PRIMARY CARE DIABETES XXX (2017) XXX–XXX

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original Research

Trends in breast cancer incidence among women with type-2 diabetes in British general practice

Heleen K. Bronsveld[a,b], *Paul J.H.L. Peeters*[a], *Mark C.H. de Groot*[a,c], *Anthonius de Boer*[a], *Marjanka K. Schmidt*[b], *Marie L. De Bruin*[a,d,*]

[a] *Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

[b] *Division Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

[c] *Department of Clinical Chemistry and Haematology, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands*

[d] *Copenhagen Centre for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

ARTICLE INFO

Article history:
Received 3 December 2016
Received in revised form
3 February 2017
Accepted 4 February 2017
Available online xxx

Keywords:
Breast cancer
Diabetes mellitus
Incidence rates
Time-trends
Age
Epidemiology
Public health

ABSTRACT

Aims: To quantify breast cancer incidence in women with type-2 diabetes and assess age-standardized trends in invasive breast cancer incidence over time and by age groups.

Methods: A population-based cohort study was conducted using the British general practice database (Clinical Practice Research Datalink) using data from 1989 to 2012. All adult women prescribed anti-hyperglycemic medication were selected and matched (1:1) on age and clinical practice to a reference cohort without diabetes.

Results: During approximately 1.6 million person years (py), 2371 breast cancer cases were diagnosed in the diabetes cohort (n = 147,998) and 2252 in the reference cohort (n = 147,998). Incidence of breast cancer, overall or by age groups, among women with diabetes remained stable over time. The (overall) age-standardized breast cancer IR per 100,000 py of the diabetes cohort (150, 95%CI:143–157) resembled that observed in the reference cohort (148, 95%CI:141–156); with an incidence rate ratio (IRR) of 1.01 (95%CI:0.94–1.08, p > 0.05).

Conclusions: Currently, around 2880 women with type-2 diabetes are diagnosed with breast cancer per year in the United Kingdom. However, breast cancer incidence remained stable in the last 10 years and seems to be comparable in women with and without diabetes.

Abbreviations: BMI, body-mass index; CPRD, Clinical Practice Research Datalink; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; NIADS, non-insulin anti-diabetic drugs; py, person years; UK, United Kingdom.

* *Corresponding author at*: Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, Utrecht 3584 CG, The Netherlands.

E-mail addresses: H.Bronsveld@nki.nl (H.K. Bronsveld), P.J.H.L.Peeters@uu.nl (P.J.H.L. Peeters), M.C.H.deGroot-3@umcutrecht.nl (M.C.H. de Groot), A.deBoer@uu.nl (A. de Boer), mk.schmidt@nki.nl (M.K. Schmidt), M.L.DeBruin@uu.nl (M.L. De Bruin).

http://dx.doi.org/10.1016/j.pcd.2017.02.001
1751-9918/

1. Introduction

Type-2 diabetes mellitus and breast cancer are two major global health problems with partially shared risk factors such as overweight [1]. Recent estimates indicate that diabetes prevalence is 9.1% and life-time risk for breast cancer is 9.7% among women in Europe [2,3]. Female breast cancer incidence rates (IRs) have increased strongly since the late-1970s [4], with a 62%-increase in the United Kingdom (UK) [5]. Between 2001–2012 the increases in IRs have been relatively stabilized with a total increase of ~6% [5]. For diabetes the incidence and prevalence is still rising in most European countries [6–8]. The number of women with type-2 diabetes in the UK has doubled since 1994. Age-standardized IRs of diabetes increased from 1.6 women per 1000 person years (py) in 1994 to 3.1 women per 1,000 py in 2003 [9].

Meta-analyses have reported that women with type-2 diabetes having a 1.2-fold risk to develop breast cancer [10–14]. Changes in population lifestyle patterns over time, such as increased high-caloric diet and decreased physical activity, resulting in obesity, led to an increase in the number of people developing type-2 diabetes [15]. Possible explanations for the increased risk of breast cancer in patients with diabetes include shared risk factors such as obesity (high BMI), high blood glucose levels and hyperinsulinemia [12,16,17].

