SYSTEMATIC REVIEW OF EFFICACY OUTCOMES REPORTED IN RANDOMISED CONTROLLED TRIALS OF FIRST-LINE (1L) THERAPIES FOR METASTATIC BREAST CANCER (MBC)

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OBJECTIVES: There is currently some debate around the optimal role of overall survival (OS) as a gold standard in assessing the benefits of oncology products. The objective of this analysis was to provide evidence to inform this discussion from a review of the clinical outcomes in 1L mBC trials reported over the last 10 years.

METHODS: MEDLINE and Cochrane databases were searched to identify randomised controlled trials of 1L mBC published between January 2009 and February 2009. Studies in exclusively human epidural growth factor receptor 2-positive populations were excluded. RESULTS: Clinical efficacy data were extracted from 36 trials. All 36 trials reported response rate (RR), 34 reported a progression-based end point and 33 reported OS. The most commonly stated primary efficacy end points were progression-based; only 6 trials stated OS as the primary end point. Improvement in median OS ranged from 0.1 to 7.8 months, improvement in median progression-free survival (PFS) ranged from 0.1 to 6.4 months and improvement in RR ranged from 0.3% to 28%. Fourteen trials (39%) reported a significant progression-based benefit, 4 of which (36%) reported significant median OS. Each of these 4 trials also reported a significant benefit in RR and median PFS. CONCLUSIONS: Overall, very few 1L mBC trials have reported a significant median OS benefit. Where a significant OS benefit was reported, a significant overall RR and PFS benefit was also reported. These findings are important in light of the ongoing debate on the relevance of currently used clinical end points in mBC trials.

STATIN USE AND THE RISK OF COLORECTAL CANCER: A POPULATION-BASED COHORT STUDY

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OBJECTIVES: Basic scientific evidence suggests that statins inhibit the growth of colon-cancer cell lines, and secondary analyses of some randomized clinical trials suggest that they reduce the risk of colorectal cancer. However, evidence from observational studies has been conflicting on whether the risk of colorectal cancer is reduced in statin users. We sought to assess the association between statin use and the rate of colorectal cancer in a large cohort of residents in Emilia-Romagna, Italy.

METHODS: We conducted a population-based cohort study using the longitudinal health database of Emilia-Romagna, Italy, a region with approximately 4.2 million inhabitants. This comprehensive database contains information on all health care services rendered to the population, including hospital, outpatient pharmacy and specialty data. We identified all initiators of statins; initiators of glaucoma medications served as a comparison group. Colorectal cancer cases were identified by hospital discharge data. Multivariable logistic regression analyses were used to adjust for confounding. RESULTS: Patient characteristics were similar in both groups, but statin initiators (30,334) were prevalently male, were slightly younger, and used hospital services more frequently than glaucoma medication initiators (78,361). During a maximum of 3 years of follow-up, the incidence rate of colorectal cancer was lower in the statin users than in the glaucoma medication users (0.49% vs. 0.79%; Relative Risk, 0.69, 95% CI, 0.52 to 0.92). The adjusted odds ratio for statin use compared with nonuse was 0.67 (95% CI, 0.57 to 0.79).

CONCLUSIONS: The use of statins was associated with a 33% relative reduction in the risk of colorectal cancer after adjustment for observable risk factors. Because the analysis may not have accounted for every potential confounder, further investigation of the overall benefits of statins in preventing colorectal cancer is warranted.

CANCER INCIDENCE IS INFLUENCED BY INSULIN DOSE AND METFORMIN IN TYPE 2 DIABETES

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OBJECTIVES: Patients with type-treated type 2 diabetes are more likely to be diagnosed with cancer than those on metformin. We looked for evidence of a relationship between insulin dose and cancer incidence in type 2 diabetes, and examined the effect of concomitant metformin upon this relationship. METHODS: Three treatment cohorts: metformin monotherapy, insulin plus metformin, and insulin only, were compared in a retrospective analysis of data from UK general practice. Relative insulin exposure was determined by the number of insulin prescriptions per year (<7, 7–10, >10 days, and >15). Cox proportional hazards models were used to adjust for differences in baseline characteristics and for differences in insulin use exposure using a time-dependent analysis. RESULTS: The adjusted hazard ratios (HRs) for a diagnosis of cancer in the four subgroups treated with insulin alone relative to metformin monotherapy were: 1.24 (95% CI 0.90–1.70), 1.40 (1.05–1.87), 1.99 (1.52–2.61), and 2.75 (2.01–3.75) with increasing exposure to insulin. The corresponding HRs for insulin combination with metformin were 1.01 (0.72–1.40), 1.14 (0.76–1.64), 1.08 (1.03–1.18), 1.05 (0.98–1.13), 2.05 (1.07–3.93), and 1.80 (0.93–2.11). Introduced as a continuous variable, for those with insulin plus metformin the HR for prescribed insulin dose in IUs/kg/day was exactly 1.00 (0.76–1.29; p = 0.9999). For insulin only, the HR for dose expressed in IUs/kg/day was 1.83 (1.50–2.24; p < 0.0001). CONCLUSIONS: There was a dose-related association between insulin exposure and cancer risk in type 2 diabetes. The highest observed rates were in those with lower weight and higher levels of prescribed insulin. Co-administration of metformin was associated with a lower incidence of cancer at all levels of insulin exposure.

