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Concordant colon tumors in monozygotic twins previously treated for prostate cancer

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Abstract This report describes the quasi-simultaneous occurrence of colon cancers in monozygotic twin brothers (age 63 years) who had undergone androgen deprivation therapy for prostate cancers 4 years earlier. Concordance among male twins for both of these cancers has never been reported. Although the family history suggested possible genetic predispositions to both cancers, the twins have no evidence of the genetic alterations associated with hereditary colorectal tumors. We explore the possibility that colorectal tumorigenesis in these twins was fuelled by a combination of genetic and iatrogenic factors, in particular the androgen deprivation therapy used to treat their prostate cancers.

Keywords Androgen deprivation · Colon cancer · Monozygotic twins · Prostate cancer · Wnt signalling

Introduction

Prostate and colorectal cancers are common in western populations. The epidemiology of these diseases suggests that, in a substantial proportion of cases, genetic factors play a role [1–3]. Twin studies have been used to estimate the relative contributions of inherited genetic alterations and environmental factors to the development of these two cancers [4–8]. The dizygotic twin brothers of men with prostate cancer have a relative risk for developing this cancer of around three, but this figure is four times higher for monozygotic twins [1]. Indeed, probandwise concordance rates reported for prostate cancer are around 5% in dizygotic twins and approximately 20% in those who are monozygotic [1, 7, 8]. Men whose twin brothers have colorectal cancer are also more likely to develop this cancer. In this case, however, the relative risk for a monozygotic twin (around seven) is decidedly lower than that described for prostate cancer and similar to that of his dizygotic counterpart (around six). Colon cancer concordance rates (8 and 9% in dizygotic and monozygotic male twins) are also unrelated to zygosity [1].

These figures suggest that, while predisposing genetic factors contribute to the development of both prostate and colorectal cancer, nongenetic factors play a more substantial role in the latter disease. This conclusion appears to be strongly supported by the clinical and molecular evidence we collected on a pair of monozygotic twins who developed adenocarcinomas of the prostate and 4 years later adenocarcinomas of the colon. Genetic testing has excluded the presence of mutations currently known to cause predisposition to colorectal cancer. We explore the possibility that the development of their colon tumors might have been triggered by a combination of shared genetic and nongenetic factors, the latter including the treatment they received for their prostate cancers.

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Patients and procedures

Patients 1 and 2 were male monozygotic twins of Caucasian origin. (Monozygosity was confirmed [probability: 99.96%] by the analysis of nine autosomal STR (short tandem repeat) markers.) Neither was married. They worked together in the same office, shared an apartment, had similar diets and normal body mass indexes, and both were smokers.

In October 1997, patient 1 (subject III-1 in Fig. 1), then 58 years old, underwent transurethral resection for what proved to be prostate cancer (T3-4N0M0 based on imaging data; Gleason score 7 [3 + 4]). He received 3 months of percutaneous radiotherapy with neoadjuvant and adjuvant androgen ablation therapy based on goserelin and bicalutamide (details in Fig. 2). Three years later (June 2001), the cancer recurred with bone and biopsy-confirmed liver metastases. Goserelin treatment was resumed, and intermittent chemotherapy with docetaxel was then given for several months.

In March 2002, the patient was completely asymptomatic, but computed tomography performed for therapy control revealed a suspicious lesion in the sigmoid colon. Colonoscopy disclosed a sigmoid adenocarcinoma (2.7 × 2.5 cm) and a severely dysplastic tubular adenoma (5.5 × 4.3 cm) in the ascending colon. The tumors were removed by anterior colonic resection and partial resection of the ascending colon, and the colon cancer was classified as pT3pN0M0, G3. Nine months after surgery (January 2003), colonoscopy was repeated to determine the cause of the patient's persistent diarrhea, and nine new adenomas (tubular or tubulo-villous, diameters, 2–20 mm) were removed. These lesions varied in terms of the degree of dysplasia, and one polyp located in the right flexure proved to be a well-differentiated, stage I adenocarcinoma.

