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 23 February 2017

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

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

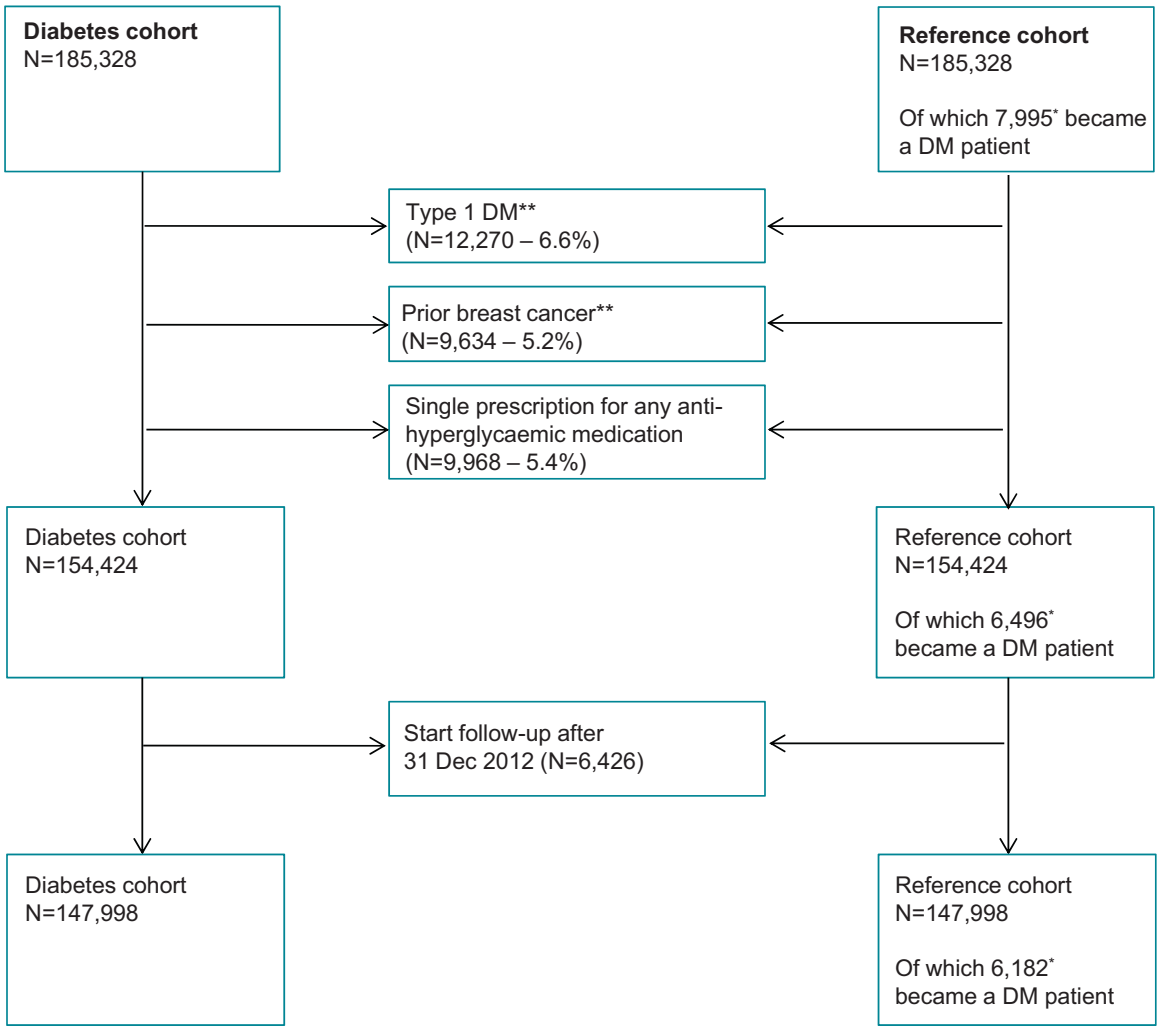
To estimate breast cancer rates among women with and without type-2 diabetes during 1989–2012, we used a cohort of prevalent and incident anti-hyperglycemic drug users (diabetes cohort) and a matched reference cohort. The diabetes cohort consisted of registered adult women (aged ≥18 years) with at least 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 anti-diabetic 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-



* Women who were diagnosed with diabetes after attributing to the reference cohort. Follow-up was censored in the reference cohort, upon which the women with newly diagnosed diabetes was included in the diabetes cohort. A new reference patient was matched to the women with newly diagnosed diabetes. ** Several women score in multiple categories (N=968). *DM= Diabetes Mellitus*

Fig. 1 – Flow chart of the selection of the diabetes and matched reference cohorts in the CPRD (1989–2012).

vals, starting with '18–20 years' and ending with '85+ years'. For calendar year period, two-year intervals were created; but 1989–2000 were aggregated due to small numbers.

