Analysis of Fibroblast Growth Factor Receptor 3 S249C Mutation in Cervical Carcinoma

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Carcinoma of the uterine cervix is the most common gynecologic cancer encountered worldwide (1). Infection with human papillomavirus (HPV) is a major risk factor in cervical cancer, and HPV is present in nearly all cervical carcinomas examined (2). Additional recurrent genetic alterations in cervical cancer include loss of heterozygosity at several chromosomal regions, including 3p, 4p, 5p, 6p, 11q, 17p, 18q, and 19q, and gene amplification on chromosome 3q (3). However, specific genes at these loci have yet to be identified. Recently, Cappellen et al. (4) reported that the gene encoding fibroblast growth factor receptor 3 (FGFR3) is frequently mutated in cervical carcinomas, representing the most common specific molecular genetic alteration in cervical cancer identified to date.

FGFR3 is a transmembrane tyrosine kinase receptor that mediates signals for cell proliferation, differentiation, angiogenesis, and embryogenesis (5–7). Distinct germline missense mutations in FGFR3 result in the autosomal dominant human skeletal diseases of achondroplasia, hypochondroplasia, and thanatophoric dysplasia (8). Cappellen et al. (4) reported that the FGFR3 messenger RNA is expressed in 92% of bladder (70 of 76) and 93% of cervical (27 of 29) cancers as well as in normal urothelia and normal cervical epithelia. In addition, these authors (4) reported that 25% (three of 12) of cervical carcinomas contain the same somatic missense mutation at codon 249 of the FGFR3 gene, TCC(Ser)→TGC(Cys). The S249C mutation results in the presence of a cysteine residue in the extracellular ligand-binding domain and may lead to constitutive activation of FGFR3 by ligand-independent dimerization of the receptor; when present in the germline, this mutation causes thanatophoric dysplasia, a lethal short-limb skeletal dysplasia (9). The findings that FGFR3 is commonly expressed in the cervical epithelium and that the S249C mutation is present in 25% of cervical carcinomas suggest that FGFR3 may play an important role in cervical tumorigenesis (4).

Because the number of cervical cancer specimens examined was relatively small (n = 12) in the study by Cappellen et al. (4), we sought to clarify the role of the FGFR3 S249C mutation in a larger sample of cervical carcinomas (n = 104). We analyzed tumors from a consecutive series of unselected patients who underwent primary cervical cancer surgery at this institution over a 10-year period (1990–1999). This study was approved by the Institutional Review Board of the Memorial Sloan-Kettering Cancer Center. Pathologic review was performed on each case to confirm a diagnosis of invasive cervical carcinoma. With regard to histologic subtype, 95 (91%) of the cervical cancers were squamous cell and nine (9%) were adenocarcinoma. With regard to surgical stage, eight were stage I, 78 were stage IB, nine were stage IIA, five were stage IIB, two were stage IIIB, and one was stage IVB, according to criteria described previously (10). Stage was unavailable for one case. Histologic and stage distributions were typical for those generally seen in the cervical carcinoma population. After microdissection of tumor tissue from formalin-fixed, paraffin-embedded, or flash-frozen tissue specimens, genomic DNA was isolated with the use of standard procedures. A 161-base-pair polymerase chain reaction product containing codon 249 was generated with the use of the primers 5’-AGTTGCCTGTTGGTGATGAGGAG-3’ and 5’-TGTGCCTCACCTGCACCTGAC-3’, then subjected to direct sequence analysis. Of the 104 cervical carcinomas examined, all contained only the wild-type sequence (TCC) at codon 249 of FGFR3 (Fig. 1). These data suggest that the FGFR3 S249C mutation is likely to be very rare in this population of cervical carcinoma patients.

It is difficult to account for the discrepancy between the data of Cappellen et al. (4) and our data. Absence of the FGFR3 S249C mutation in a large sample of cervical carcinomas from our institution may reflect differences in the molecular genetics of cervical cancers from the population studied here (urban northeastern United States) and the French population studied by Cappellen et al., which could result from any number of ethnic, socioeconomic, lifestyle, or environmental influences that affect cervical tumorigenesis in the two patient populations. Such HPV strain differences have been hypothesized, but not proven, to underlie an observed discrepancy in the association between polymorphic p53 alleles and cervical cancer risk in different populations (11). Furthermore, our data pertain only to the S249C mutation in FGFR3. Even though this was the only mutation seen in cervical cancers following a mutation screen of the entire FGFR3 coding region by Cappellen et al., additional mutations affecting this gene in different patient populations could exist. Nevertheless, our data are consistent with the conclusion that FGFR3 S249C is unlikely to represent a common oncogenic mutation in cervical cancer generally.

REFERENCES


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