Diabetologia (2020) 63:34–48
https://doi.org/10.1007/s00125-019-04995-7

ARTICLE

Breast, cervical and colorectal cancer screening in adults with diabetes: a systematic review and meta-analysis

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Received: 2 April 2019 / Accepted: 9 August 2019 / Published online: 24 October 2019

Abstract

Aims/hypothesis Individuals with diabetes are at increased risk of developing and dying from cancer. Evidence-based guidelines recommend universal screening for breast, cervical and colorectal cancer; however, evidence on the uptake of these tests in individuals with diabetes is mixed. We conducted a meta-analysis to quantify the association between diabetes and participation in breast, cervical and colorectal cancer screening.

Methods MEDLINE, EMBASE and CINAHL were searched systematically for publications between 1 January 1997 and 18 July 2018. The search was supplemented by handsearching of reference lists of the included studies and known literature reviews. Abstracts and full texts were assessed in duplicate according to the following eligibility criteria: study conducted in the general population; diabetes included as a predictor vs a comparison group without diabetes; and breast (mammography), cervical (Papanicolaou smear) or colorectal (faecal and endoscopic tests) cancer screening uptake included as an outcome. Random-effects meta-analyses were performed using the most-adjusted estimates for each cancer site.

Results Thirty-seven studies (25 cross-sectional, 12 cohorts) were included, with 27 studies on breast, 19 on cervical and 18 on colorectal cancer screening. Having diabetes was associated with significantly lower likelihood of breast (adjusted OR 0.83 [95% CI 0.77, 0.90]) and cervical (OR 0.76 [95% CI 0.71, 0.81]) cancer screening, relative to not having diabetes. Colorectal cancer screening was comparable across groups with and without diabetes (OR 0.95 [95% CI 0.86, 1.06]); however, women with diabetes were less likely to receive a colorectal cancer screening test than women without diabetes (OR 0.86 [95% CI 0.77, 0.97]).

Conclusions/interpretation Our findings suggest that women with diabetes have suboptimal breast, cervical and colorectal cancer screening rates, compared with women without diabetes, although the absolute differences might be modest. Given the increased risk of cancer in this population, higher quality prospective evidence is necessary to evaluate the contribution of diabetes to cancer screening disparities in relation to other patient-, provider- and system-level factors.

Registration PROSPERO registration ID CRD42017073107.

Keywords Breast cancer · Cancer screening · Cervical cancer · Colorectal cancer · Diabetes management · Diabetes mellitus · Healthcare barriers · Healthcare disparities · Meta-analysis · Systematic review

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-019-04995-7) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Abbreviations

FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
NOS	Newcastle–Ottawa Scale
Pap	Papanicolaou
PR	Prevalence ratio
RCT	Randomised controlled trial

Research in context

What is already known about this subject?

- Individuals with diabetes are at increased risk of developing and dying from cancer
- Evidence-based guidelines recommend routine universal screening for breast, cervical and colorectal cancer
- Current evidence reviews suggest possible cancer screening disparities in patients with chronic disease; however, the uptake of cancer screening tests in individuals with diabetes is unclear

What is the key question?

- What is the effect of diabetes on the uptake of recommended routine screening for breast, cervical and colorectal cancer, compared with not having diabetes?

What are the new findings?

- Women with diabetes were significantly less likely to receive breast and cervical cancer screening than women without diabetes
- Women with diabetes were also less likely to be screened for colorectal cancer than women without diabetes, with no such difference in men
- Absolute differences might be modest and the included studies had high heterogeneity, low methodological quality and showed a risk of publication bias

How might this impact on clinical practice in the foreseeable future?

- Suboptimal cancer screening rates in women with diabetes may be putting them at risk of poorer cancer outcomes. Higher quality prospective methods are needed to evaluate the contribution of diabetes to cancer screening disparities; population-based and targeted approaches are needed for improving cancer screening uptake and reducing the burden of diabetes management in this population

Introduction

Cancer is a leading cause of death worldwide, with rapidly growing incidence and mortality rates [1]. Diabetes has been associated with 30% higher incidence of certain cancers [2–4] and 40% higher mortality after cancer diagnosis [5]. Individuals with diabetes are also more likely to be diagnosed with advanced-stage tumours [6–8] and to experience greater toxicity during treatment [9, 10], leading to more conservative regimens [11, 12]. Beyond shared risk factors, such as socioeconomic status [13], lifestyle behaviours [14–17] and being overweight or obese [18–20], diabetes is hypothesised to be causally related to cancer through tumorigenic effects of insulin resistance and hyperinsulinaemia [21–23].

Screening for breast, cervical and colorectal cancer has been associated with up to 33% [24], 70% [25] and 37% [26] reduction, respectively, in cancer-specific deaths. Breast cancer screening detects early-stage tumours, which have a better prognosis [24], while cervical and colorectal cancer screening also detect pre-malignant lesions [25, 26]. Evidence-based guidelines recommend universal screening with mammography for breast cancer, Papanicolaou ('Pap') smear for cervical cancer, and faecal and endoscopic tests for colorectal cancer [27–34]. Many jurisdictions have also implemented organised programmes to deliver population-wide screening [35–40].

The importance of cancer screening and early detection is especially salient for individuals with diabetes. Previous studies have suggested that people with diabetes may experience poorer preventive care due to the competing priorities of chronic disease management [41–47], which place a substantial burden on patients and their healthcare teams [42]. The extent to which diabetes impacts the receipt of recommended cancer screenings, however, is unclear. In this systematic review and meta-analysis, we aimed to quantify the association between diabetes and breast, cervical and colorectal cancer screening participation.

Methods

Data sources We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [48, 49] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [50] guidelines (see electronic supplementary material [ESM] Checklists 1 and 2), and used a protocol to guide the review [51, 52] (PROSPERO: CRD42017073107). We developed an electronic search

strategy in consultation with a public health information specialist and searched MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (EBSCO) between 1 January 1997 and 18 July 2018 for English-language studies in adults (ESM Table 1). To ensure saturation, we reviewed reference lists of the included studies and known literature reviews [53–55]. Duplicates were removed using the Bramer algorithm, validated for use with EndNote reference management software (Version X7; Thompson Reuters, USA) [56].