Since June 2001, the patient's metastatic prostate cancer had been controlled with docetaxel, but in March 2003 new liver metastases appeared, and prostate-specific antigen (PSA) levels rose. Repeat colonoscopy revealed two new tubular adenomas (diameters, 3 mm) that were promptly removed. The patient was still receiving goserelin (Fig. 2), and experimental capecitabine therapy was started, but in June 2003—69 months after the prostate cancer had been diagnosed, 14 months after the diagnosis of colon cancer—the patient died of progressive prostate cancer (verified by autopsy).

Patient 2's prostate cancer (T1cN0M0; Gleason score 6 [3 + 3]) was diagnosed in February 1998 (4 months after the discovery of his twin's tumor—Fig. 2) as a result of PSA-based screening and ultrasound-guided needle biopsy. Like his brother, patient 2 (III-2 in Fig. 1) received percutaneous radiotherapy and dual-agent androgen-deprivation therapy (Fig. 2). In May 2002, when his brother's colon cancer was diagnosed, he had a colonoscopy (although he was completely asymptomatic), which revealed a cecal carcinoma (3.5 × 2.8 cm) and three metachronous tubular and tubulo-villous adenomas of the proximal colon (diameters 5–20 mm). These lesions were eliminated with a right hemicolectomy, and the colon cancer was classified as pT2pN0M0, G2-3. Colonoscopy was repeated postoperatively to remove six small polyps (diameters 2–5 mm), including a 5 mm tubular adenoma. Because of his brother's history, patient 2 received close endoscopic follow-up. Eight months after his hemicolectomy (January 2003), a tubular adenoma was removed from the sigmoid colon. Since then over ten hyperplastic polyps have been removed from various parts of the remaining colon. In September 2007, PSA levels rose, but the patient is currently completely asymptomatic without treatment.

Genetic testing

Prostate and colorectal cancers are both common in the general population, so we cannot exclude the possibility that the cancers diagnosed in these twins are phenocopies.

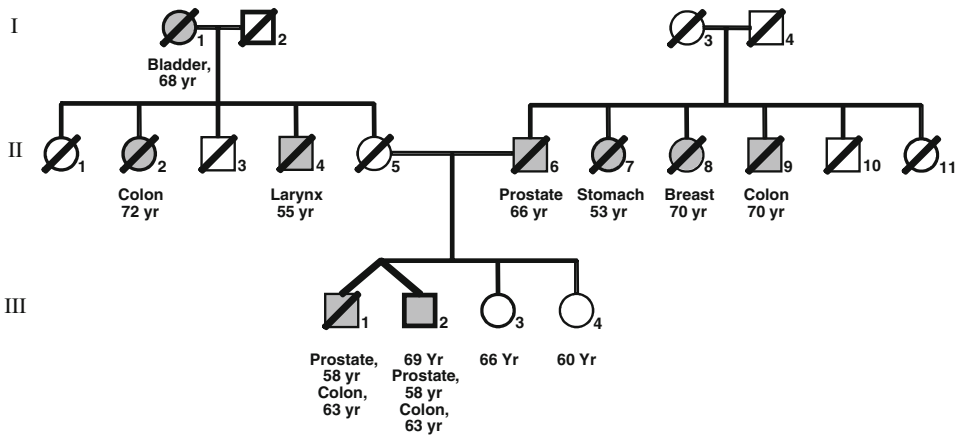

Fig. 1 Pedigree of the twins' family. *Circles* represent females; *squares* stand for males. *Slashes* indicate deceased family members. *Gray* symbols represent individuals who developed cancer (site and age at onset specified below the symbol). When the pedigree was created, patient 1 (III-1) had died, patient 2 (III-2) was 69 years old, and their only living relatives (III-3 and III-4) were asymptomatic and refused to be screened for colon cancer