In addition, we assessed IRs in age groups (<45, 45–54, 55–64, 65–69, 70–79, ≥ 80 years) over time, and in BMI categories (<25, ≥25 to <30, ≥30 to <35, ≥35 kg/m^2, unknown), and in pre- and postmenopausal women (age 55 years was used as proxy) over the entire follow-up period. Within the age groups we also standardized for age in 5-years intervals. Age was determined per calendar year as the year difference with the year of birth. One woman could thus contribute to different age-specific IRs in different calendar years. Rates for women <45 years over time are not presented separately as numbers were too small and we had insufficient numbers to present IRs over time stratified for BMI categories. Since menopausal status is an effect modifier in the relation between BMI and breast cancer risk, we described breast cancer incidence rates per BMI category among pre- and postmenopausal women separately. BMI was determined time-dependently, where BMI was updated with each new recording at the date of measurement. If the last measurement was older than 1 year, BMI was labeled as 'unknown'. Stratification for BMI in the reference cohort was not possible since for 76% of the women BMI was not available in the year prior to cohort entry.

Follow-up time for all women was divided in periods with variable length, depending on the occurrence of a new recording of BMI. Subsequently, IRs per BMI category were produced as the number of events within each category, divided by the total amount of follow-up time; i.e. the sum of all time periods within this category. All IRs are provided as the number of new breast cancer events per 100,000 py. Differences between IRs were determined by calculating incidence rate ratios (age-standardized IR diabetes/age-standardized IR reference) with 95% CI [26]. If this interval includes 1.0, the standardized rates are not significantly different at a 5% level. The same method was used to compare IRs in calendar year periods.

To exclude the influence of potential diagnostic bias in the comparison between women with and without diabetes (i.e. increased breast cancer screening around the time of initiation of diabetes treatment) [27], we performed a sensitivity analysis, in which the first year of follow-up was excluded for all women with and without diabetes. Additionally, we ran sensitivity analyses to assess whether the results in pre- and postmenopausal women were similar when using age 50 as proxy for menopausal status.

3. Results

3.1. Characteristics of the diabetes and reference cohort

In total, 147,998 women with diabetes and 147,998 women without diabetes were included in the study with a median age of 64 years at cohort entry (Table 1). Of the women with diabetes 11% was treated with insulin and 66% with metformin at cohort entry. In the diabetes cohort, 26% of the women were obese (BMI 30–35 kg/m^2) and 31% severe obese (BMI ≥ 35 kg/m^2), according to the most recent measurement in the year prior to cohort entry; in the reference cohort this was 17% and 11%, respectively.

3.2. Overall incidence

During a total follow-up of approximately 1.6 million py, 2371 women were diagnosed with invasive breast cancer in the diabetes cohort (crude IR: 295/100,000 py) and 2252 in the reference cohort (crude IR: 290/100,000 py). Incidence of breast cancer among women with diabetes increased slightly between 1989–2008 and incidence rates declined between 2009–2012 (Fig. 2a), but none of these secular trends were significant, with IRRs of respectively 1.11 (95%CI:0.94–1.31, $p > 0.05$) and 0.87 (95%CI:0.74–1.01, $p > 0.05$). The IRs of the diabetes cohort resembled those observed in the reference cohort over time. Overall, age-standardized breast cancer IRs per 100,000 py were similar between the diabetes (150, 95%CI:143–157) and reference cohort (148, 95%CI:141–156) with an incidence rate ratio (IRR) of 1.01 (95%CI:0.94–1.08, $p > 0.05$). The sensitivity analysis, in which the first year of follow-up was excluded, resulted in a lower age-standardized IRs per 100,000 py for the diabetes cohort (140, 95%CI:132–148, n = 141,902), but not for the reference cohort (148, 95%CI:140–157, n = 141,902), with an IRR of 0.94 (95%CI:0.87–1.02, $p > 0.05$).

3.3. Incidence by age groups

Age-specific IRs showed a constant rise by age for women with diabetes (except for a drop at age 70–74 years); the same was seen for women without diabetes but with a flattening around the age of 64 years (Fig. 3). Incidence rates in women with diabetes between 80–84 years and ≥85 years were significantly higher as compared to women without diabetes; IRR 1.15 (95%CI:1.01–1.32, $p < 0.05$) and IRR 1.25 (95%CI:1.08–1.44, $p < 0.05$), respectively. Incidence rates per age category were reasonably stable over time (Fig. 2b–f). We observed a trend of increasing IRs of breast cancer in women aged 65–69 years with significant increased incidence between 2001–2006 for women with diabetes (IRR:1.59, 95%CI:1.08–2.35, $p > 0.05$) and without diabetes (IRR:2.18, 95%CI:1.33–3.55, $p > 0.05$). In women with diabetes, IRs were higher in women over 80 years compared to women without diabetes, which was significant in periods 1989–2000 and 2007–2008. This is in line with the age-specific IRs presented in Fig. 3.