Aging populations and better treatment (resulting in lower mortality rates) further contribute to the increasing prevalence of diabetes. Hence, a significant proportion of women is living with diabetes, and these women may be at increased risk of developing breast cancer. It is important for public health decisions to quantify this double burden of disease and get insight in the absolute numbers of breast cancer incidence stratified by type-2 diabetes over time. However, these numbers are largely missing. Therefore, we examined age-standardized IRs of breast cancer among women with type-2 diabetes in British general practice and investigated trends in incidence over time (1989–2012) and by age groups. To support our findings, we compared breast cancer incidence trends to a non-diabetes reference group. Since underlying risk factors changed over time we also stratified IRs by menopause (using age as a proxy) and BMI to explore whether we could identify specific subgroups of women with diabetes that might benefit from e.g. intensified breast cancer screening.

2. Methods

2.1. Source of data

Data were obtained from the Clinical Practice Research Datalink (CPRD) [18]. This database comprises electronic medical records from patients registered at general practices since 1987 and represents approximately 7% of the UK population. Patients in the CPRD are broadly representative of the UK general population in terms of age, sex, ethnicity, and mortality rates [18,19]. The accuracy and completeness of CPRD data have been well validated in previous studies [20,21]. Data recorded in CPRD include demographic information, prescribed medication, clinical events including cancer diagnosis, preventive care provided, specialist referrals and hospital admissions. The CPRD's Independent Scientific Advisory Committee approved the protocol of this study (number: 13_050).

2.2. Study population, follow-up and case definition

To estimate breast cancer rates among women with and without type-2 diabetes during 1989–2012, we used a cohort of prevalent and incident anti-hyperglycemic drug users (diabetes cohort) and a matched reference cohort. The diabetes cohort consisted of registered adult women (aged ≥18 years) with at least 1 prescription for any anti-hyperglycemic agent recorded in CPRD during follow-up. The date of the first anti-hyperglycemic drug prescription during follow-up was taken as the date of cohort entry; though women might also have used anti-hyperglycemic drugs prior to cohort entry. The diabetes cohort was matched (1:1) on age and practice to a reference cohort of women without any recorded prescriptions for anti-hyperglycemic agents. If a woman in the reference cohort started using anti-hyperglycemic drugs during follow-up, she was censored and categorized as a patient with diabetes from that day onwards. As a newly diagnosed patient with diabetes, she was then matched to a new woman that was added to the reference cohort. By creating two dynamic cohorts we avoided immortal time bias [22].

To select our final cohort, we excluded patients with type-1 diabetes. Women with a prescription for insulin on the index date, without a concomitant prescription for non-insulin antidiabetic drugs (NIADS) were considered as patients with type-1 diabetes, if (a) they had a recorded diagnosis for type-1 diabetes or (b) they were under the age of 30 at cohort entry. In addition, women with primary breast cancer prior to cohort entry, and women in the diabetes cohort without any subsequent prescription for an anti-hyperglycemic agent after the initial prescription recorded at cohort entry were excluded. If a woman with diabetes or a matched woman without diabetes met any of the exclusion criteria, the woman was excluded, together with her matched counterpart. A flowchart of the selection of the diabetes and reference cohort is presented in Fig. 1.

All women were followed from cohort entry until the occurrence of breast cancer, death, transfer out of practice, or end of data collection (October 31, 2013), whichever came first. The first-ever diagnostic code for invasive breast cancer (Supplementary material Table S1 in the online version at DOI: 10.1016/j.pcd.2017.02.001) in CPRD after cohort entry was taken as the date of diagnosis. Medical records from CPRD are regarded as a valid measure to capture breast cancer occurrence [23].

2.3. Data analysis

For the diabetes and reference cohorts, IRs for primary invasive breast cancer were calculated and standardized for age using direct standardization by weighting all the strata according to the age distribution in the 2012 European (EU-27) standard population [24]. Confidence intervals (CI) were calculated for crude [25] and age-standardized IRs [26]. To assess secular trends, IRs are presented by calendar year period. Age categories for standardization consisted of 5-year inter-

Please cite this article in press as: H.K. Bronsveld, et al., Trends in breast cancer incidence among women with type-2 diabetes in British general practice, Prim. Care Diab. (2017), http://dx.doi.org/10.1016/j.pcd.2017.02.001