CASTRATION-RESISTANT PROSTATE CANCER (CRPC): A UK POPULATION-LEVEL STUDY

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OBJECTIVES: To determine the epidemiology of castration-resistant prostate cancer (CRPC). METHODS: Primary care data for males aged >40 years with a diagnosis of prostate cancer (PC) based on the Read classification were selected from The Health Improvement Network (THIN) between 1998 and 2008. Patients with CRPC were defined by a Read code indicative of medical/surgical castration and evidence of increasing levels of prostate specific antigen (PSA) following hormone/androgen therapy. Incidence and mortality rates were based on person years at risk. Survival was estimated using Cox regression analyses. To compare survival between CRPC and non-CRPC, non-CRPC controls were matched by age, year of diagnosis and baseline survival. RESULTS: Between 2003/2007, 8,678 patients with PC were identified. Incidence was 22.4 per 10,000 patient years and prevalence was 153.0 per 10,000 patients. 969 patients (11.2%) progressed to CRPC. Amongst patients with PC the prevalence was 1,530 per 10,000 cases. Rate of first recorded metastases was 34.9 per 1,000 patient years for CRPC; compared with 24.8 for non-CRPC. Following CRPC onset, the mortality rate was 201.2 per 1,000 patient years compared with 86.7 per 1,000 for non-CRPC. Based on matched data, the hazard ratio for CRPC relative to non-CRPC was 2.61 (p = 0.001). Extrapolated to the UK the data from this study would predict approximately 220,000 prevalent cases of PC, 7,000 CRPC and 2,000 CRPC with recorded metastatic spread. Similarly the annual incidence would predict approximately 37,000 PC, 8,400 CRPC and 820 CRPC with recorded metastatic spread. CONCLUSIONS: The extrapolated prevalence and incidence estimates of PC are comparable to other studies in the UK. CRPC status was associated with a significantly greater rate of metastases and mortality. Due to the reliance on PA reads in defining CRPC status it is acknowledged that we may underestimate the incidence of CRPC.

BREAST CANCER PATIENTS ARE TWICE AS LIKE TO DEVELOP ARTERIAL THROMBOEMBOLIC EVENTS BEFORE DIAGNOSIS COMPARED TO CANCER-FREE WOMEN

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OBJECTIVES: To study occurrence of arterial thromboembolic events before and after breast cancer (BC) diagnosis compared to cancer-free controls as this information is lacking in published literature. METHODS: Women who had a first hospitalization for BC between 2002 and 2007 were selected from the PHARMO Record Linkage System, which includes drug use and hospitalization data of approximately 3 million residents in the Netherlands. BC patients were matched 1:10 by age with cancer-free controls, using the date of diagnosis as the index date for all BC patients and their controls. ATEE were defined as a myocardial infarction, ischemic stroke, unstable angina and transient ischemic attack requiring hospitalization and were assessed 12 months before and 12 months after the index date. RESULTS: The analysis included 11,473 BC patients, with a mean (SD) age of 59 (±14) years. ATEE before the index date were twice as frequent among BC patients compared with cancer-free controls (Odds Ratio = 2.0 [95%CI:1.6–2.6]), though prevalence was <1% in both groups. The incidence of developing ATEE in the 12-month follow-up period was 6.2 per 1000 person years among patients and 3.8 among controls. BC patients experienced a higher risk of ATEE compared with controls (Hazard Ratio = 1.7 [95%CI:1.3–2.2]). This risk was attenuated but remained statistically significant after adjusting for prior cardiovascular or TEE hospitalization and prior antithrombotic or cardiovascular drug use (Hazard Ratio = 1.3 [95%CI:1.0–1.7]). Independent risk factors for developing ATEE in 12 months after diagnosis were age (253 versus <65 years), prior use of antihypertensives or antidiabetic drugs and total hospital stay >10 days during the first 6 months of follow-up. CONCLUSIONS: In this population-based study, BC patients were twice as likely to develop ATEE compared to cancer-free controls, although the frequency of events was low. These results emphasize the need for careful observation of BC patients after diagnosis.