3.4. Incidence by menopausal status and BMI

The observed IR in premenopausal women (<55 years) with diabetes was 77 (95%CI:67–88) and 82 (95%CI:71–93) in women without diabetes, with an IRR of 0.95 (95%CI:0.78–1.14, $p > 0.05$). Among postmenopausal women (≥55 years) with diabetes the IR was 342 (95%CI:327–357) and the IR in women without diabetes was 330 (95%CI:315–345), with an IRR of 1.04 (95%CI:0.97–1.10, $p > 0.05$). Sensitivity analysis, using age 50 as proxy for menopausal status gave similar results; the IRR for premenopausal women (<50 years) with diabetes compared to those without diabetes was 0.97 (95%CI:0.73–1.28, $p > 0.05$) and for postmenopausal women (≥50 years) the IRR was 1.02 (95%CI:0.96–1.09, $p > 0.05$). Among premenopausal women with diabetes, age-standardized IRs of breast cancer (per 100,000 py) decreased with increasing BMI (Fig. 4a), but IRRs were not significantly different (BMI ≥ 35 vs BMI < 25 kg/m^2; IRR 0.70, 95%CI:0.40–1.22). Among postmenopausal women with diabetes, age-standardized IRs of breast cancer (per 100,000 py) increased with increasing BMI (Fig. 4b). Breast cancer incidence was significantly higher among postmenopausal extreme obese (BMI ≥ 35 kg/m^2) women with diabetes compared to not-overweight (BMI < 25 kg/m^2) women with diabetes; IRR 1.35 (95%CI:1.13–1.61, $p < 0.05$). The IRR for women with obesity (BMI ≥ 30 kg/m^2) compared to not-overweight women was 1.17 (95%CI:0.99–1.38, $p > 0.05$). Age-standardized IRs for women with diabetes with missing BMI were comparable to those with a BMI < 25 kg/m^2.

4. Discussion

Our study described time-trends and age-specific breast cancer IRs among women with type-2 diabetes in British general practice between 1989–2012, aiming to quantify the double burden of disease and to provide figures for public health policies. Breast cancer incidence in the diabetes cohort was similar to the reference cohort. Overall and age-specific rates of breast cancer have remained relatively stable between 2001 and 2012, apart from a temporary increase in incidence since the early 2000s among women aged 65–69 years, in both cohorts. This increase can probably to a great extent be attributed to increasing screening[28,29], which was introduced in 1988 for women aged 50–64 years and was expanded to women aged 65–70 years in 2000.

We stratified IRs by age, menopause and BMI because of the potential modifying impact of these factors and to explore whether a subgroup of women might benefit from intensified breast cancer screening. Overall, women with and without diabetes had similar IRs by age and menopause. However, we observed that the IR of breast cancer in women >80 years was

Table 1 – Characteristics and number of person years of follow-up for each calendar period in the diabetes and reference cohort in the CPRD.

	Diabetes cohort (n = 147,998)		Reference cohort (n = 147,998)	
Age in years (median, IQR)	64	(51–74)	64	(51–74)
Person years of follow-up				
Entire follow-up	805,005		777,746	
1989–2000	116,005		114,679	
2001–2002	63,047		61,437	
2003–2004	85,283		82,086	
2005–2006	106,852		102,005	
2007–2008	126,002		120,159	
2009–2010	144,473		138,833	
2011–2012	163,043		158,548	
	n	%	n	%
Prior cancer[a]	10,034	6.8	10,058	6.8
BMI (kg/m^2)[b]				
<20	1578	1.9	2804	7.9
20–25	10,627	13.1	11,487	32.3
25–30	22,321	27.5	11,439	32.2
30–35	21,398	26.3	6050	17.0
>35	25,343	31.2	3779	10.6
Unknown	66,731	45.1	112,439	76.0
Smoking[b]				
Current	20,318	21.2	20,599	22.1
Ex	19,046	19.9	15,847	17.0
Never	56,582	59.0	56,600	60.8
Unknown	52,052	35.2	54,952	37.1
Alcohol use[b]				
Yes	49,092	63.2	54,953	74.6
No	28,645	36.8	18,697	25.4
Unknown	70,261	47.5	74,348	50.2
Type of anti-hyperglycemic drug[c]				
Insulin	15,773	10.7		
Metformin	98,259	66.4		
Sulfonylurea	45,208	30.5		
Thiazolidinediones	3158	2.1		
Other oral anti-hyperglycemic drugs	2251	1.5		

Abbreviations: IQR, interquartile range; BMI, body mass-index.

[a] Any type, except non-melanoma skin cancer or breast cancer.

[b] BMI, alcohol and smoking information is based on the most recent record in the year prior to cohort entry. The denominator of the category 'unknown' is the overall number of individuals, while the percentage of sub-categories of BMI, smoking, and alcohol use is calculated relative to all those who are not 'unknown'.