Selection process and eligibility criteria Titles were screened by one reviewer (DB). To verify the quality of the screening process, the abstracts of a random sample of the excluded titles (5%) were reviewed. Abstracts and full texts of the included articles were assessed for eligibility in duplicate by two independent reviewers (DB, WW). Inter-rater reliability was assessed using Cohen's κ statistic, reflecting agreement beyond that attributable to chance [57]. Disagreements were settled through discussion and involvement of a third independent reviewer (IL). Study eligibility was defined using the following PECO (population, exposure, comparison group, outcome) criteria: (1) study was conducted in the general population; (2) study included diabetes as a predictor; (3) study included a comparison group without diabetes and (4) study reported breast, cervical or colorectal cancer screening uptake as an outcome. We excluded studies conducted in special populations ineligible for routine screening, along with case reports or series, commentaries, dissertations and conference abstracts.

Data abstraction and quality assessment Data were abstracted by one reviewer (DB) and critical appraisal was performed in duplicate by two independent reviewers (DB, WW). Disagreements were resolved by discussion and involvement of a third independent reviewer (IL). We used the Cochrane Handbook for Systematic Reviews-recommended Newcastle–Ottawa Scale (NOS) to evaluate the quality of observational studies [57, 58], including the secondary analysis of one randomised controlled trial (RCT) [59]. The NOS allocates up to 9 points to studies according to three quality domains: selection of the study groups; comparability of the groups and ascertainment of the outcome. A modified NOS was used for cross-sectional studies [60]. The scoring of the 'comparability' criterion can be customised by specifying important covariates that studies should control for. Controlling for age and personal or family history of cancer was deemed to be particularly important due to the influence of these factors on screening recommendations' risk categories [27–34]. Publication bias was assessed by visually inspecting funnel plots [57].

Meta-analysis We performed random-effects meta-analyses to obtain summary effects for breast, cervical and colorectal cancer screening uptake. The random-effects approach assumes the existence of a distribution of distinct (yet related) exposure effects, rather than a single true effect, and thus reports the average effect of the exposure on the outcome [57]. Studies that reported an adjusted OR or prevalence ratio (PR) and a 95% CI for receipt of a screening test in individuals with diabetes relative to those without were combined using the DerSimonian–Laird inverse variance method, which assigns weights to individual estimates based on their precision level [57, 61]. Although PRs and ORs indicate the same directionality of effect in cross-sectional studies of non-rare outcomes, such as cancer screening, ORs may overestimate the strength of the association compared with PRs [62–64]. Since only two studies (one on breast cancer screening [65] and one on colorectal cancer screening [66]) reported PRs and their exclusion in sensitivity analyses did not meaningfully modify findings (data not shown), a decision was made to combine ORs and PRs together. Only the most-adjusted estimates were pooled to minimise confounding [67, 68]. If studies reported the likelihood of not screening [65] or used diabetes as a reference group [59], the reciprocal of the effect estimate was pooled in the meta-analyses, as ORs are mathematically symmetrical [69]. If studies reported multiple unique ORs, they were entered separately in the meta-analyses. In studies with overlapping groups of participants, we chose the most representative estimate [65] or calculated the weighted average [70].

Heterogeneity was assessed using the I^2 statistic, describing the results' variability attributable to study heterogeneity, rather than chance [57]. We explored heterogeneity through subgroup analyses by study design, quality rating (high quality >6 points on NOS) [58] and setting, provided at least three unique estimates were available. Since most studies were conducted in the USA, subgroup analyses by setting were dichotomised into USA and non-USA studies. For studies on colorectal cancer screening, we performed subgroup analyses by type of screening test and sex of participants. Data were analysed using Cochrane Review Manager (RevMan) software (version 5.3; Copenhagen, Denmark).

Results

Cohen's κ statistic for all duplicate-screened sections was 0.78, reflecting excellent agreement between reviewers [57].

Characteristics of included studies Our search yielded 5200 unique records, of which 37 met the inclusion criteria (ESM Fig. 1). Individual study characteristics are presented in Table 1 and aggregate study characteristics in Table 2 (additional detail in ESM Table 2). Nine studies examined breast cancer screening [65, 71–78], two examined cervical cancer screening [79, 80], and eight examined colorectal cancer screening alone [59, 65, 66, 70, 81–85]; eight studies examined both breast and cervical cancer screening [86–93], one examined breast and colorectal cancer screening [94], and nine examined all three cancer screenings [95–103]. All studies were observational, with 25 cross-sectional [65, 70, 77–80, 82–85, 87–93, 95–100, 102, 103] and

