Androgen deprivation therapy and the risk of colorectal cancer in patients with prostate cancer

Jonathan Assayag · Hui Yin · Serge Benayoun · Michael N. Pollak · Samy Suissa · Laurent Azoulay

Abstract

Purpose Androgens are known to play an important protective role on colorectal carcinogenesis, and thus the objective of this study was to determine whether androgen deprivation therapy (ADT) is associated with an increased risk of incident colorectal cancer in patients with prostate cancer.

Methods We conducted a population-based cohort study within the UK General Practice Research Database population which included all patients newly diagnosed with prostate cancer between 1 January 1988 and 31 December 2008, followed until 31 December 2009. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) of incident primary colorectal cancer associated with the use of ADT. Secondary analyses considered cumulative duration of use and specific ADTs.

Results The cohort included a total of 21,503 patients, of whom 184 were diagnosed with colorectal cancer during a mean (SD) follow-up 4.0 (3.0) years (rate 2.4/1,000 person-years). Overall, use of ADT was not associated with an increased risk of colorectal cancer (HR 0.99, 95 % CI 0.73–1.35). Similarly, no association was observed in terms of duration use, although this secondary analysis may have been limited by statistical power. With respect to specific ADTs, bilateral orchiectomy was the only therapy associated with an increased risk of colorectal cancer (HR 2.50, 95 % CI 1.13–5.52).

Conclusion Overall, the use of ADT is not associated with an increased risk of incident colorectal cancer. The increased risk observed with bilateral orchiectomy may possibly be due to the prolonged androgen suppression of this therapy.

Keywords Androgen deprivation therapy · Colorectal cancer · Prostate cancer · Population based · Safety

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Introduction

Androgen deprivation therapy (ADT) remains the most common form of treatment for advanced prostate cancer [1]. ADT can be achieved either through surgical (bilateral orchiectomy) or chemical castration (gonadotropin-releasing hormone (GnRH) agonists or oral anti-androgens). While this therapy was traditionally reserved for patients with advanced disease, ADT is increasingly being used earlier in the course of the disease, such as in patients with biochemical relapse that have no evidence of metastatic

disease [2], thus allowing the chronic manifestations of the hypogonadal state to emerge [3].

The prolonged suppression of androgens has been associated with several adverse effects often called the "androgen deprivation syndrome." This is a condition characterized by metabolic changes, such as dyslipidemia [4–6], insulin resistance [7], and modification of body composition toward an increase of fat mass [6, 8], which have all been identified as risk factors of colorectal cancer [9]. Furthermore, several studies have shown that androgens exert a protective effect on colorectal carcinogenesis [10, 11]. Evidence for this potential adverse effect is limited, with just one study reporting an increased risk of colorectal cancer associated with ADT [9]. Specifically, the use of GnRH agonists was associated with a 31 % [hazard ratio (HR) 1.31, 95 % confidence interval (CI) 1.12–1.53] increased risk after 25 months on therapy, whereas bilateral orchiectomy was associated with a 37 % increased risk of colorectal cancer (HR 1.37, 95 % CI 1.14–1.66) [9]. While this study was novel in supporting a role for androgens in the prevention of colorectal carcinogenesis, it lacked information on other ADTs, such as oral antiandrogens which are often used alone or in combination with GnRH agonists. Thus, carefully designed studies are needed to assess the association between ADT and the risk of colorectal cancer.

Given the expanding indication for early use of ADT, particularly in men with localized prostate cancer [12], it is imperative to adequately assess its risks and benefits. Thus, the objective of this study is to determine whether ADT is associated with an increased risk of developing colorectal cancer in patients with prostate cancer.