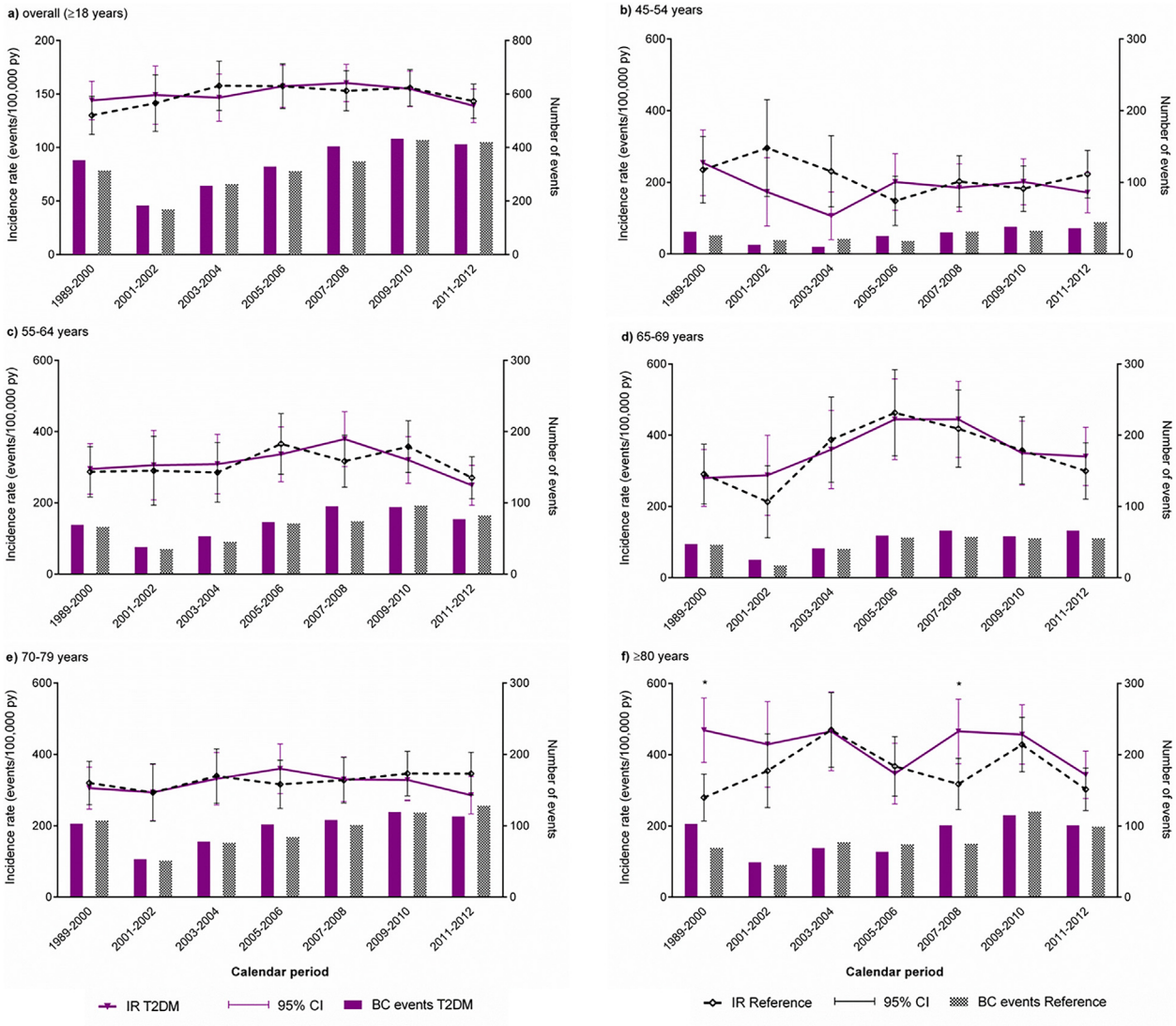
[c] Several patients have multiple prescriptions on the index date.

higher in women with diabetes compared to women without diabetes. Since women >80 years are not screened, it might be that breast cancer was more likely to be diagnosed due to more intensive health checks in women with diabetes.

Due to lack of completeness of BMI data, we could not make a comparison between women with and without diabetes for different BMI categories. We observed that within post-menopausal women with diabetes those with a BMI ≥35 kg/m^2 had significantly higher IRs than those not-overweight, which is in line with previous findings in women without diabetes [17]. Even though we had indications that BMI among women with diabetes was higher than among women without diabetes in our study, we did not find an overall higher IR for breast cancer in the diabetes cohort. This might be related to lack of screening participation by obese women, possibly in particular those with diabetes [30]. Screening leads to an increase in breast cancer incidence [31], and normal weight women without diabetes are more likely to participate in screening programs [30].

Another potential modifying factor of breast cancer incidence in women with diabetes might be the use of anti-hyperglycemic agents. However, since recent published meta-analyses showed that insulin [32], as well as metformin [33], are unlikely to increase or decrease risk of breast cancer, we suspect that this, if at all, had only a minor influence on breast cancer incidence in women with diabetes.

