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Polymorphisms in *COX-2*, NSAID use and risk of basal cell carcinoma in a prospective study of Danes

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Abstract

We investigated the risk of basal cell carcinoma (BCC) in relation to a number of single nucleotide polymorphisms in genes involved in the inflammatory response. A case–control study including 322 BCC cases and a similar number of controls was nested in a population-based prospective study of 57,053 individuals (aged 50–64 at inclusion) in Denmark. NSAID use was associated with a slightly decreased risk of BCC (IRR = 0.85, 95% CI = 0.66–1.10). We found that two polymorphisms in *COX-2*, *COX-2* A-1195G and T8473C were associated with risk of BCC. Carriers of the variant allele of *COX-2* A-1195G had lower risk of BCC than homozygous wild type carriers (IRR = 0.54, 95% CI = 0.47–0.89). Homozygous carriers of the variant allele of COX-2 T8473C were at 2.27-fold higher risk of BCC (95% CI = 1.31–3.92) than homozygous wild type allele carriers.

The polymorphisms *IL6* G-174C, *IL8* T-251A, *PPARγ2* Pro[12]Ala, *IL1β* T-31C, and *IL10* C-592A were not associated with risk of BCC. We found no statistically significant interaction between polymorphisms and NSAID use in relation to risk of BCC. While it cannot be ruled out that the present findings are due to chance, the results indicate that high *COX-2* expression may increase risk of BCC while NSAID use may be protective.

Keywords: SNP; Population based; Genetic epidemiology; Inflammation; NSAID

1. Introduction

Basal cell carcinoma (BCC) is the most common cancer in the Western World, and its incidence is increasing. Risk factors include sunlight exposure, fair skin and nevi [1–3]. Inflammation is an important part of UV-light induced skin carcinogenesis. Exposure to UV-light, including sunlight, results in induction of several cytokines including IL 10, TNF and IL1β [4,5]. *COX-2* (also called *PTGS2*) encodes the prostaglandin

Abbreviations: BCC, basal cell carcinoma; 95% CI, 95% confidence interval; NSAID, non-steroid anti-inflammatory drugs; RR, rate ratio; SNP, single nucleotide polymorphism; SSC, squamous cell carcinoma

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H synthase which is a key enzyme in prostaglandin synthesis. Over-expression of COX-2 in basal epidermal cells in mice increases the sensitivity towards genotoxic agents [6], indicating that high levels of COX-2 are associated with an increased cancer risk. Furthermore, there is in vitro evidence that inhibition of prostaglandin E2 production by specific COX-2 inhibitors and other NSAIDs partly prevents UV-light induced skin carcinogenesis [7]. Only few epidemiological studies, however, have examined the association between NSAIDs and BCC and the results are inconclusive [8–10].

The promoter polymorphisms *COX-2* A-1195G and G-765C have been shown to modify the *COX-2* transcription levels [11]. The A-allele of *COX-2* A-1195G had a much higher transcriptional level than the G-allele in *in vivo* studies of esophageal tissues and in luciferase reporter assays performed in HeLa cells [11]. A-allele carriers were found to be at higher risk of esophageal cancer than G-allele carriers in a Chinese population [11]. The *COX-2* T8473C polymorphism in the 3′UTR region of the transcript has been associated with lung cancer risk. However, while carriers of the variant C-allele were found to be at higher risk of lung cancer in one study [12], variant carriers were found to be at lower risk in another study [13].

COX-2 expression is positively regulated by the cytokine IL6 [7,14]. The *IL6* G-174C promoter polymorphism affects the transcription of the gene [15,16] with the G-allele having a higher transcriptional level than the C-allele [16]. Carriers of the variant C-allele were found to be at 50% higher risk of colorectal cancer than homozygous carriers of the G-allele [17], whereas no association with risk of lung cancer was found in another study [12]. The *IL8* T-251A promoter polymorphism has been shown to modify IL8 production in vitro [18], with an increased IL8 response associated with the variant A-allele. In the former two studies, carriers of the variant A-allele were at lower risk of colorectal cancer than homozygous carriers of the wild type T-allele [17], whereas no association was found with risk of lung cancer [12].

The gene *PPARγ* encodes the peroxisome profilerator-activated receptor γ, which is a transcription factor and member of the nuclear hormone receptor super-family. PPARγ regulates among other genes *COX-2* expression and PPARγ is activated by UV-B light [19]. In vitro studies have shown that the variant allele of the PPARγ2 $Pro^{12}Ala$ polymorphism gives less transcriptional activation of target genes [20]. Carriers of the variant allele were found to have 50% lower risk of colorectal cancer than homozygous carriers of the wild type allele [17].

The promoter polymorphism *IL1β* T-31C has been found to affect the transcriptional level of *IL1β*. Carriers of the TT genotype had higher mucosal IL-1β levels than variant allele carriers in a Japanese study of *Helicobacter pylori*-infected patients [21]. Finally, the promoter polymorphism *IL10* C-592A forms a haplotype with two other SNPs, G-1082A and C-819T, which is associated with changes in the IL-10 level [22]. An interaction between the *IL10* C-592A polymorphism and NSAID use in relation to colorectal cancer has been reported [23].

We investigated whether polymorphisms modifying the inflammatory response are associated with risk of BCC, in a nested case–control study within the Danish "Diet, Cancer, and Health" cohort. Furthermore, we evaluated potential interaction by NSAID use and tanning during summer.

2. Materials and methods

The case–control study of BCC has been described previously [24–26]. Study subjects were selected from the Danish prospective study "Diet, Cancer and Health" [27,28]. Between December 1993 and May 1997, 160,725 individuals aged 50–64 years were invited to participate, of whom 57,053 individuals with no previous cancer diagnosis were recruited. At enrolment at two study centres, detailed information on diet and lifestyle, including information on skin type, were obtained. Blood samples were collected and buffy coat samples were stored at −150 °C.

Of the initial 57,053 participants, 547 persons were excluded from the study because they later were reported with cancer diagnosed prior to enrolment. Cohort members were identified by the unique identification number, assigned to every Danish citizen by the Central Population Registry. The identification number for all 56,506 cohort members was linked to the Central Population Registry for information on vital status and immigration. Information on cancer occurrence among cohort members was obtained through record linkage to the Danish Cancer Registry, which has recorded incident cases of cancer on a nationwide basis since 1943. Each cohort member was followed-up for BCC occurrence from date of entry, i.e. date of visit to the study centre, until the date of diagnosis of any cancer, date of death, date of emigration, or 31 December 1998, whichever came first. A total of 322 participants were diagnosed with BCC during the follow up period.

2.1. Matching of cases and controls

We used a nested case–control design [29]. One control was selected for each of the 322 cases. The control was cancer-free at the exact age at diagnosis of the case and was further matched on sex (male/female) and age at inclusion into the cohort (half-year intervals) but otherwise selected at random from the 'Diet, Cancer and Health' cohort.