	Patient 1 (III-1)		Patient 2 (III-2)
Oct 1997	Diagnosis of prostate adenocarcinoma (T3-4N0M0, Gleason 7 [3+4])	Feb 1998	Diagnosis of prostate adenocarcinoma (T1cN0M0, Gleason 6 [3+3])
Nov 1997-May 1998	Androgen deprivation with goserelin and bicalutamide	Mar-Aug 1998	Androgen deprivation with goserelin and bicalutamide
Feb-Apr 1998	Percutaneous radiotherapy (74 Gy)	May-Jun 1998	Percutaneous radiotherapy (72 Gy)
June 2001	Prostate cancer metastases to liver and bone. Androgen deprivation with goserelin resumed ; intermittent chemotherapy with docetaxel given through March 2003		
Mar 2002	Diagnosis and surgical removal of a sigmoid adenocarcinoma (pT3pN0M0, G3)	May 2002	Diagnosis and surgical removal of a cecal adenocarcinoma (pT2pN0M0, G2-3) and 3 proximal colon adenomas. Endoscopic removal of 6 additional small adenomas
Jan 2003	Diagnosis and removal of 2nd adenocarcinoma of the colon (pT1) and 9 metachronous adenomas (tubular or tubulo-villous)	Jan 2003-present	Endoscopic removal of 11 metachronous colon polyps (1 adenomatous and 10 hyperplastic)
Mar 2003	Progressive prostate cancer (increase of PSA and new liver metastases). Goserelin continued ; capecitabine started.		
Mar 2003	Two new colon adenomas removed		
June 2003	Death from progressive prostate cancer		
		Sept 2007	Biochemical recurrence of prostate cancer

Fig. 2 Overview of the twins' clinical histories. Immediately after the diagnosis of prostate cancer, both patients received percutaneous radiotherapy with neoadjuvant and adjuvant androgen deprivation therapy based on goserelin (10.8 mg every 3 months) with bicalutamide (50 mg daily for 2 weeks before and 2 weeks after the first goserelin injection) to prevent testosterone flare-ups, as well as percutaneous radiotherapy. When Patient 1 developed metastatic disease, he received goserelin (at the original dosage; continued until his death in 2003) and docetaxel (35 mg per square meter of body surface area every 4 weeks [on days 1, 8, and 15] for several months). During the last 3 months he also received experimental treatment with capecitabine

However, their family history was suggestive of a genetic cancer predisposition (Fig. 1). Although the cancer aggregation pattern was not indicative of any of the well-known cancer predisposition syndromes, we assessed the brothers' cancers for microsatellite instability, a hallmark of the mismatch repair deficiency that leads to the hereditary non-polyposis colon cancer syndrome. Defective mismatch repair was excluded by the absence of instability at three sensitive microsatellite markers (*BAT25*, *BAT26*, *BAT40*) and by immunohistochemical studies showing normal expression in the tumors of five mismatch repair proteins (MLH1, PMS2, MSH2, MSH6, and MSH3). The tumors also displayed normal immunohistochemical labelling for the cell-cycle checkpoint factor CHEK2. (Alterations of the gene that encodes this protein are reportedly associated with increased rates of both prostate and colon cancer [9].) Since both men had presented multiple colon adenomas, they were also tested for germline mutations involving the *adenomatous polyposis coli* gene (the protein truncation test); the *MutY homolog* (*MUTYH*) gene (denaturing high-performance liquid chromatography and direct sequencing); and the *tumor suppressor p53* (*TP53*) gene (direct sequencing of exons 5–8), but no pathogenic alterations were detected.

Discussion

These monozygotic twins were 58 years old when they were diagnosed with prostate cancer. Patient 1's tumor was advanced (T3-4, Gleason score 7) at the time of diagnosis, and his father had had the same type of cancer at age 66. Consequently, PSA-based screening was suggested for his twin brother, who was completely asymptomatic, and this precaution led to the diagnosis of an early-stage prostate cancer (T1c, Gleason score 6). Both men underwent percutaneous radiotherapy and dual-agent androgen deprivation (Fig. 2). Four years later the twins were found to have colon cancers as well. Again, patient 1's tumor was detected first, and its discovery led his twin to undergo colonoscopic screening, which revealed an earlier stage malignant neoplasm in the cecum.

