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Genomic imbalances in endometrial adenocarcinomas – Comparison of DNA ploidy, karyotyping and comparative genomic hybridization

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ABSTRACT

DNA ploidy analysis is useful for prognostication in cancer patients, but the genomic details underlying ploidy changes are not fully understood. To improve this understanding, we compared DNA ploidy status with karyotypic and comparative genomic hybridization data on 51 endometrial adenocarcinomas. Out of 34 DNA diploid tumors evaluated by CGH, 16 (47%) showed imbalances, though only two had more than four copy number changes. Ten (29%) had aberrations involving chromosome 1, seven (21%) involving chromosome 10, while one tumor had a chromosome 8 aberration. Four of the seven DNA tetraploid tumors (57%) had imbalances detected by CGH with two (29%) having more than four. Six out of eight DNA aneuploid tumors showed imbalances by CGH, with five (63%) having more than four. The aberrations were observed on chromosomes 1 and 8 in five/eight (63%) cases while four imbalances (50%) involved chromosomes 5, 7 and X. Not surprisingly, we observed a significant correlation between increasing DNA ploidy complexity and increasing number of copy alterations. Gains of material from chromosomes 8 and 7 might be specifically correlated to DNA aneuploidy in endometrial adenocarcinomas since 63% and 50% of the aneuploid compared to 3% of the diploid tumors showed imbalances involving these chromosomes.

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1. Introduction

Assessment of DNA ploidy status has been shown to be clinically useful in the prognostic evaluation of patients with epithelial cancers, including gynecological cancers (Pisani et al., 1995; Kristensen et al., 2003; Terada et al., 2004). In general, patients with DNA diploid tumors have a more favorable outcome than do patients with DNA aneuploid tumors

Abbreviations: Endometrial adenocarcinoma, EAC; comparative genomic hybridization, CGH; average number of copy alterations, ANCA.

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(Kristensen et al., 2003; Terada et al., 2004). Mostly, one does not know in any detail which genomic changes are behind the observed ploidy patterns, at least not on the same set of tumors, and we therefore undertook the present study to compare findings from DNA ploidy analyses with those obtained by comparative genomic hybridization (CGH) and karyotyping. Ideally, this might reveal patterns of genetic changes in diploid, tetraploid and aneuploid carcinomas that could shed some light on the mechanisms behind aneuploidization and polyploidization. So far the mechanisms are not fully understood, but a recent paper suggests that activation of oncogenes and inactivation of tumor suppressor genes could lead to aneuploidy (Solomon et al., 2011). Endometrial adenocarcinomas (EAC) are of two main subtypes (Bokhman, 1983). Type I carcinomas typically develop in peri-menopausal women, show mainly endometrioid differentiation and patients with these tumors generally have a favorable prognosis (Bokhman, 1983). The tumors frequently show mutations of DNA mismatch repair genes, *PTEN*, *KRAS* and *CTNNB1*. Type II carcinomas are typically characterized by DNA aneuploidy, *TP53* mutations and *ERBB2* amplifications (Lax et al., 2000), the tumors are of the serous, clear cell, and/or undifferentiated histological subtypes and the patients have a less favorable prognosis (Bokhman, 1983).

Contrary to non-endometrioid carcinomas where over 50% are non-diploid, most endometrioid EAC are DNA diploid (Prat, 2004; Pradhan et al., 2006). The DNA diploid tumors are often grade 1 or 2 carcinomas and the patients typically have longer survival than do patients with aneuploid carcinomas (Geisinger et al., 1986; Britton et al., 1989; van der Putten et al., 1989; Sorbe et al., 1990; Stendahl et al., 1991; Pisani et al., 1995; Terada et al., 2004; Pradhan et al., 2006; Susini et al., 2007). One report showed up to 91% 10-year disease free survival for patients with DNA diploid carcinomas, compared to 53% for DNA aneuploid carcinomas (Susini et al., 2007). For this study we specifically selected EAC of the endometrioid subtype because we primarily wanted to examine the pattern of acquired genomic aberrations in aneuploid but close to diploid tumor cell nuclei.

Cytogenetic studies of endometrioid EAC have shown many tumors to have hyperdiploid karyotypes with only few chromosomal aberrations, mostly partial or whole chromosome gains, although cases with complex karyotypes do exist (Sonoda et al., 1997; Suzuki et al., 1997; Pere et al., 1998; Suehiro et al., 2000; Mitelman et al., 2010). Often the aberrations involve chromosome 1 leading to gain of material from the long arm, followed by gains of or from chromosomes 2, 7, 10 and 12 (Mitelman et al., 2010). Also CGH analyses usually show only minor genomic imbalances in endometrioid EAC (Sonoda et al., 1997; Suehiro et al., 2000), the most common being gains from chromosomes 1, 3, 8, 10 and 20 and losses from chromosomes X, 4 and 13 (Sonoda et al., 1997; Suzuki et al., 1997; Pere et al., 1998; Suehiro et al., 2000). Our study is based on the karyotypic and CGH analyses performed by Micci et al. (2004) which showed that endometrioid EAC mostly harbor gains from chromosome arms 1q and 8q and losses from Xp, 9p, 9q, 17p, 19p and 19q. In that study, a gradually increasing number of aberrations from well to poorly differentiated type I carcinomas was seen (Micci et al., 2004).

2. Material and methods

The material consisted of paraffin embedded tissue samples from a consecutive series of 51 EAC of the endometrioid histological subtype surgically removed at The Norwegian Radium Hospital between 2000 and 2002. Eight of the 51 endometrioid tumors showed squamous differentiation. Tumors from six of the patients contained a component of another histological subtype (i.e., they were mixed type), and of these three had a component with mucinous differentiation, one had a clear cell component, one had serous papillary differentiation, and one had both a mucinous and a serous papillary component. There were 16 well, 20 moderately, and 15 poorly differentiated tumors, 27 were in FIGO Stage I, 10 in Stage II and 14 in Stage III.

DNA ploidy measurements were performed as previously described (Kristensen et al., 2003; Kildal et al., 2004). On average, 1087 (ranging from 259 to 1373) tumor cell nuclei were examined for each case. The mean coefficient of variation of the DNA diploid population was 2.92. Karyotyping and CGH had been performed previously, on fresh tissue from the same tumors, and the results of these analyses have been presented in Micci et al. (2004).

Concordance between CGH and DNA ploidy was defined as ≤four average number of copy alterations (ANCA), as measured by CGH in DNA diploid or tetraploid lesions, and above four ANCA in aneuploid lesions (Kildal et al., 2004).

Comparison of groups was performed by Fisher's exact test. *P*-values <0.05 were considered statistically significant.

Table 1 – Relationship between DNA ploidy classification and histological grade, FIGO stage and ANCA.[a]

	FIGO stage				Histological grade				ANCA		
	I	II	III	*p*-value[b]	Well	Moderate	Poor	*p*-value	<=4	>4	*p*-value
Diploid	19	6	11	0.730	14	16	6	0.021	32	2	<0.001
Tetraploid	4	1	2		0	2	5		5	2	
Aneuploid	4	3	1		2	2	4		3	5	

a Abbreviations: ANCA – average number of copy alterations, FIGO – International Federation for Obstetrics and Gynaecology.
b *p*-values from Fisher's exact test (2-sided).

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