The overall lack of difference in breast cancer incidence between the women with and without diabetes was against our expectations since previous meta-analyses of case-control and cohort studies [10,11] showed a positive association between diabetes and breast cancer risk. Although our aim was not to perform an association study, we considered pre-



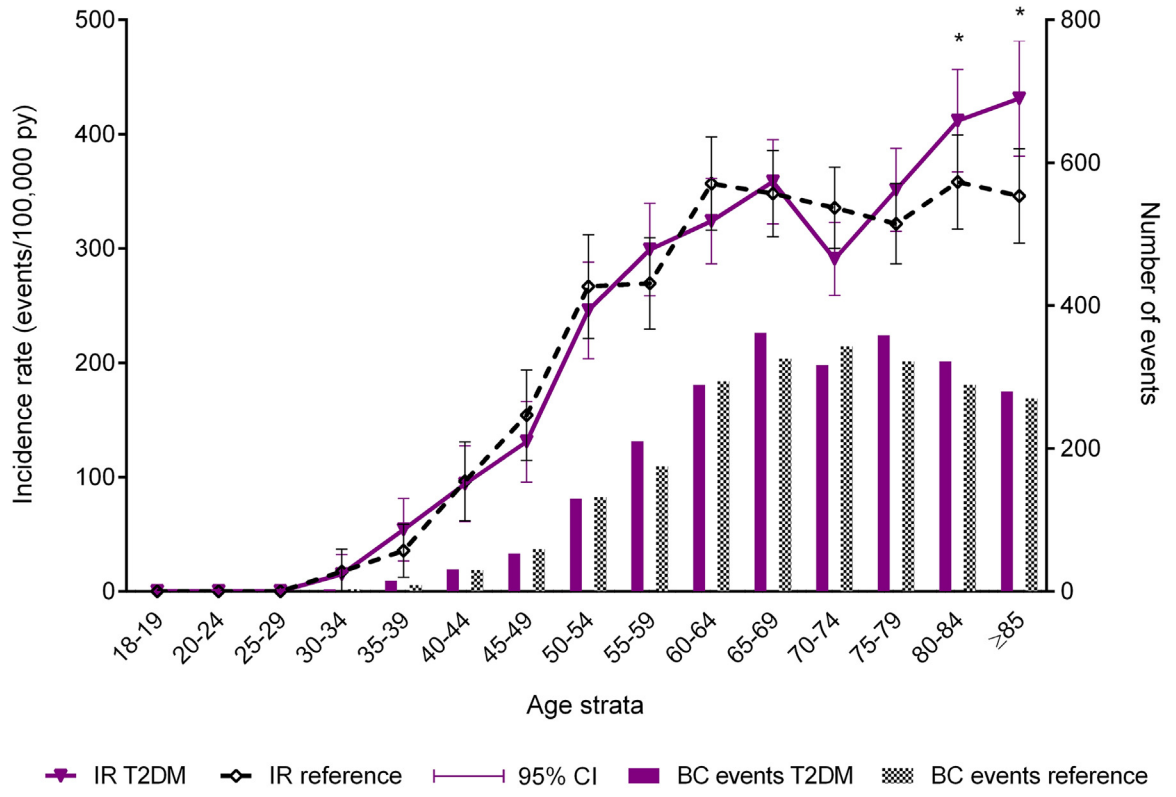
* IRs of women with and without type-2 diabetes are significantly different; Rates are standardized for age in 5-year intervals, also within the age groups. *IR, incidence rate; BC, breast cancer; T2DM, Type-2 diabetes mellitus; py, person years; CI, confidence interval*

Fig. 2 – Time trends in age-standardized incidence rates for breast cancer among women with and without type-2 diabetes in the CPRD (1989–2012), overall and by age group.

viously performed studies and compared the methodology to elaborate on this difference in outcome. Some studies included in published meta-analyses, with a large contribution to the pooled estimate, compared breast cancer risk in their cohorts of women with diabetes to IRs derived from national cancer registries [10,11]. We estimated IRs in an age and practice-matched reference cohort of women without diabetes and we have used two dynamic cohorts to prevent immortal time bias [22]. Our design and analyses are therefore less likely to be biased than some previous studies. Another explanation for the observed discrepancies might be differences in diabetes ascertainment. We defined diabetes based on anti-hyperglycemic drug use while previous studies in the meta-analyses used hospital registries, health care databases, or questionnaires for diabetes ascertainment. Studies that included only women hospitalized for their diabetes possibly suffered from more advanced disease compared to women with diabetes in the CPRD. On the other hand, we might have missed some women with diabetes who were only treated with diet. Furthermore, the time window of observation is slightly different between our study and previous studies. Our study covers data until 2012, while previous studies ended data collection around 2000.