Cancers of the prostate and colon are among the most common forms of neoplastic disease in Western men, and both are known to be caused in part by hereditary factors. The Swedish Twin Registry is one of the most informative registries of this type in the world [10]. It contains data on over 29,000 pairs of male twins, including eight cases (five monozygotic pairs, three dizygotic pairs) in which one twin has prostate *and* colon cancers, and the second has prostate

or colon cancer. But there is not one case in which colon *and* prostate cancers have been found in both twins (P. Lichtenstein, pers. comm.).

Concordance rates for prostate cancer among monozygotic male twins (20%) are markedly higher than those observed among their dizygotic counterparts (5%) [1, 7, 8] a pattern that is indicative of a substantial heritable component in this type of cancer. However, identification of the genetic alteration(s) that predispose a patient to this type of disease is currently a complicated process, and the results are far from conclusive. A few genetic loci have displayed associations with prostate cancer susceptibility in linkage analyses [11], but in some cases, the association is based solely on the analysis of a few kindreds. In others, causative roles have not been confirmed in subsequent studies. Very recently, certain common gene variants have been reported to increase the risk of prostate cancer [12], but the list of variants and their combinations will probably be refined in future genome-wide association studies and prospective trials. For these reasons, we have not attempted thus far to identify genetic alteration(s) that might have predisposed these two men to prostate cancer.

Indeed, our primary objective has been to characterize the twins' colon-cancer concordance, where the role played by genetic factors is even harder to pinpoint. In both cases, the cancers were associated with multiple synchronous and metachronous colon adenomas, which were suggestive of an inherited predisposition to this type of neoplasia, and two of the brothers' second-degree relatives had died of colon cancer (Fig. 1). However, the results of genetic testing have excluded the principal inherited causes of elevated colon cancer risk, including the classic and attenuated forms of familial adenomatous polyposis and the hereditary nonpolyposis colon cancer syndrome [3, 13]. The possibilities of inheritable changes in the multiorgan cancer susceptibility gene CHEK2 [9] or in the mutational hotspot region of *TP53* have also been ruled out.

These twins were also exposed to the same environmental risk factors for cancer, including those related to diet and smoking habits. The importance of shared nongenetic factors in colon cancer concordance among twins is reflected in the similar relative risks observed among the mono- and dizygotic twin brothers of affected males. With reference to their colon cancers, the fact that our patients had received identical treatment for their prostate tumors might be particularly relevant. The radiotherapy probably played no significant role in the development or evolution of the men's multiple colorectal tumors. The cancer-containing colon segments were not included in the treatment volume nor were they located close to the portal fields of irradiation. Moreover, the interval between the radiotherapy and the development of colon cancer was also rather short. A more interesting possibility is that the colon tumors were somehow related to the dual-agent androgen deprivation therapy that both men had received. Androgen receptors are expressed in both healthy and neoplastic colon tissues [14], and data from various studies suggest that androgens exert protective effects in the colon [15–19]. For example, chemical castration has been shown to enhance chemically induced colon carcinogenesis in rats [19], and there is a large body of evidence indicating that androgen-receptor activation in colon cancer cells can repress canonical Wnt signalling (i.e., signalling through the beta-catenin/TCF pathway) [20–22], which—in its deregulated form—is believed to be responsible for the vast majority of colorectal cancers—familial and sporadic [23].

It is tempting to speculate that colon carcinogenesis in these twins might have been fuelled—at least in part—by iatrogenic androgen deprivation resulting in inappropriate Wnt signalling. To our knowledge, the incidence of colon tumors in subjects who receive androgen deprivation therapy has never been specifically assessed in epidemiological studies. It is possible that the impact of androgen suppression on malignant transformation of the colon mucosa is genetically influenced. In the patients described here, this impact might have been increased by the genetic factors that led to the development of prostate cancer, and the fact that the two men were genetically identical may have enhanced the visibility of an effect that has thus far escaped notice in the general population. If so, identification of these genetic factors could represent an important step forward in our search for cancer susceptibility loci.

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