Letters
www.elsevier.com/locate/canlet

Association of *p73* G4C14-to-A4T14 polymorphism at exon 2 and *p53* Arg72Pro polymorphism with the risk of endometrial cancer in Japanese subjects

Yoshimitsu Niwa[a,*], Kaoru Hirose[b], Keitaro Matsuo[b], Kazuo Tajima[b], Yoko Ikoma[c], Toru Nakanishi[c], Akihiro Nawa[c], Kazuo Kuzuya[c], Akiko Tamakoshi[a], Nobuyuki Hamajima[a]

[a]*Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan*
[b]*Department of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan*
[c]*Department of Gynecology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan*

Received 19 August 2004; received in revised form 12 October 2004; accepted 15 October 2004

Abstract

To test the association of endometrial cancer with the *p73* G4C14-to-A4T14 polymorphism in exon 2 and the *p53* Arg72Pro polymorphism, an incident case-control study was performed in Japanese subjects. The cases comprised 114 endometrial cancer patients, and the controls were 320 healthy females and 122 noncancer female outpatients. An unconditional logistic regression model demonstrated a significant association between the *p73 AA* genotype and an increased risk of endometrial cancer (OR = 2.82, 95% CI = 1.36–5.82), especially of type-I tumors (OR = 3.24, 95% CI = 1.53–6.87). In contrast, there was no significant difference in the *p53* Arg72Pro genotype frequency between the controls and cases.

Keywords: *p73* two linked polymorphisms; *p53* Arg72Pro polymorphism; Endometrial cancer; Polymerase chain reaction with confronting two-pair primers

1. Introduction

Endometrial cancer is one of the most common gynecologic malignancies. Although the frequency of endometrial cancer in Japan is low relative to the rates in many Western countries [1], the age-standardized incidence rate is now rising in Japan possibly due to changing lifestyles and dietary patterns.

Reproductive events and obesity are risk factors for endometrial cancer [2], but these do not explain a large proportion of endometrial cancer cases. Currently, two pathways are distinguished for the tumorigenesis of endometrial cancer; estrogen-related and estrogen-unrelated pathways, designated type-I

* Corresponding author. Tel.: +81 52 744 2133; fax: +81 52 744 2971.
E-mail address: ytt-niwa@xg7.so-net.ne.jp (Y. Niwa).

0304-3835/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2004.10.018

and type-II tumors, respectively [3]. These pathways lead to different tumor histological subtypes with different clinical behavior. The 80–90% of endometrial cancers are type-I tumors [4] which are generally associated with endometrial hyperplasia, and are overall characterized by favorable clinical behavior. It has been suggested that the majority of type-I tumors correspond to endometrioid adenocarcinoma [5,6]. Type-I tumors also include mucinous carcinoma and adenoacanthoma that show favorable clinical behavior. The other 10–20% of endometrial cancers are type-II tumors [4], which usual develop at an old age than type-I tumors, and show aggressive behavior and are associated with poor outcome [5,6]. They are typically nonendometrioid subtypes, such as serous carcinoma, clear-cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinoma [5]. Endocrine and nutritional factors are thought to affect the risk of type-I but not type-II tumors. Identifying genetic differences associated with cancer susceptibility, from the point of view of histologic subtypes, would be of great value to understanding their clinical behavior.

The *p53* is associated with many crucial cellular functions, including cell cycle regulation, DNA repair, inhibition of spontaneous mutations, cellular differentiation, and apoptosis. Codon 72 of the *p53* contains a single-nucleotide polymorphism resulting in the amino-acid substitution of arginine to proline that might have oncogenic properties [7]. Storey and co-workers first reported that the risk of cervical cancer was higher among females homozygous for the arginine allele with the *p53* Arg72Pro polymorphism [8]. Many studies have investigated the association between this polymorphism and the risk of various cancers, including endometrial cancer, but with inconsistent results [9–11].

p73 codes a protein that shares considerable homology with the p53 protein [12]. Jost et al. reported that p73 protein can, at least when overproduced, activate the transcription of p53-responsive genes and inhibit cell growth in a p53-like manner by inducing apoptosis [13]. The 1p36.3 region (where *p73* maps) is often deleted by the loss of heterozygosity in various human malignancies [14–18]. This suggests that genetic changes in *p73* are important in human malignancies. *p73* has two linked polymorphisms, at positions 4 and 14 of exon 2 (G4C14 to A4T14, termed G4A hereafter), which exist in a region of the transcript that could form a stem-loop structure and affect gene expression, and therefore could have functional consequences [19]. Previous reports revealed that individuals with at least one *A4T14* allele were at a higher risk of cervical cancer [20] and squamous cell carcinoma of the head and neck [21]. However, to our knowledge no report has been published on the association between *p73* polymorphism and the risk of endometrial cancer.

To investigate whether *p73* G4A and *p53* Arg72-Pro polymorphisms influence the likelihood of endometrial cancer, we conducted an incident case-control study in Japanese subjects.

2. Materials and methods

2.1. Study subjects

The cases comprised 114 Japanese endometrial cancer patients who were diagnosed at Aichi Cancer Center Hospital between October 2001 and March 2004; these cases were enrolled in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II) [22]. All were confirmed histologically to have endometrial cancer, comprising 96 cases with endometrioid adenocarcinoma (43 with grade 1, 38 with grade 2, and 15 with grade 3), four with adenosquamous carcinoma, one with adenoacanthoma, seven with serous adenocarcinoma, three with clear-cell carcinoma, two with undifferentiated carcinoma, and one with mucinous carcinoma. Controls were recruited from two sources [20]. Group I consisted of examinees who attended a health checkup provided by the Nagoya Municipal Government on 3 days during 2000. Written informed consent for the anonymous use of their residual blood for research purposes was obtained from 468 of 489 (95.7%) examinees. After excluding males and those with a past history of cancer, 320 blood samples were analyzed. Group II comprised 122 noncancer first-visit female outpatients who underwent gastroscopy in 1999 at the Aichi Cancer Center Hospital. The female controls were derived from the same subjects reported in our previous paper [23]. The Aichi Cancer Center has an ethical committee to