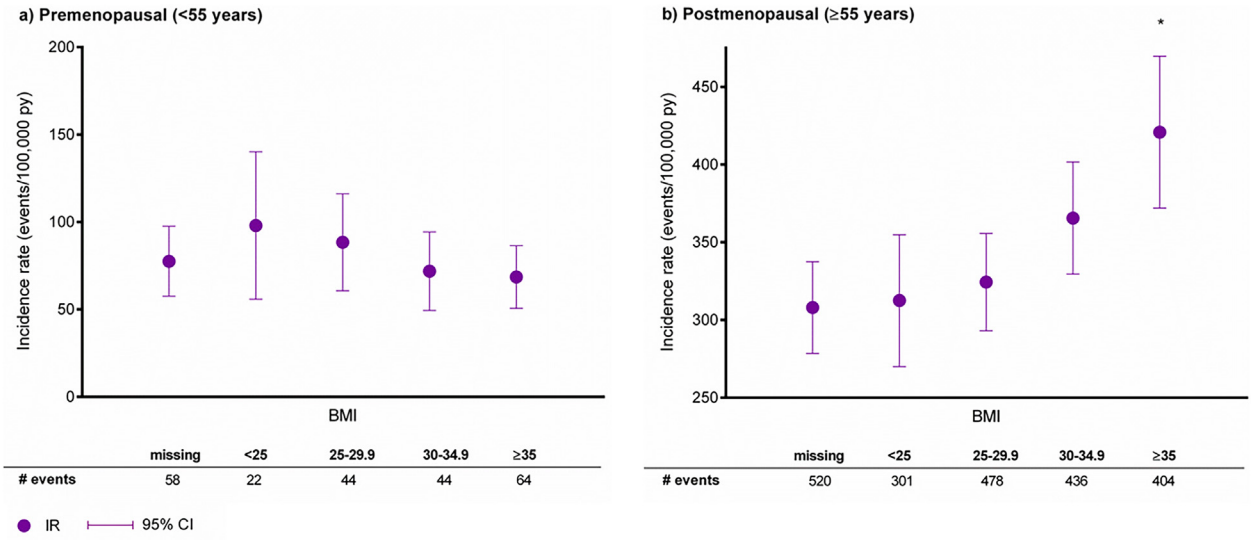
The Dutch Cancer Society also reported prevalence rates of diabetes among a sample of Dutch women visiting their GP and among women who were diagnosed with breast cancer [34]. They found that diabetes prevalence rates were similar among women with breast cancer (35–64 years: 3%; ≥65 years: 13.4%) compared to women without breast cancer (35–64 years: 3.1%; ≥65 years-13.2%). These statistics are in line with our results.

If we compare our results with age-specific breast cancer IRs and time-trends in the general population published by UK cancer research [5] these were largely comparable. How-



* IRs of women with and without type-2 diabetes are significantly different. IRs in age strata were calculated over the entire follow-up period (1989-2012). *IR, incidence rate; BC, breast cancer; T2DM, Type 2 diabetes mellitus; py, person years, CI, confidence interval*

Fig. 3 – Age-specific crude incidence rates for breast cancer in women with and without type-2 diabetes in the CPRD (1989–2012).



* Significantly different compared to BMI <25. IRs in BMI categories were calculated over the entire follow-up period (1989-2012). *BMI, body mass index in kg/m2; py, person years; #, number; CI, confidence interval*

Fig. 4 – Age-standardized incidence rates for breast cancer among pre- and postmenopausal women with type-2 diabetes by BMI category in the CPRD (1989–2012).

ever, the overall age-standardized IR of our reference cohort was somewhat higher than that reported by the UK cancer registry (148 vs 125/100,000 py). This is hard to explain as 98% of the UK population is registered at a GP practice, however, the CPRD may not be representative of all practices in the UK based on geography [18]. Underlying risk factors for breast cancer

such as social status, hormone use and reproductive history might have been different between our cohort and that of the registry.

This study used a large and accurate healthcare database in which clinical records are regarded as a valid measure to capture breast cancer incidence as compared to the National Cancer Registry [23]. However, this study also had limitations. First of all, we defined diabetes based on anti-hyperglycemic drugs. Consequently, we might have missed some women with diabetes who were only treated with diet which might have biased results toward zero. Secondly, we were unable to determine trends in incidence over time before 2001 because of the limited follow-up time and number of cancer events. However, IRs restricted to 2001 onwards were very similar to the entire follow-up period in the diabetes (151, 95%CI:143–159) and reference cohort (151, 95%CI:143–159). However, since overall incidence rates remained relatively stable over time, and the IRs were comparable between women with and without diabetes, we do not expect that these analyses would have given us new insights. Thirdly, potential diagnostic bias at the start of follow-up might be present, as the age-standardized IR for breast cancer among the diabetes cohort decreased from 150 to 140/100,000 py after elimination of the first year of follow-up. Finally, we could not match women with and without diabetes on BMI because of information asymmetry between the two cohorts. In addition, for the women without diabetes we were unable to stratify IRs for BMI categories because the majority had no recently recorded BMI measure. BMI is less frequently measured in (normal weight) women without diabetes as the Quality and Outcome Framework in the UK specifically rewards practices for the registration of BMI among patients with diabetes and among women with a BMI >30 kg/m^2 [35]. We assume that unmeasured BMI, reflects normal BMI.

The UK has approximately 1.92 million women living with diagnosed diabetes [36], of whom, assuming a similar age distribution as the women in our study and an age-standardized IR of 150/100,000 py, each year 2880 will be diagnosed with breast cancer. This is a high number, but incidence of breast cancer among women with diabetes remained seemingly stable between 2000–2012 and breast cancer incidence in women with diabetes was comparable to incidence in women without diabetes. Therefore, based on this research there is no indication that points toward a need for a different screening approach, such as for example intensified screening for breast cancer among women with type-2 diabetes. Even so, further research is recommended in women with high BMI and diabetes since they are at higher risk and based on other studies might be less likely to attend the mammography screening.