Materials and methods

Data sources

This study was conducted using the General Practice Research Database (GPRD), a primary care database from the United Kingdom (UK) [13]. The GPRD is the world's largest computerized database of longitudinal records from primary care. It contains the complete primary care medical record for more than 12 million people enrolled in more than 650 general practices. The geographic distribution of the practices participating in the GPRD has been shown to be representative of the UK population, and age and sex distributions of patients in the GPRD are similar to those reported by the National Population Census. Participating general practitioners have been trained to record medical information including demographic data, medical diagnoses, procedures, and deaths using a standardized form. Prescriptions issued by GPRD physicians are automatically transcribed into the computer record. In addition, the GPRD collects information regarding lifestyle variables, such as body mass index (BMI), and quantitative and qualitative data pertaining to smoking and alcohol use. The Read classification is used to enter medical diagnoses and procedures, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposures and diagnoses has been validated and proven to be of high quality [14–16]. The study protocol was approved by the Independent Scientific Advisory Committee of the GPRD and the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

Study population

We conducted a cohort study using a population-based cohort of patients newly diagnosed with prostate cancer between 1 January 1988 and 31 December 2008, followed until 31 December 2009. Patients included in the cohort were required to be at least 40 years of age at the time of their prostate cancer diagnosis, and have at least 1 year of medical history in the GPRD prior to their diagnosis. Furthermore, we excluded patients diagnosed with metastatic disease at cohort entry, and those previously diagnosed with colorectal cancer at any time prior to cohort entry. The latter criterion was to ensure that incident cases are identified during follow-up. Finally, the cohort was restricted to patients with at least 1 year of follow-up after their prostate cancer diagnosis, necessary for latency considerations. Thus, cohort entry for all patients consisted of the year after the prostate cancer diagnosis.

Patients were followed until a first-ever primary diagnosis of colorectal cancer (outcome), death from any cause, end of registration with the general practice, or end of the study period (31 December 2009), whichever came first. Cancer diagnoses, including prostate and colorectal cancer, have shown high validity in the GPRD, with sensitivities and positive predictive values exceeding 90 % [17–20], and with case ascertainment rates comparable to UK cancer registries [21].

Exposure to androgen deprivation therapy

We considered all ADTs available on the UK market during the study period. Exposure to ADT was defined in a time-dependent fashion, allowing patients to move from a period of non-exposure to a period of exposure during follow-up. For the primary analysis, exposure was defined as ever use of any of the following ADTs: (1) GnRH agonists (leuprolide, goserelin, triptorelin) monotherapy (which may have included up to 4 weeks of an oral antiandrogen treatment at start of therapy), (2) oral anti-

androgens (cyproterone acetate, flutamide, bicalutamide, nilutamide) monotherapy, (3) combined androgen blockade (use of both GnRH agonists and >4 weeks of an oral anti-androgen), (4) bilateral orchiectomy, (5) estrogens and/or combinations of the above, and (6) no use of any ADT up until the event date.

In a secondary exposure definition, we assessed whether there was a dose–response in terms of cumulative duration of use which was entered as a time-dependent variable, calculated by adding the specified durations of each ADT prescription up until the date of the event. For patients who underwent bilateral orchiectomy, cumulative duration of use was calculated from the date of surgery. We also assessed whether the risk varied across the different ADTs listed above. All exposures were lagged by one year to account for a biologically meaningful latency time period, as it unlikely that ADT would increase the risk over a short duration of exposure. For all analyses, the reference category consisted of patients who were never exposed to any ADT up until the event date.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort. Person-time at risk was calculated from cohort entry to date of event or end of follow-up. Thus, the crude incidence rate of colorectal cancer, along with CIs based on the Poisson distribution, was calculated by dividing the number of patients diagnosed with colorectal cancer during the study period over the total person-time at risk.

Time-dependent Cox proportional hazards models, with duration of follow-up as the time axis, was used to estimate adjusted HRs and 95 % CIs for the association between use of any ADT, specific ADTs, and cumulative duration of use, entered in tertiles in the model based on the distribution in the cohort, on the risk of incident colorectal cancer. Exposure to ADT was treated as a unidirectional time-dependent variable (i.e., the time from cohort entry until a patient receives a first prescription was considered unexposed, and exposed from that point forward, even if the patient discontinued the treatment).