Table 1 Characteristics of the included studies

Study	Design	Year	Country	Cancer	Sample size	Age range (years)	Percentage with diabetes	Percentage with diabetes screened	Percentage without diabetes screened	Effect	Quality
Abdullah et al (2016) [79]	CS	2014	Malaysia	Cervix	515	≥50	46.8	29.5	47.8	LD	Low
Banks et al (2002) [76]	Cohort	1998	UK	Breast	1064	≥50	4	77.5	83.1	NS	Low
El Bcheraoui et al (2015) [77]	CS	2013	Saudi Arabia	Breast	875	50–74	35.7	9.3	5.8	NS	Low
Beckman et al (2001) [71][a]	Cohort	1997–2000	USA	Breast	1269	50–75	33.4	78.1	84.9	LD	High
Bell et al (2001) [85]	CS	1993–1997	USA	Colon	5700	≥50	–	21.9	19.5	NS	Low
Blustein et al (1998) [72][a]	Cohort	1991–1992	USA	Breast	2352	≥75	13.9	26.6	26.8	NS	High
Brittain et al (2015) [82]	CS	Mid-2000s	USA	Colon	129	≥50	23	–	–	NS	Low
Chan et al (2014) [73][a]	Cohort	1999–2010	Canada	Breast	504,288	50–69	1:2 matched cohort	60.3	65.8	LD	High
Chuck et al (2017) [87][a]	CS	2007–2009	South Korea	Breast	6069	≥40	12.3	38.8	44.6	LD	Low
				Cervix	7946	≥30	9.9	35.1	51.2	LD	
Constantinou et al (2016) [88][a]	CS	2008	France	Breast	2056	50–74	7.6	59.7	75.9	LD	Low
				Cervix	4226	25–65	2.9	63.6	76.4	NS	
Coughlin et al (2004) [89]	CS	1999	USA	Breast	49,564	≥40	–	74.3	75.9	NS	Low
				Cervix	60,479	≥18	–	84.9	86.4	NS	
Fleming et al (2011) [96][a]	CS	2008	USA	Breast	–	≥40	–	66	76.8	NS	Low
				Cervix	681	≥18	14.5	70.2	84.3	NS	
				Colon	675	≥50	15.9	24.8 (FOBT) 63.1 (FS/CP)	20.1 61.4	NS	
Fontana et al (1997) [97][a]	CS	1991–1992	USA	Breast	1447	50–65	2	Screened overall	88	LD	Low
				Cervix	1447	50–65	2	Screened overall	81	LD	
				Colon	2166	50–65	8	Screened overall	58 (FOBT), 38.5 (FS)	LD	
Greiner et al (2014) [59][a]	RCT	2009–2011	USA	Colon	470	≥50	–	–	–	LD	Low
Heflin et al (2002)[a] [95]	CS	1992	USA	Breast	1481	≥65	24.6	Screened overall	44	NS	Low
				Cervix	1482	≥65	24.6	Screened overall	58	NS	
				Colon	2225	≥65	24.3	Screened overall	54 (FOBT)	NS	
Hsia et al (2000)[a] [98]	CS	1994–1997	USA	Breast	55,278	50–79	5.2	Screened overall	85–87	LD	Low
				Cervix	55,278	50–79	5.2	Screened overall	88–93	LD	
				Colon	55,278	50–79	5.2	Screened overall	57–64	LD	
Jensen et al (2015) [65][a]	Cohort	2008–2009	Denmark	Breast	144,264	50–69	2	70.4	79.1	LD	High
Jimenez-Garcia et al (2009) [92][a]	CS	2006	Spain	Breast	12,429	≥40	9.8	57.9	61.9	LD	Low
				Cervix	13,739	18–69	4.5	61.5	65.6	LD	
Jimenez-Trujillo et al (2015) [99]	CS	2009–2011	Spain	Breast	11,074	40–69	45.2	75.4	72	NS	Low
				Cervix	–	40–64	45.2	52.4	67.4	LD	
				Colon	20,948	40–69	7.9	8.1	5.7	NS	

Table 1 (continued)

Study	Design	Year	Country	Cancer	Sample size	Age range (years)	Percentage with diabetes	Percentage with diabetes screened	Percentage without diabetes screened	Effect	Quality
Karathanasi et al (2009) [100]	CS	2000–2005	Greece	Breast	3462	–	9	16.7	22.6	LD	Low
				Cervix	3462	–	9	30.8	46.9	LD	
				Colon	6447	–	10.5	11 (FOBT) 10.1 (FS/CP)	12 11	NS	
Katz et al (2018) [74][a]	Cohort	2008–2014	Israel	Breast	44,318	56–74	22.2	21.7	41.9	LD	High
Kiefe et al (1998) [86][a]	Cohort	1995	USA	Breast	937	≥40	–	Screened overall	58	NS	Low
				Cervix	1764	40–64	–	Screened overall	66.5	NS	
Lipscombe et al (2005) [75][a]	Cohort	1999–2002	Canada	Breast	732,687	50–69	9.4	38.1	47.3	LD	High
Liu et al (2014) [101][a]	Cohort	1998–2009	USA	Breast	1859	≥55	–	Screened overall	49	NS	Low
				Cervix	740	≥55	–	Screened overall	52	NS	
				Colon	3433	≥55	–	Screened overall	37	NS	
Lopez-de-Andres et al (2010) [91]	CS	2004–2005	Spain	Breast	2580	≥40	6.5	65.1	62	NS	Low
				Cervix	3200	18–69	2.9	78.3	77.4	NS	
Marshall et al (2010) [90]	CS	2003	USA	Breast	23,033	≥40	6.9	66	68	NS	Low
				Cervix	30,141	21–70	6.9	78	86	LD	
Martinez-Huedo et al (2012) [93][a]	CS	2009–2010	USA	Breast	8708	≥40	10.7	37.9	53.8	LD	Low
				Cervix	9070	18–69	4.6	49.1	64	LD	
McBean et al (2007) [94][a]	Cohort	1999–2000	USA	Breast	16,394	≥67	1:1 matched cohort	39.6	43	LD	High
		1999–2002		Colon	16,394	≥67	1:1 matched cohort	14.9	17.9	LD	
Miller et al (2014) [66][a]	CS	2008–2010	USA	Colon	14,885	50–74	17.4	56.6–63.3	57.9–58	NS	Low
Oluyemi, et al (2014)[a] [70]	CS	2006–2010	USA	Colon	155,020–229,202	50–75	–	66.4	61.7	HD	Low
Owens et al (2008) [102]	CS	2005	USA	Breast	–	≥40	–	66.8	66.8	NS	Low
				Cervix	19,114	≥18	7.6	79.2	78.4	NS	
				Colon	–	≥50	–	48.2	48.9	NS	
Porter et al (2016) [83][a]	CS	2012	USA	Colon	55,825	≥50	11.8	52.4	42.6	HD	Low
Richard et al (2015) [80][a]	CS	2012	Switzerland	Cervix	7319	20–69	2.6	Screened overall	72.9	NS	Low
Sanderson et al (2014) [78][a]	CS	2002–2009	USA	Breast	14,665–30,846	≥40	20.2–24.6	31–32.2	28.8–33.2	NS	Low
Singh et al (2015) [84][a]	CS	2012	Canada	Colon	61,707	50–74	12.1	Screened overall	55.2	NS	Low
Wernli et al (2014) [81]	Cohort	1996–2010	USA	Colon	81,223	50	7	37	41.2	LD	High
Zhao et al (2009) [103][a]	CS	2006	USA	Breast	140,936	≥40	11.5	76.4	77.1	NS	Low
				Cervix	10,634	18–69	7.7	74.2	79	LD	
				Colon	103,601	≥50	13.7	63.2	60.4	HD	