Funding

The research leading to the results of this study has received funding from the European Community's Seventh Framework Programme (FP-7) under grant agreement number 282526, the CARING project. The funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Ethical approval and consent to participate

The CPRD's Independent Scientific Advisory Committee approved the protocol of this study (protocol no: 13_050).

Author contributions

HKB contributed to the formulation of the study design, analyzed the data together with PJHLP, and wrote the manuscript. PJHLP, MCHG, MKS and MLDB contributed to the design of study, the data management strategies, the interpretation of the results, and reviewed and edited the manuscript. ADB reviewed and edited the manuscript and contributed to the interpretation of the results. All authors approved the final version.

Competing interests

Heleen K. Bronsveld is employed by The Netherlands Cancer Institute and her employment is funded by the CARING project. Paul J.H.L. Peeters' employment at the Utrecht University is funded by the CARING project as well.

Mark C.H. de Groot received unrestricted support from the Innovative Medicine Initiative Joint Undertake (IMI-PROTECT: www. imi. europa. eu) under Grant Agreement No. 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in kind contribution.

Anthonius de Boer is employed by Utrecht University as professor Pharmacotherapy and has no conflicts of interest. His full profile can be found on http://www.uu.nl/medewerkers/AdeBoer.

Marjanka K. Schmidt is employed by The Netherlands Cancer Institute and was funded by the Dutch Cancer Society project number DCS-NKI2009-4363.

M.L. De Bruin, I am appointed as professor in Regulatory Science, which chair is funded by the University of Copenhagen. In addition, I am director of the Copenhagen Insitute of Regulatory Science (CORS), based at the same university. CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organizations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related.

Apart from my position at the University of Copenhagen, I am part-time employed by Utrecht University as senior researcher conducting research under the umbrella of the Utrecht-WHO Collaborating Center for Pharmaceutical Policy and Regulation. This Center receives no direct funding or donations from private parties, including pharma industry. Research funding from public-private partnerships, e.g. IMI, The Escher Project (http://escher.lygature.org/) is accepted under the condition that no company-specific product or company related study is conducted. The Center has received unrestricted research funding from public sources,

e.g. World Health Organisation (WHO), Netherlands Organisation for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health.

None of the abovementioned funding sources had a role in the design, conduct, analysis, or reporting of this study. None of the authors have any competing interests.

Acknowledgements

We acknowledge the CARING team for their valuable input and we acknowledge Michael Hauptman for his advice on the calculation of incidence rate ratios with 95% CI.