All models were adjusted for the following potential baseline confounders known to be associated with colorectal cancer which might also influence the use of ADT: year of cohort entry, age, excessive alcohol use, obesity (BMI > 30 kg/m^2), smoking status, inflammatory bowel disease (consisting of Crohn's disease and ulcerative colitis), previous cancer (other than non-melanoma skin cancer), history of polyps, cholecystectomy, type 2 diabetes, and ever use of aspirin, other anti-platelets, non-steroidal anti-inflammatory drugs, and statins. In addition, to control for possible increased colorectal screening intensity in ADT users, the models were further adjusted for referrals to colonoscopy, sigmoidoscopy, and radiation therapy, entered as time-dependent covariates in the models. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 39,607 patients diagnosed with prostate cancer during the study period, a total of 21,503 met the study inclusion criteria (Fig. 1). Within the first 6 months of diagnosis, 57.2 % of the patients received ADT, 20.0 % had undergone prostatectomy, while 5.0 % received radiation therapy. These low rates of prostatectomy and radiation therapy are consistent with the active surveillance approach adopted in the UK [22]. The characteristics of the cohort are presented in Table 1. The mean (standard deviation [SD]) age at cohort entry was 72.0 (8.9) years, and the mean (SD) duration of follow-up was 4.0 (3.0) years. During follow-up, the majority of patients received, on at least one occasion, GnRH agonists (58.4 %), followed by oral anti-androgens (48.5 %), estrogens (6.7 %), and bilateral orchiectomy (2.9 %). The characteristics of patients using the different ADTs were generally similar overall, although GnRH agonist users tended to be more on aspirin, statins, and have diabetes (Online appendix Table 1).

During the study period, 184 patients were diagnosed with colorectal cancer during 75,425 person-years of follow-up, yielding an overall colorectal cancer rate of 2.4/1,000 (95 % CI 2.1–2.8) persons per year.

Table 2 presents the results of the primary analysis. Overall, ever use of ADT was not associated with an increased risk of colorectal cancer (adjusted HR 0.99, 95 % CI 0.73–1.35). This result remained virtually the same even