[a] Studies included in the meta-analysis

CP, colonoscopy; CS, cross-sectional study; FS, flexible sigmoidoscopy; HD, higher in diabetes; LD, lower in diabetes; NS, not significant

Table 2 Aggregate characteristics of the included studies by cancer screening site

Study characteristic	Breast cancer screening		Cervical cancer screening		Colorectal cancer screening	
	In meta-analysis (19 studies)	Not in meta-analysis (8 studies)	In meta-analysis (12 studies)	Not in meta-analysis (7 studies)	In meta-analysis (12 studies)	Not in meta-analysis (6 studies)
Study design						
Cross-sectional	10 (52.6)	7 (87.5)	10 (83.3)	7 (100)	9 (75)	5 (83.3)
Cohort	9 (47.4)	1 (12.5)	2 (16.7)	–	3 (25)	1 (16.7)
Data sources						
Self-report	10 (52.6)	7 (87.5)	10 (83.3)	7 (100)	9 (75)	5 (83.3)
Admin. claims	6 (31.6)	1 (12.5)	–	–	1 (8.3)	1 (16.7)
Medical records	3 (15.8)	–	2 (16.7)	–	2 (16.7)	–
Screening interval						
<1 year	–	1 (12.5)	–	–	1 (8.3), all tests	–
1–3 years[a]	19 (100)	7 (87.5)	12 (100)	6 (85.7)	8 (66.7), faecal	3 (50), faecal
3–5 years	–	–	–	–	3 (25), all tests	1 (16.7), all tests
5–10 years	–	–	–	–	10 (83.3), Endo	2 (33.3), Endo
Ever	–	–	–	1 (14.3)	–	2 (33.3), Endo
Screening start age						
18–24 years	–	–	5 (41.7)	4 (57.1)	–	–
25–30 years	–	–	2 (16.7)	–	–	–
40–45 years	7 (36.8)	5 (62.5)	1 (8.3)	1 (14.3)	–	1 (16.7)
50–55 years	9 (47.4)	2 (25)	3 (25)	1 (14.3)	10 (83.3)	4 (66.7)
>65 years	3 (15.8)	–	1 (8.3)	–	2 (16.7)	–
Not reported	–	1 (12.5)	–	1 (14.3)	–	1 (16.7)
Screening end age						
64–69 years	4 (21)	1 (12.5)	8 (66.7)	2 (28.6)	1 (8.3)	1 (16.7)
70–79 years	4 (21)	1 (12.5)	1 (8.3)	1 (14.3)	4 (33.3)	–
No upper age limit	11 (57.9)	5 (62.6)	3 (25)	3 (42.8)	7 (58.3)	4 (66.7)
Not reported	–	1 (12.5)	–	1 (14.3)	–	1 (16.7)
Screening programme						
Organised	8 (42.1)	3 (37.5)	2 (16.7)	2 (28.6)	1 (8.3)	2 (33.3)
Opportunistic	–	2 (25)	3 (25)	2 (28.6)	–	1 (16.7)
Not reported	11 (57.9)	3 (37.5)	7 (58.3)	3 (42.8)	11 (91.7)	3 (50)
Screening modality (CRC only)[b]						
Faecal test: FOBT or FIT	–	–	–	–	12 (100)	5 (83.3)
Endoscopy: FS or CP	–	–	–	–	11 (91.7)	5 (83.3)
Endoscopy: other[c]	–	–	–	–	3 (25)	3 (50)
Women-only sample (CRC only)	–	–	–	–	3 (25)	1 (16.7)

Data show no. of studies (% of column total)

[a] 1–3 years for breast cancer screening; 2–3 years for cervical cancer screening; 1–2 years for colorectal cancer screening

[b] Screening modalities are not mutually exclusive across studies (i.e. a single study could report on multiple screening modalities)

[c] Other endoscopic tests include double-contrast barium enema, proctoscopy and computed tomographic (CT) colonography

CP, colonoscopy; CRC, colorectal cancer; Endo, endoscopy; FS, flexible sigmoidoscopy

12 cohort [59, 65, 71–76, 81, 86, 94, 101] designs, including one RCT assessing the effect of diabetes on colorectal cancer screening completion independent of the intervention [59]. Over half of the studies were conducted in North America, with 21 studies from the USA [59, 66, 70–72, 78, 81–83, 85, 86, 89, 90, 94–98, 101–103] and three from Canada [73, 75, 84]. The remaining studies were from Europe [65, 76, 80, 88, 91–93, 99, 100], the Middle East [74, 77] and Asia [79, 87]. Sample sizes

ranged from 129 to 732,687 individuals and the mean sample diabetes prevalence was 15.1% for breast, 9.7% for cervical and 12.4% for colorectal cancer screening.

Assessment of methodological quality Methodological quality varied across studies (ESM Table 3). Overall, only nine studies [59, 65, 71–75, 81, 94] were rated as high quality (>6 points) and all were cohort designs. Nearly all studies were conducted in large population-based samples. Over half of the cross-sectional studies did not justify their sample sizes [70, 77, 78, 83, 85, 87–90, 96–98, 100, 103], which poses a risk of underpowered analyses. Most cross-sectional surveys also had low response rates [80, 91, 96, 97] or did not report either the response rate or the characteristics of non-respondents [66, 70, 78, 83–85, 87, 89, 90, 92, 93, 95, 98–100, 102]. Three cohort studies did not provide information on loss to follow-up [71, 86, 101], posing the risk of attrition bias. Six cohort studies had overlapping or ambiguous intervals over which diabetes and cancer screening status were determined [71, 72, 74, 76, 86, 101], which raises concerns around the exposure and outcome temporal order. Thirty-six studies controlled for either age or personal or family history of cancer [59, 65, 66, 70–89, 91–103] and 22 controlled for both [19–28, 30, 31, 35, 39, 40, 43, 44, 48, 50, 52, 54, 55].