REFERENCES

[1] A.A. Onitilo, J.M. Engel, I. Glurich, R.V. Stankowski, G.M. Williams, S.A. Doi, Diabetes and cancer II: role of diabetes medications and influence of shared risk factors, Cancer Causes Control 23 (2012) 991–1008.
[2] Diabetes Atlas Internal Diabetes Federation, 7th ed., 2015.
[3] M.H. Forouzanfar, K.J. Foreman, A.M. Delossantos, R. Lozano, A.D. Lopez, C.J. Murray, M. Naghavi, Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis, Lancet (London, England) 378 (2011) 1461–1484.
[4] GLOBOCAN, International Agency for Reserarch on Cancer, Section of Cancer Surveillance, Breast, 2012, http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. (Accessed 29 March 2016).
[5] Breast cancer incidence statistics, Cancer Research UK, 2017, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive. (Accessed 10 August 2015).
[6] Diabetes Atlas Internal Diabetes Federation, 6th ed., 2013.
[7] Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants, Lancet (London, England) 387 (2016) 1513–1530.
[8] M. de Sousa-Uva, L. Antunes, B. Nunes, A.P. Rodrigues, J.A. Simoes, R.T. Ribeiro, J.M. Boavida, C. Matias-Dias, Trends in diabetes incidence from 1992 to 2015 and projections for 2024: a Portuguese General Practitioner's Network study, Prim. Care Diabetes 10 (2016) 329–333.
[9] J. Hippisley-Cox, R. Ryan, Diabetes in the United Kindgom: Analysis of QRESEARCH Data, 2007 http://www.qresearch.org/Public_Documents/DataValidation/Diabetes%20in%20the%20UK%20analysis%20of%20QRESEARCH%20data.pdf.
[10] J. Starup-Linde, O. Karlstad, S.A. Eriksen, P. Vestergaard, H.K. Bronsveld, F. de Vries, M. Andersen, A. Auvinen, J. Haukka, V. Hjellvik, M.T. Bazelier, A. Boer, K. Furu, M.L. De Bruin, CARING (CAncer Risk and INsulin analoGues): the association of diabetes mellitus and cancer risk with focus on possible determinants—a systematic review and a meta-analysis, Curr. Drug Saf. 8 (2013) 296–332.
[11] S.C. Larsson, C.S. Mantzoros, A. Wolk, Diabetes mellitus and risk of breast cancer: a meta-analysis, Int. J. Cancer 121 (2007) 856–862.
[12] F. Xue, K.B. Michels, Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence, Am. J. Clin. Nutr. 86 (2007) s823–s835.
[13] S. Liao, J. Li, W. Wei, L. Wang, Y. Zhang, J. Li, C. Wang, S. Sun, Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature, Asian Pac. J. Cancer Prev. 12 (2011) 1061–1065.
[14] K.S. Peairs, B.B. Barone, C.F. Snyder, H.C. Yeh, K.B. Stein, R.L. Derr, F.L. Brancati, A.C. Wolff, Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis, J. Clin. Oncol. 29 (2011) 40–46.
[15] World Health Organisation, Prevention of Diabetes Mellitus. Report of a WHO study Group, World Health Organisation, Geneva, 1994.
[16] D.P. Rose, L. Vona-Davis, The cellular and molecular mechanisms by which insulin influences breast cancer risk and progression, Endocr. Relat. Cancer 19 (2012) R225–R241.
[17] Z. Cheraghi, J. Poorolajal, T. Hashem, N. Esmailnasab, A. Doosti Irani, Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis, PLoS One 7 (2012) e51446.
[18] E. Herrett, A.M. Gallagher, K. Bhaskaran, H. Forbes, R. Mathur, T. van Staa, L. Smeeth, Data resource profile: Clinical Practice Research Datalink (CPRD), Int. J. Epidemiol. 44 (2015) 827–836.
[19] J. Campbell, D.J. Dedman, S.C. Eaton, A.M. Gallagher, T.J. Williams, Is the CPRD GOLD population comparable to the U.K. population? 29th ICPE Pharmacoepidemiology and Drug Savety (2013), pp. 280.
[20] E. Herrett, S.L. Thomas, W.M. Schoonen, L. Smeeth, A.J. Hall, Validation and validity of diagnoses in the General Practice Research Database: a systematic review, Br. J. Clin. Pharmacol. 69 (2010) 4–14.
[21] N.F. Khan, S.E. Harrison, P.W. Rose, Validity of diagnostic coding within the General Practice Research Database: a systematic review, Br. J. Gen. Practice 60 (2010) e128–136.
[22] L.E. Levesque, J.A. Hanley, A. Kezouh, S. Suissa, Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes, BMJ 340 (2010) b5087.
[23] R. Boggon, T.P. van Staa, M. Chapman, A.M. Gallagher, T.A. Hammad, M.A. Richards, Cancer recording and mortality in the General Practice Research Database and linked cancer registries, Pharmacoepidemiol. Drug Saf. 22 (2013) 168–175.
[24] European Standard Population, Eurostat, 2017, http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database. (Accessed 12 January 2015).
[25] K. Rothman, J. Boice, Epidemiologic Analysis with a Programmable Calculator, US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH publication, 1979.
[26] P. Boyle, D.M. Parkin, Chapter 11. Statistical Methods for Registries, in: International Agency for Research on Cancer, pp. 135–136 (age-standardized rate), 138–139 (age-standardized rate ratio).
[27] J.L. Harding, J.E. Shaw, A. Peeters, B. Cartensen, D.J. Magliano, Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation, Diabetes Care 38 (2015) 734–735.
[28] B. Junod, P.H. Zahl, R.M. Kaplan, J. Olsen, S. Greenland, An investigation of the apparent breast cancer epidemic in France: screening and incidence trends in birth cohorts, BMC Cancer 11 (2011) 401.
[29] Independent UK Panel on Breast Cancer Screening, The benefits and harms of breast cancer screening: an independent review, Lancet (London, England) 380 (2012) 1778–1786.
[30] S.S. Hellmann, S.H. Njor, E. Lynge, M. von Euler-Chelpin, A. Olsen, A. Tjonneland, I. Vejborg, Z.J. Andersen, Body mass index and participation in organized mammographic screening: a prospective cohort study, BMC Cancer 15 (2015) 294.

[31] J.B. Austoker V., A. Berrington, R.G. Blanks, N.E. Day, T.J. Day, I.O. Ellis, Screening for breast cancer in England: past and future, NHSBSP Publication, 61 (2006).
[32] H.K. Bronsveld, B. ter Braak, O. Karlstad, P. Vestergaard, J. Starup-Linde, M.T. Bazelier, M.L. De Bruin, A. de Boer, C.L. Siezen, B. van de Water, J.W. van der Laan, M.K. Schmidt, Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence, Breast Cancer Res. 17 (100) (2015).
[33] S. Gandini, M. Puntoni, B.M. Heckman-Stoddard, B.K. Dunn, L. Ford, A. DeCensi, E. Szabo, Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders, Cancer Prev. Res. (Phila. PA) 7 (2014) 867–885.
[34] KWF kanker bestrijding, Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. Data from IKZ and RIVM, (2004) 218.
[35] Quality and Outcomes Framework for 2012/13; Guidance for PCOs and Practices. NHS Employers, 2017, http://www.hscic.gov.uk/media/14017/QOF-Guidance-GMS-Contract-2012-13/pdf/QOF_guidance_GMS_contract_2012_13.pdf. (Accessed 7 August 2015).
[36] Diabetes: Facts and Stats. DIABETES UK, 2017, https://www.diabetes.org.uk/About_us/What-we-say/Statistics/. (Accessed 5 October 2015).