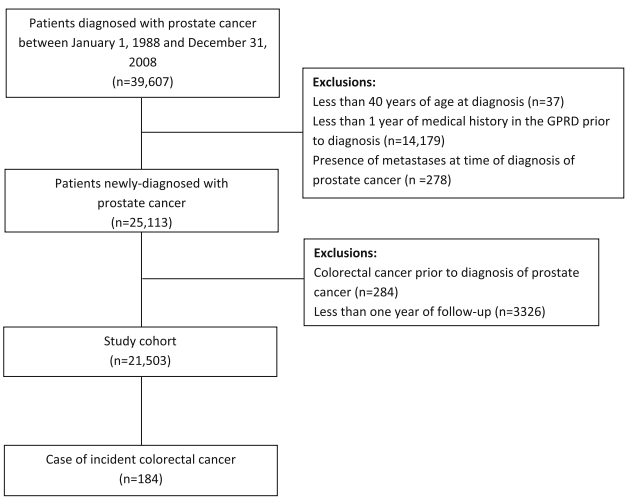

Fig. 1 Study flow chart

Table 1 Characteristics of the cohort

Characteristics measured at baseline	Cohort (n = 21,503)	Crude HR for CRC (95 % CI)
Age, mean (SD)	72.0 (8.9)	1.04 (1.02, 1.06)
Excessive alcohol use, *n* (%)	1,462 (6.8)	1.08 (0.58, 1.98)
Body mass index, *n* (%)		
<30 kg/m^2	15,880 (73.9)	1.00 (reference)
≥30 kg/m^2	2,480 (11.5)	1.14 (0.76, 1.70)
Unknown	2,480 (11.5)	1.23 (0.77, 1.96)
Smoking status, *n* (%)		
Ever	10,523 (48.9)	1.58 (1.14, 2.18)
Never	9,022 (42.0)	1.00 (reference)
Unknown	1,958 (9.1)	1.71 (1.11, 2.65)
Inflammatory bowel disease, *n* (%)	271 (1.3)	1.97 (0.73, 5.32)
Previous cancer, *n* (%)	2,980 (13.9)	0.81 (0.51, 1.28)
History of polyps, *n* (%)	398 (1.9)	1.04 (0.33, 3.27)
Cholecystectomy, *n* (%)	719 (3.3)	0.85 (0.35, 2.07)
Diabetes, *n* (%)	1,947 (9.1)	1.21 (0.73, 2.03)
Referrals to colonoscopy[a], *n* (%)	1,158 (5.4)	2.07 (1.69, 2.54)
Referrals to sigmoidoscopy[a], *n* (%)	687 (3.2)	1.45 (1.14, 1.83)
Radiation therapy[a], *n* (%)	2,501 (11.6)	0.87 (0.55, 1.37)
Ever use of statins, *n* (%)	4,842 (22.5)	1.07 (0.72, 1.59)
Ever use of aspirin, *n* (%)	6,892 (32.1)	1.09 (0.79, 1.51)
Ever use of other anti-platelet drugs, *n* (%)	903 (4.2)	1.38 (0.65, 2.93)
Ever use of non-steroidal anti-inflammatory drugs, *n* (%)	10,162 (47.3)	1.12 (0.84, 1.50)

HR hazard ratio, *CI* confidence interval, *SD* standard deviation, *CRC* colorectal cancer

[a] Entered as time-dependent covariates in the model

Table 2 Androgen deprivation therapy and the risk of colorectal cancer

Androgen deprivation therapy	Cases (n = 184)	Person-years	Crude rate (per 1,000/year)	Crude HR	Adjusted HR (95 % CI)[a]
Non-use	68	30,663	2.2	1.00	1.00 (reference)
Ever use	116	44,762	2.6	1.13	0.99 (0.73, 1.35)

HR hazard ratio, *CI* confidence interval

[a] Adjusted for year of cohort entry, age, excessive alcohol use, obesity (≥ 30 kg/m^2), smoking status, inflammatory bowel disease, previous cancer, history of polyps, cholecystectomy, and diabetes, ever use of aspirin, other anti-platelet drugs, non-steroidal anti-inflammatory drugs, and statins. The model was also adjusted for referrals to colonoscopy, sigmoidoscopy, and radiation therapy which were entered as time-dependent covariates

after removing referrals to colonoscopy and sigmoidoscopy from the model (adjusted HR 0.99, 95 % CI 0.73–1.35). Similarly, no dose–response was observed in terms of cumulative duration of use when all ADTs were considered, although a trend was observed with longer durations (Table 3). In terms of duration of use of specific ADTs, the median was 0.9 years for GnRH agonists, 0.2 years for oral anti-androgens, 0.8 years for combined androgen blockade, 1.7 years for bilateral orchiectomy, and 1.0 year for other ADT therapies. Due to the few exposed cases in each of these ADT categories, it was not possible to perform cumulative duration analyses.

When ADT was categorized according to type (Table 4), no increased risk of colorectal cancer was observed with the use of GnRH agonists, oral anti-androgens, combined androgen blockade, other therapies (such as estrogen), and combinations of the above. In contrast, a significant increased risk of incident colorectal cancer was observed with bilateral orchiectomy (adjusted HR 2.50, 95 % CI 1.13–5.52).