Funnel plots for each cancer site indicate possible small study effects (ESM Figs. 2–4), suggesting that we cannot rule out the risk of publication bias. Low-precision studies showed lower screening participation in individuals with diabetes and a larger screening uptake gap between the groups, while higher-precision studies were closely and symmetrically distributed about the pooled effect size estimates.

Assessment of the exposure Diabetes status was self-reported in 26 studies [59, 66, 70, 72, 77–80, 82–85, 88–93, 95–100, 102, 103], of which 17 considered ever-diagnosis [66, 70, 72, 78, 80, 83, 85, 90, 92, 93, 95–99, 102, 103], two considered current diagnosis [88, 100] and seven did not provide a look-back period [59, 77, 79, 82, 84, 89, 91]. The remaining studies defined diabetes up to 10 years before baseline using administrative data [65, 71, 73, 75, 81, 94], medical charts [74, 86, 101], records of prescription medications [76] and records of direct physical and laboratory examinations performed at the time of survey administration [87]. Two self-reported [78, 88] and four administrative data definitions [71, 73, 75, 94] were independently validated by healthcare professionals against medical charts [71, 73, 75, 78, 94] and responses to other survey questions [88].

Breast cancer screening Breast cancer screening with a bilateral mammogram was defined using self-report in 17 studies [77, 78, 87–93, 95–100, 102, 103], administrative claims in seven studies [65, 71–73, 75, 76, 94] and medical records in three studies [74, 86, 101]. Most studies were conducted in age-eligible women and defined screening as receiving a mammogram within 1–3 years, which is consistent with clinical guidelines [27–30] (Table 2). To minimise inclusion of non-screening mammograms, studies excluded women with a history of breast cancer [65, 71–75, 78, 88, 95, 101], any cancer [94, 97, 100], mastectomy [71, 100, 101], recent abnormal mammogram [101] or mammogram performed after a recent breast cancer diagnosis [75]. Mammograms performed by invitation within organised programmes were considered as screening tests [65, 76, 88].

The prevalence of breast cancer screening ranged from 9.3% to 78.1% in women with diabetes and from 5.8% to 84.9% in women without diabetes. Adjusted ORs for breast cancer screening were reported by 19 studies [65, 71–75, 78, 86–88, 92–98, 101, 103] (Fig. 1). The remaining studies only reported the proportions of women screened in each group, due to the descriptive focus of the studies [76, 89, 90, 99, 100, 102], non-significant bivariate associations between diabetes and screening [91], or statistical model selection procedures [77]. One descriptive study [100] and 12 of the 19 analytical studies found that breast cancer screening participation was significantly lower in women with diabetes [65, 71, 73–75, 87, 88, 92–94, 97, 98].

The pooled OR for breast cancer screening uptake in women with diabetes relative to those without was 0.83 (95% CI 0.77, 0.90; 19 studies, 23 subgroups, $I^2 = 97\%$) (Fig. 1). Heterogeneity was partially explained by study designs and quality ratings; however, the effect size estimate remained robust in subgroup analyses across these factors (ESM Table 4). The likelihood of breast cancer screening in women with diabetes relative to those without was lower in studies conducted outside of the USA compared with those conducted in the USA [71, 72, 78, 86, 94–98, 101, 103] (outside USA: 0.78 [95% CI 0.69, 0.88], 8 studies, 8 subgroups, $I^2 = 99\%$; in USA: 0.89 [95% CI 0.84, 0.96], 11 studies, 15 subgroups, $I^2 = 54\%$).

Cervical cancer screening Cervical cancer screening was determined using self-report in 17 studies [79, 80, 87–93, 95–100, 102, 103] and medical records in two studies [86, 101]. Consistent with clinical guidelines [31–33], most studies considered age-eligible women and defined screening as receipt of a Pap test within 2–3 years (Table 2). To approximate a screen-eligible population, some studies excluded women with a history of cervical cancer [88, 95, 101], any cancer [97, 100], hysterectomy [88, 89, 100, 101], or a recent abnormal Pap test [101].

The prevalence of cervical cancer screening ranged from 29.5% to 84.9% in women with diabetes and from 46.9% to 86.4% in women without diabetes. Seven studies did not report adjusted estimates due to the descriptive focus of the studies [89, 90, 99, 100, 102] or non-significant bivariate associations between diabetes and screening [79, 91]. Lower uptake of cervical cancer screening in women with diabetes was observed in four descriptive [79, 90, 99, 100] and six analytical studies [87, 92, 93, 97, 98, 103], while three descriptive [89, 91, 102] and six analytical studies [80, 86, 88, 95, 96, 101] found non-significant differences.

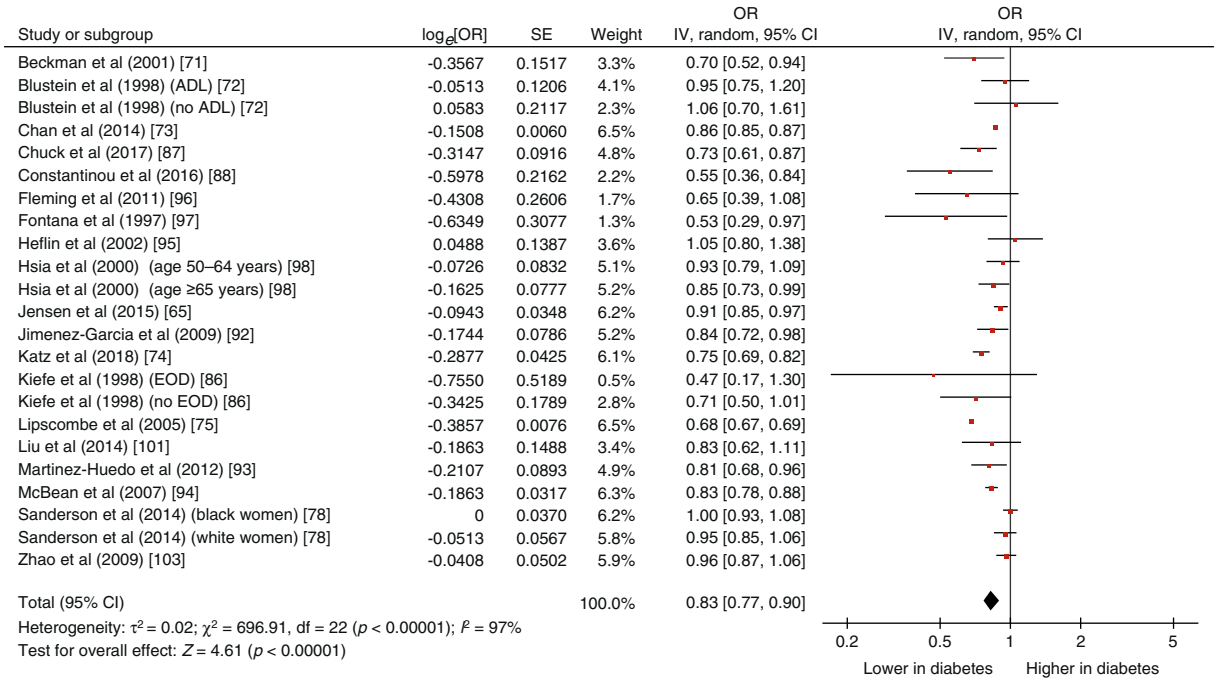

Fig. 1 Forest plot depicting breast cancer screening (mammography) in women with vs without diabetes. ADL, activities of daily living (subgroups by individuals with and without ADL limitations); EOD, end-organ damage (subgroups by individuals with and without EOD); IV, inverse variance

The pooled OR for cervical cancer screening uptake in women with diabetes relative to those without was 0.76 (95% CI 0.71, 0.81; 12 studies, 14 subgroups), with low heterogeneity ($I^2 = 0\%$) (Fig. 2). This finding was robust across subgroup analyses by study design and setting (ESM Table 4). Subgroup analyses by quality rating could not be performed, as all studies on cervical cancer screening were rated as lower quality.

Colorectal cancer screening Colorectal cancer screening was determined using administrative data [81, 94] and medical records in two studies each [59, 101], and was self-reported in the remaining studies. Individuals were considered screened if they received a faecal or an endoscopic test, with faecal occult blood test (FOBT), flexible sigmoidoscopy and colonoscopy being the most frequently used tests. As recommended by clinical guidelines [34], screening intervals were 1–2 years for faecal tests [66, 70, 83–85, 95, 96, 99–101, 103] and 5–10 years for endoscopic tests [66, 70, 83–85, 96, 100, 101, 103], and target populations included adults over the age of 50 (Table 2). To minimise inclusion of non-screening tests, studies excluded individuals with a history of colorectal cancer

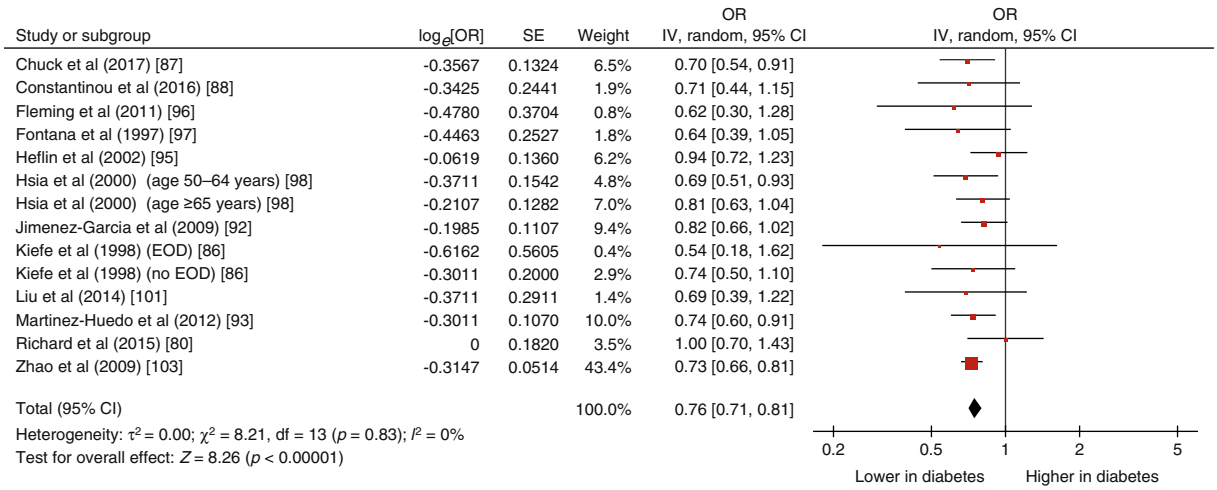

Fig. 2 Forest plot depicting cervical cancer screening (Pap smear) in women with vs without diabetes. EOD, end-organ damage (subgroups by individuals with and without EOD); IV, inverse variance

[59, 66, 81–83, 95, 101], any cancer [94, 97, 100], inflammatory bowel disease [59, 81], colonic polyps or gastrointestinal bleeding [59], family history of colorectal cancer [59], hereditary polyposis/non-polyposis syndrome [59], colonoscopy before the age of 50 years [81], colectomy [81], colorectal cancer-related surgery [100], or recent abnormal screening results [101].

The prevalence of colorectal cancer screening ranged from 8.1% to 66.4% in individuals with diabetes and from 5.7% to 61.7% in individuals without diabetes. Twelve of the 18 studies reported adjusted ORs or PRs [59, 66, 70, 83, 84, 94–98, 101, 103]. The remaining studies had a descriptive focus [85, 99, 100, 102] or reported effect measures that could not be pooled with ORs [81, 82]. All four descriptive studies found that colorectal cancer screening was comparable between individuals with and without diabetes [85, 99, 100, 102]. The results of the analytical studies were mixed, with three studies showing significantly greater likelihood of screening in diabetes [70, 83, 103], five studies showing significantly lower likelihood of screening in those with diabetes [59, 81, 94, 97, 98] and six studies finding no significant difference [66, 82, 84, 95, 96, 101].