Discussion

The results of this study indicate that overall, the use of ADT is not significantly associated with an increased risk of colorectal cancer. However, in a secondary analysis, bilateral orchiectomy was associated with more than a two-

Table 3 Cumulative duration of androgen deprivation therapy and the risk of colorectal cancer

Androgen deprivation therapy	Cases ($n = 184$)	Person-years	Crude rate (per 1,000/year)	Crude HR	Adjusted HR (95 % CI)[a]
Non-use	68	30,663	2.2	1.00	1.00 (reference)
Cumulative duration of use (months)[b]					
<14.3	27	14,736	1.8	0.84	0.79 (0.51, 1.24)
14.3–33.5	37	15,239	2.4	1.10	0.92 (0.60, 1.41)
>33.5	52	14,787	3.5	1.49	1.29 (0.86, 1.95)

HR hazard ratio, *CI* confidence interval

[a] Adjusted for year of cohort entry, age, excessive alcohol use, obesity (≥30 kg/m^2), smoking status, inflammatory bowel disease, previous cancer, history of polyps, cholecystectomy, and diabetes, ever use of aspirin, other anti-platelet drugs, non-steroidal anti-inflammatory drugs, and statins. The model was also adjusted for referrals to colonoscopy, sigmoidoscopy, and radiation therapy which were entered as time-dependent covariates

[b] Based on tertile categories

Table 4 Androgen deprivation therapy and the risk of colorectal cancer

Ever use of androgen deprivation therapy	Cases ($n = 184$)	Person-years	Crude rate (per 1,000/year)	Crude HR	Adjusted HR (95 % CI)[a]
Non-use	68	30,663	2.2	1.00	1.00 (reference)
Gonadotropin-releasing hormone agonists only	61	26,522	2.3	1.03	0.87 (0.61, 1.24)
Oral anti-androgens only	19	7,118	2.7	1.19	1.13 (0.68, 1.88)
Combined androgen blockade[b]	21	7,982	2.6	1.08	0.93 (0.56, 1.54)
Bilateral orchiectomy	7	1,215	5.8	2.73	2.50 (1.13, 5.52)
Other therapies or combinations	8	1,925	4.2	1.61	1.57 (0.75, 3.31)

HR hazard ratio, *CI* confidence interval

[a] Adjusted for year of cohort entry, age, excessive alcohol use, obesity (≥30 kg/m^2), smoking status, inflammatory bowel disease, previous cancer, history of polyps, cholecystectomy, and diabetes, ever use of aspirin, other anti-platelet drugs, non-steroidal anti-inflammatory drugs, and statins. The model was also adjusted for referrals to colonoscopy, sigmoidoscopy, and radiation therapy which were entered as time-dependent covariates

[b] Composed of patients prescribed GnRH agonists with more than 4 weeks of an oral anti-androgen

fold increased risk of colorectal cancer. In contrast to other ADTs, this therapy had the longest duration of use, and thus supports to the notion that prolonged androgen deprivation may be associated with an increased risk of colorectal cancer.

While we observed no increased risk of colorectal cancer with ADT overall, the increased risk observed with bilateral orchiectomy is concordant with the one observed in the previous study where this therapy was associated with 37 % increased risk (HR 1.37, 95 % CI 1.14–1.66) [9]. In contrast, we did not observe a dose–response relationship in terms of ADT cumulative duration of use. Gillessen et al. [9] reported an increased risk of colorectal cancer with the use of GnRH agonist therapy for 25 months or longer (HR 1.31, 95 % CI 1.12–1.53). In our study, only 61 cases were ever exposed to GnRH agonists. As such, we did not have the statistical power to evaluate whether the long-term use of this therapy is associated with an increased risk of colorectal cancer. Therefore, it is not possible to rule out an increased risk with longer durations of use, specifically when we take into consideration the strong association observed with bilateral orchiectomy. Indeed, it is unlikely that GnRH agonists and bilateral orchiectomy act differently on colorectal tissues. By perturbations at different level of the hypothalamic–pituitary–gonadal axis, GnRH agonists are just as effective as bilateral orchiectomy in impairing production of testosterone to castrate levels. The association observed between bilateral orchiectomy and colorectal cancer is better explained by the duration of castration. Since bilateral orchiectomy is an older and definitive therapy (not eligible to intermittent androgen deprivation therapy), patients on this therapy had longer durations of castration compared with patients on GnRH agonists. This hypothesis is supported by the fact that the median castration duration with bilateral orchiectomy was almost 2 years, which corroborates the results of the previous study showing a modest effect only after 13–24 months of castration [9].