The pooled OR for colorectal cancer screening uptake in individuals with vs without diabetes was 0.95 (95% CI 0.86, 1.06; 12 studies, 16 subgroups, $I^2 = 90\%$) (Fig. 3). Heterogeneity was partially explained by differences in study design, participant sex and screening modalities (ESM Table 4). Cohort studies showed lower likelihood of screening in diabetes (0.77 [95% CI 0.70, 0.86], $I^2 = 0\%$), though this represented only four subgroups from three studies [59,94,101]. Women with diabetes were less likely to be screened compared with women without diabetes (0.86 [95% CI 0.77, 0.97]; 7 studies, 8 subgroups, $I^2 = 85\%$), while among men, no such association was observed. The analysis was robust across screening modality subgroups (FOBT vs flexible sigmoidoscopy or colonoscopy). We could not perform subgroup analyses by quality rating or study setting, as only two studies were rated to be of high quality [59, 94] and only one was conducted outside the USA [84]. Excluding each of these studies in sensitivity analyses did not meaningfully influence the results (ESM Table 4).

Discussion

Principal findings This systematic review and meta-analysis of 37 studies suggested that women with diabetes are significantly less likely to undergo recommended breast, cervical and colorectal cancer screening than women without diabetes, though the absolute differences might be modest. The findings were particularly robust for cervical cancer screening, with low heterogeneity across studies. Suboptimal cancer screening rates in women with diabetes may be putting them at risk of poorer cancer outcomes.

Strengths and limitations in relation to other studies To our knowledge, this is the first systematic review and meta-analysis of the effect of diabetes on cancer screening participation. Three literature reviews on cancer screening participation in adults with chronic comorbidities have been conducted to date, with mixed findings. A narrative review concluded that diabetes may negatively impact cancer screening uptake in elderly individuals [53], although the findings were based on only five studies conducted in the USA [71, 72, 86, 94, 95]. Another systematic review of seven studies found that chronic disease may be associated with increased likelihood of colorectal cancer screening, without specific inferences about diabetes [54]. Neither review performed a meta-analysis. A meta-analysis of 22 studies showed inconclusive evidence regarding the impact of composite comorbidity measures on breast and cervical cancer screening participation [55].

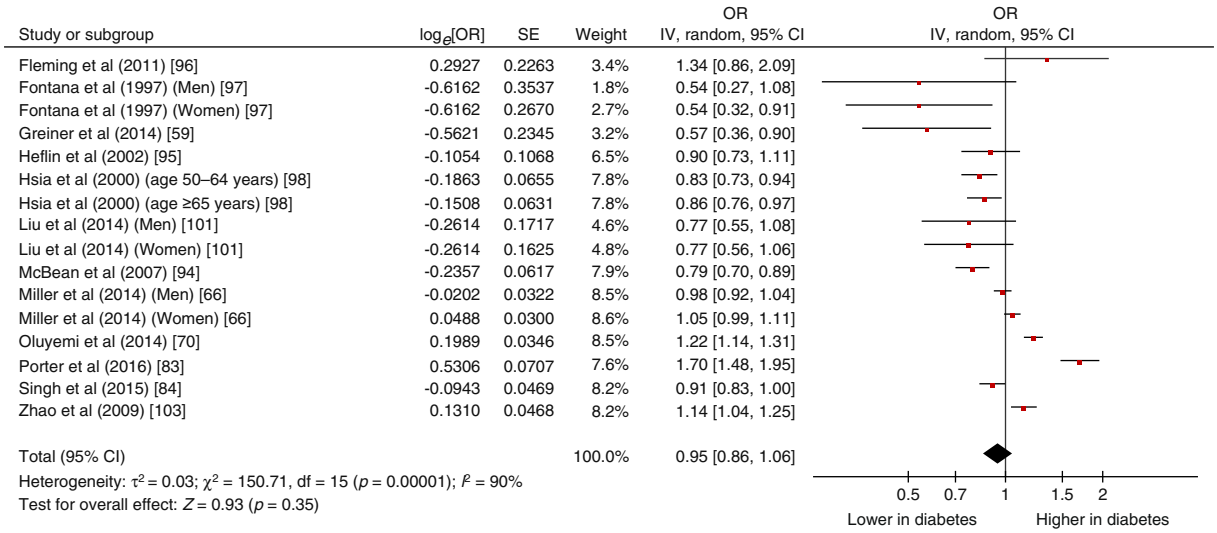

Fig. 3 Forest plot depicting colorectal cancer screening (faecal and endoscopic tests) in individuals with vs without diabetes. IV, inverse variance

The strengths of our study include quantifying the specific effects of diabetes on all three recommended cancer screenings and a rigorous review process. Compared with prior research, our review resulted in a larger pool of eligible studies for each cancer site.

Our findings should be interpreted in light of a number of important limitations. First, most studies had low methodological quality ratings and the extent to which non-response bias and lack of power in cross-sectional studies and loss to follow-up in cohort studies may have affected our results is unclear. In addition, 25 of the 37 studies were cross-sectional, while another six studies had overlapping or unclear intervals in which the exposure and the outcome status were defined [71, 72, 74, 76, 86, 101]. Many studies were therefore unable to determine whether the diabetes diagnosis preceded cancer screening participation, limiting our ability to infer causality. Nonetheless, since lifetime ('ever') diabetes diagnosis was considered in over half of these studies [66, 70, 72, 78, 80, 83, 85, 90, 92, 93, 95–99, 102, 103] while screening was established over intervals of under 10 years, instances of reversed exposure–outcome temporal sequences are likely to be few. Further, diabetes and outcome status were self-reported in most studies. While self-reported diabetes status has been shown to have high accuracy [104–108], cancer screening participation tends to be overestimated [109–111]. The true cancer screening participation gap in diabetes may thus be greater than that found.

Second, despite our efforts to only pool the most-adjusted effect estimates, meta-analyses of observational studies are particularly vulnerable to residual confounding [67, 68]. Unexamined factors known to be associated with both diabetes status and cancer screening participation, such as socioeconomic status [112, 113], may thus underlie our findings. Interestingly, a Canadian study showed that diabetes was associated with lower mammographic breast cancer screening participation across all socioeconomic strata [73], suggesting that diabetes and socioeconomic status are distinct and independent barriers. The evidence on other possible confounding factors, including other comorbidities [55, 101], patient health and functional status [72], and patient preferences [114], is less clear. This residual confounding may also explain the high statistical heterogeneity that was observed in breast and colorectal cancer screening meta-analyses. In subgroup analyses, the heterogeneity was only partially accounted for by study designs, study quality ratings, healthcare systems (USA vs non-USA; breast cancer screening only), sex of participants (colorectal cancer screening only), and screening modalities (FOBT vs flexible sigmoidoscopy or colonoscopy; colorectal cancer screening only).

Third, we could not confidently rule out publication bias in our review. This is worth noting because, to gage between-study variance, random-effects meta-analyses award relatively more weight to smaller studies than fixed effects meta-analyses [57], thus potentially biasing the result away from the null, should publication bias be present. However, in meta-analyses of observational studies, funnel plot asymmetry may also be attributed to residual confounding, methodological limitations and statistical heterogeneity, rather than publication bias alone [115].

Fourth, measures representing relative reductions in the likelihood of adequate screening, such as ORs, should be interpreted with caution, as absolute differences are likely to be more modest. While it is not possible to directly convert adjusted relative estimates into absolute ones [42], it is important to consider that diabetes may not be the most important, and thus actionable, determinant of cancer screening participation, compared with other characteristics of individuals.

Finally, it should be noted that our search was limited to studies written in English. However, according to a prior comprehensive review by evidence synthesis experts, the use of language restrictions is unlikely to result in systematic biases that could alter the interpretation of results [116].

Implications of findings and future directions The burden of diabetes management in primary care may contribute to lower cancer screening uptake among individuals with diabetes. It has been shown that as the number of guideline-recommended preventive services for which a person is eligible increases, the likelihood of their utilisation decreases [117]. Providing guideline-adherent chronic disease care also requires more consultation time than physicians have available per patient [43, 118–120], which may lead to prioritisation of diabetes-related care over routine preventive care [41, 119, 120]. This is especially relevant for cervical cancer screening, as Pap tests are performed during office-based primary care visits, while breast and colorectal cancer screenings are performed outside of this setting. All tests nonetheless require physician orders, which may explain the modest reductions in both breast and colorectal cancer screening we found in women with diabetes.

Regional differences may also underlie our findings. We noted that the gap in breast cancer screening between women with and without diabetes was more pronounced in studies conducted outside the USA, including Canada [73, 75], France [88], Spain [92, 93], Denmark [65], Israel [74] and South Korea [87]. In contrast to the USA, all of these jurisdictions have universal healthcare systems and thus, more equitable access to preventive care. Since regular healthcare contact and health insurance status have shown to be independent predictors of cancer screening in the USA [98, 121], it is possible that individuals with diabetes receive more opportunistic screening than those without diabetes in non-universal healthcare settings due to increased healthcare contact. This may also explain our null findings for colorectal cancer screening, as all but one [84] of those studies were set in the USA. Sex-based differences in colorectal cancer screening participation in the present review are consistent with overall screening patterns in the USA, as women are less likely to

undergo screening regardless of diabetes status [122]. Interestingly, research in other jurisdictions suggests the opposite trend, with women having higher colorectal cancer screening participation rates than men [123]. Our findings suggest that diabetes status may modify this trend in universal settings; however, more primary evidence in such settings is required. Other contextual factors, such as the overall population screening uptake rate and the presence of an organised screening programme, should also be examined.

Novel screening approaches may increase cancer screening uptake in groups presenting high healthcare burden and competing demands. The use of mail- and telephone-based invitations has been shown to improve first and repeat screening for all three cancers [124, 125]. Direct mailing of self-screening kits, such as the faecal immunochemical test (FIT) for colorectal cancer [40, 126, 127] and human papilloma virus (HPV) test for cervical cancer [128–130], is associated with even greater screening uptake, particularly in under-screened populations [126–128, 131]. Emphasising colorectal cancer screening in women may be particularly important, as some women perceive colorectal cancer to mainly affect men [132, 133].

Beyond population-based interventions, targeted approaches may be particularly beneficial in individuals with diabetes. Shared-care between primary care physicians and diabetes specialists has been associated with better adherence to diabetes-related health services and higher likelihood of receiving breast and cervical cancer screening when compared with care by either practitioner alone [134]. Integrated diabetes management models may therefore improve attention to other recommended preventive health services by offloading diabetes care from primary care physicians. Supporting diabetes self-management may also yield better screening participation. Recent evaluations of patient navigator interventions in primary care have been associated with improved glycaemic control and appointment-keeping in patients with diabetes [135], as well as greater likelihood of colonoscopy attendance in the general population [136].

Conclusion

This systematic review and meta-analysis suggests that women with diabetes are significantly less likely to receive recommended breast, cervical and colorectal cancer screening than women without diabetes. Caution is warranted in interpreting these findings due to high study heterogeneity, low methodological quality of included studies, and risk of publication bias. Given the increased risk of cancer in this population, future studies should consider using higher quality prospective methods to evaluate the contribution of diabetes status to cancer screening disparities in relation to other patient-, provider- and system-level factors.

Acknowledgements We would like to thank V. Lui (Gerstein Science Information Centre, University of Toronto) for her guidance in the design of the electronic database search strategy. DB is supported by the Enid Walker Award in Women's Health Research from Women's College Hospital. LL is supported by the Diabetes Investigator Award from Diabetes Canada.

Contribution statement DB, IL and LL conceived and designed the study. WW provided methodological and statistical advice. IL and LL provided clinical guidance in interpreting the results. DB, WW and IL assessed citations for eligibility and risk of bias. DB was involved in data abstraction, synthesis and drafting of the first version of the manuscript. All authors contributed critically to subsequent revisions and approved the final manuscript. All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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