The association between ADT and colorectal cancer is biologically plausible. First, androgen receptors are present

in both normal and malignant human colonic tissues [23, 24]. Furthermore, several animal studies have shown that androgens can protect against colorectal carcinogenesis, while suppression of androgens can promote it. [10, 11, 25] Finally, studies have shown that abnormal activation of Wnt/b-catenin/T cell factor signaling is related to the majority of colorectal cancers [26], and evidence has shown that androgen receptor activation can strongly repress this signaling in colon cancer cells [27, 28].

This population-based study has a number of strengths and some limitations. First, we assembled a large population-based cohort of patients newly diagnosed with prostate cancer, followed for up to 21 years. However, despite this large sample, we may have lacked statistical power in secondary analyses assessing the risk according to cumulative duration of use and by type of ADT. Second, the use of population-based data limited the potential for selection bias. Third, because information is prospectively recorded in the GPRD, the possibility of recall bias was eliminated. However, drug information in the GPRD represents prescriptions written by general practitioners. As such, it was unknown whether prescriptions were actually filled at the pharmacy and whether patients fully complied with the treatment regimen. Such misclassification of exposure would dilute the point estimates toward the null. Fourth, our exposure definitions were time-dependent, avoiding biases related to misclassification of exposure during follow-up [29]. Another limitation of the GPRD is the lack of information on certain colorectal cancer risk factors, such as diet, race, ethnicity, family history, and inherited syndromes. It is unclear why these unmeasured variables would be differentially distributed between users and nonusers of ADT, and therefore it is unlikely that this lack of information affected the validity of our results. We also did not have access to testosterone levels to assess if perfect castration was achieved, however, this lack of information is not a concern for bilateral orchiectomy. Furthermore, the GPRD database contains information on a number of important potential confounders, such as BMI, excessive alcohol use, and smoking, and thus we were able to adjust for a number of important confounders often absent in administrative databases. As for our outcome ascertainment, we specifically searched for diagnostic codes related to a primary diagnosis of colorectal cancer. As part of this outcome definition, we did not include diagnostic codes of secondary colorectal cancers or diagnostic codes related to cancers that have metastasized in the colon or rectal area, although it is not possible to exclude possible misclassifications. Finally, the susceptibility to bias from confounding by indication is invariably a concern in non-experimental designs [30], however, confounding by indication is generally not a problem if a study focuses on unexpected drug effects, such as colorectal cancer in this study [31].

Conclusions

The results of this study indicate that, overall, the use of ADT is not associated with an increased risk of colorectal cancer in patients with prostate cancer. However, the strong increased risk observed with bilateral orchiectomy supports the possibility that prolonged castration may increase the risk of colorectal neoplasia. Additional well-designed population-based studies are needed to assess the risk of colorectal cancer associated with the different ADT therapies, and with longer durations of use.

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References

1. Taylor LG, Canfield SE, Du XL (2009) Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer 115(11):2388–2399
2. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, Milani RV, Sagalowsky AI, Smith MR, Zakai N; American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association (2010) Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation 121(6):833–840
3. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS (2005) Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 103(8):1615–1624
4. Braga-Basaria M, Muller DC, Carducci MA, Dobs AS, Basaria S (2006) Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. Int J Impot Res 18(5): 494–498
5. Braga-Basaria M, Dobs AS, Muller DC et al (2006) Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 24(24):3979–3983
6. Smith MR, Finkelstein JS, McGovern FJ et al (2002) Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 87(2):599–603
7. Smith MR, Lee H, Fallon MA, Nathan DM (2008) Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology 71(2):318–322
8. Smith MR (2004) Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology 63(4):742–745
9. Gillessen S, Templeton A, Marra G, Kuo YF, Valtorta E, Shahinian VB (2010) Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. J Natl Cancer Inst 102(23):1760–1770
10. Izbicki JR, Hamilton SR, Wambach G et al (1990) Effects of androgen manipulations on chemically induced colonic tumours and on macroscopically normal colonic mucosa in male Sprague-Dawley rats. Br J Cancer 61(2):235–240
11. Aoki K, Nakajima A, Mukasa K, Osawa E, Mori Y, Sekihara H (2003) Prevention of diabetes, hepatic injury, and colon cancer

with dehydroepiandrosterone. J Steroid Biochem Mol Biol 85(2–5):469–472
12. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR (2003) National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst 95(13):981–989
13. Walley T, Mantgani A (1997) The UK General Practice Research Database. Lancet 350(9084):1097–1099
14. Jick H, Jick SS, Derby LE (1991) Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 302(6779):766–768
15. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD (2000) Validation of the diagnosis of venous thromboembolism in general practice database studies. Br J Clin Pharmacol 49(6):591–596
16. Jick SS, Kaye JA, Vasilakis-Scaramozza C et al (2003) Validity of the general practice research database. Pharmacotherapy 23(5):686–689
17. Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR (1997) Calcium-channel blockers and risk of cancer. Lancet 349(9051):525–528
18. Garcia-Rodriguez LA, Huerta-Alvarez C (2001) Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. Epidemiology 12(1):88–93
19. Hall GC, Roberts CM, Boulis M, Mo J, MacRae KD (2005) Diabetes and the risk of lung cancer. Diabetes Care 28(3): 590–594
20. Gonzalez-Perez A, Garcia Rodriguez LA (2005) Prostate cancer risk among men with diabetes mellitus (Spain). Cancer Causes Control 16(9):1055–1058
21. van Staa TP, Patel D, Gallagher AM, de Bruin ML (2012) Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. Diabetologia 55(3):654–665
22. Prostate cancer: Diagnosis and treatment. National Collaborating Centre for Cancer. London (UK):National Institute for Health and Clinical Excellence (NICE); 2008 Feb. 146 p. (NICE clinical-guideline; no. 58). http://guidelines.gov/content.aspx?id=14315&search=prostate+cancer+2008. Accessed 21 Dec 2012
23. Castagnetta L, Traina A, Campisi I et al (2002) Androgen receptor status in nontumoral and malignant human colorectal tissues. Ann NY Acad Sci 963:322–325
24. Meggouh F, Lointier P, Saez S (1991) Sex steroid and 1,25-dihydroxyvitamin D3 receptors in human colorectal adenocarcinoma and normal mucosa. Cancer Res 51(4):1227–1233
25. Rao S, Porter DC, Chen X, Herliczek T, Lowe M, Keyomarsi K (1999) Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-CoA reductase. Proc Natl Acad Sci USA 96(14):7797–7802
26. Van der Flier LG, Sabates-Bellver J, Oving I et al (2007) The intestinal Wnt/TCF signature. Gastroenterology 132(2):628–632
27. Chesire DR, Isaacs WB (2002) Ligand-dependent inhibition of beta-catenin/TCF signaling by androgen receptor. Oncogene 21(55):8453–8469
28. Shah S, Hecht A, Pestell R, Byers SW (2003) Trans-repression of beta-catenin activity by nuclear receptors. J Biol Chem 278(48):48137–48145
29. Suissa S (2008) Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 167(4):492–499
30. Strom BL, Melmon KL (1994) The use of pharmacoepidemiology to study beneficial drug effects. Pharmacoepidemiology. Wiley, Chichester
31. Strom BL, Melmon K (1994) The use of pharmacoepidemiology to study beneficial drug effects. In: Strom BL (ed) pharmacoepidemiology, 2nd edn. Wiley, Chichester, pp 611–628